Notice of Award

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 08/01/2020

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 1R01GM140459-01 REVISED
FAIN: R01GM140459

Principal Investigator(s):
David Kennedy

Project Title: US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

John W Hanold
Associate VP for Research
Pennsylvania State University
Office of Sponsored Programs
110 Technology Center Building
University Park, PA 168027000

Award e-mailed to: osp@psu.edu

Period Of Performance:
Budget Period: 08/01/2020 – 04/30/2021
Project Period: 08/01/2020 – 04/30/2025

Dear Business Official:

The National Institutes of Health hereby revises this award (see “Award Calculation” in Section I and “Terms and Conditions” in Section III) to PENNSYLVANIA STATE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the “Terms and Conditions” is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as “Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM140459. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.” Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator’s Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Connie Murphy
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 1R01GM140459-01 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$141,523
Fringe Benefits	$37,099
Personnel Costs (Subtotal)	$178,622
Materials & Supplies	$17,834
Travel	$6,800
Other	$6,731
Tuition Remission	$32,822
Federal Direct Costs	$242,809
Federal F&A Costs	$127,042
Approved Budget	$369,851
Total Amount of Federal Funds Obligated (Federal Share)	$369,851
TOTAL FEDERAL AWARD AMOUNT	$369,851
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$369,851	$369,851
2	$369,851	$369,851
3	$369,851	$369,851
4	$369,851	$369,851
5	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1246000376A1
Document Number:	RGM140459A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2020

IC	CAN	2020	2021	2022	2023	2024
GM	8019957	$369,851	$369,851	$369,851	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: G242DJ / **OC**: 41021 / **Released**: (b)(6) 07/27/2020
Award Processed: 08/01/2020 12:02:07 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R01GM140459-01 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1R01GM140459-01 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.

c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM140459. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made

publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.
Treatment of Program Income:
Additional Costs

SECTION IV – GM Special Terms and Conditions – 1R01GM140459-01 REVISED

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

This revised award adds a 5th year of funding as requested in the original application since the PD/PI qualifies as an Early Stage Investigator according to the NIH guidelines: https://grants.nih.gov/policy/early-investigators/index.htm

TERMS AND CONDITIONS FROM PREVIOUS AWARD:

1. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-20-068: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-068.html.

2. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap. Therefore, this award and/or future years are adjusted accordingly, if applicable.
Current salary cap levels can be found at the following URL:
http://grants.nih.gov/grants/policy/salcap_summary.htm

3. As appropriate, the grant recipient is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

4. **IMPORTANT**: The grant recipient is reminded that payments made for educational assistance (e.g., scholarships, fellowships, and student aid costs) may not be paid from NIH research grant funds even when they would appear to benefit the research project. See the explanation of "Fringe Benefits/IHE Tuition/Tuition Remission" in the NIH Grants Policy Statement, Section 7.9.1. at:
https://grants.nih.gov/grants/policy/nihgps/HTML5/section_7/7.9_allowability_of_costs_activities.htm#Selected

5. The Year -01 budget period is slightly less than 12 months in length (full 12-month level of funds provided) so that the anniversary date for future non-competing awards will be May 1st. The Research Performance Progress Report (RPPR) will be due 45 days prior to this date (60 days for non-SNAP awards) each year. Guidance on RPPR submission is documented in the RPPR Instruction Guide found at: http://grants.nih.gov/grants/rppr/index.htm.

This anniversary date may change the receipt date for the next competing continuation (Type 2) application. Consult the submission dates/deadlines on the NIH Office of Extramural Research Grants (OER) Home page at http://grants.nih.gov/grants/dates.htm.

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an

Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Robert Altieri
Email: Robert.Altieri@nih.gov **Phone**: (631) 849-1872 **Fax**: (301) 480-2554

Program Official: Daniel E Janes
Email: daniel.janes@nih.gov

SPREADSHEET SUMMARY
GRANT NUMBER: 1R01GM140459-01 REVISED

INSTITUTION: PENNSYLVANIA STATE UNIVERSITY

Budget	Year 1	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$141,523	$141,523	$141,523	$141,523	$141,523
Fringe Benefits	$37,099	$37,099	$37,099	$37,099	$37,099
Personnel Costs (Subtotal)	$178,622	$178,622	$178,622	$178,622	$178,622
Materials & Supplies	$17,834	$17,834	$17,834	$17,834	$17,834
Travel	$6,800	$6,800	$6,800	$6,800	$6,800
Other	$6,731	$6,731	$6,731	$6,731	$6,731
Tuition Remission	$32,822	$32,822	$32,822	$32,822	$32,822
TOTAL FEDERAL DC	$242,809	$242,809	$242,809	$242,809	$242,809
TOTAL FEDERAL F&A	$127,042	$127,042	$127,042	$127,042	$127,042
TOTAL COST	$369,851	$369,851	$369,851	$369,851	$369,851

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	60.5%	60.5%	60.5%	60.5%	60.5%
F&A Cost Base 1	$209,987	$209,987	$209,987	$209,987	$209,987
F&A Costs 1	$127,042	$127,042	$127,042	$127,042	$127,042

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 07/21/2020

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 1R01GM140459-01
FAIN: R01GM140459

Principal Investigator(s):
David Kennedy

Project Title: US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

John W Hanold
Associate VP for Research
Pennsylvania State University
Office of Sponsored Programs
110 Technology Center Building
University Park, PA 168027000

Award e-mailed to: osp@psu.edu

Period Of Performance:
Budget Period: 08/01/2020 – 04/30/2021
Project Period: 08/01/2020 – 04/30/2024

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $369,851 (see “Award Calculation” in Section I and “Terms and Conditions” in Section III) to PENNSYLVANIA STATE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the “Terms and Conditions” is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as “Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM140459. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.” Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator’s Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Connie Murphy
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 1R01GM140459-01

Award Calculation (U.S. Dollars)

Salaries and Wages	$141,523
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AMOUNT OF THIS ACTION (FEDERAL SHARE)	$369,851

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YR	**THIS AWARD**	**CUMULATIVE TOTALS**
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Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1246000376A1
Document Number:	RGM140459A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2020

IC	CAN	2020	2021	2022	2023
GM	8019957	$369,851	$369,851	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: G242DJ / **OC**: 41021 / **Released**: (b)(6) 07/13/2020
Award Processed: 07/21/2020 12:55:25 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R01GM140459-01

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1R01GM140459-01

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a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.

d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

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Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

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This award has been assigned the Federal Award Identification Number (FAIN) R01GM140459. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

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Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.
Treatment of Program Income:
Additional Costs

SECTION IV – GM Special Terms and Conditions – 1R01GM140459-01

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

1. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-20-068: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-068.html.

2. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap. Therefore, this award and/or future years are adjusted accordingly, if applicable.
Current salary cap levels can be found at the following URL:
http://grants.nih.gov/grants/policy/salcap_summary.htm

3. As appropriate, the grant recipient is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

4. **IMPORTANT**: The grant recipient is reminded that payments made for educational assistance (e.g., scholarships, fellowships, and student aid costs) may not be paid from NIH research grant funds even when they would appear to benefit the research project. See the explanation of "Fringe Benefits/IHE Tuition/Tuition Remission" in the NIH Grants Policy Statement, Section 7.9.1. at:
https://grants.nih.gov/grants/policy/nihgps/HTML5/section_7/7.9_allowability_of_costs_activities.htm#Selected

5. The Year -01 budget period is slightly less than 12 months in length (full 12-month level of funds provided) so that the anniversary date for future non-competing awards will be May 1st. The Research Performance Progress Report (RPPR) will be due 45 days prior to this date (60 days for non-SNAP awards) each year. Guidance on RPPR submission is documented in the RPPR Instruction Guide found at: http://grants.nih.gov/grants/rppr/index.htm.

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SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

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Grants Management Specialist: Robert Altieri
Email: Robert.Altieri@nih.gov **Phone**: (631) 849-1872 **Fax**: (301) 480-2554

Program Official: Daniel E Janes
Email: daniel.janes@nih.gov

SPREADSHEET SUMMARY
GRANT NUMBER: 1R01GM140459-01

INSTITUTION: PENNSYLVANIA STATE UNIVERSITY

Budget	Year 1	Year 2	Year 3	Year 4
Salaries and Wages	$141,523	$141,523	$141,523	$141,523
Fringe Benefits	$37,099	$37,099	$37,099	$37,099
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Travel	$6,800	$6,800	$6,800	$6,800
Other	$6,731	$6,731	$6,731	$6,731
Tuition Remission	$32,822	$32,822	$32,822	$32,822
TOTAL FEDERAL DC	$242,809	$242,809	$242,809	$242,809
TOTAL FEDERAL F&A	$127,042	$127,042	$127,042	$127,042
TOTAL COST	$369,851	$369,851	$369,851	$369,851

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4
F&A Cost Rate 1	60.5%	60.5%	60.5%	60.5%
F&A Cost Base 1	$209,987	$209,987	$209,987	$209,987
F&A Costs 1	$127,042	$127,042	$127,042	$127,042

Form Approved Through 03/31/2020 OMB No. 0925-0001

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ength restrictions indicated.

PI: **KENNEDY, DAVID**
1 R01 GM140459-01
Dual: TW
IRG: ZRG1 IDM-U(55) R

Council: 05/2020
Received: 03/25/2020

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*

US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☐ YES
(If "Yes," state number and title)
Number: PAR-20-001 Title: NIH-NSF Ecology and Evolution of Infectious Diseases Program: A J

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Kennedy, David	Ph. D.	(b)(6)

3c. POSITION TITLE
Assistant Professor Of Biology

3d. MAILING ADDRESS *(Street, city, state, zip code)*
W229B Millennium Science Bldg
University Park, PA 16802-7000

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT

3f. MAJOR SUBDIVISION
Eberly College of Science

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 814-863-5461 FAX:

E-MAIL ADDRESS:
dak30@psu.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
■ No ☐ Yes	☐ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
	☐ No ☐ Yes	☐ No ☐ Yes

5. VERTEBRATE ANIMALS ☐ No ■ Yes — 5a. Animal Welfare Assurance No. A3141-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
08/01/20	07/31/2025	284,961	427,614	1,570,374	2,361,226

9. APPLICANT ORGANIZATION
Name The Pennsylvania State University
Address
Office of Sponsored Programs
110 Technology Center Building
University Park, PA 16802-7000

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ■ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
1246000376A1
DUNS NO. 0003403953 Cong. District PA-012

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name John W. Hanold
Title Associate VP for Research
Address
Office of Sponsored Programs
110 Technology Center Building
University Park, PA 16802-7000
Tel: 814-865-1372 FAX: 814-863-3413
E-Mail: osp@psu.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name John W. Hanold
Title Associate VP for Research
Address
Office of Sponsored Programs
110 Technology Center Building
University Park, PA 16802-7000
Tel: 814-865-1372 FAX: 814-863-3413
E-Mail: osp@psu.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*
(b)(6)

DATE
3/24/2020

PROJECT SUMMARY (See instructions):

Vaccination can be one of the most efficient and effective tools for controlling infectious diseases, but in many settings, including wildlife and farm animal diseases, logistical and economic hurdles make it impractical to vaccinate large enough fractions of hosts to achieve herd immunity. Transmissible vaccines, defined as vaccines capable of disseminating from vaccinated to non-vaccinated hosts, offer one potential solution to these challenges by amplifying the impact of vaccination campaigns. However, transmissible vaccines are not without risk. Reversion to virulence or recombination with wildtype pathogens could cause transmissible vaccines to make matters worse or complicate elimination efforts. This proposed work will for the first time quantify the effects of transmissible vaccines on disease ecology and evolution using an economically important, naturally transmissible vaccine currently in widespread use on poultry farms.

Marek's disease, a poultry-specific disease that is a threat to sustainable poultry production, is currently controlled by the "Rispens" vaccine, a live, attenuated vaccine that has been widely used for two decades. Recent experiments have found that this vaccine is capable of efficiently transmitting from vaccinated to non-vaccinated birds. These results are consistent with recent field surveillance studies that have found vaccine isolates in cohorts that have not been directly vaccinated. In addition, advances in whole genome sequencing have revealed recombination between the vaccine virus and the wildtype virus, which is concerning given that the vaccine virus harbors highly virulent forms of the oncogenic meq gene. Together, these observations demonstrate that the Rispens vaccine is a transmissible vaccine capable of evolving and potentially facilitating adverse evolution of wildtype Marek's disease virus. Our primary objective is to quantify the consequences of transmissible vaccine use. Specifically, we will:

1) Develop a general model of transmissible vaccination to identify key knowledge gaps
2) Characterize vaccine transmission and its impact on wildtype virus transmission
3) Characterize the genetic evolution of wildtype virus and vaccine virus
4) Model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine

RELEVANCE (See instructions):

Transmissible vaccines are being widely considered to control zoonotic diseases in animal populations, including Ebola, Marburg, Sin Nombre hantavirus, and rabies. However, before transmissible vaccines are introduced, the benefits and risks must be considered. This study will provide the first empirical estimate of how well a transmissible vaccine spreads, and it will determine whether adverse evolution has occurred due to the widespread use of a transmissible vaccine, or if not, whether it is likely to occur.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location			
Organizational Name: The Pennsylvania State University			
DUNS: 003403953			
Street 1: W229B Millennium Science Bldg		Street 2:	
City: University Park	County: Centre		State: Pennsylvania
Province:	Country: United States		Zip/Postal Code: 16802-7000
Project/Performance Site Congressional Districts: PA-012			

Additional Project/Performance Site Location			
Organizational Name:			
DUNS:			
Street 1:		Street 2:	
City:	County:		State:
Province:	Country:		Zip/Postal Code:
Project/Performance Site Congressional Districts:			

SENIOR/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other senior/key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Szpara, Moriah	(b)(6)	The Pennsylvania State University	Co-I

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ■ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: https://grants.nih.gov/stem_cells/registry/current.htm. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

The name of the program director/principal investigator must be provided at the top of each printed page and each continuation page.

RESEARCH GRANT
TABLE OF CONTENTS

* Follow the page limits for these sections indicated in the application instructions, unless the Funding Opportunity Announcement specifies otherwise.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 08/01/20 THROUGH 07/31/21

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
David Kennedy	PD/PI	(b)(6)				11065	4187	15252
Moriah Szpara	Co-I					25375	9604	34979
Chris Bown	Technician					11907	4507	16414
Daniel Renner	Technician					18230	6900	25130
TBN-Postdoctor scholar	Postdoc	12				51361	12081	63442
2 TBN-Graduate Assitants	Graduate assist.		9			48154	6260	54414
	SUBTOTALS →					166092	43539	209631

CONSULTANT COSTS

EQUIPMENT *(Itemize)*

SUPPLIES *(Itemize by category)*

Two laptops for the grad students - $4,000
Arbor BioSciences oligo sets - $11,930
Laboratory consumables - $5,000

20930

TRAVEL

Domestic travel - $4,500 International travel - $3,480 — 7980

INPATIENT CARE COSTS

OUTPATIENT CARE COSTS

ALTERATIONS AND RENOVATIONS *(Itemize by category)*

OTHER EXPENSES *(Itemize by category)*

ICS-ACI services - $7,200
Participant support, scholarships - $700
Tuition Remission - $38,520

46420

CONSORTIUM/CONTRACTUAL COSTS | DIRECT COSTS

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* $ 284961

CONSORTIUM/CONTRACTUAL COSTS | FACILITIES AND ADMINISTRATIVE COSTS

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD $ 284961

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	209631	232408	238214	244167	250270
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES	20930	16225	14225	5000	
TRAVEL	7980	26550	4500	21550	4500
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	46420	54577	65981	52992	54254
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	284961	329760	322920	323709	309024
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	284961	329760	322920	323709	309024

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD $ 1570374

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Salaries and Wages

Principal Investigator – David Kennedy ((b)(6) month effort year 1 and (b)(6) months effort years 2-5): Dr. Kennedy will coordinate and oversee the work conducted for this project, including supervision of a graduate student and a postdoctoral researcher. He will also contribute to conference calls, experimental design, progress reports, and the dissemination and publication of results.

Co-Principal Investigator – Moriah Szpara ((b)(6) months effort): Dr. Szpara will oversee the work in Aim 3, including supervision of a research technician and a bioinformatician. She will also contribute to conference calls, experimental design, progress reports, and the dissemination and publication of results.

Bio Technician – Chris Bowen ((b)(6) months effort): This technician's role will be to conduct DNA extractions, sample preparation, and other molecular biology methods required in Aim 3.

Computational Technician – Daniel Renner ((b)(6) months effort): This technician's role will be to process the sequencing reads for de novo genome assembly and contig reconstruction.

Post Doctoral Scholar – TBN (12 calendar months effort): The Postdoc's role will be to integrate the experimental results with mathematical models of Marek's disease virus transmission (Aims 3 and 4).

Graduate Assistant – TBN (4.5 academic months effort): The student's role will be to construct and analyze general models of the consequences of transmissible vaccination (Aims 1 and 2).

Graduate Assistant – TBN (4.5 academic months effort): The student's role will be to conduct the computational evolutionary analyses in Aim 3. The student will also assist in DNA extractions, sample preparation, and genome assembly.

The principal investigator is budgeted at the percentage of time shown using his/her actual salary in the calculation. The principal investigator's time includes both technical and project management functions. Any other individuals/positions shown are technical staff with the percentage of time shown and actual salaries used. For project time occurring after July 1 of any given year, the salaries have been adjusted at the University approved rate of 2.5%.

Fringe Benefits
Fringe benefits are computed using the provisional rates of 37.85% applicable to Category I Salaries, 13.00% applicable to Category II Graduate Assistants, 7.86% applicable to Category III Salaries and Wages, 0.25% applicable to Category IV Student Wages, and 23.52% for Category V, Postdoctoral Scholars and Fellows, for fiscal year 2020 (July 1, 2019, through June 30, 2020). If this proposal is funded, the rates quoted above shall, at the time of funding, be subject to adjustment for any period subsequent to June 30, 2020, if superseding Government approved rates have been established. Fringe benefit rates are negotiated and approved by the Office of Naval Research, Penn State's cognizant federal agency.

Travel
All travel will be in accordance with University travel regulations and mileage will be charged at the current rate on the date of travel.

Funds are requested for Dr. Kennedy, Dr. Szpara, and three trainees to travel to the International Symposium on Marek's Disease and Avian Herpesviruses in years 2 (international) and 4 (domestic) of this proposal. Registration for this year's meeting is $550 ($350 for graduate students). The meeting alternates between being hosted in North America (typically the United States) and being hosted internationally. We estimate a cost of $300 per day per person for food and lodging, and an average of $1000 per flight ($500 per flight for domestic, $1500 per flight for international).

In addition, funds are requested for Dr. Kennedy and two trainees to travel to the Ecology and Evolution of Infectious Diseases conference in years 1 through 5 of this proposal. Estimated costs are $200 per person for registration, $200 per day per person for food and lodging, and $500 per person per flight.

Lastly, funds are requested for Dr. Kennedy and two trainees to travel to Pirbright in year 2 for 6 days during one of the experimental studies. Per diem and lodging and meal costs are based on Department of Defense rates for "other" cities in the United Kingdom ($330 per person per day). Flights are estimated at $1500 per person.

Participant Support Costs
$700 per year is requested for scholarships to 2 youth attending Penn State's educational summer camp "Science-U".

Materials and Supplies
Funds are requested in year 1 for two laptops, one for each graduate student ($4000). Funds are also requested for one laptop in year 2 for the postdoctoral scholar ($2,000). In addition, funds are requested for a custom designed Arbor BioSciences oligo set in year 1 ($11,930), and for library prep and MiSeq sequencing of dust samples ($9,225 per year) in years 2 and 3. For consumables that will be used in prepping and handling samples, we request an additional $5000 per year in years 1 through 4.

Publication Costs
We are requesting $3000 in each of years 2 through 5 for publication costs.

Computer Services
To attain the computational requirements of Aims 1, 3, and 4, we are requesting funds for a subscription to PSU's high-performance computing infrastructure, ICS-ACI. This subscription is $25 per core per month, where the recommended minimum subscription being 20 cores ($6000 per year). We are additionally requesting funds to subscribe to the minimum storage allotment ($1200 per year).

Purchased Services
Funds are requested to cover PacBio sequencing at the Penn State Genomics Core. These expenses include $4000 for a pilot study in year 2. $1100 for indexing materials, $850 for indexing labor, $2392 for eight SMRTbell Express Template Preps, and $9872 for Sequel Sequencing of 8 SMRTcells in year 3.

Tuition
Computed using the approved tuition charges for a one-half (1/2) time graduate assistant of $9,350 (pre-comprehensive) and $3050 (post-comprehensive) for fall and spring semesters 2019/2020, and $4,675 for summer session 2020. The charges quoted above are increased by three percent (3%) for any project period occurring after summer session 2020, and each summer session thereafter.

F&A – On Campus Research
F&A rates are negotiated and approved by the Office of Naval Research, Penn State's cognizant federal agency. Penn State's current provisional on-campus rate for research is 58.05% of MTDC from July 1, 2019, through June 30, 2020. New awards and new competitive segments with an effective date of July 1, 2020, or later shall be subject to adjustment when superseding Government approved rates are established. Per 2 CFR 200 (Appendix III, Section C.7), the actual F&A rates used will be fixed at the time of the initial award for the duration of the competitive segment.

Definition of a Year
The University defines the term "year" as the fiscal year (July – June).

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☐ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☒ Domestic Grant with foreign involvement List Country(ies) Involved: United Kingdom

INVENTIONS AND PATENTS *(Renewal appl. only)* ☒ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
	0.00	

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in the NIH Grants Policy Statement, Section 4: Public Policy Requirements, Objectives and Other Appropriation Mandates. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☐ HHS Agreement dated: _____ ☐ No Facilities And Administrative Costs Requested.

☐ HHS Agreement being negotiated with _____ Regional Office.

☒ No HHS Agreement, but rate established with Office of Naval Research Date 07/16/2019

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	245,741	x Rate applied	58.05	% = F&A costs	$	142,653
b. 02 year	Amount of base $	289,383	x Rate applied	58.05	% = F&A costs	$	167,987
c. 03 year	Amount of base $	281,353	x Rate applied	58.05	% = F&A costs	$	163,325
d. 04 year	Amount of base $	280,917	x Rate applied	58.05	% = F&A costs	$	163,072
e. 05 year	Amount of base $	264,970	x Rate applied	58.05	% = F&A costs	$	153,815
					TOTAL F&A Costs	$	790,852

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

List of Suggested Reviewers or Reviewers Not To Include (optional)

SUGGESTED REVIEWERS:
Not Listed

REVIEWERS NOT TO INCLUDE:
Not Listed

PennState
Eberly College of Science

David Kennedy
Assistant Professor
Biology Department
Eberly College of Science
Phone: (814) 863-5461

The Pennsylvania State University
W229B Millennium Science Bldg
Pollock Road
University Park, PA 16802 US

To whom it may concern:

On behalf of the proposal investigators, I, Dr. David Kennedy, consent that the proposal as well as its unattributed reviews will be shared with the EEID partner-funding agencies.

Signed: (b)(6)

Organization: The Pennsylvania State University

Date: 11/19/19

The following information regarding collaborators and other affiliations (COA) must be separately provided for each individual identified as senior project personnel. The COA information must be provided through use of this COA template.

Please complete this template (e.g., Excel, Google Sheets, LibreOffice), save as .xlsx or .xls, and upload directly as a Fastlane Collaborators and Other Affiliations single copy doc. Do not upload .pdf.

Please note that some information requested in prior versions of the PAPPG is no longer requested. THIS IS PURPOSEFUL AND WE NO LONGER REQUIRE THIS INFORMATION TO BE REPORTED. Certain relationships will be reported in other sections (i.e., the names of postdoctoral scholar sponsors should not be reported, however if the individual collaborated on research with their postdoctoral scholar sponsor, then they would be reported as a collaborator). The information in the tables is not required to be sorted, alphabetically or otherwise.

There are five separate categories of information which correspond to the five tables in the COA template:

COA template Table 1:
List the individual's last name, first name, middle initial, and organizational affiliation in the last 12 months.

COA template Table 2:
List names as last name, first name, middle initial, for whom a personal, family, or business relationship would otherwise preclude their service as a reviewer.

COA template Table 3:
List names as last name, first name, middle initial, and provide organizational affiliations, if known, for the following:
- **The individual's Ph.D. advisors; and**
- **All of the individual's Ph.D. thesis advisees.**

COA template Table 4:
List names as last name, first name, middle initial, and provide organizational affiliations, if known, for the following:
- **Co-authors on any book, article, report, abstract or paper with collaboration in the last 48 months (publication date may be later); and**
- **Collaborators on projects, such as funded grants, graduate research or others in the last 48 months.**

COA template Table 5:
List editorial board, editor-in chief and co-editors with whom the individual interacts. An editor-in-chief must list the entire editorial board.
- **Editorial Board: List name(s) of editor-in-chief and journal in the past 24 months; and**
- **Other co-Editors of journal or collections with whom the individual has directly interacted in the last 24 months.**

The template has been developed to be fillable, however, the content and format requirements must not be altered by the user. This template must be saved in .xlsx or .xls format, and directly uploaded into FastLane as a Collaborators and Other Affiliations Single Copy Document. Using the .xlsx or .xls format will enable preservation of searchable text that otherwise would be lost. It is therefore imperative that this document be uploaded in .xlsx or .xls only. Uploading a document in any format other than .xlsx or .xls may delay the timely processing and review of the proposal.

This information is used to manage reviewer selection. See Exhibit II-2 for additional information on potential reviewer conflicts.

1 Note that graduate advisors are no longer required to be reported.
2 Editorial Board does not include Editorial Advisory Board, International Advisory Board, Scientific Editorial Board, or any other subcategory of Editorial Board. It is limited to those individuals who perform editing duties or manage the editing process (i.e., editor in chief).

List names as Last Name, First Name, Middle Initial. Additionally, provide email, organization, and department (optional)
Fixed column widths keep this sheet one page wide; if you cut and paste text, set font size at 10pt or smaller, and
To insert *n* blank rows, select *n* row numbers to move down, right click, and choose Insert from the menu.
You may fill-down (crtl-D) to mark a sequence of collaborators, or copy affiliations. Excel has arrows that enable sorting.
For "Last Active Date" and "Last Active" columns dates are optional, but will help NSF staff easily determine which information remains relevant for reviewer selection.
"Last Active Date" and "Last Active" columns may be left blank for ongoing or current affiliations.

<u>Table 1:</u> List the individual's last name, first name, middle initial, and organizational affiliation in the last 12 months.

1	Your Name:	Your Organizational Affiliation(s), last 12 r	Last Active Date
	Kennedy, David A	Pennsylvania State University	

<u>Table 2:</u> List names as last name, first name, middle initial, for whom a personal, family, or business relationship would otherwise preclude their service as a reviewer.

R: Additional names for whom some relationship would otherwise preclude their service as a reviewer.

to disambiguate common names

2	Name:	Type of Relationship	Optional (email, Department)	Last Active

<u>Table 3:</u> List names as last name, first name, middle initial, and provide organizational affiliations, if known, for the following.

G: The individual's Ph.D. advisors; and
T: All of the individual's Ph.D. thesis advisees.

to disambiguate common names

3	Advisor/Advisee Name:	Organizational Affiliation	Optional (email, Department)
G:	Dwyer, Greg	University of Chicago	gdwyer@uchicago.edu

Table 4: List names as last name, first name, middle initial, and provide organizational affiliations, if known, for the following:

A: Co-authors on any book, article, report, abstract or paper with collaboration in the last 48 months (publication date may be later); and

C: Collaborators on projects, such as funded grants, graduate research or others in the last 48 months.

to disambiguate common names

4	Name:	Organizational Affiliation	Optional (email, Department)	Last Active
A:	Dukic, Vanja	University of Colorado, Boulder		12/31/15
C:	Dunn, John R	USDA-ARS		
C:	Dunn, Patricia A	Pennsylvania State University		
C:	Jones, Matthew J	Pennsylvania State University		
C:	Kurath, Gael	US Geological Survey		
A:	Nair, Venugopal K	The Pirbright Institute		
A:	Yao, Yongxiu	The Pirbright Institute		
A:	Pandey, Utsav	Children's Hospital Los Angeles		
A:	Purcell, Maureen K	US Geological Survey		12/31/16
A:	Read, Andrew F	Pennsylvania State University		
A:	Salathe, Rahel M	Pennsylvania State University		12/31/17
A:	Szpara, Moriah L	Pennsylvania State University		
C:	Wargo, Andrew R	Virgina Institute of Marine Science		
A:	Winton, James R	US Geological Survey		12/31/16
A:	Walkden-Brown, Stephen W	University of New England		12/31/15
A:	Bell, Andrew S	Pennsylvania State University		
A:	Renner, Daniel W	Pennsylvania State University		
A:	Shreve, Jacob T	Pennsylvania State University		12/31/16
A:	Cairns, Chris L.	Pennsylvania State University		
A:	Brito, Ilana L	Cornell University		12/31/16
C:	Boni, Maciej F	Pennsylvania State University		
C:	Shaw, Clara L	Pennsylvania State University		
C:	Bhattacharya, Amrita	Pennsylvania State University		
C:	Day, Troy	Queens University		
C:	Rachel Breyta	US Geological Survey		

Table 5: List editorial board, editor-in chief and co-editors with whom the individual interacts. An editor-in-chief must list the entire editorial board.

B: Editorial Board: List name(s) of editor-in-chief and journal in the past 24 months; and

E: Other co-Editors of journal or collections with whom the individual has directly interacted in the last 24 months.

to disambiguate common names

5	Name:	Organizational Affiliation	Journal/Collection	Last Active
E:	Richardson, Lauren A	NA	PLOS Biology	9/10/19

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List names as Last Name, First Name, Middle Initial. Additionally, provide email, organization, and department (optional)
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To insert *n* blank rows, select *n* row numbers to move down, right click, and choose Insert from the menu.
You may fill-down (crtl-D) to mark a sequence of collaborators, or copy affiliations. Excel has arrows that enable sorting.
For "Last Active Date" and "Last Active" columns dates are optional, but will help NSF staff easily determine which information remains relevant for reviewer selection.
"Last Active Date" and "Last Active" columns may be left blank for ongoing or current affiliations.

Table 1: List the individual's last name, first name, middle initial, and organizational affiliation in the last 12 months.

1	Your Name:	Your Organizational Affiliation(s), last 12 r	Last Active Date
	Szpara, Moriah L.	Pennsylvania State University	

Table 2: List names as last name, first name, middle initial, for whom a personal, family, or business relationship would otherwise preclude their service as a reviewer.

R: Additional names for whom some relationship would otherwise preclude their service as a reviewer.

to disambiguate common names

2	Name:	Type of Relationship	Optional (email, Department)	Last Active
(b)(6)				

Table 3: List names as last name, first name, middle initial, and provide organizational affiliations, if known, for the following.

G: The individual's Ph.D. advisors; and

T: All of the individual's Ph.D. thesis advisees.

to disambiguate common names

3	Advisor/Advisee Name:	Organizational Affiliation	Optional (email, Department)
G:	Ngai, John	University of California Berkeley	

T:	Pandey, Utsav	Children's Hospital Los Angeles	
T:	Shipley, Mackenzie	Fred Hutchinson Cancer Research Institute	
T:	Rathbun, Molly	Pennsylvania State University	

Table 4: List names as last name, first name, middle initial, and provide organizational affiliations, if known, for the following:

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C: Collaborators on projects, such as funded grants, graduate research or others in the last 48 months.

to disambiguate common names

4	Name:	Organizational Affiliation	Optional (email, Department)	Last Active
C:	Johnston, Christine	University of Washington		
C:	Grose, Charles	University of Iowa		10/1/19
C:	Weitzman, Matthew	University of Pennsylvania		10/1/19
C:	Akhtar, Lisa	University of Pennsylvania		
C:	Sawtell, Nancy	Cinncinnati Children's Hospital Medical Center		11/1/19
C:	Thompson, Richard	University of Cinncinnati		11/1/19
A:	Pandey, Utsav	Children's Hospital Los Angeles		11/1/19
A:	Mangold, Colleen	Pennsylvania State University		
A:	Read, Andrew F	Pennsylvania State University		
A:	Shipley, Mackenzie	Fred Hutchinson Cancer Research Institute		
A:	Renner, Daniel W	Pennsylvania State University		
A:	Bloom, David	University of Florida		
A:	Paavilainen, Henrik	Turku University (Finland)		
A:	Bell, Andrew S	Pennsylvania State University		
A:	Shreve, Jacob T	Pennsylvania State University		8/31/19
A:	Cairns, Chris L.	Pennsylvania State University		
A:	Norberg, Peter	University of Gothenburg (Sweden)		
A:	Hukkanen, Veijo	Turku University (Finland)		
A:	Kennedy, David	Pennsylvania State University		
A:	Jones, Matthew	Pennsylvania State University		
A:	Dunn, Patricia	Pennsylvania State University		
A:	Whitley, Richard	University of Alabama Birmingham		
A:	Prichard, Mark	University of Alabama Birmingham		5/8/18
A:	Koelle, David	University of Washington		
A:	Kuny, Chad	Pennsylvania State University		
A:	Derby, Nina	Population Council		
A:	Trimpert, Jakob	Freie Universitat (Berlin)		
A:	Osterrieder, Nikolaus	Freie Universitat (Berlin)		
A:	Spatz, Stephen	USDA		
A:	McMahon, Dino	Freie Universitat (Berlin)		10/1/18
A:	Kunec, Dusan	Freie Universitat (Berlin)		10/1/18
A:	Yao, Pamela	NIH		5/1/18
A:	Benkovic, Stephen	Pennsylvania State University		
A:	Gatherer, Derek	Lancaster University (UK)		3/1/16
A:	Enquist, Lynn	Princeton University		
A:	Kinchington, Paul (Kip)	University of Pittsurgh		5/15/19
A:	Dix, Richard	Georgia State University		7/25/19

Table 5: List editorial board, editor-in chief and co-editors with whom the individual interacts. An editor-in-chief must list the entire editorial board.

B: Editorial Board: List name(s) of editor-in-chief and journal in the past 24 months; and

E: Other co-Editors of journal or collections with whom the individual has directly interacted in the last 24 months.

to disambiguate common names

5	Name:	Organizational Affiliation	Journal/Collection	Last Active
B:	Pybus, Oliver	NA	Virus Evolution	11/19/19
B:	Elena, Santi	NA	Virus Evolution	11/19/19
E:	Maes, Piet	NA	eLife	10/1/19

COVER SHEET FOR PROPOSAL TO THE NATIONAL SCIENCE FOUNDATION

PROGRAM ANNOUNCEMENT/SOLICITATION NO./DUE DATE
NSF 19-592 11/20/19

☐ Special Exception to Deadline Date Policy

FOR NSF USE ONLY
NSF PROPOSAL NUMBER
2011143

FOR CONSIDERATION BY NSF ORGANIZATION UNIT(S) (Indicate the most specific unit known, i.e. program, division, etc.)
DEB - Ecology of Infectious Diseases

DATE RECEIVED	NUMBER OF COPIES	DIVISION ASSIGNED	FUND CODE	DUNS# (Data Universal Numbering System)	FILE LOCATION
11/20/2019	1	08010000 DEB	7242	003403953	11/20/2019 3:02pm

EMPLOYER IDENTIFICATION NUMBER (EIN) OR TAXPAYER IDENTIFICATION NUMBER (TIN)
246000376

SHOW PREVIOUS AWARD NO. IF THIS IS
☐ A RENEWAL
☐ AN ACCOMPLISHMENT-BASED RENEWAL

IS THIS PROPOSAL BEING SUBMITTED TO ANOTHER FEDERAL AGENCY? YES ☐ NO ☒ IF YES, LIST ACRONYM(S)

NAME OF ORGANIZATION TO WHICH AWARD SHOULD BE MADE
Pennsylvania State Univ University Park

AWARDEE ORGANIZATION CODE (IF KNOWN)
0033290000

ADDRESS OF AWARDEE ORGANIZATION, INCLUDING 9 DIGIT ZIP CODE
Pennsylvania State Univ University Park
110 Technology Center Building
University Park,PA.168027000

NAME OF PRIMARY PLACE OF PERF
Pennsylvania State Univ University Park

ADDRESS OF PRIMARY PLACE OF PERF, INCLUDING 9 DIGIT ZIP CODE
Pennsylvania State Univ University Park
University park ,PA ,168027000 ,US.

IS AWARDEE ORGANIZATION (Check All That Apply) ☐ SMALL BUSINESS ☐ MINORITY BUSINESS ☐ FOR-PROFIT ORGANIZATION ☐ WOMAN-OWNED BUSINESS

☐ IF THIS IS A PRELIMINARY PROPOSAL THEN CHECK HERE

TITLE OF PROPOSED PROJECT **US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study**

REQUESTED AMOUNT	PROPOSED DURATION (1-60 MONTHS)	REQUESTED STARTING DATE	SHOW RELATED PRELIMINARY PROPOSAL NO. IF APPLICABLE
$ 2,361,226	60 months	08/01/20	

THIS PROPOSAL INCLUDES ANY OF THE ITEMS LISTED BELOW
☐ BEGINNING INVESTIGATOR
☐ DISCLOSURE OF LOBBYING ACTIVITIES
☐ PROPRIETARY & PRIVILEGED INFORMATION
☐ HISTORIC PLACES
☐ VERTEBRATE ANIMALS IACUC App. Date _____
PHS Animal Welfare Assurance Number _____
☒ TYPE OF PROPOSAL **Research**

☐ HUMAN SUBJECTS Human Subjects Assurance Number _____
Exemption Subsection _____ or IRB App. Date _____
☐ FUNDING OF INT'L BRANCH CAMPUS OF U.S IHE ☐ FUNDING OF FOREIGN ORG
☒ INTERNATIONAL ACTIVITIES: COUNTRY/COUNTRIES INVOLVED
XX
☒ COLLABORATIVE STATUS
Not a collaborative proposal

PI/PD DEPARTMENT

PI/PD FAX NUMBER

PI/PD POSTAL ADDRESS
110 Technology Center Building
UNIVERSITY PARK,PA 168027000
United States

NAMES (TYPED)	High Degree	Yr of Degree	Telephone Number	Email Address
PI/PD NAME **David Kennedy**	PhD	2012		dak30@psu.edu
CO-PI/PD **Moriah Szpara**	PhD	2004	814-865-1372	mls164@psu.edu
CO-PI/PD				
CO-PI/PD				
CO-PI/PD				

CERTIFICATION PAGE

Certification for Authorized Organizational Representative (or Equivalent) or Individual Applicant

By electronically signing and submitting this proposal, the Authorized Organizational Representative (AOR) or Individual Applicant is: (1) certifying that statements made herein are true and complete to the best of his/her knowledge; and (2) agreeing to accept the obligation to comply with NSF award terms and conditions if an award is made as a result of this application. Further, the applicant is hereby providing certifications regarding conflict of interest (when applicable), drug-free workplace, debarment and suspension, lobbying activities (see below), nondiscrimination, flood hazard insurance (when applicable), responsible conduct of research, organizational support, Federal tax obligations, unpaid Federal tax liability, and criminal convictions as set forth in the NSF Proposal & Award Policies & Procedures Guide (PAPPG). Willful provision of false information in this application and its supporting documents or in reports required under an ensuing award is a criminal offense (U.S. Code, Title 18, Section 1001).

Certification Regarding Conflict of Interest

The AOR is required to complete certifications stating that the organization has implemented and is enforcing a written policy on conflicts of interest (COI), consistent with the provisions of PAPPG Chapter IX.A.; that, to the best of his/her knowledge, all financial disclosures required by the conflict of interest policy were made; and that conflicts of interest, if any, were, or prior to the organization's expenditure of any funds under the award, will be, satisfactorily managed, reduced or eliminated in accordance with the organization's conflict of interest policy. Conflicts that cannot be satisfactorily managed, reduced or eliminated and research that proceeds without the imposition of conditions or restrictions when a conflict of interest exists, must be disclosed to NSF via use of the Notifications and Requests Module in FastLane.

Drug Free Work Place Certification

By electronically signing the Certification Pages, the Authorized Organizational Representative (or equivalent), is providing the Drug Free Work Place Certification contained in Exhibit II-3 of the Proposal & Award Policies & Procedures Guide.

Debarment and Suspension Certification

(If answer "yes", please provide explanation.)

Is the organization or its principals presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from covered transactions by any Federal department or agency? Yes ☐ No ☒

By electronically signing the Certification Pages, the Authorized Organizational Representative (or equivalent) or Individual Applicant is providing the Debarment and Suspension Certification contained in Exhibit II-4 of the Proposal & Award Policies & Procedures Guide.

Certification Regarding Lobbying

This certification is required for an award of a Federal contract, grant, or cooperative agreement exceeding $100,000 and for an award of a Federal loan or a commitment providing for the United States to insure or guarantee a loan exceeding $150,000.

Certification for Contracts, Grants, Loans and Cooperative Agreements

The undersigned certifies, to the best of his or her knowledge and belief, that:
(1) No Federal appropriated funds have been paid or will be paid, by or on behalf of the undersigned, to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with the awarding of any Federal contract, the making of any Federal grant, the making of any Federal loan, the entering into of any cooperative agreement, and the extension, continuation, renewal, amendment, or modification of any Federal contract, grant, loan, or cooperative agreement.
(2) If any funds other than Federal appropriated funds have been paid or will be paid to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with this Federal contract, grant, loan, or cooperative agreement, the undersigned shall complete and submit Standard Form-LLL, "Disclosure of Lobbying Activities," in accordance with its instructions.
(3) The undersigned shall require that the language of this certification be included in the award documents for all subawards at all tiers including subcontracts, subgrants, and contracts under grants, loans, and cooperative agreements and that all subrecipients shall certify and disclose accordingly.

This certification is a material representation of fact upon which reliance was placed when this transaction was made or entered into. Submission of this certification is a prerequisite for making or entering into this transaction imposed by section 1352, Title 31, U.S. Code. Any person who fails to file the required certification shall be subject to a civil penalty of not less than $10,000 and not more than $100,000 for each such failure.

Certification Regarding Nondiscrimination

By electronically signing the Certification Pages, the Authorized Organizational Representative (or equivalent) is providing the Certification Regarding Nondiscrimination contained in Exhibit II-6 of the Proposal & Award Policies & Procedures Guide.

Certification Regarding Flood Hazard Insurance

Two sections of the National Flood Insurance Act of 1968 (42 USC §4012a and §4106) bar Federal agencies from giving financial assistance for acquisition or construction purposes in any area identified by the Federal Emergency Management Agency (FEMA) as having special flood hazards unless the:
(1) community in which that area is located participates in the national flood insurance program; and
(2) building (and any related equipment) is covered by adequate flood insurance.

By electronically signing the Certification Pages, the Authorized Organizational Representative (or equivalent) or Individual Applicant located in FEMA-designated special flood hazard areas is certifying that adequate flood insurance has been or will be obtained in the following situations:
(1) for NSF grants for the construction of a building or facility, regardless of the dollar amount of the grant; and
(2) for other NSF grants when more than $25,000 has been budgeted in the proposal for repair, alteration or improvement (construction) of a building or facility.

Certification Regarding Responsible Conduct of Research (RCR)
(This certification is not applicable to proposals for conferences, symposia, and workshops.)

By electronically signing the Certification Pages, the Authorized Organizational Representative is certifying that, in accordance with the NSF Proposal & Award Policies & Procedures Guide, Chapter IX.B. , the institution has a plan in place to provide appropriate training and oversight in the responsible and ethical conduct of research to undergraduates, graduate students and postdoctoral researchers who will be supported by NSF to conduct research. The AOR shall require that the language of this certification be included in any award documents for all subawards at all tiers.

CERTIFICATION PAGE - CONTINUED

Certification Regarding Organizational Support

By electronically signing the Certification Pages, the Authorized Organizational Representative (or equivalent) is certifying that there is organizational support for the proposal as required by Section 526 of the America COMPETES Reauthorization Act of 2010. This support extends to the portion of the proposal developed to satisfy the Broader Impacts Review Criterion as well as the Intellectual Merit Review Criterion, and any additional review criteria specified in the solicitation. Organizational support will be made available, as described in the proposal, in order to address the broader impacts and intellectual merit activities to be undertaken.

Certification Regarding Federal Tax Obligations

When the proposal exceeds $5,000,000, the Authorized Organizational Representative (or equivalent) is required to complete the following certification regarding Federal tax obligations. By electronically signing the Certification pages, the Authorized Organizational Representative is certifying that, to the best of their knowledge and belief, the proposing organization:
(1) has filed all Federal tax returns required during the three years preceding this certification;
(2) has not been convicted of a criminal offense under the Internal Revenue Code of 1986; and
(3) has not, more than 90 days prior to this certification, been notified of any unpaid Federal tax assessment for which the liability remains unsatisfied, unless the assessment is the subject of an installment agreement or offer in compromise that has been approved by the Internal Revenue Service and is not in default, or the assessment is the subject of a non-frivolous administrative or judicial proceeding.

Certification Regarding Unpaid Federal Tax Liability

When the proposing organization is a corporation, the Authorized Organizational Representative (or equivalent) is required to complete the following certification regarding Federal Tax Liability:

By electronically signing the Certification Pages, the Authorized Organizational Representative (or equivalent) is certifying that the corporation has no unpaid Federal tax liability that has been assessed, for which all judicial and administrative remedies have been exhausted or lapsed, and that is not being paid in a timely manner pursuant to an agreement with the authority responsible for collecting the tax liability.

Certification Regarding Criminal Convictions

When the proposing organization is a corporation, the Authorized Organizational Representative (or equivalent) is required to complete the following certification regarding Criminal Convictions:

By electronically signing the Certification Pages, the Authorized Organizational Representative (or equivalent) is certifying that the corporation has not been convicted of a felony criminal violation under any Federal law within the 24 months preceding the date on which the certification is signed.

Certification Dual Use Research of Concern

By electronically signing the certification pages, the Authorized Organizational Representative is certifying that the organization will be or is in compliance with all aspects of the United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern.

AUTHORIZED ORGANIZATIONAL REPRESENTATIVE	SIGNATURE	DATE
NAME **Lisa Sergeant**	**Electronic Signature**	**Nov 20 2019 3:01PM**

TELEPHONE NUMBER	EMAIL ADDRESS	FAX NUMBER
814-865-3335	**lus22@psu.edu**	

Direct for Biological Sciences
Division of Environmental Biology
Ecology of Infectious Diseases

Proposal Classification Form
PI: / Proposal Number: 2011143

CATEGORY I: INVESTIGATOR STATUS (Select ONE)

- ☐ Beginning Investigator - No previous Federal support as PI or Co-PI, excluding fellowships, dissertations, planning grants, etc.
- ☐ Prior Federal support only
- ☑ Current Federal support only
- ☐ Current & prior Federal support

CATEGORY II: FIELDS OF SCIENCE OTHER THAN BIOLOGY INVOLVED IN THIS RESEARCH (Select 1 to 3)

☐ Astronomy	☐ Engineering	☐ Psychology
☐ Chemistry	☐ Mathematics	☐ Social Sciences
☐ Computer Science	☐ Physics	☑ None of the Above
☐ Geosciences		

CATEGORY III: SUBSTANTIVE AREA (Select 1 to 4)

☐ BIOGEOGRAPHY	☐ Decomposition	☐ Molecular Evolution
☐ Island Biogeography	☐ Biogeochemistry	☐ Methodology/Theory
☐ Historical/ Evolutionary Biogeography	☐ Limnology/Hydrology	☐ Isozymes/ Electrophoresis
☐ Phylogeography	☐ Climate/Microclimate	☐ Nucleic Acid Analysis (general)
☐ Methods/Theory	☐ Whole-System Analysis	☐ Restriction Enzymes
☐ CHROMOSOME STUDIES	☐ Productivity/Biomass	☑ Nucleotide Sequencing
☐ Chromosome Evolution	☐ System Energetics	☐ Nuclear DNA
☐ Chromosome Number	☐ Landscape Dynamics	☐ Mitochondrial DNA
☐ Mutation	☐ Chemical & Biochemical Control	☐ Chloroplast DNA
☐ Mitosis and Meiosis	☐ Global Change	☐ RNA Analysis
☐ COMMUNITY ECOLOGY	☐ Climate Change	☐ DNA Hybridization
☐ Community Analysis	☐ Regional Studies	☐ Recombinant DNA
☐ Community Structure	☐ Global Studies	☐ Amino Acid Sequencing
☐ Community Stability	☐ Forestry	☐ Gene/Genome Mapping
☐ Succession	☐ Resource Management (Wildlife, Fisheries, Range, Other)	☐ Natural Products
☐ Experimental Microcosms/ Mesocosms	☑ Agricultural Ecology	☐ Serology/Immunology
☐ Disturbance	☐ EXTREMOPHILES	☐ PALEONTOLOGY
☐ Patch Dynamics	☐ GENOMICS (Genome sequence, organization, function)	☐ Floristic
☐ Food Webs/ Trophic Structure	☐ Viral	☐ Faunistic
☐ Keystone Species	☐ Microbial	☐ Paleoecology
☐ COMPUTATIONAL BIOLOGY	☐ Fungal	☐ Biostratigraphy
☐ CONSERVATION & RESTORATION BIOLOGY	☐ Plant	☐ Palynology
☐ DATABASES	☐ Animal	☐ Micropaleontology
☐ ECOSYSTEMS LEVEL	☐ MARINE MAMMALS	☐ Paleoclimatology
☐ Physical Structure	☐ MOLECULAR APPROACHES	☐ Archeozoic
		☐ Paleozoic
		☐ Mesozoic

- ☐ Cenozoic
- ☑ POPULATION DYNAMICS & LIFE HISTORY
- ☐ Demography/ Life History
- ☐ Population Cycles
- ☐ Distribution/Patchiness/ Marginal Populations
- ☐ Population Regulation
- ☐ Intraspecific Competition
- ☐ Reproductive Strategies
- ☐ Gender Allocation
- ☐ Metapopulations
- ☐ Extinction
- ☐ POPULATION GENETICS & BREEDING SYSTEMS
- ☐ Variation
- ☐ Microevolution
- ☐ Speciation
- ☐ Hybridization
- ☐ Inbreeding/Outbreeding
- ☐ Gene Flow Measurement
- ☐ Inheritance/Heritability
- ☐ Quantitative Genetics/ QTL Analysis
- ☐ Ecological Genetics
- ☐ Gender Ratios
- ☐ Apomixis/ Parthenogenesis
- ☐ Vegetative Reproduction
- ☐ SPECIES INTERACTIONS
- ☐ Predation
- ☐ Herbivory
- ☐ Omnivory
- ☐ Interspecific Competition
- ☐ Niche Relationships/ Resource Partititioning
- ☐ Pollination/ Seed Dispersal
- ☐ Parasitism
- ☐ Mutualism/ Commensalism
- ☐ Plant/Fungal/ Microbial Interactions
- ☐ Mimicry
- ☐ Animal Pathology
- ☐ Plant Pathology
- ☐ Coevolution
- ☐ Biological Control
- ☐ STATISTICS & MODELING
- ☐ Methods/ Instrumentation/ Software
- ☑ Modeling (general)
- ☐ Statistics (general)
  - ☐ Multivariate Methods
  - ☐ Spatial Statistics & Spatial Modeling
  - ☐ Sampling Design & Analysis
  - ☐ Experimental Design & Analysis
- ☐ SYSTEMATICS
- ☐ Taxonomy/Classification
- ☐ Nomenclature
- ☐ Monograph/Revision
- ☐ Phylogenetics
- ☐ Phenetics/Cladistics/ Numerical Taxonomy
- ☐ Macroevolution
- ☐ NONE OF THE ABOVE

CATEGORY IV: INFRASTRUCTURE (Select 1 to 3)

- ☑ COLLECTIONS/STOCK CULTURES
- ☑ Natural History Collections
- ☐ DATABASES
- ☐ FACILITIES
- ☐ Controlled Environment Facilities
- ☐ Field Stations
  - ☐ Field Facility Structure
  - ☐ Field Facility Equipment
- ☐ LTER Site
- ☐ INDUSTRY PARTICIPATION
- ☐ Technique Development
- ☐ TRACKING SYSTEMS
- ☐ Geographic Information Systems
- ☐ Remote Sensing
- ☐ NONE OF THE ABOVE

CATEGORY V: HABITAT (Select 1 to 2)

TERRESTRIAL HABITATS

- ☐ GENERAL TERRESTRIAL
- ☐ TUNDRA
- ☐ BOREAL FOREST
- ☐ TEMPERATE
  - ☐ Deciduous Forest
  - ☐ Coniferous Forest
  - ☐ Rain Forest
  - ☐ Mixed Forest
  - ☐ Prairie/Grasslands
  - ☐ Desert
- ☐ SUBTROPICAL
  - ☐ Rain Forest
  - ☐ Seasonal Forest
  - ☐ Savanna
  - ☐ Thornwoods
  - ☐ Deciduous Forest
  - ☐ Coniferous Forest
  - ☐ Desert
- ☐ TROPICAL
  - ☐ Rain Forest
  - ☐ Seasonal Forest
  - ☐ Savanna
  - ☐ Thornwoods
  - ☐ Deciduous Forest
  - ☐ Coniferous Forest
  - ☐ Desert
- ☐ CHAPPARAL/ SCLEROPHYLL/ SHRUBLANDS
- ☐ ALPINE
- ☐ MONTANE
- ☐ CLOUD FOREST
- ☐ RIPARIAN ZONES
- ☐ ISLANDS (except Barrier Islands)
- ☐ BEACHES/ DUNES/ SHORES/ BARRIER ISLANDS
- ☐ CAVES/ ROCK OUTCROPS/ CLIFFS
- ☐ CROPLANDS/ FALLOW FIELDS/ PASTURES
- ☐ URBAN/SUBURBAN
- ☐ SUBTERRANEAN/ SOIL/ SEDIMENTS
- ☐ EXTREME TERRESTRIAL ENVIRONMENT
- ☐ AERIAL

AQUATIC HABITATS

- ☐ GENERAL AQUATIC
- ☐ FRESHWATER
  - ☐ Wetlands/Bogs/Swamps
  - ☐ Lakes/Ponds
  - ☐ Rivers/Streams
  - ☐ Reservoirs
- ☐ MARINE
  - ☐ Open Ocean/Continental Shelf
  - ☐ Bathyal
  - ☐ Abyssal
  - ☐ Estuarine
  - ☐ Intertidal/Tidal/Coastal
  - ☐ Coral Reef
  - ☐ HYPERSALINE
- ☐ EXTREME AQUATIC ENVIRONMENT
- ☐ CAVES/ ROCK OUTCROPS/ CLIFFS
- ☐ MANGROVES
- ☐ SUBSURFACE WATERS/ SPRINGS
- ☐ EPHEMERAL POOLS & STREAMS
- ☐ MICROPOOLS (Pitcher Plants, Tree Holes, Other)

MAN-MADE ENVIRONMENTS

- ☐ LABORATORY
- ☐ THEORETICAL SYSTEMS
- ☑ OTHER ARTIFICIAL SYSTEMS

NOT APPLICABLE

- ☐ NOT APPLICABLE

CATEGORY VI: GEOGRAPHIC AREA OF THE RESEARCH (Select 1 to 2)

- ☑ WORLDWIDE
- ☐ NORTH AMERICA
  - ☐ United States
    - ☐ Northeast US (CT, MA, ME, NH, NJ, NY, PA, RI, VT)
    - ☐ Northcentral US (IA, IL, IN, MI, MN, ND, NE, OH, SD, WI)
    - ☐ Northwest US (ID, MT, OR, WA, WY)
    - ☐ Southeast US (DC, DE, FL, GA, MD, NC, SC, WV, VA)
    - ☐ Southcentral US (AL, AR, KS, KY, LA, MO, MS, OK, TN, TX)
    - ☐ Southwest US (AZ, CA, CO, NM, NV, UT)
    - ☐ Alaska
    - ☐ Hawaii
    - ☐ Puerto Rico
  - ☐ Canada
  - ☐ Mexico
- ☐ CENTRAL AMERICA (Mainland)
  - ☐ Caribbean Islands
  - ☐ Bermuda/Bahamas
- ☐ SOUTH AMERICA
  - ☐ Eastern South America (Guyana, Fr. Guiana, Suriname, Brazil)
  - ☐ Northern South America (Colombia, Venezuela)
  - ☐ Southern South America (Chile, Argentina, Uruguay, Paraguay)
  - ☐ Western South America (Ecuador, Peru, Bolivia)
- ☐ EUROPE
  - ☐ Eastern Europe
  - ☐ Russia
  - ☐ Scandinavia
  - ☐ Western Europe
- ☐ ASIA
  - ☐ Central Asia
  - ☐ Far East
  - ☐ Middle East
  - ☐ Siberia
  - ☐ South Asia
  - ☐ Southeast Asia
- ☐ AFRICA
  - ☐ North Africa
  - ☐ African South of the Sahara
    - ☐ East Africa
    - ☐ Madagascar
    - ☐ South Africa
    - ☐ West Africa
- ☐ AUSTRALASIA
  - ☐ Australia
  - ☐ New Zealand
  - ☐ Pacific Islands
- ☐ ANTARCTICA
- ☐ ARCTIC
- ☐ ATLANTIC OCEAN
- ☐ PACIFIC OCEAN
- ☐ INDIAN OCEAN
- ☐ OTHER REGIONS (Not defined)
- ☐ NOT APPLICABLE

CATEGORY VII: CLASSIFICATION OF ORGANISMS (Select 1 to 4)

- ☑ VIRUSES
- ☐ Bacterial
- ☐ Plant
- ☑ Animal
- ☐ PROKARYOTES
  - ☐ Archaea
  - ☐ Cyanobacteria
  - ☐ Bacteria
  - ☐ Noncultured Organisms
- ☐ PROTISTA (PROTOZOA)
  - ☐ Amoebae
  - ☐ Apicomplexa
  - ☐ Ciliophora
  - ☐ Flagellates
  - ☐ Foraminifera
  - ☐ Microspora
  - ☐ Radiolaria
- ☐ FUNGI
  - ☐ Ascomycota
  - ☐ Basidiomycota
  - ☐ Chytridiomycota
  - ☐ Mitosporic Fungi
  - ☐ Oomycota
  - ☐ Zygomycota
- ☐ LICHENS
- ☐ SLIME MOLDS
- ☐ ALGAE
  - ☐ Bacillariophyta (Diatoms)
  - ☐ Charophyta
  - ☐ Chlorophyta
  - ☐ Chrysophyta
  - ☐ Dinoflagellata
  - ☐ Euglenoids
  - ☐ Phaeophyta
  - ☐ Rhodophyta
- ☐ PLANTS
  - ☐ NON-VASCULAR PLANTS
    - ☐ BRYOPHYTA
      - ☐ Anthocerotae (Hornworts)
      - ☐ Hepaticae (Liverworts)
      - ☐ Musci (Mosses)
  - ☐ VASCULAR PLANTS
    - ☐ FERNS & FERN ALLIES
    - ☐ GYMNOSPERMS
      - ☐ Coniferales (Conifers)

- ☐ Cycadales (Cycads)
- ☐ Ginkgoales (Ginkgo)
- ☐ Gnetales (Gnetophytes)
- ☐ ANGIOSPERMS
- ☐ Monocots
- ☐ Arecaceae (Palmae)
- ☐ Cyperaceae
- ☐ Liliaceae
- ☐ Orchidaceae
- ☐ Poaceae (Graminae)
- ☐ Dicots
- ☐ Apiaceae (Umbelliferae)
- ☐ Asteraceae (Compositae)
- ☐ Brassicaceae (Cruciferae)
- ☐ Fabaceae (Leguminosae)
- ☐ Lamiaceae (Labiatae)
- ☐ Rosaceae
- ☐ Solanaceae

☐ ANIMALS

- ☐ INVERTEBRATES
- ☐ MESOZOA/PLACOZOA
- ☐ PORIFERA (Sponges)
- ☐ CNIDARIA
- ☐ Hydrozoa (Hydra, etc.)
- ☐ Scyphozoa (Jellyfish)
- ☐ Anthozoa (Corals, Sea Anemones)
- ☐ CTENOPHORA (Comb Jellies)
- ☐ PLATYHELMINTHES (Flatworms)
- ☐ Turbellaria (Planarians)
- ☐ Trematoda (Flukes)
- ☐ Cestoda (Tapeworms)
- ☐ Monogenea (Flukes)
- ☐ GNATHOSTOMULIDA
- ☐ NEMERTINEA (Rynchocoela) (Ribbon Worms)
- ☐ ENTOPROCTA (Bryozoa) (Plant-like Animals)
- ☐ ASCHELMINTHES
- ☐ Gastrotricha
- ☐ Kinorhyncha
- ☐ Loricifera
- ☐ Nematoda (Roundworms)
- ☐ Nematomorpha (Horsehair Worms)
- ☐ Rotifera (Rotatoria)
- ☐ ACANTHOCEPHALA (Spiny-headed Worms)
- ☐ PRIAPULOIDEA
- ☐ BRYOZOA (Ectoprocta) (Plant-like Animals)
- ☐ PHORONIDEA (Lophophorates)
- ☐ BRACHIOPODA (Lamp Shells)
- ☐ MOLLUSCA
- ☐ Monoplacophora
- ☐ Aplacophora (Solenogasters)
- ☐ Polyplacophora (Chitons)
- ☐ Scaphopoda (Tooth Shells)
- ☐ Gastropoda (Snails, Slugs, Limpets)
- ☐ Pelecypoda (Bivalvia) (Clams, Mussels, Oysters, Scallops)
- ☐ Cephalopoda (Squid, Octopus, Nautilus)
- ☐ ANNELIDA (Segmented Worms)
- ☐ Polychaeta (Parapodial Worms)
- ☐ Oligochaeta (Earthworms)
- ☐ Hirudinida (Leeches)
- ☐ POGONOPHORA (Beard Worms)
- ☐ SIPUNCULOIDEA (Peanut Worms)
- ☐ ECHIUROIDEA (Spoon Worms)
- ☐ ARTHROPODA
- ☐ Cheliceriformes
- ☐ Merostomata (Horseshoe Crabs)
- ☐ Pycnogonida (Sea Spiders)
- ☐ Scorpionida (Scorpions)
- ☐ Araneae (True Spiders)
- ☐ Pseudoscorpionida (Pseudoscorpions)
- ☐ Acarina (Free-living Mites)
- ☐ Parasitiformes (Parasitic Ticks & Mites)
- ☐ Crustacea
- ☐ Branchiopoda (Fairy Shrimp, Water Flea)
- ☐ Ostracoda (Sea Lice)
- ☐ Copepoda
- ☐ Cirripedia (Barnacles)
- ☐ Amphipoda (Skeleton Shrimp, Whale Lice, Freshwater Shrimp)
- ☐ Isopoda (Wood Lice, Pillbugs)
- ☐ Decapoda (Lobster, Crayfish, Crabs, Shrimp)
- ☐ Hexapoda (Insecta) (Insects)
- ☐ Apterygota (Springtails, Silverfish, etc.)
- ☐ Odonata (Dragonflies, Damselflies)
- ☐ Ephemeroptera (Mayflies)
- ☐ Orthoptera (Grasshoppers, Crickets)
- ☐ Dictyoptera (Cockroaches, Mantids, Phasmids)
- ☐ Isoptera (Termites)
- ☐ Plecoptera (Stoneflies)
- ☐ Phthiraptera (Mallophaga & Anoplura) (Lice)
- ☐ Hemiptera (including Heteroptera) (True Bugs)
- ☐ Homoptera (Cicadas, Scale Insects, Leafhoppers)
- ☐ Thysanoptera (Thrips)
- ☐ Neuroptera (Lacewings, Dobsonflies, Snakeflies)
- ☐ Trichoptera (Caddisflies)
- ☐ Lepidoptera (Moths, Butterflies)
- ☐ Diptera (Flies, Mosquitoes)
- ☐ Siphonaptera (Fleas)
- ☐ Coleoptera (Beetles)
- ☐ Hymenoptera (Ants, Bees, Wasps, Sawflies)
- ☐ Chilopoda (Centipedes)
- ☐ Diplopoda (Millipedes)
- ☐ Pauropoda
- ☐ Symphyta (Symphyla)
- ☐ PENTASTOMIDA (Linguatulida) (Tongue Worms)
- ☐ TARDIGRADA (Tardigrades, Water Bears)
- ☐ ONYCHOPHORA (Peripatus)
- ☐ CHAETOGNATHA (Arrow Worms)
- ☐ ECHINODERMATA
- ☐ Crinoidea (Sea Lilies, Feather Stars)
- ☐ Asteroidea (Starfish, Sea Stars)
- ☐ Ophiuroidea (Brittle Stars, Serpent Stars)
- ☐ Echinoidea (Sea Urchins, Sand Dollars)
- ☐ Holothuroidea (Sea Cucumbers)
- ☐ HEMICHORDATA (Acorn Worms, Pterobranchs)
- ☐ UROCHORDATA (Tunicata) (Tunicates, Sea Squirts, Salps, Ascideans)
- ☐ CEPHALOCHORDATA (Amphioxus/Lancelet)
- ☐ VERTEBRATES
- ☐ AGNATHA (Hagfish, Lamprey)
- ☐ FISHES
- ☐ Chondrichthyes (Cartilaginous Fishes) (Sharks, Rays, Ratfish)
- ☐ Osteichthyes (Bony Fishes)
- ☐ AMPHIBIA
- ☐ Anura (Frogs, Toads)
- ☐ Urodela (Salamanders, Newts)
- ☐ Gymnophiona (Apoda) (Caecilians)
- ☐ REPTILIA
- ☐ Chelonia (Turtles, Tortoises)
- ☐ Serpentes (Snakes)
- ☐ Sauria (Lizards)
- ☐ Crocodylia (Crocodilians)
- ☑ AVES (Birds)
- ☐ Passeriformes (Passerines)
- ☐ MAMMALIA
- ☐ Monotremata (Platypus, Echidna)
- ☐ Marsupalia (Marsupials)
- ☐ Eutheria (Placentals)
- ☐ Insectivora (Hedgehogs, Moles, Shrews, Tenrec, etc.)
- ☐ Chiroptera (Bats)
- ☐ Primates
- ☐ Humans
- ☐ Rodentia
- ☐ Lagomorphs (Rabbits, Hares, Pikas)
- ☐ Carnivora (Bears, Canids, Felids, Mustelids, Viverrids, Hyena, Procyonids)
- ☐ Perissodactyla (Odd-toed Ungulates) (Horses, Rhinos, Tapirs, etc.)

☐ Artiodactyla (Even-toed Ungulates) (Cattle, Sheep, Deer, Pigs, etc.) ☐ Marine Mammals (Seals, Walrus, Whales, Otters, Dolphins, Porpoises)	☐ TRANSGENIC ORGANISMS ☐ FOSSIL OR EXTINCT ORGANISMS	☐ NO ORGANISMS

CATEGORY VIII: MODEL ORGANISM (Select ONE)		
☑ NO MODEL ORGANISM MODEL ORGANISM (Choose from the list)	☐ Escherichia coli ☐ Mouse-Ear Cress (Arabidopsis thaliana)	☐ Fruitfly (Drosophila melanogaster)

PROJECT SUMMARY

Overview:

Vaccination can be one of the most efficient and effective tools for controlling infectious diseases, but in many settings, including wildlife and farm animal diseases, logistical and economic hurdles make it impractical to vaccinate large enough fractions of hosts to achieve herd immunity. Transmissible vaccines, defined as vaccines capable of disseminating from vaccinated to non-vaccinated hosts, offer one potential solution to these challenges by amplifying the impact of vaccination campaigns. However, transmissible vaccines are not without risk. Reversion to virulence or recombination with wildtype pathogens could cause transmissible vaccines to make matters worse or complicate elimination efforts. This proposed work will for the first time quantify the effects of transmissible vaccines on disease ecology and evolution using an economically important, naturally transmissible vaccine currently in widespread use on poultry farms.

Marek's disease, a poultry-specific disease that is a threat to sustainable poultry production, is currently controlled by the "Rispens" vaccine, a live, attenuated vaccine that has been widely used for two decades. Recent experiments have found that this vaccine is capable of efficiently transmitting from vaccinated to non-vaccinated birds. These results are consistent with recent field surveillance studies that have found vaccine isolates in cohorts that have not been directly vaccinated. In addition, advances in whole genome sequencing have revealed recombination between the vaccine virus and the wildtype virus, which is concerning given that the vaccine virus harbors highly virulent forms on the oncogenic meq gene. Together, these observations demonstrate that the Rispens vaccine is a transmissible vaccine capable of evolving and potentially facilitating adverse evolution of wildtype Marek's disease virus. Our primary objective is to quantify the consequences of transmissible vaccine use. Specifically, we will:

1) Develop a general model of transmissible vaccination to identify key knowledge gaps
2) Characterize vaccine transmission and its impact on wildtype virus transmission
3) Characterize the genetic evolution of wildtype virus and vaccine virus
4) Model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine

Intellectual Merit:

This work will be the first to link empirical and theoretical studies to explore the impacts of transmissible vaccines on disease ecology and evolution. Transmissible vaccines are being widely considered to control zoonotic diseases of animal populations, including Ebola, Marburg, Sin Nombre hantavirus, and rabies. However, before transmissible vaccines are introduced, the benefits and risks must be considered, such as how well transmissible vaccines spread and how likely they are to drive adverse evolution. This study will provide the first empirical estimate of how well a transmissible vaccine disseminates. It will explore the effects of transmissible vaccines on disease control, by using mathematical models to quantify the reduction in disease that can be attributed to the vaccine's transmissibility. The main risk for transmissible vaccines is that they may drive adverse evolution of the vaccine or wildtype pathogen. This study will determine whether adverse evolution has already occurred, or if not, whether it is likely to occur. An output of this project will be the first empirical estimate of recombination rates between a transmissible vaccine and the wildtype pathogen it is intended to control.

Broader Impacts:

This study has direct relevance to the poultry industry. Marek's disease costs the worldwide poultry industry more than USD 2 billion per year, most of which is attributable to the cost of vaccination. A component of this proposal will address whether vaccination costs can be reduced by utilizing vaccine transmissibility. Moreover, two earlier generations of Marek's disease vaccines have been undermined by virus evolution in response to vaccination. This proposal will address whether adverse evolution is likely to undermine the currently effective Rispens vaccine, which would be devastating to food security. The investigators will also disseminate their findings to industry stakeholders, K-12 youth, and the broader public. Stakeholders will be engaged through presentations at industry meetings, and through Co-PI Nair's international consulting work on Marek's disease. Youth will be engaged through a presentation at Penn State's youth-focused "Science-U", demonstrating how genetic data can be used to infer relatedness. The broader public will be engaged through the development of a four-part lecture at Penn State's Osher Lifelong Learning Institute (OLLI) on the ecological and evolutionary consequences of vaccines.

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US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

Introduction: Wildlife diseases and other animal diseases pose substantial threats to human and animal health [37, 59, 73]. Spillovers of zoonotic pathogens are responsible for non-transmissible human diseases such as rabies and Lyme disease [72, 96], emerging diseases such as Ebola and monkeypox [14, 28], and the potential re-emergence of diseases such as plague [118]. Spillover of diseases from wildlife into animal populations such as for foot and mouth disease [119] or highly pathogenic avian influenza [46] can also threaten food security. Conservation efforts can also be hindered by animal diseases, such as for the problems faced by amphibians in response to the chytrid fungus, *Batrachochytrium dendrobatidis* [17].

The tools available to control animal diseases are limited. Animals can be culled, quarantined, or relocated in response to disease outbreaks [22, 45, 125]. For some diseases, treatment such as antibiotics drugs and vaccines may also be an option [45, 125]. However, each of these interventions have the same limitations, which are the logistical challenges associated with accessing sufficient numbers of animals to achieve herd immunity [2, 45, 114]. Even when every animal can be accessed, such as for farm animal diseases, costs of vaccination can cut into narrow profit margins.

One potential solution to this conundrum is transmissible vaccines. Transmissible vaccines, or self-disseminating vaccines, are vaccines capable of transmitting between individuals [19, 80, 85, 86, 88]. Such vaccines, by nature of their ability to disseminate to hosts that were themselves not directly vaccinated, show substantial promise for interventions in wildlife populations, because each administered vaccine has the potential to reach otherwise inaccessible potential hosts [12, 86]. They may also be useful on farmed populations such as fish or chickens where vaccinating every animal at the correct doses can be technically challenging and can substantially reduce profit margins [23, 79]. Moreover, such vaccines might be capable of persisting in the animal population over time, reducing the urgency to vaccinate every time populations turn over, such as during reproductive seasons or between different cohorts on a farm.

Yet transmissible vaccines have the potential to drive adverse evolution in several ways. First, transmissible vaccines, like other vaccines, may alter the way in which selection acts on standing pathogen variation. Second, transmissible vaccines may provide genetic material via recombination that allows wildtype pathogens to become better adapted to transmission in host populations. Third, transmissible vaccines may acquire genetic material from wildtype pathogens and themselves become pathogenic. Fourth, transmissible vaccines may mutate and evolve over time, potentially regaining virulence. While none of these effects are unique to transmissible vaccines [25, 71, 78, 99], the risk of adverse evolution may be higher since transmissible vaccines, by definition, persist longer in the host population than conventional vaccines.

A key question is therefore whether the use of transmissible vaccines will make things better or worse. With the exception of a handful of short-term lab and field studies on a vaccine for myxomatosis and rabbit hemorrhagic disease [8, 9, 100, 120], previous work in this area has been entirely theoretical [11, 12, 18, 19, 86-88, 115, 122]. However, the impact of transmissible vaccines in these theoretical studies depends critically on the model structure and parameter estimates, and data-tested models and parameter estimates for these models do not yet exist for any transmissible vaccine system. Therefore, the impact of transmissible vaccines on disease dynamics and pathogen evolution are uncertain and will remain so until empirical and theoretical studies are performed in a single system. What is therefore needed is a system where theory and empirical data can be combined to ask what the overall consequences of transmissible vaccines are on disease ecology and evolution.

Study system: Two classes of transmissible vaccines exist – recombinant transmissible vaccines and attenuated transmissible vaccines [19]. Recombinant transmissible vaccines are vaccines that are generated by inserting antigens into a transmissible vector, such as a nonpathogenic virus. Attenuated transmissible vaccines are vaccines that have been derived from isolates of a pathogen that have been attenuated in the lab, typically by growing the isolate for numerous rounds in cell culture. To our knowledge, no transmissible recombinant vaccines have yet been licensed for use in any capacity. In addition, most attenuated vaccines are unable to efficiently transmit [12]. These facts substantially limit the number of potential systems available to study transmissible vaccines.

An ideal study system would have seven key features: 1) a transmissible vaccine that is in widespread use, 2) a wildtype pathogen targeted by vaccination that circulates in the same host

populations as the transmissible vaccine, 3) potential for controlled experiments in settings that replicate field-like conditions, 4) known or knowable host and disease ecology so that the system can be modeled, 5) a historical library of pathogen and vaccine isolates, and 6) the capacity to screen for phenotypic change in both the wildtype pathogen and the vaccine. Ideally, 7) this system would also have public health or economic importance.

Extremely few systems satisfy these requirements. In fact, extremely few systems satisfy the first criterion alone. Transmissible vaccines are generally not used, in large part because the consequences of their use are unknown. In humans, several attenuated vaccines have had rare instances of transmission [60, 77, 105, 124], but the only vaccine that is routinely capable of transmission is the live oral poliovirus vaccine [36]. The oral Sabin polio vaccine is shed from vaccinated hosts, and it can transmit to non-vaccinated hosts through host-to-host contact or through the environment. The transmissibility of this vaccine virus, which is frequently associated with a reversion to virulence [78], has almost certainly aided in disease control despite causing challenges in final eradication [30], demonstrating the dichotomous impacts of transmissible vaccination. The usefulness of the poliovirus system for studying the consequences of transmissible vaccines on disease ecology and pathogen evolution is limited, however, because it is not possible to perform controlled experiments to quantify the transmissibly of the vaccine.

Vaccines of farm animals include a few more transmissible vaccines, but often these systems are poorly studied. Vaccine transmission has been documented for vaccines against porcine circovirus type 2 virus in pigs [90], infectious laryngotracheitis virus [106] and Marek's disease virus [104] in chickens, and bluetongue virus in ruminants [110]. How readily transmission occurs in these systems, however, and the degree to which that transmission confers protection to non-primary vaccinated hosts is typically difficult to measure, and thus largely unknown. Using the Marek's disease vaccine CVI988, often referred to as the "Rispens vaccine," we have collected preliminary data that can be used to estimate its ability to transmit from vaccinated to cohoused hosts. This system possesses all seven key features mentioned above for an ideal system.

Marek's disease, caused by Marek's disease virus, has a storied history. It was first described in 1907 as a mild polyneuritis [15, 82]. Over time, the list of clinical signs has expanded to include immune suppression, paralysis, tumor formation, and death [91]. During the industrialization of farming in the middle of the twentieth century, chicken rearing moved from taking place predominantly outdoors at low density to predominantly indoors at high densities. Concurrently, Marek's disease emerged as a threat to the sustainability of poultry farming [79]. That changed in 1970 with the introduction of the first Marek's disease vaccine [89], the "herpesvirus of turkeys" or HVT vaccine. The HVT vaccine effectively controlled Marek's disease for nearly a decade until new virus isolates, termed "very virulent" (vv), emerged. These virus strains had increased virulence and were capable of escaping vaccine protection [126, 129]. In response, a second-generation vaccine was introduced in 1982 [20], termed the "bivalent" vaccine, because it is a mixture of the HVT vaccine and a non-oncogenic virus belonging to a sister-species of Marek's disease virus that naturally circulates in chicken populations [20, 111]. After a decade of use of the bivalent vaccine, again new virus isolates emerged, termed "very virulent plus" (vv+), that had even higher virulence and were able to escape bivalent vaccine protection [126]. A third generation of vaccine, termed "CVI988" or the "Rispens vaccine", was licensed in 1996 that could effectively protect animals against disease from all circulating virus isolates [26]. The Rispens vaccine is an attenuated version of an initially mild isolate of Marek's disease virus [103, 104]. Attenuation was achieved by passaging the virus isolate in duck embryo fibroblast cells [103]. For the passage cycle at which the vaccine is used, the Rispens vaccine virus is still capable of transmission [103]. Increasing the number of passaging cycles decreased the efficacy of the vaccine, while decreasing the number of passaging cycles increased the pathogenicity of the vaccine [53]. Today, the Rispens vaccine is still in use, and it is still effective against currently circulating viral isolates [27, 32, 82, 128].

The Rispens vaccine shows substantial protective efficacy against disease for all known circulating isolates of Marek's disease virus [26]. It substantially reduces the shedding of wildtype virus [58, 98], and the widespread use of the Rispens vaccine has been associated with decreased prevalence of Marek's disease and Marek's disease virus [65]. Whether its impact has been amplified by its transmissibility is currently unknown, but the reduction in disease that accompanied the licensing of the Rispens vaccine extends beyond the farms on which it is used [65]. However, the vaccine is imperfect, meaning that wildtype virus can infect vaccinated individuals and transmit from them. Recombination between wildtype virus and vaccine is therefore a risk. This risk is particularly acute, given a recent study,

which found that the Rispens vaccine harbors an oncogene allele that is more potent that the wildtype allele [25]. In that study, the authors found that inserting the vaccine isoform of the gene into a wildtype virus backbone increased the pathogenicity of the virus [25].

Intellectual Merit

Recently, Marek's disease has developed into a premier model for understanding vaccine-driven evolution [83, 91, 93, 99]. The decades-long interleaving of vaccine introductions, followed by virulence evolution of wildtype virus isolates in the field is quite possibly the clearest example of how vaccination can drive the evolution of increased pathogen virulence [99]. With historical strain collections allowing access to virus evolution trajectories over time, Marek's disease virus has also been one of the few systems where vaccine resistance evolution has been documented [67, 68]. Here we propose to extend the value of the Marek's disease system by developing it into a model system for studying the ecological and evolutionary consequences of transmissible vaccines. To achieve this goal, we will:

1) **Develop a general model of transmissible vaccination to identify key knowledge gaps**
2) **Characterize vaccine transmission and its impact on wildtype virus transmission**
3) **Characterize the genetic evolution of wildtype virus and vaccine virus**
4) **Model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine**

Aim 1: Develop a general model of transmissible vaccination to identify key knowledge gaps

Rationale. Identifying knowledge gaps is a critical first step for scientific discovery. Developing mathematical models forces us to identify knowledge gaps and to be explicit about our assumptions. In addition, once a model has been generated, simulating the model or performing sensitivity analyses can identify which assumptions and which knowledge gaps are key to our understanding of biological outcomes. This data can inform experiments that will in turn facilitate model refinement. A key component of our work will therefore be the iterative feedback between model development and experimental design. We will start by developing a general mathematical model to describe the impacts of transmissible vaccines in a cohort-structured host population. While Marek's disease dynamics in chickens may be described by such a model, the generality of the structure of the model will enhance its applicability to many host-pathogen systems.

Hypothesis. We hypothesize that the effects of transmissible vaccination on overall disease will be most sensitive to the relative rates of vaccine transmission and pathogen transmission. We also hypothesize that vaccine reversion will complicate final eradication efforts when the effective reproductive ratio of the revertant vaccine is greater than one.

Background/Preliminary data. We have developed a preliminary model of vaccine transmission in a cohort-structured population. This preliminary model is inspired by Marek's disease virus dynamics, but its structure applies more generally to disease dynamics in any cohort-structured populations. We have modeled systems with similar structure in prior work [62, 66]. We begin by describing dynamics within a cohort, since the structure of these dynamics is more likely to be broadly applicable than the dynamics between cohorts, which may differ substantially between wildlife and farmed populations. We start with a two strain Susceptible-Infected (SI) model that allows for coinfection:

$$\frac{dS}{dt} = -\beta_v S(I_v + \epsilon_v I_{vp}) - \beta_p S(I_p + \epsilon_p I_{vp}) - \phi S$$

$$\frac{dI_p}{dt} = \beta_p S(I_p + \epsilon_p I_{vp}) - e_p \beta_v I_p (I_v + \epsilon_v I_{vp}) + \mu_v I_v + \mu_{vp} I_{vp} - \alpha_p I_p - \epsilon_p \phi I_p$$

$$\frac{dI_v}{dt} = \beta_v S(I_v + \epsilon_v I_{vp} - e_v \beta_p I_v (I_p + \epsilon_p I_{vp}) - \mu_v I_v + \phi S$$

$$\frac{dI_{vp}}{dt} = e_v \beta_p I_v (I_p + \epsilon_p I_{vp}) + e_p \beta_v I_p (I_v + \epsilon_v I_{vp}) - \mu_{vp} I_{vp} - \alpha_{vp} I_{vp} + \epsilon_p \phi I_p$$

Above, the subscript v refers to vaccine and the subscript p refers to pathogen. S is the number of susceptible hosts, I_v is the number of hosts infected with vaccine, I_p is the number of hosts infected with pathogen, and I_{vp} is the number of hosts infected with both vaccine and pathogen. $\beta_n$is the transmission rate of strain n, $\epsilon_n$is the relative change in the transmission rate of strain n caused by coinfection, and e_n is the relative change in susceptibility of I_n caused by infection with strain n. The

vaccination effort is ϕ. Finally, μ_v and μ_{vp} are the respective rates of vaccine reversion to virulence in vaccinated and coinfected hosts, and α_p and α_{vp} are the respective rates of death in hosts infected or coinfected with the pathogen.

Between-cohort dynamics occur on a separate timescale from within-cohort dynamics. By taking advantage of this separation of timescales as we have done in previous work [62, 66], we can model between-cohort dynamics as a set of difference equations. These difference equations may take various forms to describe different types of systems. To be most in line with the farm setting, we assume that total host density is the same at the beginning of every cohort and a fraction of the vaccinated I_v, pathogen-infected I_p, or coinfected hosts I_{vp} transmit infection on to hosts in the next cohort. Thus:

$$S_{c+1}(0) = N - fI_{v,c}(\tau) - gI_{p,c}(\tau) + hI_{vp,c}(\tau)$$
$$I_{v,c+1}(0) = fI_{v,c}(\tau)$$
$$I_{p,c+1}(0) = gI_{p,c}(\tau)$$
$$I_{vp,c+1}(0) = hI_{vp,c}(\tau)$$

Above, c indexes cohorts with 0 marking the start of the cohort and τ marking the end of it. N is the total host population size at the start of a cohort, f, g, and h are the respective fractions of hosts that pass their infection status on to hosts in the next generation.

Methodology. We will characterize the above model by identifying equilibria and stability around those equilibria. In particular, we are interested in endemic equilibria where vaccine and pathogen can coexist. We are also interested in the set of conditions where the pathogen competitively excludes the vaccine and where the vaccine competitively excludes the pathogen. We will first develop analytical solutions for the values of R_0 for the vaccine and for the wildtype pathogen, to identify conditions under which the vaccine or pathogen are able to persist indefinitely in the host population [29, 107]. We will use invasion analyses to identify conditions under which the vaccine or wildtype pathogen are capable of competitive exclusion or coexistence [38]. We will then perform sensitivity analyses to identify the importance of each of the parameters on the outcome of competition between the vaccine and the pathogen. These steps will allow us to quantify the importance of vaccine transmission on overall disease dynamics.

After those initial analyses are performed, we will consider the structural uncertainty in the model. In particular, there are several key assumptions made in the above model that may lack biologically plausibility. First, the model assumes that primary vaccination is no more or less effective than vaccination that is acquired through transmission, so called “secondary” vaccination. We will extend the model by adding state-variables to separately represent primary-vaccinated hosts and hosts that acquire vaccination through transmission. We will then ask how dynamics differ if we allow the parameters that describe infection rates or shedding rates to differ. Second, the model assumes no incubation period between when a host is exposed to a pathogen or vaccine and when it becomes infectious. This incubation period may, however, be important to the disease dynamics [109]. We will extend the model to allow for distributed delays using the gamma-chain method [123]. These delays may increase the opportunity for coinfection [62]. We will therefore explore the sensitivity of the model’s predictions to the duration of the delay between exposure and immunity. Third, the model as written assumes that host population sizes are infinite, which simplifies analytical analyses, but removes the stochastic effects of small population sizes. We will therefore convert the model into its finite-population-size version following standard methods to explore disease elimination.

Expected results. We expect to find that the transmission rate of the vaccine from primary and secondary vaccinated hosts are critically important to understanding the effects of vaccine transmission on disease dynamics. We similarly expect to find that vaccine-induced protection against infection in primary and secondary vaccinated hosts has a disproportionately large impact on disease dynamics. We further expect to find that when the time between exposure and immunity is long, the number of co-infected hosts increases, which increases the potential for recombination between pathogen and vaccine strains. Lastly, we expect to find that reversion to virulence may complicate efforts to locally eliminate disease, increasing the likelihood that vaccination will be needed in perpetuity.

Aim 2: Characterize vaccine transmission and its impact on wildtype virus transmission

Rationale. From our preliminary analysis and in Aim 1, we identify key parameters and knowledge gaps that can be experimentally explored to better understand the impact of transmissible vaccines on disease

ecology and evolution. Here, we will estimate key parameters and fill in knowledge gaps to further our understanding of how the transmissible Rispens vaccine impacts Marek's disease virus ecology and evolution. We intend to have iterative feedback between models and experiments, allowing for experiments to change based on new results in Aims 1 and 4. Based on our preliminary analyses, we infer several knowledge gaps to be important, and we begin by prioritizing those experiments here. Others will be included if/when additional knowledge gaps are identified. We will: a) *Quantify the transmission rate of the vaccine virus*, b) *Characterize how selection on standing virus variation is affected by Rispens vaccination*, c) *Disentangle the protective effects of the transmissible vaccine*.

Background and preliminary data: In a preliminary experiment, we found that the Rispens vaccine can transmit from directly vaccinated birds to co-housed birds. We also found that Rispens vaccine does not favor the transmission of a hypervirulent vv+ isolate over less virulent v and vv isolates, which contrasts with published data showing that the earlier generation HVT vaccine favors hypervirulent strains over less virulent strains [99]. The Rispens vaccine therefore may drive fundamentally different patterns of evolution than seen in the past.

Methods: The methods used in our preliminary experiment are similar to those that will be used in the proposed work. We therefore present those methods in detail here. Our experimental setups are shown pictorially in Figure 1. Note that our preliminary experiment closely follows that of Aim 2b in Figure 1.

In our preliminary experiment, 180 specified-pathogen-free (SPF), maternal-antibody-free chickens were hatched from embryonated eggs at The Pirbright Institute. We used Rhode Island Red chickens, a breed that has not been subject to the intensive selective breeding and outcrossing that characterizes modern commercial chicken strains. However, in our proposed work, we will use commercial SPF layer-type birds to provide a level of genetic diversity more similar to the field conditions. Birds were individually wing-banded at one day of age and transferred to six, positive pressure, high efficiency particulate air (HEPA)-filtered avian isolators (Controlled Isolation Systems, US) within rooms in the BSU animal facility at The Pirbright Institute. Each isolator contained a total of 30 birds. Twenty of these birds were vaccinated or mock-vaccinated, hereafter referred to as "primary birds". The remaining 10 birds were non-vaccinated, hereafter referred to as "sentinel birds". Primary birds were also exposed to one of three challenge strains of wildtype Marek's disease virus that spanned the range of the virulence spectrum: HPRS-B14 (v), Md5 (vv), and 675A (vv+). We performed vaccination at one-day-of-age by administering approximately 1000 pfu of the Rispens vaccine (virus strain CVI988), in a volume of 100 μL, via the sub-cutaneous route. Challenge with MDV was performed at eight-days-of-age by administration of approximately 750 pfu of wildtype virus in a volume of 100 μL, via the intra-abdominal route.

Birds were inspected up to four times per day, depending on the severity of clinical signs in each group. Any chicken considered to have reached the humane endpoint was culled by cervical dislocation. When experiments were terminated, any surviving birds were culled. Post-mortem examination was performed on all culled chickens and the presence or absence of gross Marek's disease lesions recorded.

Since the vaccine or virus is found in the lymphocytes of vaccinated or infected birds [1], the detection of vaccine or viral DNA in peripheral blood is a marker of host

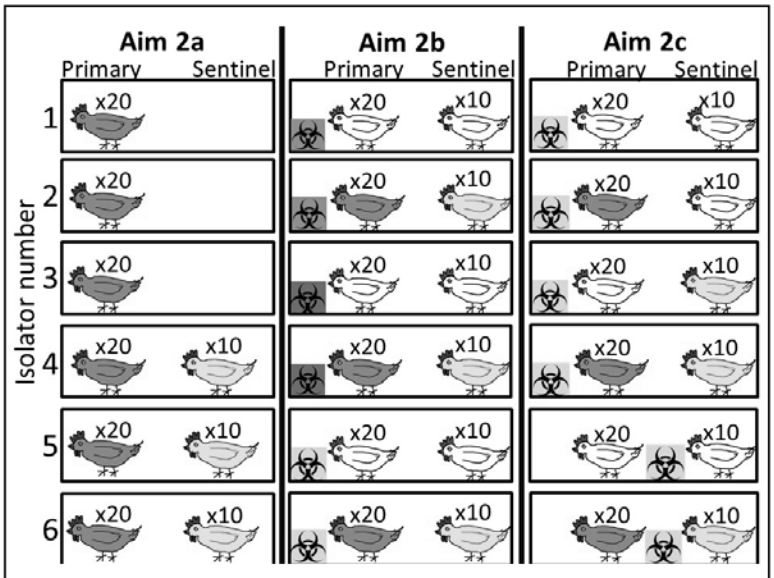

Figure 1: Experimental setup. Each column shows a different experiment and each row shows a different isolator. Blue birds were directly vaccinated, and aqua birds were cohoused with vaccinated birds. Biohazard symbols represent experimental infection with wildtype virus, where different colors depict different virus strains.

vaccination or infection status [43]. Since infectious vaccine or virus is produced and shed from feather epithelial cells [84], the detection of vaccine or virus DNA in feather pulp is a marker of shedding [5]. Since poultry dust, which consists of shed skin cells, dander, bacteria, and food particulate, is the infectious vehicle in the Marek's disease system [21, 24], the detection of vaccine or virus DNA in poultry dust is a proxy for transmission potential [99]. Therefore, on pre-specified sampling days (days post vaccination (dpv): 10, 13, 17, 20, 24, 27, 34, 38, 45, 48, 52, 55, 59 and 62), we collected 150 μl of blood from each primary and sentinel bird, four blood feathers from the axillary feather tract of primary birds, and poultry dust from the pre-filter of the ventilation fans in each isolator.

We processed blood, feathers, and dust for DNA extraction following our standard methods [5-7, 63, 99]. Each DNA sample was run in two real-time PCR assays: one specific for the Rispens vaccine virus, and the other specific for wildtype strains of Marek's disease virus [6, 63]. The above protocol was approved by the UK Home Office under license PPL 30/3169.

Preliminary results: Our main results from this preliminary experiment are as follows (Figure 2). First, as expected, we found that vaccination kept primary birds alive after challenge with wildtype virus. Second, we found that the Rispens vaccine substantially suppressed the shedding of all wildtype isolates of virus, including hypervirulent isolates. Third, we found that vaccine virus transmitted efficiently to sentinel chickens, with approximately 80% of sentinel chickens testing positive for vaccine DNA in blood by day 30, demonstrating that the Rispens vaccine is transmissible. Fourth, we found that for all three wildtype virus isolates, more sentinel birds became positive for the vaccine than the wildtype virus when sentinel birds were cohoused with vaccinated primary birds, suggesting that the vaccine virus may be capable of outcompeting the wildtype virus. Fifth, we found no significant differences between virus isolates of different virulence level in their ability to escape the protection of the vaccine in primary birds. Moreover, the direction of the non-significant effect on wildtype virus shedding was such that the vaccinated primary birds were better at transmitting less virulent v and vv isolates of virus to sentinels than they were at spreading the hypervirulent vv+ isolate. Thus, unlike in our previous work on the earlier generation HVT vaccine [99], the Rispens vaccine reduced transmission to sentinels for all wildtype isolates of virus, including hypervirulent isolates.

Caveats: While these data are promising, co-exposure of hosts to wildtype virus and vaccine is known to change shedding profiles of vaccine and virus [55, 56, 58]. We cannot therefore use this data to calculate an unbiased estimate of vaccine transmission rates. In addition, since space limitations restricted this study to three virus strains, we cannot assess whether the differences seen between treatments are due to strain-specific variation or virulence-associated differences. Finally, while this study demonstrates that vaccination reduces transmission of wildtype virus, in its current design, we are unable to assess whether this reduction is due to direct protection, indirect protection, or secondary protection acquired during virus transmission. In what follows, we design experiments to address each of these issues.

Aim 2a: *Quantify the transmission rate of the vaccine virus*. The value of transmissible vaccines comes from the ability of these vaccines to spread through host populations, which protects non-directly vaccinated hosts from infection or disease [19, 80, 88]. However, virtually nothing is known about how readily these vaccines transmit through host populations. While our preliminary data demonstrate that transmission is possible for the Rispens vaccine (Figure 2), we do not have a quantitative estimate for the transmission rate of the vaccine. This project will thus generate the first empirical estimates of the transmission rate of a licensed, commercial, transmissible vaccine.

Hypothesis. The Rispens vaccine virus will transmit efficiently to sentinel birds. Vaccine virus will be detectable in the feather pulp of sentinel birds at similar levels to that of primary birds, suggesting the potential for multiple rounds of vaccine transmission.

Methodology. We will experimentally quantify the transmissibility of the Rispens vaccine. Following our standard methodology [99], we will perform an experiment at The Pirbright Institute using 150 commercial SPF layer-type chickens. Details will be as described above with the following modifications. Each of the isolators will contain 20 birds vaccinated at one day of age, which we refer to as "primary birds". Three of the isolators will additionally contain 10 non-vaccinated birds, which we refer to as "sentinel birds", such that there will be three replicates for both experimental treatments. Blood and feathers will be collected from both primary and sentinel birds at the same sampling times as above along with dust from ventilation fans. Since no wildtype virus will be used in this experiment, DNA samples will be processed for real-time PCR using only the Rispens-specific assay [6].

To quantify the transmission potential of the vaccine, we will first measure the vaccine copy number per milligram (mg) of dust in each of the isolators, because dust is the infectious vehicle in the Marek's disease system [21, 24]. We will transform these data into total copies of vaccine virus using methods that we have previously developed that account for changes in dust shedding as a function of bird age [4, 99]. We will also measure vaccine copy number in the feathers of birds from all isolators, since virus copy number in feathers is tightly correlated with virus copy number in dust [5]. These data will provide an estimate of transmission potential over time [99]. To convert transmission potential into transmission rates, we will employ a statistical model that relates dust copy number to vaccine-positivity in sentinel birds, which can be determined from blood samples. This model essentially states that the number of sentinel birds uninfected with vaccine virus at time t depends on the initial number of sentinel birds multiplied by the probability that a bird would not have become infected by that time. Note that we will perform these calculations assuming a 7-day lag between infection and detection of virus in blood [55-57, 99]. We will model the system using:

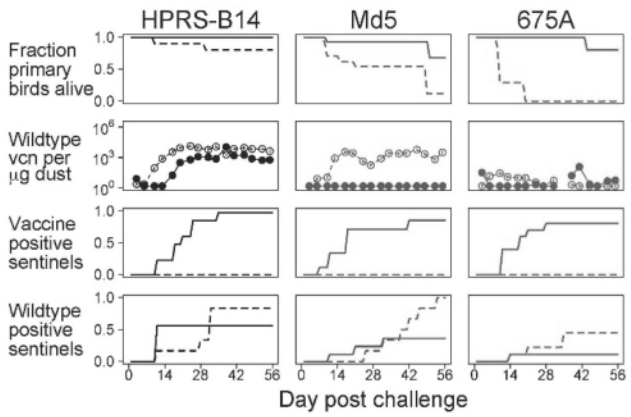

Figure 2: Results from preliminary experiment. Dotted lines and open circles show non-vaccinated treatments. Solid lines and filled circles, vaccinated.

$$S_t = S_0 e^{-\alpha \int_0^t \tau V_\tau d\tau}$$

Above, S_t is the number of sentinel birds that do not have detectable vaccine virus in their blood by time t, V_t is the number of vaccine virus copies in the dust at time t, and α is the per copy transmission rate of the vaccine virus. Rearranging this model, we can solve for the transmission rate α:

$$\alpha = \frac{\ln\left(\frac{S_0}{S_t}\right)}{\int_0^t \tau V_\tau d\tau}$$

Note that the underlying error structure in S_t is binomial. As we have previously shown using wildtype virus shedding, we can also estimate our uncertainty in V_t using the within-sample variation in our qPCR analysis [63, 99]. We will therefore be able to use likelihood-based approaches to estimate α and its uncertainty [34, 64, 65]. In addition, we will have observations at multiple timepoints for both S_t and V_t, which will greatly improve the precision of our estimate of α. A power analysis, based on our preliminary data that 80% of sentinels will become infected, shows that our sample sizes will allow us to estimate α with a standard error of approximately 19%.

Expected results. We expect to generate the first estimates for both the lifetime transmission potential and the transmission rate of a transmissible vaccine. We expect these estimates to show that the vaccine transmits efficiently from primary birds to secondary birds. We do not yet have a prediction regarding how much vaccine virus will be produced from birds that have been secondarily vaccinated, despite model predictions likely being strongly sensitive to this outcome [86].

Aim 2b: *Characterize how selection on standing virus variation is affected by Rispens vaccination.* As we described, the historical evolution of Marek's disease virus has been largely driven by the first two generations of vaccines [3, 26, 27, 99, 108, 126]. In the past, Marek's disease virus evolved vaccine resistance and increased virulence in response to the widespread use of these older vaccines. The potential and realized impacts of the Rispens vaccine on Marek's disease virus evolution are still unknown, but data on virus pathotypes over time show a correlation between the introduction of the Rispens vaccine and a decrease in average pathogen virulence (Figure 3). Moreover, our preliminary data presented above suggest that primary vaccination with the Rispens vaccine reduces the transmission of wildtype virus regardless of the pathotype of the virus isolate. It also suggests that the Rispens vaccine may be capable of outcompeting wildtype virus. This indicates potential for long-term disease control with the Rispens vaccine, making a comprehensive understanding of the reasons for this

success crucial to the development and implementation of other transmissible vaccines. We will explore the generality of the preliminary results using a second set of virus isolates.

Hypothesis. Vaccinated primary hosts will shed wildtype virus at significantly lower rates than mock-vaccinated primary hosts. Wildtype virus infection rates will be lower in sentinel hosts cohoused with vaccinated primary hosts than those cohoused with mock-vaccinated hosts. In treatments with both vaccinated and mock-vaccinated primary hosts, high virulence isolates will transmit less well to sentinel hosts than low virulence isolates.

Methodology. We will perform an experiment similar to that described in the preliminary data, with slight modifications (Figure 1). We will again experimentally challenge groups of 20 primary birds (vaccinated or mock-vaccinated) to virus isolates of different virulence, and these primary birds will again be co-housed with sentinel birds (non-vaccinated). The first modification from the preliminary study is that we will use a different set of virus isolates to see whether the patterns seen above depend on virus pathotype, or if they instead differ in unpredictable ways for each virus isolate. The second modification is that we will use commercial SPF layer type birds as described above. The third modification is that we will collect feathers from sentinel birds, to quantify the onward transmission potential of both wildtype virus and vaccine virus from sentinel birds. In addition, spleen samples from each host will be preserved at -80 °C when hosts reach experimental endpoints. Wildtype and vaccine virus found in feathers and spleens will be used in Aim 3 to study recombination rates between wildtype and vaccine virus. Transmission rates of vaccine and wildtype virus will be estimated as described in Aim 2a above. The detection of vaccine virus in the feathers of sentinel birds does not necessarily indicate the potential for transmission of the vaccine from sentinel birds to future non-vaccinated birds, because wildtype virus is capable of recombination with vaccine virus. For this reason, we will test for recombination and reversion to virulence in Aim 3.

Expected Results. We expect to find that the transmission of wildtype virus in vaccinated treatments is similar for all viral isolates regardless of their level of virulence. We will interpret the consequences of our results for virulence evolution using the model in Aim 4.

Potential pitfalls. One potential pitfall is that our qPCR assays show some interference between wildtype virus DNA and vaccine virus DNA [6, 63]. Since the assay is based on a single-base-pair polymorphism, high levels of wildtype virus DNA or vaccine virus DNA obscures our ability to accurately quantify the other. If this proves to be problematic, we will use the sequences generated in Aim 3a to develop new qPCR assays with decreased interference between the vaccine and our challenge viruses.

Aim 2c: *Disentangle the protective effects of the transmissible vaccine*. Vaccines typically reduce disease in a population through a combination of direct and indirect protection [47]. Transmissible vaccines introduce an additional type of protection, "secondary protection", which we define as direct protection against disease that is conferred to non-directly-vaccinated hosts due to exposure to the transmissible vaccine. Disentangling secondary protection from indirect protection (i.e. reduced disease due to herd immunity), however, would be extremely challenging in field settings [48, 49]. We thus designed an experiment to separately measure the direct, indirect, and secondary protection of the Rispens vaccine.

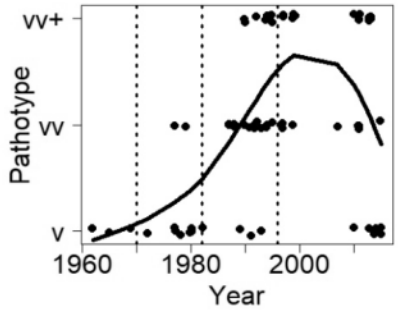

Figure 3: Pathotype of virus isolates collected over time [32]. Curve denotes mean pathotype. Dotted lines denote the introduction of HVT, bivalent, and Rispens vaccination. Note that mean virulence has declined since the introduction of the Rispens vaccine.

Hypothesis. We hypothesize that the Rispens vaccine will confer secondary protection smaller in magnitude than direct protection and greater in magnitude than indirect protection.

Methodology. This experiment will involve 180 chickens reared as described above. The experiment will contain 6 treatment arms (Figure 1). Each treatment arm will contain 20 primary birds (either vaccinated or mock-vaccinated) and 10 sentinel birds (non-vaccinated). Based on our preliminary data, the vaccine virus is detectable in sentinel birds at 28 days post vaccination, and so the sentinel birds in treatment groups 2 and 3 (Figure 1) will be flipped at this time, generating a set of secondary-protected sentinel birds that are

cohoused with mock-vaccinated primary birds, and a set of non-secondary-protected sentinel birds that are cohoused with vaccinated primary birds. On this same day, all primary birds in Treatment groups 1-4 as well as all sentinel birds in treatment groups 5-6 will be exposed to the hypervirulent wildtype virus isolate 675A (vv+). These treatments are designed to distinguish between primary, indirect, and secondary protection. We will again collect blood, feather, and dust samples. Birds that reach experimental endpoints will be removed from the experiment, at which time spleen samples will be removed and preserved at -80 °C for later genetic analysis in **Aim 3**. We will test each blood, feather, and dust sample for the presence of vaccine virus and wildtype virus by qPCR, to study the dynamics of infection, within-host replication, and shedding rate.

We will **quantify the direct effects of Rispens vaccination** on mortality, infection, and shedding by comparing data from vaccinated and mock-vaccinated primary birds (Isolators 1 vs. 2 and 3 vs. 4 in Figure 1). We will **quantify the indirect effects of Rispens vaccination** on mortality, infection, and shedding by comparing data from sentinel birds of the same vaccine status that are cohoused with vaccinated or mock-vaccinated primary birds (Isolators 1 vs. 2 and 3 vs. 4). We will **quantify the secondary protection of the Ripsens vaccine** by comparing data from sentinel birds that have or have not been previously cohoused with vaccinated primary birds (Isolators 1 vs. 3, 2 vs. 4, and 5 vs. 6).

Aim 3: Characterize the genetic evolution of wildtype virus and vaccine virus

Rationale. One of the key unknowns regarding transmissible vaccines is how such vaccines will evolve or drive the evolution of the pathogens they are meant to control [19, 80, 88]. All live vaccines have some risk of reverting to virulence, and all transmissible vaccines are by necessity live vaccines. Attenuated vaccines may reversion to virulence as they re-adapt to their original host, such as for the polio vaccine [78]. Transmissible vaccines have an increased risk of reversion to virulence relative to traditional vaccines, because transmissible vaccines may be able to evolve over multiple rounds of transmission. In addition, transmissible vaccines that co-circulate with the wildtype pathogens they are designed to control, have opportunities for recombination or horizontal gene transfer between vaccine and pathogen isolates [71]. The rate at which these evolutionary events take place are thus key to understanding whether transmissible vaccines may lead to adverse evolutionary outcomes. Using experimental samples from Aim 2 along with a library of over 25,000 dust samples collected from farms in central Pennsylvania USA [63] and a library of 120 dust sampled collected from farms in several countries in Europe, we will explore the risk of vaccine virus evolution and recombination between wildtype virus and vaccine virus. In particular, we will: a) *Characterize genetic diversity of vaccine and wildtype virus isolates collected on two continents*, b) *Quantify the rate of recombination in co-infected experimental birds*, and c) *Identify recombination events and their association with gain or loss of virulence*.

Background/Preliminary data. To date, there have been few published cases documenting recombination between wildtype Marek's disease virus and vaccine virus [50, 51]. Part of the reason why, however, may be that few studies have looked for recombination. Recombination may be rampant given that only a single polymorphic site has proven to be globally reliable for distinguishing between wildtype virus and the Rispens vaccine [6, 44, 101].

In previous work, we conducted routine surveillance for wildtype Marek's disease virus and the Rispens vaccine virus on farms in central Pennsylvania, to establish the distribution of Marek's disease virus on commercial poultry farms [63]. That work generated a library of over 25,000 dust samples from 102 farms in Pennsylvania, which are currently stored in a -80 °C freezer at Penn State University. A smaller library of samples, currently stored at Pirbright, was collected by Co-PI Nair during a similar surveillance project conducted across several countries in Europe. In both studies, samples were assayed for the presence of wildtype virus or the Rispens vaccine using probe-based qPCR assays developed by Co-PI Nair that are capable of distinguishing between wildtype and vaccine virus [6]. Over 4,000 of the Pennsylvania samples and all 120 of the European samples were assayed [63]. Approximately one third of the Pennsylvania samples were positive for wildtype virus or vaccine virus while about two thirds of the European isolates tested positive. However, only a small fraction of the positive European isolates were positive for wildtype virus. We have already utilized these libraries in prior studies [13, 63, 66, 93], and we will build on these prior data to guide our future work. In one of our previous studies, we identified at least 12 haplotypes of wildtype Marek's disease virus and a Rispens vaccine haplotype circulating on Pennsylvania farms [13]. In that study, we found that many of the wildtype virus haplotypes had marker regions that were identical to the Rispens vaccine, suggesting the

potential for recombination [13]. However, the Sanger sequencing method employed in that study could not definitively discern recombination from shared phylogenetic history. The whole genome sequencing planned here will be able to distinguish between these possibilities.

In an ongoing project, we sequenced full genomes from 64 viral isolates that have been pathotyped at the USDA Animal Diagnostics and Oncology lab. These isolates were collected under the research program of Richard Witter, and they comprises the largest collection of virus isolates that have been phenotyped (often referred to as "pathotyped" in this system) for their ability to escape the protection of different generations of Marek's disease vaccines [32, 126]. Moreover, this is the only collection of isolates that have been pathotyped using the Witter method, which is the gold standard method for phenotyping Marek's disease virus isolates [31, 127]. The isolates in the Witter collection were gathered from farms across the United States over 60 years, thus representing the diversity of Marek's disease virus over space and time [33].

Three preliminary outputs have emerged from this sequencing and comparative genomics analysis. First, we developed a pipeline for whole-genome sequencing and reference-guided *de novo* assembly of the Marek's disease virus genome, using 300 bp paired-end Illumina MiSeq reads, or 250 bp paired-end HiSeq reads. This pipeline is a modification of previous pipelines developed by Co-PI Szpara [93, 94]. Second, we performed preliminary genome wide association mapping using mixed linear models of association in the "GCTA" software package [130, 131] to identify polymorphic sites in this set of Marek's disease virus isolates that serve as markers of virulence. As a component of this work, we confirmed that a genetic marker previously posited to associate with virulence correlates extremely well with virulence in this collection, which is the largest set of samples for which parallel phenotypic data is available [13, 33, 92], and we identified several other putative markers of virulence. Third, we performed a recombination analysis using the program 3Seq to identify recombination breakpoints [16, 70] in the phylogenetic history of the virus genomes contained in the Witter collection. From this analysis, we found a strong signature of phylogenetic incongruence between different loci within the viral genomes, suggesting that recombination had occurred between wildtype isolates of the virus in the past.

Aim 3a: *Characterize genetic diversity of vaccine and wildtype virus isolates collected on two continents*. A necessary step towards characterizing evolution is to first characterize genetic diversity. Towards this end, we will leverage our libraries of field surveillance samples to identify the genetic variation present in wildtype and vaccine virus isolates circulating on two continents.

Hypothesis. We hypothesize that the loci harboring genetic diversity within continents will be different than the loci harboring diversity between continents. We also hypothesize that identical virus haplotypes will frequently have different whole-genome sequences.

Methodology. We will begin by generating whole genome sequences for each of the 12 virus haplotypes that we identified in previous work in our US library of dust samples [13]. Where possible, we will sequence three replicate isolates where the same haplotype was collected on different farms for a total of 36 US isolates. We will sequence an additional 10 dust samples in which we detected the Rispens vaccine. We will use a similar procedure to characterize virus diversity in the European dust samples. However, since only three European samples tested positive for wildtype virus, we will leverage our network of collaborators to find 33 additional European isolates to sequence. We will additionally sequence 10 Rispens vaccine samples in such a way as to maximize the geographic and temporal dispersion. In addition, we will sequence the 6 virus isolates and the vaccine virus used to infect birds in Aim 2, giving us a total of 99 isolates to sequence.

Sequencing virus from field isolates can be challenging because less than 0.1% of DNA in a chicken dust sample is Marek's disease virus DNA [93]. In previous work, we have developed a method, based on a series of enzymatic-digestion, filtration, and centrifugation steps, to enrich samples for viral DNA, allowing us to sequence virus directly from dust without introducing biases likely to arise from typical methods such as culturing samples prior to sequencing [53, 93, 116]. Co-PI Szpara has since applied more efficient methods for enrichment of viral DNA in samples to her work on herpes simplex virus type 1 [112, 113]. This method involves using Arbor Biosciences myBaits, which are custom oligonucleotide baits designed to bind to regions of the viral genome, thus enriching samples for downstream high-throughput sequencing. In practice, we will use the oligo library previously developed and successfully applied by Nikolaus Osterrieder and colleagues (including Co-PI Szpara) for sequencing Marek's disease virus [121]. We will use this method to enrich our field and lab samples for viral DNA prior to sequencing. Sequencing libraries will be prepared using the Illumina TruSeq Nano DNA Sample

Prep Kit following manufacturer instructions. The target DNA fragment size selected for library construction will be 550 base pairs (bp). We will sequence samples on an Illumina MiSeq, housed in Co-PI Szpara's laboratory, using version 3 chemistry to obtain paired-end sequence fragments of 300 by 300 bp. *De novo* assembly of consensus genomes will be performed using the viral genome assembly (VirGA) workflow developed by Co-PI Szpara [94]. Briefly, VirGA combines quality control preprocessing of reads, *de novo* assembly, genome linearization and annotation, and post-assembly quality assessments into a user-friendly web interface [94]. After assembly, we will test for the presence of minor variants within each dust sample using VarScan [69]. We will characterize the minor variants, as well as the sites at which these minor variants occur within and between samples to determine whether minor variants more likely arose *de novo* or represent co-circulation of multiple viral lineages [62].

Potential pitfalls. If some of the dust samples contain mixtures of virus genotypes, the analysis pipeline that we are planning to employ will not be capable of resolving haplotypes. In that event, for the subset of samples that harbor mixtures, we will employ haplotype reconstruction approaches [35] or long-read sequencing technology such as that of Pacific Biosciences (PacBio) [102], as described in Aim 3b.

Aim 3b: *Quantify the rate of recombination in co-infected experimental birds*. While we know from our preliminary data that recombination in the Marek's disease virus system is possible over evolutionary time, we do not know how readily recombination occurs. By looking for recombination in birds known to be vaccinated and infected with wildtype virus, we can ask how readily recombination events occur within a bird. In Aim 2, we will have generated samples from 100 birds that were experimentally infected with wildtype virus after direct vaccination. One of the challenges in identifying recombination is that convergent evolution and shared phylogenetic history can be difficult to distinguish from recombination when the parent strains of a recombinant are unknown [75, 76]. In our experimentally infected birds, however, it will be more straightforward to identify recombination between vaccine virus and wildtype virus because both parental isolates of any recombinant virus will be known to us. We will therefore be able to readily quantify the rate of recombination and the breakpoints of recombination in our experiments.

Hypothesis. We hypothesize that recombination will readily occur within hosts, suggesting numerous opportunities for selection to act on recombinant genotypes in the field.

Methodology. We will use long-read sequencing technology to detect recombination in the virus shed from experimentally vaccinated and infected birds. The vaccine virus genome and one of the 6 virus genomes, which we will sequence in Aim 3a above, will serve as parental genotypes in each of our observed recombination events. The high error rates of long-read sequencing can complicate the use of this technology for variant discovery, but our knowledge of the parental genotypes in the experiments will allow us to overcome this obstacle. We will sequence viral DNA in the feather pulp of the 100 birds that were experimentally vaccinated and then infected in Aim 2, since feather pulp contains the transmissible vaccine and virus. As before, we will enrich our samples for target DNA using Arbor Biosciences custom oligonucleotide baits [112, 113]. We will then follow standard procedures to prepare barcoded libraries for sequencing these samples using a PacBio Sequel sequencer. This process, along with PacBio sequencing, will be handled by the Penn State Genomics Core. The Penn State Genomics Core PacBio Sequel sequencer typically produces about 4,000,000 reads of length greater than 10 kb per run for indexed samples, which translates to approximately 2500x coverage per sample for 100 samples [102]. By identifying all polymorphic sites as belonging to the wildtype virus parent or the vaccine virus parent, we will be able to use our sequence reads in a non-parametric runs test to assess the fraction of reads in which there is statistically significant evidence of recombination [70]. If the runs test is underpowered to detect recombination given the high read error of PacBio sequencing, we will use model selection with maximum likelihood to classify reads as "recombined" or "not identifiable" based on the relative ratio between the maximum likelihood and the likelihood of being derived from a single parent. Based on the fraction of reads with a breakpoint between each set of neighboring segregating loci, we will estimate recombination rates across the genome to identify recombination hotspots [81]. One caveat is that a single recombination event may appear in multiple reads because of amplification within the host, and so we will bound the recombination rate by running a similar analysis using only reads that show evidence of a unique recombination event.

Potential pitfalls. PacBio sequencing can fail if DNA isolates are not extremely pure, or if DNA quantity is too low. If we find our samples to lack quality or quantity, we may opt to first generate amplicons prior to

sequencing, or to sequence from spleen samples. We may alternatively look to other long read technologies such as the Oxford Nanopore MinION.

Aim 3c: ***Identify recombination events and their association with gain or loss of virulence***. In the above, we will have identified the rate at which recombination occurs in concurrently vaccinated and infected hosts. Whether recombinant isolates will persist long enough to influence the ecology and evolution of disease is however an open question. Here we will address to what degree recombinant isolates circulate in the field and to what degree recombination influences the severity of disease in birds exposed to recombinant virus or recombinant vaccine.

Hypothesis. We hypothesize that recombination will be readily evident in the field. We also hypothesize that when markers of virulence are altered by recombination in a given isolate, the phenotype of that associated vaccine or virus isolate will also change.

Methodology. We will identify recombinants in our samples by using the approach that we have used in our preliminary analysis of the Witter collection of 64 virus isolates. Briefly, using MAFFT [61], we will generate an alignment of the genomes. The alignment will be analyzed using the 3Seq program to determine recombination breakpoints [16, 70]. 3Seq imports a nucleotide sequence file and tests triplets drawn from the alignment for mosaic recombination signals, to determine if any member of a triplet is a recombinant of the other two (i.e. child vs. parents). 3Seq performs a non-parametric test for mosaicism and uses pre-computed p-values to determine statistical significance. Overlapping break points will be combined to identify genome segments. We will then generate maximum likelihood trees using the RaXML program for all of the genome segments to look for phylogenetic incongruence [117].

If time and money allows, we will test the phenotype of a subset of isolates that show strong evidence of recombination between the vaccine isolate and a wildtype virus isolate or between wildtype isolates of differing putative virulence [13]. This experiment will be performed at The Pirbright Institute following bird rearing methods explained in Aim 2. Using 5 isolates that have genetic markers associated with hypervirulence [33], and 5 isolates that have genetic markers associated with low virulence, we will test whether each isolate is virulent by exposing sets of 10 one-day-old, specified-pathogen-free, maternal-antibody-free Rhode Island Red chickens to each isolate. These birds will be exposed to isolates following our standard procedures [99]. Three control groups will receive hypervirulent isolate 675A, low virulent HPRS-B14, or the Rispens vaccine strain, which will be used as internal controls for assigning phenotypes. Birds will be monitored 1 to 3 times daily, and we will collect data on the fraction of birds that die and their time of death. Based on a power analysis using our previous data [99], this experimental setup will have 99% power to distinguish between vaccine-like isolates and vv+ or vv-like isolates, 92% power to distinguish between v-like and vv+ or vv-like isolates, and 19% power to distinguish between vaccine-like and v-like isolates. We will use this data to ask whether the recombination of putative markers of virulence alters the virulence of virus or vaccine isolates.

Potential pitfalls. We may have difficulty getting our virus isolates from dust into cell culture, which is a necessary step for virus amplification and bird exposure. If this is the case, we may opt to use recombinant virus isolates generated in Aim 2b and sequenced in Aim 3b, since spleen samples of these isolates could be used to get the virus into culture. This approach, however, adds an extra step, in that genotypes must be confirmed in culture, because samples are likely to be a mixture of both unrecombined and recombined isolates.

Aim 4: Model the overall impact of transmissible vaccination on Marek's disease and its vaccine

Rationale. The data from Aims 2 and 3 will be used to fill key knowledge gaps identified in Aim 1. This will allow us to generate for the first time a data-informed model of transmissible vaccination. To accomplish this goal, we will expand on a model that we have developed in prior work [66]. This expanded model will be used to explore optimal management practices for Marek's disease on commercial poultry farms, and it will also be used to address conceptual issues relating to how transmissible vaccination alters the ecology and evolution of infectious diseases.

Our first task will be to isolate the impacts of vaccine transmission on virus transmission and disease. One can expect that vaccine transmission will reduce the number of birds that need to be vaccinated to control disease [19, 80, 88], but the degree to which vaccine transmission effects disease depends on the rate of spread for both the wildtype pathogen and the vaccine. That is because in a cohort structured population, the vaccine and wildtype virus must compete for first access to susceptible

hosts. Therefore, if the wildtype virus spreads much more quickly than the vaccine virus, or if vaccine transmission confers only partial immunity to wildtype virus, the epidemiological benefit of vaccine transmission may be negligible. Here we will use the parameter estimates generated in Aim 2 to generate for the first time a model of transmissible vaccination that has been grounded in empirical data. We will use the model to quantify the impact of vaccine transmission on disease ecology.

Our second task will be to understand how competition between wildtype virus and vaccine virus impacts the persistence of the transmissible vaccine and wildtype virus within locations and between locations over time. Most transmissible vaccines currently being considered target pathogen prevalence in wildlife populations [19, 80, 88]. Control of infectious diseases in these systems must necessarily account for multiple spatial and temporal timescales since wildlife populations often follow metapopulation dynamics [39, 42, 52]. The inherent metapopulation structure of farmed chickens therefore provides an ideal setting for initial studies of this process [63]. We will use our model to understand the ecological competition between the wildtype virus and the vaccine virus, to understand how this competition will alter the persistence of the wildtype virus and the vaccine.

Our third task will be to understand the evolutionary consequences of transmissible vaccination. Recombination between wildtype virus and vaccine virus may lead to improved transmissibility of the vaccine virus [71], potentially increasing the ability of the vaccine to control disease. However, recombination may also increase the virulence of currently circulating virus or vaccine isolates through recombination [25]. From Aim 2, we will learn whether the transmissible vaccine alters competition between less virulent and more virulent isolates of the virus, potentially leading to evolutionary increases or decreases in mean virulence [10, 40, 41, 74, 99]. In addition, a key component of why vaccine resistance tends not to evolve is because vaccines tend to be applied prophylactically rather than therapeutically [67, 68]. For transmissible vaccines, vaccines may often transmit to hosts that are already infected with wildtype pathogen, thus setting the stage for the emergence of vaccine resistance [67]. We will use our model to probe which of these evolutionary consequences are likely to occur for this transmissible vaccine, giving insight more generally into the evolutionary consequences of transmissible vaccines.

Methodology. In previous work, we developed a model to describe the ecology of Marek's disease virus on commercial poultry flocks [66]. In this aim, we will extend this model to allow for vaccine transmission and to allow for mixed populations of vaccinated and non-vaccinated hosts. For Marek's disease virus, as with most infectious diseases, there is a delay between exposure and virus shedding [54, 55, 99]. There is also a delay between wildtype virus exposure and host mortality [97, 99]. Our first step will therefore be to extend our previous ordinary-differential-equation model of this system by generalizing the "gamma-chain" method to allow for variability in the delay between exposure and mortality [123]. A typical gamma-chain model assumes that hosts transition through multiple hidden classes before entering an infectious class in which they are infectious and at risk of pathogen-induced mortality [123]. However, the onset of infectiousness vs. mortality typically occurs at different times. An obvious approach to deal with this issue is to use a second gamma-chain in the infectious class, such that hosts die only after they transition through the hidden classes in both the exposed state and the infectious state. The drawback of this approach, however, is that it assumes that infectiousness is a prerequisite to mortality, whereas in the Marek's disease virus system, we know that this is not always the case [91]. In fact, the possible occurrence of mortality prior to infectiousness is a key driver of Marek's disease virulence evolution [99]. We will therefore generate an alternative framework for distributed-delay gamma-chain models by creating a two-dimensional set of pre-infectious and pre-death classes that allows hosts to independently progress through pre-infectious and pre-death states. We have already begun to develop this model, as outlined below. If we assume that hosts become infectious when they progress through I preinfectious classes, and we assume that hosts die when they progress through J premortality classes, then we can extend our previously published model [66] to include independent progression towards infectiousness or mortality by tracking I times J classes that depict exposed and infectious hosts. We can thus describe the dynamics within a cohort using the following model:

$$\frac{dS(t)}{dt} = -\alpha S(t) \sum_k Z_k(t)$$

$$\frac{dE_{1,1,k}(t)}{dt} = \alpha S(t) Z_k(t) - (\beta + \lambda_k) E_{1,1,k}(t)$$

$$\frac{dE_{n,m,k}(t)}{dt} = \beta E_{n-1,m,k}(t) + \lambda_k E_{n,m-1,k}(t) - (\beta + \lambda_k) E_{n,m,k}(t)$$

$$\frac{dI_{m,k}(t)}{dt} = \beta E_{N,m,k}(t) + \lambda_k I_{m-1,k}(t) - \lambda_k I_{m,k}(t)$$

$$\frac{dZ_k(t)}{dt} = -\gamma Z_k(t) - \delta Z_k(t) + a_k\, d(\tau) \sum_{r=1}^{M} I_{r,k}$$

for $(n = 1, 2, 3, \dots, N)$, $(m = 1,2,3, \dots, M)$, and $(k = v, vv, vv+, \text{or Rispens})$.

In the above equations, S_t is the density of susceptible birds at time t and $E_{n,m,k}(t)$ is the density of birds exposed to virus type k in exposed classes n and m at time t, where n denotes the N incubation classes prior to a bird becoming infectious, and m denotes the M disease classes prior to a bird dying of disease. Note that a "0" subscripts for E or I correspond to a zero value for the state variable. We assume that progression towards shedding is separate from progression towards death, because data have shown that birds can die prior to the onset of substantial virus shedding, and hosts can alternatively experience extreme shedding in the absence of any clinical signs [99]. $I_{m,k}(t)$ is the density of birds in infectious class m at time t infected with virus isolate k. $Z_k(t)$ is the density of virus isolate k at time t. The transmission rate is α and the virus shedding per mg of dust shed is a_k. Birds shed $d(\tau)$ mg of dust per day, which depends on bird age τ. Virus is removed from the system through ventilation γ and degradation δ. Exposed birds progress through incubation classes at rate β and exposed and infectious birds progress through illness classes at rate λ_k. Note that all birds, except for those that were vaccinated, begin a cohort in the susceptible class. While this model has a lot of parameters, the majority of them have already been estimated in our previous work [66] and those remaining can be estimated from previously published data [4, 99] or experiments that will be conducted as a component of this grant.

We will use this model along with data from Aim 2 to explore the impact of vaccine transmission on infection prevalence and host mortality. We will generate two versions of our model, one not allowing for vaccine transmission by setting $a_{\text{Rispens}} = 0$, and the other allowing for it by setting a_{Rispens} to its experimentally observed value. Using these models, we will quantify mortality and infection prevalence in the presence or absence of vaccine transmission to identify how many extra doses of vaccine are needed to achieve equal protection in the absence of vaccine transmission. We will run the model for host populations containing virulent (v), very virulent (vv), and very virulent plus (vv+) pathotypes of the virus, for the range of initial virus concentrations seen in our previous surveillance study [63], to explore the impact that virus phenotype and virus concentration have on optimal management practices.

Following our previous work, we will next extend the model to allow for virus and vaccine persistence across multiple sequential cohorts [66]. Between cohorts, farm housing environments experience a period of downtime, during which cleaning and disinfection may be implemented. We describe the dynamics between cohorts using the following model:

$$\Omega_k(\mathrm{c}) = (1 - \mu)(1 - C) Z_k(l)$$

Above, $\Omega_k(\mathrm{c})$ is the amount of virus of type k that will persist until the start of cohort c. $\Omega_k(\mathrm{c})$ depends on the fraction of virus that degrades between cohorts μ, the fraction of virus that is physically removed between cohorts C, and the amount of virus that was present at the end of the previous cohort $Z_k(l)$. We will use our previous estimates for the values of these parameters [66].

We will use this model to explore how competition between wildtype virus and the vaccine virus influences the long-term coexistence of the wildtype virus and the vaccine. If our results from Aim 2c show that immune protection is different in primary and secondary vaccinated birds, we will expand the model to accommodate this difference. We will also generalize the model to allow for an arbitrary number of virus phenotypes and genotypes, which in turn will allow us to model recombination between virus isolates. The rate of this recombination will be estimated in Aim 3, and we will use this model to ask how recombination between vaccine and wildtype virus influences the ecology and evolution of transmissible vaccines and the pathogens they are designed to control.

Broader Impacts

The work in this proposal is expected to have direct benefits for society through improved food biosecurity. Marek's disease is a substantial economic drain on the profitability of poultry farming, and evolution of the virus is an ever-present threat [26]. Given that chicken meat and eggs contribute more than 10% of the protein in the average American's diet [95], the impact of adverse evolution occurring in

the virus or vaccine could be severe. The proposed work will address whether such adverse evolution is likely to occur or has in fact already begun. We will ensure that our work is widely accessible to the scientific community by posting preprints on BioRXiv, a preprint academic server for Biology, and by making all code developed for this project available on GitHub. In addition, we will ensure that our work and related concepts are widely disseminated to relevant audiences through educational outreach to K-12 youth, the general public, and industry stakeholders. Dr. Jessica Kim-Schmid in the Office of Science Outreach will help to facilitate these activities by serving as a connection within Penn State.

For outreach to K-12 youth, and in particular youth from groups that are underrepresented in the STEM fields, we will take advantage of the infrastructure already in place at Penn State University. We will contribute to the Science-U summer camp program run by the Penn State Office of Science Outreach, which comprises 12-15 topic-specific weeklong summer camps for K-12 students each summer. The chief mission of Science-U is to advance science literacy in youth through the sharing and discovery of scientific knowledge. PI Kennedy has previously designed and contributed a presentation for the Science-U "Infection" camp, a camp which engaged high school students with an interest in infectious diseases. As a component of this proposal, he will design and contribute a presentation for the Science-U "Finding Your Roots" camp, which introduces middle school students to ways they can use their own genetic data to understand their ancestry and traits. As part of the camp's focus on introducing these students to real scientists using similar concepts in their work, our presentation will demonstrate how we use genetic information to understand the evolutionary history of infectious diseases. A major component of this presentation will describe work performed in this proposal, and we will emphasize how scientific research impacts aspects of their daily lives, such as food safety. To support the accessibility of Science-U's impactful programming for students from economically disadvantaged backgrounds, we will also contribute two student scholarships per year to Science-U.

For outreach to the broader public, we will again build off of the resources at Penn State. The Osher Lifelong Learning Institute (OLLI) at Penn State offers a collection of over 300 courses (with a typical course being 3 to 5 lectures) available to members of the community 50 years and older who want to learn and explore in a welcoming environment. Despite the wide variety of offerings, science courses are rarely offered, and the OLLI staff are eager for more science content. To help meet this need and share the important and widely relevant concepts from our research, PI Kennedy will develop a 4-part course entitled "The Impacts of Vaccination". Part 1 will cover how vaccines work to control disease. Part 2 will cover why antibiotic resistance readily evolves but vaccine resistance does not. Part 3 will cover the ways in which vaccines can be used to slow the emergence and spread of antibiotic resistance. Part 4 will cover the other impacts of vaccination on pathogen evolution. Additionally, to reach a younger adult audience, we will modify our course content for an informal and conversational talk at "Science on Tap", a well-established seminar series geared towards the public that is hosted by the Penn State Science Policy Society.

For outreach to industry stakeholders, we will disseminate our findings to farmers locally and widely. Co-PI Nair runs the Marek's disease virus laboratory for the OIE (World Organisation for Animal Health, the WHO equivalent for animal health) and consults internationally with stakeholders on Marek's disease problems. Nair also carries out collaborative research on Marek's disease through UK-China Centre of Excellence for Research on Avian Diseases (CERAD), which allows us to potentially examine disease dynamics in Asia should funds and time allow. The knowledge gained in this proposal will therefore directly reach stakeholders and policymakers worldwide. In addition, PI Kennedy regularly attends the Pennsylvania Poultry Sales and Service Conference and Northeast Conference on Avian Diseases (PPSSC-NECAD), a joint regional-meeting between the poultry industry and the scientific community performing industry-relevant research. Co-PI Szpara has also attended this meeting previously. PI Kennedy will present results from this proposal at this meeting.

Results from prior NSF support

Of the PIs, only Kennedy has NSF support: NSF-DEB 1754692 (08/01/2018-07/31/2021). *Virulence Evolution After Viral Host Jump and Emergence*. PI: Andrew F Wargo (VIMS), Co-PIs: Gael Kurath (USGS), David A Kennedy (PSU). Total award: $1,327,512; Kennedy subaward: $117,175. Preliminary studies have been conducted for all research aims. Preliminary code exploring the timescale at which virulence evolution can occur has been deposited by Kennedy on GitHub. **Intellectual Merit**: This project concerns the evolution of virulence in a fish pathogen, following its initial emergence in a new host. **Broader Impacts**: This work has direct relevance to the rapidly expanding aquaculture industry, in which many developing nations and under-represented groups are heavily invested.

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Biographical Sketch

David Kennedy
Assistant Professor of Biology
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(814) 863-5461
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(a) Professional Preparation

State University of New York at Binghamton	Binghamton, NY	Biology	BS, 2005
University of Chicago	Chicago, IL	Ecology and Evolution	PhD, 2012
Pennsylvania State University	State College, PA	Disease Ecology and Evolution	Post-doc, 2012-2015

(b) Appointments

2019-Present Assistant Professor of Biology, Pennsylvania State University
2015-2018 Research Associate, Pennsylvania State University, Department of Biology

(c) Publications

(i) Five publications/products most closely related to the proposed project

1. Bell AS, **Kennedy DA**, Jones MJ, Cairns CL, Pandey U, Dunn PA, Szpara ML, Read AF. 2019. Molecular epidemiology of Marek's disease virus in central Pennsylvania, USA. *Virus Evolution*, 5: vey042.

2. **Kennedy DA**, Dunn PA, Read AF. 2018. Modeling Marek's disease virus transmission: A framework for evaluating the impact of farming practices and evolution. *Epidemics*, 23: 85-95.

3. **Kennedy DA**, Cairns C, Jones MJ, Bell AS, Salathe RM, Baigent SJ, Nair VK, Dunn PA, Read AF. 2017. Industry-wide surveillance of Marek's disease virus on commercial poultry farms. *Avian Diseases*, 61: 153-164.

4. Read AF, Baigent SJ, Powers C, Kgosana LB, Blackwell L, Smith LP, **Kennedy DA**, Walkden-Brown SW, Nair VK. 2015. Imperfect vaccination can enhance the transmission of highly virulent pathogens. *PLoS Biology*, 13: e1002198.

5. **Kennedy DA**, Dunn JR, Dunn PA, Read AF. 2015. An observational study of the temporal and spatial patterns of Marek's-disease-associated leukosis condemnation of young chickens in the United States of America. *Preventive Veterinary Medicine*, 120: 328-335.

(ii) Five other significant publications/products

1. **Kennedy DA**, Read AF. 2018. Why the evolution of vaccine resistance is less of a concern than the evolution of drug resistance. *Proceedings of the National Academy of Sciences USA*, 115: 12878-12886.

2. **Kennedy DA**, Dwyer G. 2018. Effects of multiple sources of genetic drift on pathogen variation within hosts. *PLoS Biology*, 16: e2004444.

3. **Kennedy DA**, Read AF. 2017. Why does drug resistance readily evolve but vaccine resistance does not? *Proceedings of the Royal Society B: Biological Sciences*, 284: 20162562.

4. **Kennedy DA**, Kurath G, Brito IL, Purcell MK, Read AF, Winton JR, Wargo AR. 2016. Potential drivers of virulence evolution in aquaculture. *Evolutionary Applications*, 9: 344-354.

5. **Kennedy DA**, Dukic V, Dwyer G. 2014. Pathogen growth in insect hosts: inferring the importance of different mechanisms using stochastic models and response-time data. *The American Naturalist*, 184: 407-423.

(d) Synergistic Activities

- Presented yearly research presentations to industry at the joint Northeast Conference on Avian Diseases and Poultry Sales & Services Conference (2013-2018)
- Served on the Penn State Biology Climate/Diversity Committee, a committee tasked with improving the climate of inclusion and mutual respect at Penn State (2012-present)
- Contributed a presentation to Science U summer camp, *Infection*, a program designed to foster interest in STEM for high school and middle school students, particularly those from under-represented groups (2016)
- Mentored two postdocs, nine undergraduates, one high school student, and one technician. Includes three individuals from under-represented groups. (2012-present)
- Served as guest Academic Editor for *PLoS Biology* (2019)

Moriah Szpara
Associate Professor of Biochemistry and Molecular Biology
Center for Infectious Disease Dynamics, and the Huck Institutes of the Life Sciences
Pennsylvania State University
W208 Millennium Science Complex, University Park, PA 16802, USA
(814) 867-0008
mls164@psu.edu

(a) Professional Preparation

Pennsylvania State University	University Park, PA	Biology	B.S., 1998
University of California (UC)	Berkeley, CA	Neuroscience	PhD, 2004
Princeton University	Princeton, NJ	Neurovirology	Postdoc, 2005 – 2013

(b) Appointments

2019 - present	**Associate Professor,** Dept. of Biochemistry & Molecular Biology, Pennsylvania State Univ.
2013 - 2018	**Assistant Professor,** Dept. of Biochemistry & Molecular Biology, Pennsylvania State Univ.
2005 - 2013	**Postdoctoral Fellow** and **Associate Research Scholar**, Princeton University (with Dr. Lynn Enquist)

(c) Publications

(i) Five publications most closely related to the proposed project

Bell AS, Kennedy DK, Jones MJ, Cairns CL, Pandey U, Dunn PA, **Szpara ML**, Read AF. *Molecular epidemiology of Marek's disease virus in central Pennsylvania, USA*. (2019) Virus Evolution. Apr 23;5(1). https://doi.org/10.1093/ve/vey042

Trimpert J, Groenke N, Jenckel M, He S, Kunec D, **Szpara ML**, Spatz SJ, Osterrieder N, McMahon DP. *A phylogenomic analysis of Marek's disease virus reveals independent paths to virulence in Eurasia and North America*. (2017) Evolutionary Applications. 10:1091–1101. https://doi.org/10.1111/eva.12515

Pandey U, Bell AS, Renner DW, Kennedy DA, Shreve JT, Cairns CL, Jones MJ, Dunn PA, Read AF, **Szpara ML**. *DNA from dust: Comparative genomics of large DNA viruses in field surveillance samples*. (2016) mSphere. 1:e00132-16. https://doi.org/10.1128/mSphere.00132-16

Parsons LR, Tafuri YR, Shreve JT, Bowen CD, Shipley MM, Enquist LW, **Szpara ML**. *Rapid genome assembly and comparison decode intrastrain variation in human alphaherpesviruses*. (2015) mBio. Mar 31;6(2). pii: e02213-14. https://doi.org/10.1128/mBio.02213-14

Szpara ML, Gatherer D, Ochoa A, Greenbaum B, Dolan A, Bowden RJ, Enquist LW, Legendre M, Davison AJ. *Evolution and diversity in human herpes simplex virus genomes.* (2014) Journal of Virology, Jan; 88(2): 1209-27. https://doi.org/10.1128/JVI.01987-13

(ii) Five other significant publications/products

Bowen CD, Paavilainen H, Renner DW, Palomäki J, Lehtinen J, Vuorinen T, Norberg P, Hukkanen V, **Szpara ML**. *Comparison of herpes simplex virus 1 strains circulating in Finland demonstrates the uncoupling of whole-genome relatedness and phenotypic outcomes of viral infection*. (2019) Journal of Virology. Apr 3;93(8). pii: e01824-18. https://doi.org/10.1101/424408.

Shipley MM, Renner DW, Ott M, Bloom DC, Koelle DM, Johnston C, **Szpara ML**. *Genome-wide surveillance of genital herpes simplex virus type 1 from multiple anatomic sites over time.* (2018) The Journal of Infectious Diseases. 218(4): 595–605. https://doi.org/10.1093/infdis/jiy216

Pandey U, Renner DW, Thompson R, **Szpara ML**, Sawtell NM. *Inferred father-to-son transmission of herpes simplex virus results in near-perfect preservation of viral genome identity and in vivo phenotypes*. (2017) Scientific Reports. 7(1):13666. https://doi.org/10.1038/s41598-017-13936-6

Renner DW and **Szpara ML**. *The impacts of genome-wide analyses on our understanding of human herpesvirus diversity and evolution*. (2018) Journal of Virology. 92:e00908-17. **Invited review.** https://doi.org/10.1128/JVI.00908-17

Szpara ML, Tafuri YR, Parsons L, Shamim SR, Verstrepen KJ, Legendre M, Enquist LW. *A wide extent of inter-strain diversity in virulent and vaccine strains of alphaherpesviruses.* (2011) PLoS Pathogens. 7(10): e1002282. https://doi.org/10.1371/journal.ppat.1002282

(d) Synergistic Activities

Established **VirAmp** as a web-accessible, user-friendly computational workflow for viral genome assembly, on which >230 registered users in 19 different countries have assembled 2.5 TB of viral genome sequence data thus far: http://viramp.com/ (2015 – present)

Created a **3D Printable Viruses** educational outreach website, to enable easy 3D-printing of virus models in schools or in higher-education settings. Developed in collaboration with Penn State undergraduates and the College of Engineering at Penn State: https://3dvirology.github.io/downloads/ (2017 – present)

Created and coordinated the **Virology@PSU** network and seminar series, to synergize virology research campus-wide and make it accessible to all levels from undergraduate to graduate students, postdocs, staff, and faculty: http://virology.psu.edu/ (2014 – present)

Served on the **International Committee on the Taxonomy of Viruses (ICTV)**, Herpesvirales Study Group Member (2017 – present)

Mentored two postdocs, three graduate students (2 to PhD thus far) as primary mentor, fourteen graduate students as thesis committee member (including 2 under-represented minorities, URMs), eight undergraduates, and three staff scientists. Includes three individuals from under-represented groups (URMs). (2013-present)

SUMMARY PROPOSAL BUDGET

YEAR 1

FOR NSF USE ONLY		
PROPOSAL NO.	DURATION (months) Proposed	Granted
AWARD NO.		

ORGANIZATION
Pennsylvania State Univ University Park

PRINCIPAL INVESTIGATOR / PROJECT DIRECTOR
David Kennedy

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title, A.7. show number in brackets)	NSF Funded Person-months CAL	ACAD	SUMR	Funds Requested By proposer	Funds granted by NSF (if different)
1. **David Kennedy - Principal Investigator**	(b)(6)			**11,065**	
2. **Moriah Szpara - co-PI**				**25,375**	
3.					
4.					
5.					
6. (**0**) OTHERS (LIST INDIVIDUALLY ON BUDGET JUSTIFICATION PAGE)	0.00	0.00	0.00	**0**	
7. (**2**) TOTAL SENIOR PERSONNEL (1 - 6)	(b)(6)			**36,440**	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (**1**) POST DOCTORAL SCHOLARS	12.00	0.00	0.00	**51,361**	
2. (**2**) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)	(b)(6)			**30,137**	
3. (**2**) GRADUATE STUDENTS				**48,154**	
4. (**0**) UNDERGRADUATE STUDENTS				**0**	
5. (**0**) SECRETARIAL - CLERICAL (IF CHARGED DIRECTLY)				**0**	
6. (**0**) OTHER				**0**	
TOTAL SALARIES AND WAGES (A + B)				**166,092**	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS)				**43,539**	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A + B + C)				**209,631**	
D. EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $5,000.)					
TOTAL EQUIPMENT				**0**	
E. TRAVEL 1. DOMESTIC (INCL. U.S. POSSESSIONS)				**4,500**	
2. INTERNATIONAL				**3,480**	
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $ **700**					
2. TRAVEL **0**					
3. SUBSISTENCE **0**					
4. OTHER **0**					
TOTAL NUMBER OF PARTICIPANTS (**2**) TOTAL PARTICIPANT COSTS				**700**	
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				**20,930**	
2. PUBLICATION COSTS/DOCUMENTATION/DISSEMINATION				**0**	
3. CONSULTANT SERVICES				**0**	
4. COMPUTER SERVICES				**7,200**	
5. SUBAWARDS				**0**	
6. OTHER				**38,520**	
TOTAL OTHER DIRECT COSTS				**66,650**	
H. TOTAL DIRECT COSTS (A THROUGH G)				**284,961**	
I. INDIRECT COSTS (F&A)(SPECIFY RATE AND BASE) **Modified total Direct Costs (Rate: 58.0500, Base: 245741)**					
TOTAL INDIRECT COSTS (F&A)				**142,653**	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)				**427,614**	
K. FEE				**0**	
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				**427,614**	

M. COST SHARING PROPOSED LEVEL $ **0** AGREED LEVEL IF DIFFERENT $

PI/PD NAME
David Kennedy

ORG. REP. NAME*
Lisa Sergeant

FOR NSF USE ONLY		
INDIRECT COST RATE VERIFICATION		
Date Checked	Date Of Rate Sheet	Initials - ORG

 ***ELECTRONIC SIGNATURES REQUIRED FOR REVISED BUDGET**

SUMMARY PROPOSAL BUDGET

YEAR 2

FOR NSF USE ONLY		
PROPOSAL NO.	DURATION (months) Proposed	Granted
AWARD NO.		

ORGANIZATION
Pennsylvania State Univ University Park

PRINCIPAL INVESTIGATOR / PROJECT DIRECTOR
David Kennedy

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title, A.7. show number in brackets)	NSF Funded Person-months CAL	ACAD	SUMR	Funds Requested By proposer	Funds granted by NSF (if different)
1. **David Kennedy - Principal Investigator**	(b)(6)			**22,821**	
2. **Moriah Szpara - co-PI**				**26,012**	
3.					
4.					
5.					
6. (**0**) OTHERS (LIST INDIVIDUALLY ON BUDGET JUSTIFICATION PAGE)	0.00	0.00	0.00	**0**	
7. (**2**) TOTAL SENIOR PERSONNEL (1 - 6)	(b)(6)			**48,833**	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (**1**) POST DOCTORAL SCHOLARS	12.00	0.00	0.00	**52,645**	
2. (**2**) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)	(b)(6)			**30,888**	
3. (**2**) GRADUATE STUDENTS				**50,872**	
4. (**0**) UNDERGRADUATE STUDENTS				**0**	
5. (**0**) SECRETARIAL - CLERICAL (IF CHARGED DIRECTLY)				**0**	
6. (**0**) OTHER				**0**	
TOTAL SALARIES AND WAGES (A + B)				**183,238**	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS)				**49,170**	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A + B + C)				**232,408**	
D. EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $5,000.)					
TOTAL EQUIPMENT				**0**	
E. TRAVEL 1. DOMESTIC (INCL. U.S. POSSESSIONS)				**4,500**	
2. INTERNATIONAL				**22,050**	
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $ **700**					
2. TRAVEL **0**					
3. SUBSISTENCE **0**					
4. OTHER **0**					
TOTAL NUMBER OF PARTICIPANTS (**2**) TOTAL PARTICIPANT COSTS				**700**	
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				**16,225**	
2. PUBLICATION COSTS/DOCUMENTATION/DISSEMINATION				**3,000**	
3. CONSULTANT SERVICES				**0**	
4. COMPUTER SERVICES				**7,200**	
5. SUBAWARDS				**0**	
6. OTHER				**43,677**	
TOTAL OTHER DIRECT COSTS				**70,102**	
H. TOTAL DIRECT COSTS (A THROUGH G)				**329,760**	
I. INDIRECT COSTS (F&A)(SPECIFY RATE AND BASE) **Modified total Direct Costs (Rate: 58.0500, Base: 289383)**					
TOTAL INDIRECT COSTS (F&A)				**167,987**	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)				**497,747**	
K. FEE				**0**	
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				**497,747**	

M. COST SHARING PROPOSED LEVEL $ **0** AGREED LEVEL IF DIFFERENT $

PI/PD NAME
David Kennedy

ORG. REP. NAME*
Lisa Sergeant

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 ***ELECTRONIC SIGNATURES REQUIRED FOR REVISED BUDGET**

SUMMARY PROPOSAL BUDGET

YEAR 3

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PROPOSAL NO.	DURATION (months) Proposed	Granted
AWARD NO.		

ORGANIZATION
Pennsylvania State Univ University Park

PRINCIPAL INVESTIGATOR / PROJECT DIRECTOR
David Kennedy

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title, A.7. show number in brackets)	NSF Funded Person-months CAL	ACAD	SUMR	Funds Requested By proposer	Funds granted by NSF (if different)
1. **David Kennedy - Principal Investigator**	(b)(6)			**23,391**	
2. **Moriah Szpara - co-PI**				**26,662**	
3.					
4.					
5.					
6. (**0**) OTHERS (LIST INDIVIDUALLY ON BUDGET JUSTIFICATION PAGE)	0.00	0.00	0.00	**0**	
7. (**2**) TOTAL SENIOR PERSONNEL (1 - 6)	(b)(6)			**50,053**	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (**1**) POST DOCTORAL SCHOLARS	12.00	0.00	0.00	**53,961**	
2. (**2**) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)	(b)(6)			**31,660**	
3. (**2**) GRADUATE STUDENTS				**52,144**	
4. (**0**) UNDERGRADUATE STUDENTS				**0**	
5. (**0**) SECRETARIAL - CLERICAL (IF CHARGED DIRECTLY)				**0**	
6. (**0**) OTHER				**0**	
TOTAL SALARIES AND WAGES (A + B)				**187,818**	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS)				**50,396**	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A + B + C)				**238,214**	
D. EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $5,000.)					
TOTAL EQUIPMENT				**0**	
E. TRAVEL 1. DOMESTIC (INCL. U.S. POSSESSIONS)				**4,500**	
2. INTERNATIONAL				**0**	
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $ **700**					
2. TRAVEL **0**					
3. SUBSISTENCE **0**					
4. OTHER **0**					
TOTAL NUMBER OF PARTICIPANTS (**2**) TOTAL PARTICIPANT COSTS				**700**	
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				**14,225**	
2. PUBLICATION COSTS/DOCUMENTATION/DISSEMINATION				**3,000**	
3. CONSULTANT SERVICES				**0**	
4. COMPUTER SERVICES				**7,200**	
5. SUBAWARDS				**0**	
6. OTHER				**55,081**	
TOTAL OTHER DIRECT COSTS				**79,506**	
H. TOTAL DIRECT COSTS (A THROUGH G)				**322,920**	
I. INDIRECT COSTS (F&A)(SPECIFY RATE AND BASE) **Modified total Direct Costs (Rate: 58.0500, Base: 281353)**					
TOTAL INDIRECT COSTS (F&A)				**163,325**	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)				**486,245**	
K. FEE				**0**	
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				**486,245**	

M. COST SHARING PROPOSED LEVEL $ **0** AGREED LEVEL IF DIFFERENT $

PI/PD NAME
David Kennedy

ORG. REP. NAME*
Lisa Sergeant

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 ***ELECTRONIC SIGNATURES REQUIRED FOR REVISED BUDGET**

SUMMARY PROPOSAL BUDGET

YEAR 4

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PROPOSAL NO.	DURATION (months) Proposed	Granted
AWARD NO.		

ORGANIZATION
Pennsylvania State Univ University Park

PRINCIPAL INVESTIGATOR / PROJECT DIRECTOR
David Kennedy

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title, A.7. show number in brackets)	NSF Funded Person-months CAL	ACAD	SUMR	Funds Requested By proposer	Funds granted by NSF (if different)
1. **David Kennedy - Principal Investigator**	(b)(6)			**23,976**	
2. **Moriah Szpara - co-PI**				**27,326**	
3.					
4.					
5.					
6. (**0**) OTHERS (LIST INDIVIDUALLY ON BUDGET JUSTIFICATION PAGE)	0.00	0.00	0.00	**0**	
7. (**2**) TOTAL SENIOR PERSONNEL (1 - 6)	(b)(6)			**51,302**	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (**1**) POST DOCTORAL SCHOLARS	12.00	0.00	0.00	**55,310**	
2. (**2**) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)	(b)(6)			**32,451**	
3. (**2**) GRADUATE STUDENTS				**53,446**	
4. (**0**) UNDERGRADUATE STUDENTS				**0**	
5. (**0**) SECRETARIAL - CLERICAL (IF CHARGED DIRECTLY)				**0**	
6. (**0**) OTHER				**0**	
TOTAL SALARIES AND WAGES (A + B)				**192,509**	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS)				**51,658**	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A + B + C)				**244,167**	
D. EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $5,000.)					
TOTAL EQUIPMENT				**0**	
E. TRAVEL 1. DOMESTIC (INCL. U.S. POSSESSIONS)				**9,600**	
2. INTERNATIONAL				**11,950**	
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $ **700**					
2. TRAVEL **0**					
3. SUBSISTENCE **0**					
4. OTHER **0**					
TOTAL NUMBER OF PARTICIPANTS (**2**) TOTAL PARTICIPANT COSTS				**700**	
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				**5,000**	
2. PUBLICATION COSTS/DOCUMENTATION/DISSEMINATION				**3,000**	
3. CONSULTANT SERVICES				**0**	
4. COMPUTER SERVICES				**7,200**	
5. SUBAWARDS				**0**	
6. OTHER				**42,092**	
TOTAL OTHER DIRECT COSTS				**57,292**	
H. TOTAL DIRECT COSTS (A THROUGH G)				**323,709**	
I. INDIRECT COSTS (F&A)(SPECIFY RATE AND BASE) **Modified total Direct Costs (Rate: 58.0500, Base: 280917)**					
TOTAL INDIRECT COSTS (F&A)				**163,072**	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)				**486,781**	
K. FEE				**0**	
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				**486,781**	

M. COST SHARING PROPOSED LEVEL $ **0** AGREED LEVEL IF DIFFERENT $

PI/PD NAME
David Kennedy

ORG. REP. NAME*
Lisa Sergeant

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 ***ELECTRONIC SIGNATURES REQUIRED FOR REVISED BUDGET**

SUMMARY PROPOSAL BUDGET

YEAR 5

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PROPOSAL NO.	DURATION (months) Proposed	Granted
AWARD NO.		

ORGANIZATION
Pennsylvania State Univ University Park

PRINCIPAL INVESTIGATOR / PROJECT DIRECTOR
David Kennedy

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title, A.7. show number in brackets)	NSF Funded Person-months CAL	ACAD	SUMR	Funds Requested By proposer	Funds granted by NSF (if different)
1. **David Kennedy - Principal Investigator**	(b)(6)			**24,574**	
2. **Moriah Szpara - co-PI**				**28,011**	
3.					
4.					
5.					
6. (**0**) OTHERS (LIST INDIVIDUALLY ON BUDGET JUSTIFICATION PAGE)	0.00	0.00	0.00	**0**	
7. (**2**) TOTAL SENIOR PERSONNEL (1 - 6)	(b)(6)			**52,585**	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (**1**) POST DOCTORAL SCHOLARS	12.00	0.00	0.00	**56,693**	
2. (**2**) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)	(b)(6)			**33,263**	
3. (**2**) GRADUATE STUDENTS				**54,782**	
4. (**0**) UNDERGRADUATE STUDENTS				**0**	
5. (**0**) SECRETARIAL - CLERICAL (IF CHARGED DIRECTLY)				**0**	
6. (**0**) OTHER				**0**	
TOTAL SALARIES AND WAGES (A + B)				**197,323**	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS)				**52,947**	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A + B + C)				**250,270**	
D. EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $5,000.)					
TOTAL EQUIPMENT				**0**	
E. TRAVEL 1. DOMESTIC (INCL. U.S. POSSESSIONS)				**4,500**	
2. INTERNATIONAL				**0**	
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $ **700**					
2. TRAVEL **0**					
3. SUBSISTENCE **0**					
4. OTHER **0**					
TOTAL NUMBER OF PARTICIPANTS (**2**) TOTAL PARTICIPANT COSTS				**700**	
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				**0**	
2. PUBLICATION COSTS/DOCUMENTATION/DISSEMINATION				**3,000**	
3. CONSULTANT SERVICES				**0**	
4. COMPUTER SERVICES				**7,200**	
5. SUBAWARDS				**0**	
6. OTHER				**43,354**	
TOTAL OTHER DIRECT COSTS				**53,554**	
H. TOTAL DIRECT COSTS (A THROUGH G)				**309,024**	
I. INDIRECT COSTS (F&A)(SPECIFY RATE AND BASE) **Modified total Direct Costs (Rate: 58.0500, Base: 264970)**					
TOTAL INDIRECT COSTS (F&A)				**153,815**	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)				**462,839**	
K. FEE				**0**	
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				**462,839**	

M. COST SHARING PROPOSED LEVEL $ **0** AGREED LEVEL IF DIFFERENT $

PI/PD NAME
David Kennedy

ORG. REP. NAME*
Lisa Sergeant

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***ELECTRONIC SIGNATURES REQUIRED FOR REVISED BUDGET**

SUMMARY PROPOSAL BUDGET

Cumulative

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PROPOSAL NO.	DURATION (months) Proposed	Granted
AWARD NO.		

ORGANIZATION
Pennsylvania State Univ University Park

PRINCIPAL INVESTIGATOR / PROJECT DIRECTOR
David Kennedy

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title, A.7. show number in brackets)	NSF Funded Person-months CAL	ACAD	SUMR	Funds Requested By proposer	Funds granted by NSF (if different)
1. **David Kennedy - Principal Investigator**	(b)(6)			**105,827**	
2. **Moriah Szpara - co-PI**				**133,386**	
3.					
4.					
5.					
6. ( ) OTHERS (LIST INDIVIDUALLY ON BUDGET JUSTIFICATION PAGE)	0.00	0.00	0.00	**0**	
7. (**2**) TOTAL SENIOR PERSONNEL (1 - 6)	(b)(6)			**239,213**	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (**5**) POST DOCTORAL SCHOLARS	60.00	0.00	0.00	**269,970**	
2. (**10**) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)	(b)(6)			**158,399**	
3. (**10**) GRADUATE STUDENTS				**259,398**	
4. (**0**) UNDERGRADUATE STUDENTS				**0**	
5. (**0**) SECRETARIAL - CLERICAL (IF CHARGED DIRECTLY)				**0**	
6. (**0**) OTHER				**0**	
TOTAL SALARIES AND WAGES (A + B)				**926,980**	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS)				**247,710**	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A + B + C)				**1,174,690**	
D. EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $5,000.)					
TOTAL EQUIPMENT				**0**	
E. TRAVEL 1. DOMESTIC (INCL. U.S. POSSESSIONS)				**27,600**	
2. INTERNATIONAL				**37,480**	
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $ **3,500**					
2. TRAVEL **0**					
3. SUBSISTENCE **0**					
4. OTHER **0**					
TOTAL NUMBER OF PARTICIPANTS (**10**) TOTAL PARTICIPANT COSTS				**3,500**	
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				**56,380**	
2. PUBLICATION COSTS/DOCUMENTATION/DISSEMINATION				**12,000**	
3. CONSULTANT SERVICES				**0**	
4. COMPUTER SERVICES				**36,000**	
5. SUBAWARDS				**0**	
6. OTHER				**222,724**	
TOTAL OTHER DIRECT COSTS				**327,104**	
H. TOTAL DIRECT COSTS (A THROUGH G)				**1,570,374**	
I. INDIRECT COSTS (F&A)(SPECIFY RATE AND BASE)					
TOTAL INDIRECT COSTS (F&A)				**790,852**	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)				**2,361,226**	
K. FEE				**0**	
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				**2,361,226**	

M. COST SHARING PROPOSED LEVEL $ **0** AGREED LEVEL IF DIFFERENT $

PI/PD NAME
David Kennedy

ORG. REP. NAME*
Lisa Sergeant

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C *ELECTRONIC SIGNATURES REQUIRED FOR REVISED BUDGET

Budget Justification
The Pennsylvania State University

Salaries and Wages

Principal Investigator – David Kennedy ((b)(6) month effort year 1 and (b)(6) months effort years 2-5): Dr. Kennedy will coordinate and oversee the work conducted for this project, including supervision of a graduate student and a postdoctoral researcher. He will also contribute to conference calls, experimental design, progress reports, and the dissemination and publication of results.

Co-Principal Investigator – Moriah Szpara ((b)(6) months effort): Dr. Szpara will oversee the work in Aim 3, including supervision of a research technician and a bioinformatician. She will also contribute to conference calls, experimental design, progress reports, and the dissemination and publication of results.

Bio Technician – Chris Bowen ((b)(6) months effort): This technician's role will be to conduct DNA extractions, sample preparation, and other molecular biology methods required in Aim 3.

Computational Technician – Daniel Renner ((b)(6) months effort): This technician's role will be to process the sequencing reads for *de novo* genome assembly and contig reconstruction.

Post Doctoral Scholar – TBN (12 calendar months effort): The Postdoc's role will be to integrate the experimental results with mathematical models of Marek's disease virus transmission (Aims 3 and 4).

Graduate Assistant – TBN (4.5 academic months effort): The student's role will be to construct and analyze general models of the consequences of transmissible vaccination (Aims 1 and 2).

Graduate Assistant – TBN (4.5 academic months effort): The student's role will be to conduct the computational evolutionary analyses in Aim 3. The student will also assist in DNA extractions, sample preparation, and genome assembly.

The principal investigator is budgeted at the percentage of time shown using his/her actual salary in the calculation. The principal investigator's time includes both technical and project management functions. Any other individuals/positions shown are technical staff with the percentage of time shown and actual salaries used. For project time occurring after July 1 of any given year, the salaries have been adjusted at the University approved rate of 2.5%.

Fringe Benefits

Fringe benefits are computed using the provisional rates of 37.85% applicable to Category I Salaries, 13.00% applicable to Category II Graduate Assistants, 7.86% applicable to Category III Salaries and Wages, 0.25% applicable to Category IV Student Wages, and 23.52% for Category V, Postdoctoral Scholars and Fellows, for fiscal year 2020 (July 1, 2019, through June 30, 2020). If this proposal is funded, the rates quoted above shall, at the time of funding, be subject to adjustment for any period subsequent to June 30, 2020, if superseding Government approved rates have been established. Fringe benefit rates are negotiated and approved by the Office of Naval Research, Penn State's cognizant federal agency.

Travel

All travel will be in accordance with University travel regulations and mileage will be charged at the current rate on the date of travel.

Funds are requested for Dr. Kennedy, Dr. Szpara, and three trainees to travel to the International Symposium on Marek's Disease and Avian Herpesviruses in years 2 (international) and 4 (domestic) of this proposal. Registration for this year's meeting is $550 ($350 for graduate students). The meeting alternates between being hosted in North America (typically the United States) and being hosted internationally. We estimate a cost of $300 per day per person for food and lodging, and an average of $1000 per flight ($500 per flight for domestic, $1500 per flight for international).

In addition, funds are requested for Dr. Kennedy and two trainees to travel to the Ecology and Evolution of Infectious Diseases conference in years 1 through 5 of this proposal. Estimated costs are $200 per person for registration, $200 per day per person for food and lodging, and $500 per person per flight.

Lastly, funds are requested for Dr. Kennedy and two trainees to travel to Pirbright in year 2 for 6 days during one of the experimental studies. Per diem and lodging and meal costs are based on Department of Defense rates for "other" cities in the United Kingdom ($330 per person per day). Flights are estimated at $1500 per person.

Participant Support Costs
$700 per year is requested for scholarships to 2 youth attending Penn State's educational summer camp "Science-U".

Materials and Supplies
Funds are requested in year 1 for two laptops, one for each graduate student ($4000). Funds are also requested for one laptop in year 2 for the postdoctoral scholar ($2,000). In addition, funds are requested for a custom designed Arbor BioSciences oligo set in year 1 ($11,930), and for library prep and MiSeq sequencing of dust samples ($9,225 per year) in years 2 and 3. For consumables that will be used in prepping and handling samples, we request an additional $5000 per year in years 1 through 4.

Publication Costs
We are requesting $3000 in each of years 2 through 5 for publication costs.

Computer Services
To attain the computational requirements of Aims 1, 3, and 4, we are requesting funds for a subscription to PSU's high-performance computing infrastructure, ICS-ACI. This subscription is $25 per core per month, where the recommended minimum subscription being 20 cores ($6000 per year). We are additionally requesting funds to subscribe to the minimum storage allotment ($1200 per year).

Purchased Services (G.6)
Funds are requested to cover PacBio sequencing at the Penn State Genomics Core. These expenses include $4000 for a pilot study in year 2. $1100 for indexing materials, $850 for indexing labor, $2392 for eight SMRTbell Express Template Preps, and $9872 for Sequel Sequencing of 8 SMRTcells in year 3.

Tuition (G.6)
Computed using the approved tuition charges for a one-half (1/2) time graduate assistant of $9,350 (pre-comprehensive) and $3050 (post-comprehensive) for fall and spring semesters 2019/2020, and $4,675 for summer session 2020. The charges quoted above are increased by three percent (3%) for any project period occurring after summer session 2020, and each summer session thereafter.

F&A – On Campus Research
F&A rates are negotiated and approved by the Office of Naval Research, Penn State's cognizant federal agency. Penn State's current provisional on-campus rate for research is 58.05% of MTDC from July 1, 2019, through June 30, 2020. New awards and new competitive segments with an effective date of July 1,

2020, or later shall be subject to adjustment when superseding Government approved rates are established. Per 2 CFR 200 (Appendix III, Section C.7), the actual F&A rates used will be fixed at the time of the initial award for the duration of the competitive segment.

Definition of a Year

The University defines the term “year” as the fiscal year (July – June).

Current and Pending Support
Investigator – David Kennedy

Current

Project/Proposal Title: Virulence evolution after viral host jump and emergence
Source of Support: NSF DEB
Project Location: Virginia Institute of Marine Science, The Pennsylvania State University, USGS Western Fisheries Research Center
Total Award Amount: $117,175 (sub-award to PSU)
Starting Date: 08/1/2018
Ending Date: 07/31/2021
Person-months per year committed to the Project: (b)(6) per year

Project/Proposal Title: Forward genetic prediction and testing of virulence loci in herpes simplex virus 1 (R01 AI132692)
Source of Support: NIH NIAID
Project Location: The Pennsylvania State University
Total Award Amount: $1,998,203 (no direct support to Kennedy)
Starting Date: 02/23/2018
Ending Date: 01/31/2023
Person-months per year committed to the Project: (b)(6) per year

Pending

(b)(4)

Current and Pending Support
Investigator – Moriah Szpara

Current

Project/Proposal Title: **R01 AI132692** -- Forward genetic prediction and testing of virulence loci in herpes simplex virus 1
Source of Support: NIH, National Institute for Allergy & Infectious Diseases (NIAID), **R01** Research Grant
Project Location: The Pennsylvania State University, Cincinnati Children's Hospital Medical Center, University of Cincinnati
Total Award Amount: $1,321,335 (direct costs over 5 yrs.)
Starting Date: 02/23/2018
Ending Date: 01/31/2023
Person-months per year committed to the Project: (b)(6) per year

Project/Proposal Title: **R21 AI140443** -- Viral genetic correlates of invasive neonatal HSV disease
Source of Support: NIH / NIAID **R21** Exploratory/Developmental Research Grant
Project Location: The Pennsylvania State University, Children's Hospital of Philadelphia
Total Award Amount: $300,033 (direct costs over 2 yrs.)
Starting Date: 05/01/2018
Ending Date: 04/30/2020
Person-months per year committed to the Project: (b)(6) per year (ends 4/30/2020)

Project/Proposal Title: Linking viral genetic variations to outcomes in pathogenesis and disease
Source of Support: Pennsylvania (PA) Department of Health Commonwealth Universal Research Enhancement Program **(CURE) Grant** (SAP #4100072562, TSF 15/16)
Project Location: The Pennsylvania State University
Total Award Amount: $312,150 (direct costs over 3 yrs.)
Starting Date: 07/01/2016
Ending Date: 12/31/2019
Person-months per year committed to the Project: (b)(6) per year

Pending

(b)(4)

(b)(4)

FACILITIES, EQUIPMENT, AND OTHER RESOURCES

Facilities & Resources at Penn State

Scientific Environment
I (Dr. Kennedy) am a co-hire between the Department of Biology and to the Huck Institutes of the Life Sciences at The Pennsylvania State University. The Huck Institutes create an intellectual framework for interdisciplinary research, by connecting faculty with diverse expertise that are unified by a shared research interest, under the structure of topic-themed centers. The Huck Institutes also expands physical resources available to this research by providing access to shared facilities.

My lab and office are co-located with many others that belong to The Huck Institutes' **Center for Infectious Disease Dynamics (CIDD)**, including Co-PI Szpara, in the newly constructed Millennium Science Complex (MSC). CIDD includes 40+ faculty from 15+ departments at our campus and the PSU College of Medicine, who are united by a common goal of addressing infectious disease dynamics. CIDD labs study infectious disease across scales, with an emphasis on evolution, ecology, and disease transmission. Nearby CIDD labs in MSC study bacterial, fungal, viral, and parasite pathogens, using both theoretical and empirical approaches. We exchange ideas, equipment, and expertise on a daily basis. CIDD sponsors two weekly meetings: a formal seminar series every Thursday with external speakers, and an informal series of Powerpoint-free research discussions every Monday with internal speakers. Additionally, co-PI Szpara organizes a monthly Virology Club, which I regularly attend, called **Virology@PSU**, where graduate and post-doctoral trainees from virology labs across campus meet and present their data and research ideas.

Penn State also provides strong institutional support for the mathematical modeling of biological systems. In addition to regular interactions with the more quantitative members of CIDD, I am also a member of the recently formed **Center for Mathematical Biology**. This center fosters the exchange of ideas and the development of research collaborations involving mathematical models and quantitative approaches to the life sciences. It currently includes 25 faculty from 8 departments, who employ observational, laboratory, mathematical, statistical, and computational approaches to address a broad range of biological and medical questions. The center hosts monthly lunches and a weekly seminar series to discuss work at the interface between the observation of living systems and the development of appropriate quantitative methods to describe these systems.

Experimental Facilities
Both my lab and Dr. Szpara's lab are in the Millennium Science Complex (MSC), which utilizes an open-lab format to integrate and foster interactions between primarily wet-bench and primarily computational groups, such as Dr. Szpara's group and my own. My laboratory includes BSL-2-compatible wet-bench space and a dedicated computational area. Dr. Szpara's lab includes wet-bench space, a dedicated bioinformatics and computing work area, a biohazard-level 2 (BSL-2) tissue-culture (TC) room, a fume hood and chemical room, a microscope and sequencing room, an electrophoresis area, and a zone for storage and freezers. In addition, **Co-PI Szpara has a dedicated Illumina® MiSeq in the laboratory**, which will be heavily utilized in our project. Additional sequencing equipment, tools, and expertise are available through the Penn State Genomics Core, described below in the section "Genomics Infrastructure & Support."

While the open-lab design allows researchers to share specialized equipment between research groups, MSC also has communal areas for equipment that is available for all PIs to use. This equipment includes autoclaves, ultra- and high-speed centrifuges, warm and cold rooms, and additional freezers. There are also adjoining computational spaces dedicated to bioinformatics. The MSC's focus on interdisciplinary research benefits this project, by its integration of computing and bioinformatics space with wet-bench work areas.

In addition, the Biology department and the Huck Institutes for the Life Sciences also provide administrative support, with dedicated staff for grants administration, purchasing, receiving, equipment maintenance, and computer support. Several of these support staff are located directly on-site in MSC.

Computational Infrastructure & Support
Computational support for this project will be provided by the University's Institute for CyberScience. Penn State's Institute for CyberScience (ICS) operates the Advanced CyberInfrastructure (ICS-ACI), the university's state-of-the-art high-performance research cloud.

ICS-ACI equipment is located in a newly-constructed Data Center facility at Penn State's University Park Campus. This facility operates in compliance with all Penn State IT policies. The facility provides 2.15 MW power capacity and contains 12,000 square feet of floor space for computing equipment, termed as the data center "white space." The building is powered efficiently and is undergoing LEED certification. The facility is designed to operate with an annualized average Power Usage Effectiveness (PUE) of 1.21.

The ICS-ACI high-performance research cloud is composed of hardware that is interconnected over high-speed network fabrics, and that includes various software offerings and services. ICS-ACI currently maintains 26,000 computational cores. ICS-ACI offers four different core configurations: high-memory cores (1TB RAM per server), standard-memory cores (256 GB RAM per server), and basic-memory cores (128 GB RAM per server), and GPU cores (using NVidia Tesla K80 GPU accelerators). The standard-memory and basic-memory compute cores are housed within high density Dell M1000E Blade server enclosures, while the high-memory and GPU accelerator cores are in conventional 4U and 2U rack mount configurations, respectively.

ICS-ACI also maintains 20 PB of data storage capacity. The storage is comprised of 8 PB of active storage pools that provide immediate data access and retrieval, and 12 PB of near-line storage for long-term and archival purposes. The active storage operates on DDN 12KX40 and GS7K flash storage array systems, while near-line storage utilizes Oracle's FS1 flash storage appliance and a SL8500 Tape Library.

The compute and storage hardware are interconnected using Ethernet and Infiniband network fabrics. The Ethernet network utilizes Brocade VCS fabric technology and is currently comprised of 1) four aggregate and two core layer Brocade VDX 8770-8 Enterprise-level switches that provide 10, 40, and 100 Gbps link capacity, 2) four Brocade VDX 6740 switches that provide 10 Gbps link capacity, and 3) one Brocade N2024 switch per rack for host iDRAC (integrated DELL Remote Access Controller) remote management over Gbps line rate. The Infiniband network consists of 15 Mellanox SX6025 switches and two Mellanox SX6536 648 port non-blocking SDN switch systems, all operating on 56 Gbps (FDR) line rate.

ICS-ACI maintains and regularly updates an expansive software stack. The stack currently contains 240 applications, with more added at regularly-scheduled intervals. The applications include security monitoring software (e.g.,OSSEC), batch schedulers (e.g.,MOAB, Torque), compilers, file transfer programs, and communication libraries (e.g.,MPI, OpenMP). The stack also contains software applications commonly used by researchers, such as MATLAB, COMSOL, R, and Python, as well as programs for performing specialized tasks, such as Abaqus, Quantumwise, and TopHat.

ICS-ACI is maintained by the ICS staff, who provide network monitoring, backup services, software updates, code optimization, and service-desk support. ICS uses Solarwinds network monitoring software to monitor the health and status of the network, hardware, and storage. ICS-ACI is actively monitored during normal business hours (9:00 AM –5:00 PM) Monday through Friday. ICS-ACI also hosts OSSEC, an open-source host-based intrusion detection system, which is used to control the system by monitoring available logs, alerting administrators of unauthorized system modifications, and providing a mechanism to enforce security requirements. The team uses NESSUS Professional to scan the system for potential vulnerabilities such as hacking and Denial of Service (DoS) attacks.

The ICS website offers documentation to help users resolve technical issues they may encounter. This support is supplemented by the i-ASK Center, a service desk which supplies expert technical assistance for user problems. In the event of more complex issues, the engineers of the ICS Technical Support Team provide advanced in-person support to users to ensure that problems are resolved in a timely and professional manner.

ICS offers domain-specific consulting to assist researchers with optimizing code, leveraging various software applications and in general increasing the efficiency of their research operations. Consultants cover disciplines including Engineering, Chemistry and Materials Science, Data Visualization, Parallelization, and Science Gateways for Big Data Research.

Genomics Infrastructure & Support
In addition to the Illumina® MiSeq, housed in Co-PI Szpara's laboratory, we have access to a wealth of equipment relevant to this proposal through the Huck **Genomics Core Facility**. The Genomics Fore Facility has instrumentation to support whole-genome and transcriptome sequencing of non-model organisms, amplicon sequencing for metagenomics studies, differential expression analysis of mRNA and miRNA, degradome sequencing, ChIP and RIP sequencing, Sanger DNA sequencing, genotyping of SNPs and VNTRs, microarray analysis, real-time qPCR, and digital PCR. Available instrumentation includes:

- Illumina NextSeq
- Illumina MiSeq
- PacBio Sequel
- Applied Biosystems 3730XL
- Agilent Bioanalyzer
- Qubit
- Applied Biosystems QuantStudio 12K Flex Real-Time PCR System
- Applied Biosystems StepOnePlus Real-Time PCR System
- NanoString nCounter
- BluePippin
- Covaris ultrasonicator
- Illumina HiSeq 2500
- Affymetrix GeneChip Instrument System
- Molecular Devices GenePix 4000B Scanner

Facilities & Resources at Pirbright Institute

The Pirbright Institute is one of the world's leading Centres of Excellence working in the field of viral diseases of livestock through two main strategic areas of science involving the Pathogen biology and the interactions with the host. Excellent animal models in the target natural hosts allow detailed molecular studies on virus-host interactions for developing novel intervention strategies and vaccines. Following are some of the facilities and resources available at the Pirbright Institute.

BBSRC National Virology Centre
The Plowright Building became fully operational in April 2015 and is the culmination of £145m investment to develop a new containment laboratory for research of exotic viruses. The 14,000 m^2 laboratory and associated facilities houses some 160 staff, including 125 scientists, and is essential to underpin the Institute's two scientific programmes for the purposes of in vitro research into virus diseases of livestock, including poultry.

BBSRC National Vaccinology Centre
The Jenner Building is The Pirbright Institute's low-containment facility and opened in 2016 as part of phase two of the redevelopment of the Pirbright site. This facility houses a wide range of groups working on strategically important endemic and exotic viral pathogens that can be handled under low containment including Marek's disease virus.

The Nair Laboratory located in the Jenner Building has three x 1000 ft^2 laboratories, with bench space for twenty people. The laboratories have all the facilities for carrying out all the routine molecular biological experiments including quantitative PCR assays, a major requirement for the current project. In addition the laboratory has all the facilities for virological experiments including preparation of tissue culture, virus maintenance, virus titration and egg inoculation. The Nair lab routinely carries out Marek's disease virus (MDV) work using a large collection of virus stocks from all over the world procured as part of the OIE MDV Reference Laboratory (MDVRL). In addition to the routine primary cell lines prepared in the lab, we also have access to a large collection of cell lines and monoclonal antibodies as part of the Immunological Toolbox.

Bioimaging
The Pirbright Institute houses a unique Bioimaging facility containing advanced confocal and electron microscopes, flow cytometry analysers and cell sorters. Instruments are located in both the high containment Plowright and low containment Jenner buildings making them accessible to all researchers. The scope of imaging and analytical techniques available inside the SAPO4 envelope is globally unique. It is possible to image, analyse and sort live cells from host animals infected in the Institute isolation units. Microscopy and flow techniques are used to identify immune cell types, enrich special cell populations, localise host or viral proteins within cells and study the cell biology of host-pathogen interactions at high resolution.

Houghton Facility
The Houghton Facility is a Specific Pathogen Free (SPF) hatchery that allows The Pirbright Institute to hatch and grow poultry under clean conditions. This maintains the disease-free status of the birds for use in animal experiments to study viral disease important to the welfare of chickens and ultimately to ensure security of food supply for the UK. Houghton Facility is a purpose-built animal facility dedicated to the incubation, hatching and growth of SPF chickens supplied as embryonated eggs from the Roslin Institute's National Avian Research Facility (NARF) Bumstead Building in Edinburgh, or other commercial supplier, in support of the Institute's avian research.

Animal Experimental Facilities
The BSU and the forthcoming Biggs building provide excellent facilities for conducting biological experiments in chickens in isolators under containment. All the experiments involving infections in chickens will be carried out in these facilities. Entry into the rooms is restricted and involves cloth changing and showering as part of the containment requirements. All the infected materials, including the carcasses are disposed by incineration. At the end of the experiments, each room and the isolators are disinfected to prevent any cross infection from residual viruses. All these procedures are carried to ensure that no infectious viruses come out of the containment. These facilities have a long history of successfully containing infectious agents in experimental infections. Positive pressure isolators allow housing groups of up to 20 MDV-infected birds. Dust shed by the birds is collected in the air filter housed in the outflow, and dust viral titres determined by PCR. Experimentally-infected birds, if needed, can also be kept on the floor.

Data Management Plan

Physical samples collected in the course of this project will include feathers, blood, spleen, and dust from chickens containing virus isolates and vaccine isolates, as well as DNA extracted from these samples. All physical samples collected during experiments and DNA isolation (i.e. blood, feathers, spleen dust, and DNA) will stored in -80 °C freezers which are backed up by generators. All isolates of virus described here will be shared with the research community upon request. A Materials Transfer Agreement may be requested between the sending and receiving institutions for shipment of samples.

We will also generate genomic data. All genome sequence data that we generate will be deposited in NCBI's Nucleotide database (GenBank; http://www.ncbi.nlm.nih.gov/nuccore/) within 60 days of completion, even prior to publication. These data are mirrored at the Virus Pathogens Resource (ViPR) funded by NIAID: http://www.viprdb.org. All raw high-throughput sequence data will be deposited into NCBI's Sequence Read Archive (SRA; http://www.ncbi.nlm.nih.gov/sra/). Examples of our previous NCBI depositions are here:

GenBank	GU734771, GU734772, JF797217 – JF797219 (includes 3), KM222720 – KM222727 (includes 8), KT425107-KT425110 (includes 4)
SRA	SRX018173, SRX018175, SRX018176, SRX056780 – SRX056786 (includes 7), SRX056813, SAMN03152121 – SAMN03152125 (includes 5), SAMN03152078, SAMN03152079, SAMN04093860, SAMN04093861

In addition, we will generate experimental data and mathematical models. All numerical outputs from experimental data will be entered into appropriately labeled ".csv" files, which are readable across computing platforms. PIs will have access to these files through the Penn State's Box.com accounts. Local copies will also be stored on Dr. Kennedy's computer. All computer code will be stored on GitHub, as well as on Box.com, and GitHub files will be made publicly available upon publication.

As a second line of defense, all of the data collected will be backed up on The Pennsylvania State University's ScholarSphere. ScholarSphere enables the Penn State community to share research with a worldwide audience. Faculty, students, and academic programs will be able to use ScholarSphere to collect their work in one location to create a durable and cite-able record of their papers, presentations, publications, datasets, or other scholarly creations. ScholarSphere will make these works more discoverable, accessible, usable, and thus broadly recognized and known. The preservation functions include scheduled and on-demand verifications of deposited works, characterization of files to mitigate future format obsolescence, regular file backups, and replication to disaster recovery sites. Additional information on ScholarSphere can be found at: https://scholarsphere.psu.edu

Postdoctoral Researcher Mentoring Plan

This Postdoctoral Researcher Mentoring Plan has been prepared by David Kennedy, Ph.D. Assistant Professor of Biology, The Pennsylvania State University, Pennsylvania. The Plan establishes guidelines for work to be performed by a Postdoctoral Researcher in support of the NSF grant "US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study". The Postdoctoral Researcher assigned to the project will work in the Center for Infectious Disease Dynamics located in the Millennium Sciences Complex, Penn State and will conduct research on modeling the consequences of the transmissible Rispens vaccine on Marek's disease virus ecology and evolution.

1. Orientation will include in-depth conversations between David Kennedy, PhD. and the Postdoctoral Researcher. Mutual expectations will be discussed and agreed upon in advance. Orientation topics will include (a) the amount of independence the Postdoctoral Researcher requires, (b) expected conduct in interaction with coworkers, (c) productivity including the importance of scientific publications, (d) work habits and laboratory safety, and (e) documentation of research methodologies and experimental details so that the work can be continued by other researchers in the future.

2. Career Counseling will be directed at providing the Postdoctoral Researcher with the skills, knowledge, and experience needed to excel in his/her chosen career path. The Postdoctoral Researcher will develop and follow an Individual Development Plan in collaboration with Dr. Kennedy. In addition to guidance provided by Dr. Kennedy, the Postdoctoral Researcher will be encouraged to discuss career options with researchers and peers at The Center for Infectious Disease Dynamics, Penn State University and with colleagues of Dr. Kennedy. Part of this guidance will include twice yearly postdoctoral training lunches hosted by the Biology Climate and Diversity Committee of which Dr. Kennedy is a member.

3. Publications and Presentations are expected to result from the work supported by the grant. These will be prepared under the direction of Dr. Kennedy, and as appropriate, in collaboration with Dr. Szpara, Dr. Nair, and Dr. Yao. The Postdoctoral Researcher will receive training in preparation for attending and presenting at scientific conferences, as well as training in preparing manuscripts for scientific journals.

4. Teaching and Mentoring Skills will be developed within through informal interactions and formal interactions within the Center for Infectious Disease Dynamics. The Postdoctoral Researcher will be provided with opportunities to assist graduate and undergraduate students in Dr. Kennedy's lab. The Postdoctoral Researcher will be given opportunities to interact with the broader community at the Center for Infectious Disease Dynamics to describe their work to colleagues and assist with solutions to challenging research problems.

5. Instruction in Professional Practices will be provided on a regular basis in the context of the research work and will include fundamentals of data and code management, model development, and other standards of professional practice required to generate robust, repeatable scientific discoveries. In addition, the Postdoctoral Researcher will be encouraged to affiliate with one or more professional societies in his/her chosen field.

6. Success of the Mentoring Plan will be assessed by monitoring the personal progress of the Postdoctoral Researcher through a tracking of the Postdoctoral Researcher's progress toward his/her career goals after finishing the postdoctoral program.

Biographical Sketch – Professor Venugopal Nair

Prof. Venugopal Nair
Head, Viral Oncogenesis group
Pirbright Institute
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Woking, Guildford, Surrey, United Kingdom
GU24 0NF
+44 1483 231415
venugopal.nair@pirbright.ac.uk

(a) Professional Preparation

Kerala Agricultural University	Thrissur, Kerala State, India	Veterinary Science	BVSs, 1976
Kerala Agricultural University	Thrissur, Kerala State, India	Veterinary Medicine	MVSs, 1978
University of Pune	Maharashtra, India	Medical Virology	DMV, 1981
Tamil Nadu Agricultural University	Chennai, Tamil Nadu, India	Veterinary Medicine	Ph.D. 1987

(b) Appointments

2017-Present	Head, Viral Oncogenesis group, Pirbright Institute
2015-Present	Visiting Professor in Avian Virology, Department of Zoology, Oxford University
2010-2017	Head, Avian Viral Diseases, Institute Strategic Programme Grant
1997-2010	Head, Viral Oncogenesis group, Pirbright Institute
1994-1997	Senior Scientist, Viral Oncogenesis group, Pirbright Institute

(c) Products *[this section may be titled **Publications** if only publications are listed]*
(i) List up to five (5) publications/products most closely related to the proposed project

1. Kennedy DA, Cairns C, Jones MJ, Bell AS, Salathe RM, Baigent SJ, **Nair V**, Dunn PA, Read AF. 2017. Industry-wide surveillance of Marek's disease virus on commercial poultry farms. *Avian Diseases*, 61: 153-164.
2. Read AF, Baigent SJ, Powers C, Kgosana LB, Blackwell L, Smith LP, Kennedy DA, Walkden-Brown SW, **Nair V**. 2015. Imperfect vaccination can enhance the transmission of highly virulent pathogens. *PLoS Biology*, 13: e1002198.
3. **Nair V** (2018) Spotlight on avian pathology: Marek's disease, Avian Pathology, 47:5, 440-442, DOI: 10.1080/03079457.2018.1484073.
4. Baron MD, Iqbal M, **Nair V**. 2018. Recent advances in viral vectors in veterinary vaccinology. *Current Opinion in Virology*, 29: 1-7.
5. Mwangi WN, Vasoya D, Kgosana LB, Watson M, **Nair V**. 2017. Differentially-expressed genes during spontaneous reactivation of Marek's disease virus in lymphoblastoid cell lines determined by global gene expression profiling. *Journal of General Virology,* 98: 779-790.

(ii) List up to five (5) other significant publications/products, whether or not related to the proposed project.

1. Zhang Y, Luo J, Tang N, Teng M, Reddy VRAP, Moffat K, Shen Z, **Nair V**, Yao Y. 2019. Targeted editing of pp38 gene in Marek's disease virus-transformed cell lines using CRISPR/Cas9 system. *Viruses* 11: E391. doi: 10.3390/v11050391.
2. Tang N, Zhang Y, Pedrera M, Chang P, Baigent S, Moffat K, Shen Z, **Nair V**, Yao Y. 2019. Generating recombinant avian herpesvirus vectors with CRISPR/Cas9 gene editing. *Journal of Visualized Experiments*, 143: e58193.
3. Sadigh Y, Powers C, Spiro S, Pedrera M, Broadbent A, **Nair V**. 2018. *Gallid herpesvirus* 3 SB-1 strain as a novel recombinant viral vector for poultry vaccination. *npj Vaccines*, 3: 21. doi: 10.1038/s41541-018-0056-6.
4. Dunn JR, Reddy SM, Niikura M, **Nair V**, Fulton JE, Cheng HH. 2017. Evaluation and identification of Marek's disease virus BAC clones as standardized reagents for research. *Avian Diseases*, 61: 107-114.
5. Schat KA, **Nair V**. 2013. *Marek's Disease*, Chapter, Diseases of Poultry, 13th Ed, Iowa Publishers and American Association of Avian Pathologists. Pp.515-552.

(d) Synergistic Activities

- Principal Investigator & Head of the "UK-China Centre of Excellence for Research on Avian Diseases**"** (https://www.uk-china-cerad.org/) (2015-present)
- Associate Editor, Associate Editor Diseases of Poultry 13th Ed, Iowa Publishers and American Association of Avian Pathologists. ISBN: 978-0-470-95899-5. (2013-present)
- Investigator, Jenner Institute, Oxford, United Kingdom https://www.jenner.ac.uk/jenner-investigators
- Co-ordinator, Global Alliance for Research on Avian Diseases (GARAD) http://garad.org/board
- Royal Society International Research Professor (2016-2021) https://www.pirbright.ac.uk/news/2017/02/pirbright-professor-receives-prestigious-joint-royal-society-award

Biographical Sketch

Dr. Yongxiu Yao
Deputy Head, Viral Oncogenesis group
Pirbright Institute
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GU24 0NF
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(a) Professional Preparation

Shandong Agriculture University	Taian, Shandong, China	Veterinary Medicine	BSc, 1986
Shandong Agriculture University	Taian, Shandong, China	Veterinary Medicine	MSc, 1989
University of Reading	Reading, UK	Molecular Virology	PhD, 2001
University of Reading	Reading, UK	Molecular Virology	Postdoc 2001-2005

(b) Appointments

2015-present Deputy Head, Viral Oncogenesis group, Pirbright Institute
2005-present Senior Scientist, Viral Oncogenesis group, Pirbright Institute

(c) Publication

(i) five publications/products most closely related to the proposed project

1. Zhang Y, Tang N, Luo J, Teng M, Moffat K, Shen Z, Watson M, Nair V, **Yao Y**. 2019. Marek's disease virus-encoded miR-155 ortholog critical for the induction of lymphomas is not essential for the proliferation of transformed cell lines. *Journal of Virology*, 93: e00713-19. doi: 10.1128/JVI.00713-19.

2. Zhang Y, Luo J, Tang N, Teng M, Reddy VRAP, Moffat K, Shen Z, Nair V, **Yao Y**. 2019. Targeted Editing of the pp38 Gene in Marek's Disease Virus-Transformed Cell Lines Using CRISPR/Cas9 System. *Viruses*, 11: 391. doi: 10.3390/v11050391.

3. Tang N, Zhang Y, Pedrera M, Chang P, Baigent S, Moffat K, Shen Z, Nair V, **Yao Y**. 2019. Generating recombinant avian herpesvirus vectors with CRISPR/Cas9 gene editing. *Journal of Visualized Experiments*, 143: e58193. doi: 10.3791/58193.

4. Zhang Y, Tang N, Sadigh Y, Baigent S, Shen Z, Nair V, **Yao Y**. 2018. Application of CRISPR/Cas9 Gene Editing System on MDV-1 Genome for the Study of Gene Function. *Viruses*, 10: 279. doi: 10.3390/v10060279.

5. Tang N, Zhang Y, Pedrera M, Chang P, Baigent S, Shen Z, Nair V, **Yao Y**. 2018. A simple and rapid approach to develop recombinant avian herpesvirus vectored vaccine using CRISPR/Cas9 system. *Vaccine*, 36:716-722.

(ii) Five other significant publications/products.

1. **Y Yao**, Nair V. 2016. Avian leukosis virus, In: *Molecular Detection of Animal Viral Pathogens*. CRC Press ISBN 978-1-4987-0036-8. Dongyou Liu (Editor) Pg. 145-155.

2. **Yao Y**, Smith LP, Nair V, Watson M. 2014. An avian retrovirus uses canonical expression and processing mechanisms to generate viral microRNA. *Journal of Virology*, 88: 2-9.

3. **Y Yao**, Nair V. 2013. MicroRNA expressions in avian herpesviruses, In: *MicroRNAs in Medicine*, Wiley-Blackwell Pub. Pp. 137-152.

4. **Yao Y**, Zhao Y, Smith LP, Watson M, Nair V. 2009. Novel microRNAs encoded by herpesvirus of turkeys (HVT): Evidence of miRNA evolution by duplication. *Journal of Virology*, 83: 6969-6973.

5. **Yao Y**, Zhao Y, Xu H, Smith LP, Lawrie CH, Watson M, Nair V. 2008. MicroRNA profile of Marek's disease virus-transformed T-cell line MSB-1: predominance of virus-encoded microRNAs. *Journal of Virology*, 82: 4007-4015.

(d) Synergistic Activities

- Deputy Head of the "UK-China Centre of Excellence for Research on Avian Diseases**"** (UK-China CERAD) (2015-present)
- Co-organized the progress meeting of UK-China projects on UK-China-Philippines-Thailand Swine and Poultry Research Initiative projects at Pirbright, in June 2019
- Co-organized the annual Symposium on "Recent Advances in Avian Disease Research", 2015-2019
- Supervising a number of international visiting students/workers
- Invited talks in a number of Universities/Research Institutes in China

Staff

Directly Incurred Posts

			EFFORT ON PROJECT							
Role	**Name /Post Identifier**	**Start Date**	**Period on Project (months)**	**% of Full Time**	**Scale**	**Increment Date**	**Basic Starting Salary**	**London Allowance (£)**	**Super-annuation and NI (£)**	**Total cost on grant (£)**
Researcher	PDRA	01/08/2020	36	100	N/A	01/08/2020	(b)(4); (b)(6)	0	11145	178810
									Total	178810

Applicants

Role	Name	Post will outlast project (Y/N)	Contracted working week as a % of full time work	Total number of hours to be **charged** to the grant over the duration of the grant	Average number of hours per week **charged** to the grant	Rate of Salary pool/banding	Cost estimate
Principal Investigator	Professor Venugopal Nair	Y	(b)(6)			(b)(4); (b)(6)	19044
Co-Investigator	Dr YONGXIU YAO	Y					12367
						Total	31411

Equipment

Description	Country of Manufacture	Delivery Date	Basic price £	Import duty £	VAT £	Total £	Amount Sought £
Bioflex B50 Poultry Isolators x2 together with the service contract for 2 years	United Kingdom	01/08/2020	78,160.00	0.00	0.00	78,160.00	39,080.00
					Total £	78,160.00	39,080.00

Travel and Subsistence

Destination and purpose		Total £
Outside UK	Attendance of meetings with US partner, EEID meeting	13500
	Total £	13500

Other Directly Incurred Costs

Description	Total £
Research consumable costs including molecular biology, quantitative PCR, and tissue culture reagents	60000
Recruitment costs	1000
Isolator germicidal tank x 2	1792
Animal Costs	1349.99880
Total £	64141.99880

Other Directly Allocated Costs

Description	Total £
Infrastructure Technicians	3868
Total £	3868

Animal Costs

Animal Species	Type and Microbiological Quality	Genetically Altered?	No. Purchased	Average Cost per Animal (£)	No. Bred	Average Cost per Animal (£)	Maintenance duration (weeks)	Weekly Maintenance costs per Species (£)	Total Cost £
Bird	Eggs to hatch SPF commercial birds	False	460	2.93478			70	0	1349.99880
								Total £	**1349.99880**

Research Council Facilities

details of any proposed usage of national facilities
Research Council Facilities are not relevant to this application.

Ethical Information

Please answer the following questions as appropriate

a) Human Participation

Would the project involve the use of human subjects?		Yes	No✓
	If yes, would equal numbers of males and females be used?	Yes	No✓
Would the project involve the use of human tissue?		Yes	No✓
Would the project involve the use of biological samples?		Yes✓	No

Justification of Resources: The Pirbright Institute costs:

Investigator Time: Professor Nair (PI) and Dr. Yongxiu Yao (Co-PI), will lead and coordinate the activities of the project, including the supervision of the Post-doctoral scientist. They will also contribute to the regular team progress meetings, teleconferences, review of progress reports and publication for dissemination of research outcomes. They will also oversee all biosafety, biocontainment and ethical issues related to the laboratory and animal experimental work. We have requested funds to cover (b)(6) of the salary each for this.

Post-doctoral research assistant (PDRA) salary: Funding for one FTE (100%) PDRA salary is requested for the duration of the 3 year project. The length and experience of this appointment is justified by the amount of experimental work to be undertaken, both in the laboratory work in the preparation of virus stocks, quantitation of virus from the different samples as well as in organising and executing the animal experiments. PDRA will also contribute to the analysis and in the preparation of reports and manuscripts for publication, as well as in liaising with US collaborators. PDRA will also participate in the various activities of the group and for personal development (see mentoring plan).

Research consumables (Other directly incurred research costs): Funding £60,000 will be required towards the research consumables for the 3 year period. These are the standard costs for a project of this type and will include the costs of general laboratory consumable and disposable items, tissue culture reagents, plastic ware for cell culture, molecular biology kits including DNA extraction kits, PCR reagents for quantitation of virus loads, as well as minor equipment such as pipettes.

We have included the cost of £1,792 for the two germicidal tanks for the two Bioflex B50 isolators (see below) under this section, which is shown in the quote for the cost of isolators.

Animal experimentation costs: We plan to do 3 animal experiments during the duration of the project (see the science document). We will be purchasing SPF eggs which will be hatched in our facilities for experimental infection and vaccination studies. We anticipate that we would need to obtain 570 eggs to produce sufficient one-day old chicks, and have costed £1,350 on the project towards this. The cost of the animal facilities is not included in this because it will be covered by the Core Capability grant awarded by the BBSRC to the Pirbright Institute.

Recruitment costs: A standard cost of £1,000 is included as recruitment costs for recruiting the Research assistant post.

Infrastructure Technicians: Standard cost of £3,868 is requested towards the services of the Infrastructure Technicians for the different central services of the Institute.

Equipment: The critical experiments for the project will have to be carried out in biological isolators since we want to collect the poultry dust to measure the amount of virus shed by quantitative PCR measurements. We have only limited number of isolators and these are already used to its full capacity, and will not be sufficient to fit with the number of groups required for this study. There are no other isolators available at the Pirbright Institute and we do not have access to similar isolators in nearby accessible locations. Hence we are requesting for the purchase of two additional Bioflex-B50 isolators which will allow us to carry out the planned experiments within the time scales planned in the proposal. The two isolators are also critical for the effective simultaneous comparison of the output from the different experimental groups, essential for making valid scientific conclusions. The two isolators requested are similar to the ones we already have and will minimise the potential variations between isolators. We have requested a total fund of £78,160 including the

service costs for two years towards this (see the quotes attached). As per the guidance for the costs of large equipment, we are requesting 50% of the total costs, with Pirbright contributing to the remaining 50% of the costs (see letter provided by the Head of Grants and Science Adminstration).

Travel and Subsistence:

Funding £13,500 is requested towards travel costs for the duration of the project. These costs include annual travel for the PI. Co-PI and the Post-doctoral scientist for meeting of the US collaborator, participating in the EEID meetings and one international science conference on virology (for example, International Marek's disease Conference) to present the research findings.

Justification for the choice of animal species and number of animals used:

Animal experiments will be performed following the procedures and protocols listed in the Project Licence No. **PP5997056** approved by the Home Office under the terms of Animals (Scientific Procedures) Act. Marek's disease (MD) is a specific disease of poultry which predominantly a major problem in chickens. Hence as the most important natural hosts for this virus infection, we will be using this species in experimental infections. Keeping the 3Rs principle in mind, the number of chickens used will be the minimum number that will generate statistically valid data. We propose to carry out 3 different experiments as outlined in the scientific case. With 20 birds per isolators, and 3 isolators, our estimate of vaccine virus shedding will have a mean confidence interval of width 1 $\log_{10}$ unit, and there will be an 83% chance that it will be less than 1.5 $\log_{10}$ units.

Estates and Indirect costs*:* Our indirect cost rate is based on the (UK) government-agreed "Full Economic Costing" (FEC) model used by all UK universities and research institutes. These rates are calculated to recover only the ongoing operational cost of running the facilities, a single FEC rate is applied to the whole site in order to maintain sustainability. The strategic focus of the Pirbright Institute is virology; the facilities available are world class and underpin the outstanding science delivered at the Institute. All of our facilities are sophisticated and meet the very highest of standards. Accordingly, the facilities do require high maintenance costs and as a result the level of indirect cost recovery is correspondingly high, but reflects the outstanding nature of the resources being used to undertake the science. Every effort is made to ensure the site is run as efficiently as possible, this can be demonstrated when compared to facilities of a similar standard from other organisations where the Institute's running costs are lower per sq. meter.

Access/Estates costs of £83,946 and the Indirect costs of £172,412 requested are based on the standard FEC calculations of the Pirbright Institute.

To: NSF Ecology and Evolution of Infectious Diseases (EEID) Program
From: Dr. Venugopal Nair

By signing below (or transmitting electronically), I acknowledge that I am listed as a collaborator on this proposal, entitled "**US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study**," with Dr. Dave Kennedy as the Principal Investigator. I agree to undertake the tasks assigned to me or my organization, as described in the project description of the proposal, and I commit to provide or make available the resources specified therein.

(b)(6)

Signed:
Organization: Pirbright Institute, Pirbright, Woking, Guildford, Surrey, United Kingdom

Date: 8th November 2019

To: NSF Ecology and Evolution of Infectious Diseases (EEID) Program
From: Dr. Yongxiu Yao

By signing below (or transmitting electronically), I acknowledge that I am listed as a collaborator on this proposal, entitled "**US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study**," with Dr. Dave Kennedy as the Principal Investigator. I agree to undertake the tasks assigned to me or my organization, as described in the project description of the proposal, and I commit to provide or make available the resources specified therein.

Signed: (b)(6)

Organization: Pirbright Institute, Pirbright, Woking, Guildford, Surrey, United Kingdom

Date: 8th November 2019

National Science Foundation
2415 Eisenhower Avenue
Alexandria
Virginia
22314
United States of America

18 November 2019

To whom it may concern

Re: Ecology and Evolution of Infectious Disease (EEID) US - UK Collaboration "US - UK Collab: The consequence of transmissible vaccine on disease ecology and pathogen evolution: Marek's disease virus as a case study".

I confirm on behalf of The Pirbright Institute that the U.S.-U.K. Collaborative proposal between Associate Professor David Kennedy (Pennsylvania State University) and Professor Venugopal Nair, OBE, is endorsed and has been submitted by The Pirbright Institute Grants Office.

Yours faithfully

(b)(6)

Dr Louise Barton
Head of Science Administration
The Pirbright Institute
E: Louise.barton@pirbright.ac.uk, T: 01483 231341

PennState
Eberly College
of Science

Office of
Science Outreach

Office of Science Outreach
Eberly College of Science
The Pennsylvania State University
201 Ritenour Building
University Park, PA 16802

P: 814.865.0509
F: 814.865.0096

To: NSF Ecology and Evolution of Infectious Diseases (EEID) Program
From: The Pennsylvania State University, Jessica Kim-Schmid, Director of Office of Science Outreach

By signing below (or transmitting electronically), I acknowledge that I am listed as a collaborator on this proposal, entitled "US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study," with David A Kennedy as the Principal Investigator. I agree to undertake the tasks assigned to me or my organization, as described in the project description of the proposal, and I commit to provide or make available the resources specified therein.

Signed: (b)(6)

Organization: The Pennsylvania State University, Eberly College of Science – Office of Science Outreach
Date: November 14, 2019

US-UK collaboration grant – vertebrate animal usage

As part of this grant, all the animal work will be done in the facilities at The Pirbright Institute. All the experiments will be conducted in high containment facilities using procedures regulated under the UK Home Office of Her Majesty's Government & BBSRC guidelines (http://www.bbsrc.ac.uk/web/FILES/Publications/animals_in_bioscience_research.pdf). We are ethically bound to follow the '3R' principles, particularly in reducing the numbers of animals used for experiments, where possible, but without compromising the validity of the research findings.

Description of Procedures: This proposal involves three sets of animal experiments. These experiments will be used to a) Quantify the transmission rate of the vaccine virus, b) Characterize how selection on standing virus variation is affected by Rispens vaccination, c) Disentangle the protective effects of the transmissible vaccine. These experiments involve measuring vaccine shedding, virus shedding, vaccine transmission, virus shedding, vaccine protection of directly vaccinated birds, and vaccine protection of indirectly vaccinated birds. All three sets of experiments will use specified-pathogen-free, maternal antibody negative, Rhode Island Red chickens (*Gallus gallus domesticus*) hatched from embryonated eggs at The Pirbright Institute. Chickens will be vaccinated at 1 day of age and monitored for the duration of the experiments. Based on our power analyses, we will need 510 total birds for the three sets of experiments. Birds will be a mixture of males and females.

Justifications: Marek's disease is exclusively a virus infecting chickens, and there are no *in vitro* models of the disease, vaccine protection or vaccine transmission. Hence the use of animals is inevitable. Poultry are the only susceptible species for studying the oncogenicity of the virus and hence the chicken models of the disease will be used in our studies. We have long-standing experience in experimental infection in birds with this virus and have developed excellent models of MD lymphoma models in the natural chicken hosts and have published several peer reviewed publications.

All the experiments will be carried out as per the procedures in the Project License granted to Dr. Nair as the Project License Holder under the provisions of the Animal (Scientific Procedures) Act 1986. All the procedures are also approved by the IAH Ethical Committee, in which Dr. Nair is a member. All the procedures will be carried out by experienced technical staff members who hold personal licenses to carry out the procedures. The procedures envisaged under this grant have mild severity limits and will be carried out with strict humane clinical end points, which we have been using for the last several years. The estimation of sample size has been achieved from the experience from our previous experiments to use the minimum number of animals required to provide differences between groups with 95% confidence intervals.

Minimization of Pain and Distress: The Pirbright Institute has a record of maintaining very high standards in the welfare of the experimental animals. All the animals are under the supervision of designated animal care staff and the Veterinary surgeon. Marek's disease is a neoplastic disease with a gradual onset with not major suffering. However, infection with some virulent viruses could produce acute disease. All the infected birds are checked daily, 7 days/week, and several times a day when infections are acute. There are clear guidelines on clinical endpoints for avoiding the suffering of experimental animals, and those reaching a certain clinical point will be euthanized.

Method of Euthanasia: Birds infected with Marek's disease at clinical endpoints or at the end of the experiment will be euthanized by one of the schedule I killing procedures of breaking the neck or by CO_2 asphyxiation. These procedures are approved by the Animal (Scientific Procedures) Act 1986, and are similar to the international standards of euthanasia in chickens.

FACILITIES, EQUIPMENT, AND OTHER RESOURCES

Facilities & Resources at Penn State

Scientific Environment

I (Dr. Kennedy) am a co-hire between the Department of Biology and to the Huck Institutes of the Life Sciences at The Pennsylvania State University. The Huck Institutes create an intellectual framework for interdisciplinary research, by connecting faculty with diverse expertise that are unified by a shared research interest, under the structure of topic-themed centers. The Huck Institutes also expands physical resources available to this research by providing access to shared facilities.

My lab and office are co-located with many others that belong to The Huck Institutes' **Center for Infectious Disease Dynamics (CIDD)**, including Co-PI Szpara, in the newly constructed Millennium Science Complex (MSC). CIDD includes 40+ faculty from 15+ departments at our campus and the PSU College of Medicine, who are united by a common goal of addressing infectious disease dynamics. CIDD labs study infectious disease across scales, with an emphasis on evolution, ecology, and disease transmission. Nearby CIDD labs in MSC study bacterial, fungal, viral, and parasite pathogens, using both theoretical and empirical approaches. We exchange ideas, equipment, and expertise on a daily basis. CIDD sponsors two weekly meetings: a formal seminar series every Thursday with external speakers, and an informal series of Powerpoint-free research discussions every Monday with internal speakers. Additionally, co-PI Szpara organizes a monthly Virology Club, which I regularly attend, called **Virology@PSU**, where graduate and post-doctoral trainees from virology labs across campus meet and present their data and research ideas.

Penn State also provides strong institutional support for the mathematical modeling of biological systems. In addition to regular interactions with the more quantitative members of CIDD, I am also a member of the recently formed **Center for Mathematical Biology**. This center fosters the exchange of ideas and the development of research collaborations involving mathematical models and quantitative approaches to the life sciences. It currently includes 25 faculty from 8 departments, who employ observational, laboratory, mathematical, statistical, and computational approaches to address a broad range of biological and medical questions. The center hosts monthly lunches and a weekly seminar series to discuss work at the interface between the observation of living systems and the development of appropriate quantitative methods to describe these systems.

Experimental Facilities

Both my lab and Dr. Szpara's lab are in the Millennium Science Complex (MSC), which utilizes an open-lab format to integrate and foster interactions between primarily wet-bench and primarily computational groups, such as Dr. Szpara's group and my own. My laboratory includes BSL-2-compatible wet-bench space and a dedicated computational area. Dr. Szpara's lab includes wet-bench space, a dedicated bioinformatics and computing work area, a biohazard-level 2 (BSL-2) tissue-culture (TC) room, a fume hood and chemical room, a microscope and sequencing room, an electrophoresis area, and a zone for storage and freezers. In addition, **Co-PI Szpara has a dedicated Illumina® MiSeq in the laboratory**, which will be heavily utilized in our project. Additional sequencing equipment, tools, and expertise are available through the Penn State Genomics Core, described below in the section "Genomics Infrastructure & Support."

While the open-lab design allows researchers to share specialized equipment between research groups, MSC also has communal areas for equipment that is available for all PIs to use. This equipment includes autoclaves, ultra- and high-speed centrifuges, warm and cold rooms, and additional freezers. There are also adjoining computational spaces dedicated to bioinformatics. The MSC's focus on interdisciplinary research benefits this project, by its integration of computing and bioinformatics space with wet-bench work areas.

In addition, the Biology department and the Huck Institutes for the Life Sciences also provide administrative support, with dedicated staff for grants administration, purchasing, receiving, equipment maintenance, and computer support. Several of these support staff are located directly on-site in MSC.

Computational Infrastructure & Support
Computational support for this project will be provided by the University's Institute for CyberScience. Penn State's Institute for CyberScience (ICS) operates the Advanced CyberInfrastructure (ICS-ACI), the university's state-of-the-art high-performance research cloud.

ICS-ACI equipment is located in a newly-constructed Data Center facility at Penn State's University Park Campus. This facility operates in compliance with all Penn State IT policies. The facility provides 2.15 MW power capacity and contains 12,000 square feet of floor space for computing equipment, termed as the data center "white space." The building is powered efficiently and is undergoing LEED certification. The facility is designed to operate with an annualized average Power Usage Effectiveness (PUE) of 1.21.

The ICS-ACI high-performance research cloud is composed of hardware that is interconnected over high-speed network fabrics, and that includes various software offerings and services. ICS-ACI currently maintains 26,000 computational cores. ICS-ACI offers four different core configurations: high-memory cores (1TB RAM per server), standard-memory cores (256 GB RAM per server), and basic-memory cores (128 GB RAM per server), and GPU cores (using NVidia Tesla K80 GPU accelerators). The standard-memory and basic-memory compute cores are housed within high density Dell M1000E Blade server enclosures, while the high-memory and GPU accelerator cores are in conventional 4U and 2U rack mount configurations, respectively.

ICS-ACI also maintains 20 PB of data storage capacity. The storage is comprised of 8 PB of active storage pools that provide immediate data access and retrieval, and 12 PB of near-line storage for long-term and archival purposes. The active storage operates on DDN 12KX40 and GS7K flash storage array systems, while near-line storage utilizes Oracle's FS1 flash storage appliance and a SL8500 Tape Library.

The compute and storage hardware are interconnected using Ethernet and Infiniband network fabrics. The Ethernet network utilizes Brocade VCS fabric technology and is currently comprised of 1) four aggregate and two core layer Brocade VDX 8770-8 Enterprise-level switches that provide 10, 40, and 100 Gbps link capacity, 2) four Brocade VDX 6740 switches that provide 10 Gbps link capacity, and 3) one Brocade N2024 switch per rack for host iDRAC (integrated DELL Remote Access Controller) remote management over Gbps line rate. The Infiniband network consists of 15 Mellanox SX6025 switches and two Mellanox SX6536 648 port non-blocking SDN switch systems, all operating on 56 Gbps (FDR) line rate.

ICS-ACI maintains and regularly updates an expansive software stack. The stack currently contains 240 applications, with more added at regularly-scheduled intervals. The applications

include security monitoring software (e.g.,OSSEC), batch schedulers (e.g.,MOAB, Torque), compilers, file transfer programs, and communication libraries (e.g.,MPI, OpenMP). The stack also contains software applications commonly used by researchers, such as MATLAB, COMSOL, R, and Python, as well as programs for performing specialized tasks, such as Abaqus, Quantumwise, and TopHat.

ICS-ACI is maintained by the ICS staff, who provide network monitoring, backup services, software updates, code optimization, and service-desk support. ICS uses Solarwinds network monitoring software to monitor the health and status of the network, hardware, and storage. ICS-ACI is actively monitored during normal business hours (9:00 AM –5:00 PM) Monday through Friday. ICS-ACI also hosts OSSEC, an open-source host-based intrusion detection system, which is used to control the system by monitoring available logs, alerting administrators of unauthorized system modifications, and providing a mechanism to enforce security requirements. The team uses NESSUS Professional to scan the system for potential vulnerabilities such as hacking and Denial of Service (DoS) attacks.

The ICS website offers documentation to help users resolve technical issues they may encounter. This support is supplemented by the i-ASK Center, a service desk which supplies expert technical assistance for user problems. In the event of more complex issues, the engineers of the ICS Technical Support Team provide advanced in-person support to users to ensure that problems are resolved in a timely and professional manner.

ICS offers domain-specific consulting to assist researchers with optimizing code, leveraging various software applications and in general increasing the efficiency of their research operations. Consultants cover disciplines including Engineering, Chemistry and Materials Science, Data Visualization, Parallelization, and Science Gateways for Big Data Research.

Genomics Infrastructure & Support
In addition to the Illumina® MiSeq, housed in Co-PI Szpara's laboratory, we have access to a wealth of equipment relevant to this proposal through the Huck **Genomics Core Facility**. The Genomics Fore Facility has instrumentation to support whole-genome and transcriptome sequencing of non-model organisms, amplicon sequencing for metagenomics studies, differential expression analysis of mRNA and miRNA, degradome sequencing, ChIP and RIP sequencing, Sanger DNA sequencing, genotyping of SNPs and VNTRs, microarray analysis, real-time qPCR, and digital PCR. Available instrumentation includes:

- Illumina NextSeq
- Illumina MiSeq
- PacBio Sequel
- Applied Biosystems 3730XL
- Agilent Bioanalyzer
- Qubit
- Applied Biosystems QuantStudio 12K Flex Real-Time PCR System
- Applied Biosystems StepOnePlus Real-Time PCR System
- NanoString nCounter
- BluePippin
- Covaris ultrasonicator
- Illumina HiSeq 2500
- Affymetrix GeneChip Instrument System
- Molecular Devices GenePix 4000B Scanner

Biohazards
MDV is not infectious to humans. Nevertheless, all strains of MDV will be handled as BSL-2 agents, in a designated laboratory in the Millennium Science Complex (MSC) at Penn State. Researchers use personal protective equipment (PPE) (i.e.gloves, lab coat) when handling virus. Optional inhalant barrier protection (disposable face masks) is available at all times, as are appropriate biohazard waste and autoclave areas. Freezers for long-term virus storage are adjacent to the laboratory space. When transporting aliquots of infectious material, aliquots of virus will be stored in a secondary containment device (e.g. inside a screw-top tube, container, or closed cooler). All personnel receive standard laboratory safety training, biohazard safety training, and lab-specific training in procedures regarding the safe handling of infectious agents. Multiple laboratories in the MSC use other BSL-2 agents, so researchers in both buildings are familiar with these techniques and maintain all facilities and shared research areas in a BSL-2-compatible manner (e.g. no food or drink in wet-bench areas, separate BSL-2 facilities for each pathogen, cross-training in safe handling for all pathogens). The MSC lab is directly adjacent to Penn State's Student Health Center. Emergency medical services, including the University Ambulance Service (UAS), are located in the Student Health Center and provide service 24 hours a day, 7 days a week. If needed, UAS can provide transport to the Mount Nittany Medical Center, located just 2 miles away.

Facilities & Resources at Pirbright Institute

The Pirbright Institute is one of the world's leading Centres of Excellence working in the field of viral diseases of livestock through two main strategic areas of science involving the Pathogen biology and the interactions with the host. Excellent animal models in the target natural hosts allow detailed molecular studies on virus-host interactions for developing novel intervention strategies and vaccines. Following are some of the facilities and resources available at the Pirbright Institute.

BBSRC National Virology Centre
The Plowright Building became fully operational in April 2015 and is the culmination of £145m investment to develop a new containment laboratory for research of exotic viruses. The 14,000 m^2 laboratory and associated facilities houses some 160 staff, including 125 scientists, and is essential to underpin the Institute's two scientific programmes for the purposes of in vitro research into virus diseases of livestock, including poultry.

BBSRC National Vaccinology Centre
The Jenner Building is The Pirbright Institute's low-containment facility and opened in 2016 as part of phase two of the redevelopment of the Pirbright site. This facility houses a wide range of groups working on strategically important endemic and exotic viral pathogens that can be handled under low containment including Marek's disease virus.

The Nair Laboratory located in the Jenner Building has three x 1000 ft^2 laboratories, with bench space for twenty people. The laboratories have all the facilities for carrying out all the routine molecular biological experiments including quantitative PCR assays, a major requirement for the current project. In addition the laboratory has all the facilities for virological experiments including preparation of tissue culture, virus maintenance, virus titration and egg inoculation. The Nair lab routinely carries out Marek's disease virus (MDV) work using a large collection of virus stocks from all over the world procured as part of the OIE MDV Reference

Laboratory (MDVRL). In addition to the routine primary cell lines prepared in the lab, we also have access to a large collection of cell lines and monoclonal antibodies as part of the Immunological Toolbox.

Bioimaging
The Pirbright Institute houses a unique Bioimaging facility containing advanced confocal and electron microscopes, flow cytometry analysers and cell sorters. Instruments are located in both the high containment Plowright and low containment Jenner buildings making them accessible to all researchers. The scope of imaging and analytical techniques available inside the SAPO4 envelope is globally unique. It is possible to image, analyse and sort live cells from host animals infected in the Institute isolation units. Microscopy and flow techniques are used to identify immune cell types, enrich special cell populations, localise host or viral proteins within cells and study the cell biology of host-pathogen interactions at high resolution.

Houghton Facility
The Houghton Facility is a Specific Pathogen Free (SPF) hatchery that allows The Pirbright Institute to hatch and grow poultry under clean conditions. This maintains the disease-free status of the birds for use in animal experiments to study viral disease important to the welfare of chickens and ultimately to ensure security of food supply for the UK. Houghton Facility is a purpose-built animal facility dedicated to the incubation, hatching and growth of SPF chickens supplied as embryonated eggs from the Roslin Institute's National Avian Research Facility (NARF) Bumstead Building in Edinburgh, or other commercial supplier, in support of the Institute's avian research.

Animal Experimental Facilities
The BSU and the forthcoming Biggs building provide excellent facilities for conducting biological experiments in chickens in isolators under containment. All the experiments involving infections in chickens will be carried out in these facilities. Entry into the rooms is restricted and involves cloth changing and showering as part of the containment requirements. All the infected materials, including the carcasses are disposed by incineration. At the end of the experiments, each room and the isolators are disinfected to prevent any cross infection from residual viruses. All these procedures are carried to ensure that no infectious viruses come out of the containment. These facilities have a long history of successfully containing infectious agents in experimental infections. Positive pressure isolators allow housing groups of up to 20 MDV-infected birds. Dust shed by the birds is collected in the air filter housed in the outflow, and dust viral titres determined by PCR. Experimentally-infected birds, if needed, can also be kept on the floor.

PennState
Eberly College of Science

David A. Kennedy, Assistant Professor
Department of Biology
Huck Institutes of the Life Sciences
W-229B Millennium Science Complex
University Park, PA 16802
Phone: (814) 863-5461
dak30@psu.edu

March 20, 2020

To the Division of Receipt and Referral:

This cover letter accompanies the proposal, ***US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study***. This proposal is one for the NIH-NSF Ecology and Evolution of Infectious Diseases (EEID) Program: A joint Program for Multidisciplinary Research (R01). The submission is part of Program Announcement **PAR-20-001 NIH-NSF Ecology and Evolution of Infectious Diseases Program: A Joint Program (EEID)**. Please consider this proposal for assignment to Study Section **2020/05 ZRG1 IDM-U (55)R Ecology and Evolution of Infectious Diseases**.

I have discussed this application with Program Officer Dr. Christine Jessup (christine.jessup@nih.gov).

Thank you very much for your consideration.

Sincerely,

(b)(6)

David A. Kennedy

Recipient Information

1. Recipient Name
PENNSYLVANIA STATE UNIVERSITY, THE
201 OLD MAIN

UNIVERSITY PARK, PA 16802

2. Congressional District of Recipient
12

3. Payment System Identifier (ID)
1246000376A1

4. Employer Identification Number (EIN)
246000376

5. Data Universal Numbering System (DUNS)
003403953

6. Recipient's Unique Entity Identifier

7. Project Director or Principal Investigator
David Kennedy, PHD
Assistant Professor Of Biology
dak30@psu.edu; (b)(6)
814-863-5461

8. Authorized Official
JOHN W HANOLD
osp@psu.edu
814-865-1372

Federal Agency Information

9. Awarding Agency Contact Information
Michael P Mace
Grants Management Specialist
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
macem@mail.nih.gov
(301) 402-6431

10. Program Official Contact Information
DANIEL E JANES
Program Official
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
daniel.janes@nih.gov

Federal Award Information

11. Award Number
5R01GM140459-02

12. Unique Federal Award Identification Number (FAIN)
R01GM140459

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

15. Assistance Listing Number
93.859

16. Assistance Listing Program Title
Biomedical Research and Research Training

17. Award Action Type
Non-Competing Continuation

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 05/01/2021 **– End Date** 04/30/2022	
20. Total Amount of Federal Funds Obligated by this Action	$369,851
20 a. Direct Cost Amount	$242,809
20 b. Indirect Cost Amount	$127,042
21. Authorized Carryover	$0
22. Offset	$0
23. Total Amount of Federal Funds Obligated this budget period	$369,851
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$369,851
26. Project Period Start Date 08/01/2020 **– End Date** 04/30/2025	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$739,702

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Robert Altieri

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

SECTION I – AWARD DATA – 5R01GM140459-02

Principal Investigator(s):
David Kennedy, PHD

Award e-mailed to: osp@psu.edu

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $369,851 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to PENNSYLVANIA STATE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM140459. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Robert Altieri
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Federal Direct Costs	$242,809
Federal F&A Costs	$127,042
Approved Budget	$369,851
Total Amount of Federal Funds Authorized (Federal Share)	$369,851
TOTAL FEDERAL AWARD AMOUNT	$369,851
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$369,851

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$369,851	$369,851
3	$369,851	$369,851
4	$369,851	$369,851
5	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1246000376A1
Document Number:	RGM140459A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2021

IC	CAN	2021	2022	2023	2024
GM	8019957	$369,851	$369,851	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: G242DJ / **OC**: 41025 / **Released**: Altieri, Robert 04/13/2021
Award Processed: 04/15/2021 12:16:51 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM140459-02

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 5R01GM140459-02

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the

definition of “Research and Development” at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VII Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM140459. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – GM SPECIFIC AWARD CONDITIONS – 5R01GM140459-02

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

1. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-21-058.

2. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL: http://grants1.nih.gov/grants/policy/salcap_summary.htm

3. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

4. **IMPORTANT**: The grant recipient is reminded that payments made for educational assistance (e.g., scholarships, fellowships, and student aid costs) may not be paid from NIH research grant funds even when they would appear to benefit the research project. See the explanation of "Fringe Benefits/IHE Tuition/Tuition Remission" in the NIH Grants Policy Statement, Section 7.9.1.
at:https://grants.nih.gov/grants/policy/nihgps/HTML5/section_7/7.9_allowability_of_costs_activities.htm#Selected

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

SPREADSHEET SUMMARY
AWARD NUMBER: 5R01GM140459-02

INSTITUTION: PENNSYLVANIA STATE UNIVERSITY

Facilities and Administrative Costs	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	60.5%	60.5%	60.5%	60.5%
F&A Cost Base 1	$209,987	$209,987	$209,987	$209,987
F&A Costs 1	$127,042	$127,042	$127,042	$127,042

A. COVER PAGE

Project Title: US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study	
Grant Number: 5R01GM140459-02	**Project/Grant Period:** 08/01/2020 - 04/30/2025
Reporting Period: 08/01/2020 - 04/30/2021	**Requested Budget Period:** 05/01/2021 - 04/30/2022
Report Term Frequency: Annual	**Date Submitted:** 03/15/2021
Program Director/Principal Investigator Information: DAVID KENNEDY , PHD BS **Phone Number:** (814) 863-5461 **Email:** (b)(6)	**Recipient Organization:** PENNSYLVANIA STATE UNIVERSITY-UNIV PARK 201 OLD MAIN 110 Technology Center Building UNIVERSITY PARK, PA 168021503 **DUNS:** 003403953 **EIN:** 1246000376A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: JOHN W HANOLD 110 Technology Center Building University Park, PA 168027000 **Phone number:** 8148651372 **Email:** osp@psu.edu	**Signing Official:** GARTH GREGOR 110 Technology Center University Park, PA 16802 **Phone number:** 8148634685 **Email:** gag14@psu.edu
Human Subjects: No	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Vaccination can be one of the most efficient and effective tools for controlling the burden of infectious diseases, but in many settings, such as for wildlife diseases or farm animal diseases, logistical and economic hurdles make it impractical to vaccinate large enough fractions of hosts to achieve herd immunity. Transmissible vaccines, defined as vaccines capable of disseminating from vaccinated to non-vaccinated hosts, offer one potential solution to these challenges by amplifying the impact of vaccination campaigns. However, transmissible vaccines are not without risk. Reversion to virulence or recombination with wildtype pathogens could cause transmissible vaccines to make matters worse or complicate elimination efforts. This proposed work will for the first time quantify the effects of transmissible vaccines on disease ecology and evolution using the example of an economically important, naturally transmissible vaccine currently in widespread use on poultry farms.

Marek's disease, a poultry-specific disease that is a threat to sustainable chicken and egg farming, is currently controlled by the "Rispens" vaccine, a live, attenuated vaccine that has been widely used for two decades. Recent experiments have found that this vaccine is capable of efficiently transmitting from vaccinated to non-vaccinated chickens. These results are consistent with recent field surveillance studies that have found vaccine isolates in chicken cohorts that have not been directly vaccinated. In addition, advances in whole genome sequencing has revealed the presence of recombination between the vaccine virus and wildtype virus, which is concerning given that the vaccine virus harbors highly virulent forms on the oncogenic meq gene. Together, these observations demonstrate that the Rispens vaccine is a transmissible vaccine capable of evolving and potentially facilitating adverse evolution of wildtype Marek's disease virus. Our primary objective is to use this study system to quantify the consequences of transmissible vaccine use. The project goals are as follows:

1) Develop a general model of transmissible vaccination to identify key knowledge gaps
2) Characterize vaccine transmission and its impact on wildtype virus transmission
3) Characterize the genetic evolution of wildtype virus and vaccine virus
4) Model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File Uploaded : AccomplishedUnderGoals.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File Uploaded : TrainingOpportunities.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

Dissemination of this work on vaccine-driven changes to disease ecology and evolution has been critical during the COVID-19 pandemic, since so much is currently unknown regarding how pathogen evolution will alter the efficacy of current and future COVID-19 vaccines. I have taken three main approaches to disseminate relevant information to decision makers and to the public.

First, I have served on Penn State's vaccine preparedness committee. The purpose of this committee is to prepare a plan for Penn State to distribute COVID-19 vaccines should the opportunity present itself. Based on my work on this grant, I was asked to serve on this committee to provide a scientific perspective on the ecological and evolutionary impacts of vaccines, and how best to disseminate that information to the public. In addition to making comments during the meeting, I have recorded a short video to help explain the similarities and differences between the three currently approved COVID-19 vaccines. This effort is intended to fill a perceived knowledge gap in the public about whether they should wait for their first-choice vaccine, or take the first vaccine available.

Second, I have been posting messages to Twitter regarding the need to monitor for vaccine driven pathogen evolution. I have also been using this platform to help clarify what currently is and is not known regarding the novel variants and their potential impacts on vaccine efficacy. I noticed quite a bit of misinformation circulating on Twitter, and I worried that it could undermine people's trust in science and their propensity to get vaccinated. By providing a scientific perspective, I am giving the public a resource to identify which concerns are scientifically justifiable and which are more speculative. I feel that this is a necessary step towards educating the public and maintaining overall trust in science during a time when most individuals feel that they are overloaded with information to the point that they are unable to distinguish between scientific conclusions and non-scientific opinions.

Third, I have given interviews to journalists from many different news sources including the New York Times, BBC World News, CBSNews, Science Magazine, Nature, and others. The topic of these interviews has similarly focused on how to monitor for the emergence of new virus variants that will impact COVID-19 vaccine efficacy. In these written and video interviews, I discussed the vaccines, the novel variants, and how we can monitor for evolutionary-driven changes in the efficacy of the vaccines.

Fourth, I have written three articles for The Conversation to use my voice to directly disseminate scientific information and fill knowledge gaps in the public's understanding of the COVID-19 pandemic.

All of these activities have been performed in an attempt to fill an information void that was being filled with misinformation earlier in the pandemic.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

In the next reporting period, we will continue to pursue the proposed research on multiple fronts.

For Aim 1, postdoc Aniruddha Deka will continue to develop his model describing the effects of transmissible vaccines on disease ecology in a farm-like setting. Farm-like dynamics differ from wildlife-like dynamics in that host populations tend to have discrete, non-overlapping, cohorts in which host population dynamics are divorced between cohort dynamics whereas pathogen population dynamics are not. Aniruddha's model currently captures dynamics within a cohort, but does not yet extend across multiple cohorts. That complexity will be added into his model, and he will then analyze the sensitivity of his model to different model parameters such as the vaccine transmission rate, the vaccine efficacy, pathogen transmission rate, the rate of vaccine reversion to virulence, and the rate of recombination between virus and vaccine. This work will be used to identify knowledge gaps regarding which parameters are most important to estimate in Aim 2 of this grant. It will also be a publishable unit. The natural extension of this work will then be to explore how optimal farmer behavior would be altered by the presence of a transmissible vaccine. Aniruddha's background modeling game theory of vaccination makes him an ideal candidate for this line of research.

For Aim 2, we will begin animal experiments in the UK to measure the transmission potential of the Rispens vaccine. Our earlier data has demonstrated that the Rispens vaccine is capable of transmission between hosts, but we do not yet have

quantitative information on how transmissible it is relative to wild type virus. This data is likely critical to our modeling outcomes in Aim 4. We will also use this experiment to determine the degree to which vaccine transmission confers disease protection. We will also sequence the virus isolates used for these experimental infections in Aim 3, since some preliminary data from earlier experiments cannot be analyzed until these sequences are known.

For Aim 3, we will use the Arbor Biosciences MyBaits to enrich virus and vaccine DNA from our library of dust samples. We will test these methods on 14 virus samples, including two each with low, medium and high levels of virus or vaccine, and two with high levels of both virus and vaccine. After sequencing these enriched samples using a MiSeq and assembling genomes, we will know which samples from our dust-sample library will be most useful in characterizing the genetic diversity of Marek's disease virus and the Rispens vaccine. Our expectation is that we will be able to assemble complete genomes for all of our samples with medium or high levels of vaccine or virus. We expect that we will be unable to assemble genomes from samples that contain mixtures of virus and vaccine, and if that is the case, we will perform a pilot to test whether genomes can be assembled using the PacBio platform, which allows for longer reads and thus easier assembly.

For Aim 4, we will continue to r(b)(4); (b)(6)

(b)(4); (b)(6)

(b)(4); (b)(6) In the upcoming year, we will expand the model to allow for transmission of the Rispens vaccine, using transmission rates determined from Aim 2 of the grant.

To address the aims of this grant, we have pursued the proposed research on multiple fronts:

Aim 1 of this grant involves developing general models of transmissible vaccines to identify the key knowledge gaps in understanding the ecological and evolutionary consequences of these vaccines. I have so far developed a mathematical framework that describes the dynamics of a host system that has transmission of both a pathogen and a vaccine. As of March 1, 2021, postdoc Aniruddha Deka has taken over my preliminary modeling. He has so far coded up a version of the model, he has calculated the equilibria of the model, and he is performing sensitivity analyses. So far, the model has been limited to the dynamics within a single cohort of animals, but this will need to be extended to cover multiple cohorts. Any parameters that are found to be particularly important to disease dynamics will be explored further in Aims 2 and 4.

In addition, while I was working on incorporating vaccine driven evolution into my preliminary transmissible vaccine model, I realized that these same methods could be applied to ask whether COVID-19 vaccines would drive the evolution of SARS-CoV-2. In particular, it became clear to me what data would be necessary to predict the likelihood of vaccine-driven evolution. I was able to identify three critical factors that could be explored during vaccine clinical trials in humans or in animals. The manuscript was published Nov 2020 in PLOS Biology, and it has already been read over 15,000 times and cited 7.

Aim 2 of this grant involves animal experiments to measure key parameters in the mathematical models. This work is being conducted in collaboration with Dr. Nair and Dr. Yao at the Pirbright Institute in the UK. The BBSRC is funding this research and the start date of those funds have been delayed until April on account of COVID-19 delays. Nevertheless, we have examined preliminary data from previous animal experiments performed by Dr. Nair exposing chickens to Marek's disease virus after vaccinating them with the Rispens vaccine. These analyses allow us to optimize conditions for our transmission and infection experiments.

Aim 3 of this grant uses dust samples collected as part of a previous study to look at the genetic diversity of Marek's disease virus and the Rispens vaccine and the potential for recombination. One critical step in this process is to enrich our dust samples for Marek's disease virus and the Rispens vaccine. We have reached out Jakob Trimpert who has previously used oligo enrichment to successfully perform this task previously. We now have permission to use his oligo enrichment formulation on our dust samples, and we plan to order these reagents from Arbor BioSciences before the end of the fiscal year. Meanwhile, we have sequenced the genomes of 64 historical Marek's disease virus isolates of differing virulence. Employing a program called 3Seq, we have identified recombination breakpoints in these historical isolates, which allows us to better understand the evolutionary history of this virus. This analysis yielded a strong signature of phylogenetic incongruence, indicating strong evidence of recombination between wild isolates of Marek's disease virus. The next step will be to assess whether similar evidence exists between the Rispens vaccine and wild type virus.

In Aim 4 of this project, we will synthesize data from Aims 1-3 to understand the consequences of the Rispens vaccine on vaccine and virus evolution. We have so far developed a model of Marek's disease virus transmission in vaccinated and unvaccinated host populations based on parameter estimates from previous surveillance studies. The model has been adapted to span 60

years and 100 farms, and it has been applied to understand why low virulence strains of Marek's disease virus have persisted despite a long history of widespread vaccination. Results from this analysis suggest that (b)(4); (b)(6)

(b)(4); (b)(6)

Individual Development Plans (IDP) are a mandatory requirement for postdoctoral fellows at Penn State University. This involves a yearly meeting between the postdoc and myself to discuss long and short term goals, opportunities for career development, and to discuss any obstacles that have been encountered and potential solutions. In addition to this live meeting, there are online entries by the mentor and trainee to reflect on goals, obstacles, and approaches. I typically have an additional informal IDP meeting with members of my lab so that we meet every 6 months instead of 12, since I find that these meetings provide a low-stakes opportunity to give and get feedback about how things can be improved. In addition to these meetings, I meet individually with each member of my lab weekly to discuss the progress of the last week and the plan for the next week. I often let the trainee guide these meetings to ensure that they are able to discuss what they feel they most need to discuss.

I also believe that reading, presenting, attending seminars, and discussing scientific ideas are important components of academic training. To facilitate these activities, I hold weekly lab meetings where every week a different person presents their own work or a published paper relevant to their work. I encourage all members of my lab to attend at least one and preferably two research seminars per week. Also, since our lab members have been much more distanced since the start of the COVID-19 pandemic, I hold twice weekly "tea breaks" in which members of the lab meet via Zoom and are encouraged to discuss anything that is on their mind, science related or otherwise. The feedback that I have received from trainees has taught me that these opportunities are valuable for creating lab cohesion, for soliciting scientific feedback between lab members, and for starting conversations about mental health. The postdoc on this project, Aniruddha Deka, has benefitted from these activities.

Dr. Szpara, who oversees the work of two staff scientists on this project (Christopher Bowen and Daniel Renner), holds two-hour meetings every other week with members of her lab, in addition to a weekly group meeting. She also holds an annual lab retreat that focuses on professional development.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Category	Explanation
Other	https://theconversation.com/why-it-matters-that-the-coronavirus-is-changing-and-what-this-means-for-vaccine-effectiveness-152383 Article in The Conversation explaining what the emergence of new SARS-CoV-2 variants means for the efficacy of COVID-19 vaccines.
Other	https://theconversation.com/what-you-need-to-know-about-the-new-covid-19-variants-153366 Video and article in The Conversation helping to explain what the new SARS-CoV-2 variants are, and what their consequences are likely to be.
Other	https://theconversation.com/virus-evolution-could-undermine-a-covid-19-vaccine-but-this-can-be-stopped-149234 Article in The Conversation regarding how clinical trials of COVID-19 vaccines could monitor for vaccine-driven evolution of the virus.

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	Kennedy, David	BS,PHD	PD/PI	(b)(6)					NA
	Y	SZPARA, MORIAH	PHD	Co-Investigator						NA
	N	Deka, Aniruddha		Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

No

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?
Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?
NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?
Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

There were several small delays during the current reporting period. Most notably, COVID-19 slowed down the start of this project. Two technicians that were planning to work on this project became overcommitted due to pressing work on a COVID-19 study. This unforeseeable overcommitment delayed their ability to charge time to the current project. The COVID-19 study is now complete and they will be able to put extra time into this project to get the research back on track in the upcoming fiscal year so this delay should be resolved. Along similar lines, the funding for the UK component of this project (BBSRC) was delayed until April of this year due in part to COVID-19 shutdowns in the UK. This BBSRC funding will last 3 years, and so all UK work will still take place and be completed within the expected funding period of this NIGMS award. Lastly, I had to wait several months for postdoc Aniruddha Deka to finish his PhD before he could be hired to work on this project. He is now here and making good progress on the award, and I do not anticipate any further delay as a result.

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subject

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

No

G.8 PROJECT/PERFORMANCE SITES

Organization Name	DUNS	Congressional District	Address
Primary: The Pennsylvania State University	003403953	PA-012	110 Technology Center Building University Park, PA 16802
PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	003403953		ROBERT KILLOREN DIRECTOR, SPONSORED PROGRAMS

			UNIVERSITY PARK, PA 16802
PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	003403953		201 OLD MAIN 110 Technology Center Building UNIVERSITY PARK, PA 168021503
PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	003403953		ROBERT KILLOREN DIRECTOR, SPONSORED PROGRAMS UNIVERSITY PARK, PA 16802

G.9 FOREIGN COMPONENT

Organization Name: The Pirbright Institute
Country: UNITED KINGDOM
Description of Foreign Component:
This project was funded as a collaborative proposal through the Ecology and Evolution of Infectious Diseases program. DNA sequencing, mathematical modeling, and data analysis will take place in the US, while animal experiments will take place in the UK led by Venugopal Nair and Yongxiu Yao and funded by the BBSRC.

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes

Estimated unobligated balance: $80

G.10.b Provide an explanation for unobligated balance:
The unobligated budget can be explained by several factors. First, this fiscal year lasted only 6 months, when it was expected to be 12 months in the original proposal. Second, the postdoc on this project was only unable to start in March. Third, due to COVID-19, our UK collaborators had to delay the start of their BBSRC grant until April. This has in turn delayed the arrival of DNA samples, and in turn, the salary of two technicians has not yet started to flow for this project, despite them being ready to go when samples arrive, which is expected to be shortly.

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent
The remaining balance will be spent in the upcoming fiscal year as the necessary personnel are in place to complete the proposed work. The scope of work has not changes. The postdoc and two technicians will work more calendar months than originally planned in the upcoming fiscal year to make up for the shortened fiscal year and the delay in sample arrival. The total costs will therefore be shifted between fiscal years, but otherwise unchanged.

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period? No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

Recipient Information

1. Recipient Name
PENNSYLVANIA STATE UNIVERSITY, THE
201 OLD MAIN

UNIVERSITY PARK, 16802

2. Congressional District of Recipient
12

3. Payment System Identifier (ID)
1246000376A1

4. Employer Identification Number (EIN)
246000376

5. Data Universal Numbering System (DUNS)
003403953

6. Recipient's Unique Entity Identifier
NPM2J7MSCF61

7. Project Director or Principal Investigator
David Kennedy, PHD
Assistant Professor Of Biology
(b)(6)
814-863-5461

8. Authorized Official
JOHN W HANOLD
osp@psu.edu
814-865-1372

Federal Agency Information

9. Awarding Agency Contact Information
Michael P Mace
Grants Management Specialist
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
macem@mail.nih.gov
(301) 402-6431

10. Program Official Contact Information
Ronald Adkins
Scientific Review Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
ronald.adkins@nih.gov
301 435 4511

Federal Award Information

11. Award Number
5R01GM140459-03

12. Unique Federal Award Identification Number (FAIN)
R01GM140459

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

15. Assistance Listing Number
93.859

16. Assistance Listing Program Title
Biomedical Research and Research Training

17. Award Action Type
Non-Competing Continuation

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 05/01/2022 **– End Date** 04/30/2023	
20. Total Amount of Federal Funds Obligated by this Action	$369,851
20 a. Direct Cost Amount	$242,809
20 b. Indirect Cost Amount	$127,042
21. Authorized Carryover	$0
22. Offset	$0
23. Total Amount of Federal Funds Obligated this budget period	$369,851
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$369,851
26. Project Period Start Date 08/01/2020 **– End Date** 04/30/2025	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$1,109,553

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Connie Murphy

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

SECTION I – AWARD DATA – 5R01GM140459-03

Principal Investigator(s):
David Kennedy, PHD

Award e-mailed to: osp@psu.edu

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $369,851 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to PENNSYLVANIA STATE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM140459. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Connie Murphy
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$141,523
Fringe Benefits	$37,099
Personnel Costs (Subtotal)	$178,622
Materials & Supplies	$17,834
Travel	$6,800
Other	$6,731
Tuition Remission	$32,822
Federal Direct Costs	$242,809
Federal F&A Costs	$127,042
Approved Budget	$369,851
Total Amount of Federal Funds Authorized (Federal Share)	$369,851
TOTAL FEDERAL AWARD AMOUNT	$369,851
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$369,851

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
3	$369,851	$369,851
4	$369,851	$369,851
5	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1246000376A1
Document Number:	RGM140459A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2022

IC	CAN	2022	2023	2024
GM	8019957	$369,851	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: G242RN / **OC**: 41025 / **Released**: Murphy, Connie 05/10/2022
Award Processed: 05/11/2022 12:08:50 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM140459-03

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

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SECTION III – STANDARD TERMS AND CONDITIONS – 5R01GM140459-03

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VII Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM140459. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-22-105.

None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL:

http://grants1.nih.gov/grants/policy/salcap_summary.htm

As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

IMPORTANT: The grant recipient is reminded that payments made for educational assistance (e.g., scholarships, fellowships, and student aid costs) may not be paid from NIH research grant funds even when they would appear to benefit the research project. See the explanation of "Fringe Benefits/IHE Tuition/Tuition Remission" in the NIH Grants Policy Statement, Section 7.9.1. at:

https://grants.nih.gov/grants/policy/nihgps/HTML5/section_7/7.9_allowability_of_costs_activities.htm

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

SPREADSHEET SUMMARY
AWARD NUMBER: 5R01GM140459-03

INSTITUTION: PENNSYLVANIA STATE UNIVERSITY

Budget	Year 3	Year 4	Year 5
Salaries and Wages	$141,523	$141,523	$141,523
Fringe Benefits	$37,099	$37,099	$37,099
Personnel Costs (Subtotal)	$178,622	$178,622	$178,622
Materials & Supplies	$17,834	$17,834	$17,834
Travel	$6,800	$6,800	$6,800
Other	$6,731	$6,731	$6,731
Tuition Remission	$32,822	$32,822	$32,822
TOTAL FEDERAL DC	$242,809	$242,809	$242,809
TOTAL FEDERAL F&A	$127,042	$127,042	$127,042
TOTAL COST	$369,851	$369,851	$369,851

Facilities and Administrative Costs	Year 3	Year 4	Year 5
F&A Cost Rate 1	60.5%	60.5%	60.5%
F&A Cost Base 1	$209,987	$209,987	$209,987
F&A Costs 1	$127,042	$127,042	$127,042

A. COVER PAGE

Project Title: US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study	
Grant Number: 5R01GM140459-03	**Project/Grant Period:** 08/01/2020 - 04/30/2025
Reporting Period: 05/01/2021 - 04/30/2022	**Requested Budget Period:** 05/01/2022 - 04/30/2023
Report Term Frequency: Annual	**Date Submitted:** 03/14/2022
Program Director/Principal Investigator Information: DAVID KENNEDY , PHD BS **Phone Number:** (814) 863-5461 **Email:** (b)(6)	**Recipient Organization:** PENNSYLVANIA STATE UNIVERSITY, THE 201 OLD MAIN 110 Technology Center Building UNIVERSITY PARK, PA 168021503 **DUNS:** 003403953 **EIN:** 1246000376A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: JOHN W HANOLD 110 Technology Center Building University Park, PA 168027000 **Phone number:** 8148651372 **Email:** osp@psu.edu	**Signing Official:** GARTH GREGOR 110 Technology Center University Park, PA 16802 **Phone number:** 8148634685 **Email:** gag14@psu.edu
Human Subjects: No	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Vaccination can be one of the most efficient and effective tools for controlling the burden of infectious diseases, but in many settings, such as for wildlife diseases or farm animal diseases, logistical and economic hurdles make it impractical to vaccinate large enough fractions of hosts to achieve herd immunity. Transmissible vaccines, defined as vaccines capable of disseminating from vaccinated to non-vaccinated hosts, offer one potential solution to these challenges by amplifying the impact of vaccination campaigns. However, transmissible vaccines are not without risk. Reversion to virulence or recombination with wildtype pathogens could cause transmissible vaccines to make matters worse or complicate elimination efforts. This proposed work will for the first time quantify the effects of transmissible vaccines on disease ecology and evolution using the example of an economically important, naturally transmissible vaccine currently in widespread use on poultry farms.

Marek's disease, a poultry-specific disease that is a threat to sustainable chicken and egg farming, is currently controlled by the "Rispens" vaccine, a live, attenuated vaccine that has been widely used for two decades. Recent experiments have found that this vaccine is capable of efficiently transmitting from vaccinated to non-vaccinated chickens. These results are consistent with recent field surveillance studies that have found vaccine isolates in chicken cohorts that have not been directly vaccinated. In addition, advances in whole genome sequencing has revealed the presence of recombination between the vaccine virus and wildtype virus, which is concerning given that the vaccine virus harbors highly virulent forms on the oncogenic meq gene. Together, these observations demonstrate that the Rispens vaccine is a transmissible vaccine capable of evolving and potentially facilitating adverse evolution of wildtype Marek's disease virus. Our primary objective is to use this study system to quantify the consequences of transmissible vaccine use. The project goals are as follows:

1) Develop a general model of transmissible vaccination to identify key knowledge gaps
2) Characterize vaccine transmission and its impact on wildtype virus transmission
3) Characterize the genetic evolution of wildtype virus and vaccine virus
4) Model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File Uploaded : AccomplishedUnderGoals.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File Uploaded : TrainingOpportunities.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

In the last reporting period, I have presented this work as a contributed talk at the 13th International Symposium on Marek's Disease and Avian Herpesviruses which was held June 1 to June 3, 2021. I have also applied the expertise that I gained from this project to COVID-19 and disseminated that through several written articles for the popular press publication, The Conversation. I have also spoken with numerous journalists about the evolution of SARS-CoV-2 and the role that vaccines can play, positively or negatively, in altering that evolution.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

In the next reporting period, we will continue to pursue the proposed research on multiple fronts.

For Aim 1, postdoc Aniruddha Deka will finish writing up the results from his model describing the effects of transmissible vaccines on disease ecology. He is currently starting a new modeling project to understand when vaccine transmissibility increases the likelihood of recombination between a vaccine and a pathogen. The idea stems from the fact that vaccines are typically administered when pathogen is not present, but for a transmissible vaccine, the timing of application cannot be as easily controlled, and so it is highly likely that an individual will be exposed to pathogens and vaccines at similar times. Using a modeling approach, he will ask when these risks are high and when these risks are low. Aniruddha is simultaneously working on determining how to minimize costs of disease and vaccination using optimization theory. This project is in the very early planning stages, but if that goes well, the next step would be to explore how optimal farmer behavior would be altered by the presence of a transmissible vaccine. Aniruddha's background modeling game theory of vaccination makes him an ideal candidate for this line of research.

For Aim 2, we will continue animal experiments in the UK to measure the transmission potential of the Rispens vaccine. Our earlier experiments have demonstrated that the Rispens vaccine is capable of transmission between hosts. In the upcoming year, we will analyze experimental data to develop a quantitative understanding of how transmissible it is relative to wild type virus, and the degree to which vaccine and wildtype virus interfere with each other. This data is likely critical to our modeling outcomes in Aim 4. We will also use this experiment to determine the degree to which vaccine transmission confers disease protection.

For Aim 3, we will continue to use the Arbor Biosciences MyBaits to enrich virus and vaccine DNA from our library of experimental samples. We will sequence the samples generated in experimental infections using a mix of short read and long read technology to quantify risks of recombination and other forms of evolution. We will also expand these methods to apply them to our library of dust samples that were collected as part of a previous project. Our expectation is that we will be able to detect recombination using long read sequencing and we will be able to detect the emergence of minor variants using short read sequencing. We will use these data to develop a quantitative understanding of viral and vaccine evolution.

For Aim 4, we will (b)(4); (b)(6)
For the next steps in this project, we will expand the model so that it allows for the transmissible element of the Rispens vaccine. This is a non-trivial task that will require refitting the model parameters to data, although we anticipate no issues since the methods have been developed in our previous work. Once this is performed, we will simulate the model to explore how disease dynamics and pathogen evolution have played out, and simulate it again assuming the vaccine cannot transmit, to ask how things would have been different if the transmissiblity element of the vaccine were absent. We will also expand the model to allow for transmission of the Rispens vaccine, using transmission rates determined from Aim 2 of the grant.

To address the aims of this grant, we have pursued the proposed research on multiple fronts:

Aim 1 of this grant involves developing general models of transmissible vaccines to identify the key knowledge gaps in understanding the ecological and evolutionary consequences of these vaccines. We have previously identified the precise costs and benefits of vaccine transmissibility as key knowledge gaps and developed a preliminary model to assess these costs and benefits. In this reporting period, postdoc Aniruddha Deka has used this framework to analytically derive the size of the effects of transmissibility with regard to disease reduction, reversion to virulence, and recombination between vaccines and the pathogens they are meant to control. The analysis found that for a transmissible vaccine in comparison to a non-transmissible but otherwise identical vaccine, there is always a benefit of reduced disease and always a cost of increased risk of reversion to virulence, but depending on the details of the system, there can be either an increase or a decrease in the risk of recombination. The analysis also identified the biological factors (i.e. model parameters) that the magnitude of these costs and benefits are most sensitive to. This work is currently being written up for publication.

The potential for evolutionary costs of vaccine transmissibility raises the question of when it is worthwhile to pay short term costs (e.g. increased profit or reduced disease) in exchange for long term benefits (e.g. avoiding things such as virulence evolution, recombination, or resistance). In a paper published in PLOS Biology in Nov 2021, we answer exactly that question of when it is worthwhile to invest in managing evolution. The main result of this paper was a single inequality with a clear biological interpretation; it is worthwhile to invest in managing evolution when the percent increase in the longevity of an intervention is larger than the percent increase in the cost paid to manage adverse evolution.

Aim 2 of this grant involves animal experiments to measure key parameters in the mathematical models of Marek's disease virus and vaccine dynamics. This work is being conducted in collaboration with Dr. Nair and Dr. Yao at the Pirbright Institute in the UK. The BBSRC is funding this part of the research project and the start date of those funds was delayed until April 2021 on account of COVID-19. Funds are now available, personnel have been selected, and preliminary experiments have been conducted. Part of the challenge of analyzing the data from these experiments arises because the qPCR assays that are designed to quantify vaccine and the wildtype viruses interfere with each other. We have now used deep sequencing to definitively demonstrate that both the Rispens vaccine and the wildtype virus are capable of transmitting between birds in our experimental setups. We have also shown that both wildtype virus and vaccine virus can simultaneously be detected in individual sentinel birds which were neither vaccinated or experimentally infected. We are currently analyzing this data to determine the degree to which vaccine and virus transmit, and whether the presence of one prevents infection with the other (as opposed to just qPCR interference).

Aim 3 of this grant uses dust samples collected as part of a previous study and other types of samples (peripheral blood lympocyte samples, and feather tip samples) collected in Aim 2 to look at the genetic diversity of Marek's disease virus and the Rispens vaccine and the potential for recombination. One critical step in this process is to enrich our samples for Marek's disease virus and the Rispens vaccine. Since the last reporting period, we have ordered and performed oligo enrichment successfully. We have also started sequencing samples. In two pilot rounds of

MiSeq Illumina sequencing we have run respectively 4 samples and 8 samples. Using the first set of samples, we have generated de novo whole genome sequences for the three viral isolates and one vaccine isolate used to experimentally infect birds in Aim 2. These sequences are going to be used as reference genomes for the analysis of the other experimental samples. Using the 8 samples from our second MiSeq run, we are developing a pipeline for analyzing this type of data that we will be able to use to sequence many more samples and look for evidence of recombination. We also used this pilot to identify the types of samples that work best for sequencing in our hands. We learned that we have better success sequencing viral DNA collected from peripheral blood lymphocytes than from feather tips. Simultaneously, we have split a third set of 8 samples with the intention to run them both on a MiSeq and using PacBio's long read technology. The PacBio-bound portion of the samples are currently in the queue at Penn State's sequencing core. The results of this pilot will allow us to compare the efficacy of each method for detecting recombination and other evolutionary changes in our particular type of samples. The pipelines and results generated in these pilots will set us up to make substantial progress in the upcoming reporting period.

Aim 4 of this project synthesizes the data from Aims 1-3 to understand the consequences of vaccines on vaccine and virus evolution. I have previously reported efforts to develop a model of Marek's disease virus transmission on chicken farms based on surveillance data. That project is being written up and is expected to be submitted in the next reporting period. During this reporting period, I have applied the principles from this project to help develop a framework for classifying the variants that may arise, should a pathogen evolve in the face of vaccination efforts. This framework establishes that there are two relevant axes: 1) whether the variant is a generalist or a specialist on vaccinated hosts, and 2) whether the variant is inhibited or facilitated by vaccination. We show that the direction of selection changes over time such that initially most emerging vaccine-escape variants will be generalist pathogens that are better at infecting both vaccinated and nonvaccinated hosts, but that over time, most new variants will be specialist variants that grow better on vaccinated than nonvaccinated hosts. Throughout this period, we expect most variants to be vaccination inhibited. A preprint of this article was deposited to arXiv Sep 2021 and updated Jan 2022.

Individual Development Plans (IDP) are a mandatory requirement for postdoctoral fellows at Penn State University. This involves a yearly meeting between the postdoc and myself to discuss long and short term goals, opportunities for career development, and to discuss any obstacles that have been encountered and potential solutions. In addition to this live meeting, there are online entries by the mentor and trainee to reflect on goals, obstacles, and approaches. I typically have an additional informal IDP meeting with members of my lab so that we meet every 6 months instead of 12, since I find that these meetings provide a low-stakes opportunity to give and get feedback about how things can be improved. In addition to these meetings, I meet individually with each member of my lab weekly to discuss the progress of the last week and the plan for the next week. I often let the trainee guide these meetings to ensure that they are able to discuss what they feel they most need to discuss.

I also believe that reading, presenting, attending seminars, and discussing scientific ideas are important components of academic training. To facilitate these activities, I hold weekly lab meetings where every week a different person presents their own work or a published paper relevant to their work. I encourage all members of my lab to attend at least one and preferably two research seminars per week. I hold once weekly "tea breaks" in which members of the lab meet to discuss anything that is on their mind, science related or otherwise. The feedback that I have received from trainees has taught me that these opportunities are valuable for creating lab cohesion, for soliciting scientific feedback between lab members, and for starting conversations about mental health. The postdoc on this project, Aniruddha Deka, has benefitted from these activities.

Dr. Szpara, who oversees the work of two staff scientists on this project (Christopher Bowen and Daniel Renner), holds two-hour meetings every other week with members of her lab, in addition to a weekly group meeting. She also holds an annual lab retreat that focuses on professional development.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Kennedy DA, Read AF. Monitor for COVID-19 vaccine resistance evolution during clinical trials. PLoS biology. 2020 November;18(11):e3001000. PubMed PMID: 33166303; PubMed Central PMCID: PMC7676675; DOI: 10.1371/journal.pbio.3001000.
N/A	Day T, Kennedy D, Read A, McAdams D. The economics of managing evolution. PLOS Biology. 2021 November 16;19(11):e3001409-. DOI: 10.1371/journal.pbio.3001409.
N/A	Day T, Kennedy DA, Read AF, Gandon S. The evolutionary epidemiology of pathogens during vaccination campaigns. arXiv. 2021 September 28. DOI: 10.48550/arXiv.2109.13680.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	Kennedy, David	BS,PHD	PD/PI	(b)(6)					NA
	Y	SZPARA, MORIAH	PHD	Co-Investigator						NA
	N	Deka, Aniruddha		Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA
	N	Bowen, Christopher		Technician						NA
	N	Renner, Daniel		Technician						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

No

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors? No
D.2.e Multi-PI (MPI) Leadership Plan **Will there be a change in the MPI Leadership Plan for the next budget period?** NA

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?
Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?
NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?
Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

I was hoping to have recruited a graduate student to start working on Aim 4 of this project last year, but I was unable to find a suitable candidate given that the vast majority of graduate students with backgrounds suitable for disease modeling were focused on pursing COVID-19 modeling. I have since recruited a graduate student to start Fall of this year and so I do not anticipate any further delays on that front. I anticipate hiring a postdoctoral scholar to help make up for the setback in time. Aim 2 was experimental work to be carried out in collaboration with the Pirbright Institute with funding through the BBSRC. That funding was delayed due to COVID-19 until April 2021, which delayed progress on that aim. Funding is now up and progress has been resumed.

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subject

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

No

G.8 PROJECT/PERFORMANCE SITES

Organization Name	DUNS	Congressional District	Address
Primary: The Pennsylvania State University	003403953	PA-012	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK 110 Technology Center Building University Park, PA 16802

G.9 FOREIGN COMPONENT

Organization Name: Pirbright Institute
Country: UNITED KINGDOM
Description of Foreign Component:
This grant is part of a collaborative proposal with another proposal that was simultaneously funded through the BBSRC. Aim 2 of this proposal is work to be carried out by Venugopal Nair at the Pirbright Institute. That work involves experimental studies of Marek's disease virus dynamics in vertebrate chickens that were vaccinated with the Marek's disease vaccine called Rispens. These experiments are being incorporated into the other aspects of the grant and are expected to result in co-authorship.

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes

Estimated unobligated balance: $434,564

G.10.b Provide an explanation for unobligated balance:
First, due to COVID-19 shutdowns in 2020 there was a large unobligated balance carried over from the prior year. Second, slowdowns, holds, and visa challenges caused by COVID-19 made hiring particularly difficult which increased the carryover. Third, I am in the early stage of my career, meaning that I had startup funds that were expiring and I thus spent those before spending from this grant to maximize the depth of samples that I could include in this project. Fourth, due to the delay in BBSRC funding for the collaborative part of this proposal, the vast majority of samples were not yet available for processing and expenses of processing were thus not yet realized.

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent
Much of the work that was delayed during the COVID-19 shutdowns and delays can be carried out in the upcoming academic year. First, samples generated by our collaborators will be processed in the upcoming year. Second, both a postdoctoral scholar and a graduate student will be hired to take the lead on various aspects of Aim 4 of the grant. A graduate student was recently hired by Dr. Szpara to take the lead on parts of Aim 3 of the grant. In addition I will retain the current employees and increase their monthly effort if necessary for them to make up for the delays imposed by COVID-19.

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period? No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

Recipient Information

1. Recipient Name
PENNSYLVANIA STATE UNIVERSITY, THE
201 OLD MAIN

UNIVERSITY PARK, PA 16802

2. Congressional District of Recipient
12

3. Payment System Identifier (ID)
1246000376A1

4. Employer Identification Number (EIN)
246000376

5. Data Universal Numbering System (DUNS)
003403953

6. Recipient's Unique Entity Identifier
NPM2J7MSCF61

7. Project Director or Principal Investigator
David Kennedy, PHD
Assistant Professor
dak30@psu.edu
814-863-5461

8. Authorized Official
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814-865-1372

Federal Agency Information

9. Awarding Agency Contact Information
Jennifer M Lynch

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
jennifer.lynch@nih.gov
301-594-3918

10. Program Official Contact Information
Ronald Adkins
Scientific Review Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
ronald.adkins@nih.gov
301 435 4511

Federal Award Information

11. Award Number
5R01GM140459-04

12. Unique Federal Award Identification Number (FAIN)
R01GM140459

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

15. Assistance Listing Number
93.859

16. Assistance Listing Program Title
Biomedical Research and Research Training

17. Award Action Type
Non-Competing Continuation

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 05/01/2023 **– End Date** 04/30/2024	
20. Total Amount of Federal Funds Obligated by this Action	$369,851
20 a. Direct Cost Amount	$242,809
20 b. Indirect Cost Amount	$127,042
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$369,851
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$369,851
26. Project Period Start Date 08/01/2020 **– End Date** 04/30/2025	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$1,479,404

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Connie Murphy

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

SECTION I – AWARD DATA – 5R01GM140459-04

Principal Investigator(s):
David Kennedy, PHD

Award e-mailed to: osp@psu.edu

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $369,851 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to PENNSYLVANIA STATE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM140459. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Connie Murphy
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$141,523
Fringe Benefits	$37,099
Personnel Costs (Subtotal)	$178,622
Materials & Supplies	$17,834
Travel	$6,800
Other	$6,731
Tuition Remission	$32,822
Federal Direct Costs	$242,809
Federal F&A Costs	$127,042
Approved Budget	$369,851
Total Amount of Federal Funds Authorized (Federal Share)	$369,851
TOTAL FEDERAL AWARD AMOUNT	$369,851
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$369,851

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
4	$369,851	$369,851
5	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1246000376A1
Document Number:	RGM140459A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2023

IC	CAN	2023	2024
GM	8019957	$369,851	$369,851

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: G242RN / **OC**: 41025 / **Released**: Murphy, Connie 05/19/2023
Award Processed: 05/20/2023 12:01:33 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM140459-04

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 5R01GM140459-04

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.

b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VII Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM140459. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights

laws enforced by HHS. See https://www.hhs.gov/civil-rights/for-providers/provider-obligations/index.html and https://www.hhs.gov/.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html and https://www.lep.gov.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html.
- HHS funded health and education programs must be administered in an environment free of sexual harassment; see https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html. For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see https://grants.nih.gov/grants/policy/harassment.htm.
- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see https://www.hhs.gov/conscience/conscience-protections/index.html and https://www.hhs.gov/conscience/religious-freedom/index.html.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – GM SPECIFIC AWARD CONDITIONS – 5R01GM140459-04

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

1. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-23-071.

2. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL: http://grants1.nih.gov/grants/policy/salcap_summary.htm

3. **IMPORTANT:** The grant recipient is reminded that payments made for educational assistance (e.g., scholarships, fellowships, and student aid costs) may not be paid from NIH research grant funds even when they would appear to benefit the research project. See the explanation of "Fringe Benefits/IHE Tuition/Tuition Remission" in the NIH Grants Policy Statement, Section 7.9.1.
at:https://grants.nih.gov/grants/policy/nihgps/HTML5/section_7/7.9_allowability_of_costs_activities.htm#Selected

4. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

5. Unobligated Balances: As indicated in Section III of this Notice of Award, an unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval. In accordance with section 8.1.1.1 of the NIH GPS, NIGMS staff reserve the right to make budgetary reductions to award commitments in cases where recipients have accrued excessively large unobligated balances.

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

SPREADSHEET SUMMARY
AWARD NUMBER: 5R01GM140459-04

INSTITUTION: PENNSYLVANIA STATE UNIVERSITY

Budget	Year 4	Year 5
Salaries and Wages	$141,523	$141,523
Fringe Benefits	$37,099	$37,099
Personnel Costs (Subtotal)	$178,622	$178,622
Materials & Supplies	$17,834	$17,834
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Other	$6,731	$6,731
Tuition Remission	$32,822	$32,822
TOTAL FEDERAL DC	$242,809	$242,809
TOTAL FEDERAL F&A	$127,042	$127,042
TOTAL COST	$369,851	$369,851

Facilities and Administrative Costs	Year 4	Year 5
F&A Cost Rate 1	60.5%	60.5%
F&A Cost Base 1	$209,987	$209,987
F&A Costs 1	$127,042	$127,042

A. COVER PAGE

Project Title: US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study	
Grant Number: 5R01GM140459-04	**Project/Grant Period:** 08/01/2020 - 04/30/2025
Reporting Period: 05/01/2022 - 04/30/2023	**Requested Budget Period:** 05/01/2023 - 04/30/2024
Report Term Frequency: Annual	**Date Submitted:** 03/16/2023
Program Director/Principal Investigator Information: DAVID KENNEDY , PHD BS **Phone Number:** (814) 863-5461 **Email:** (b)(6)	**Recipient Organization:** PENNSYLVANIA STATE UNIVERSITY, THE 200 Innovation Blvd. Suite 110 UNIVERSITY PARK, PA 168027000 **DUNS:** 003403953 **UEI:** NPM2J7MSCF61 **EIN:** 1246000376A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: JOHN W HANOLD 110 Technology Center Building University Park, PA 168027000 **Phone number:** 8148651372 **Email:** osp@psu.edu	**Signing Official:** GARTH GREGOR 110 Technology Center University Park, PA 16802 **Phone number:** 8148634685 **Email:** gag14@psu.edu
Human Subjects: No	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Vaccination can be one of the most efficient and effective tools for controlling the burden of infectious diseases, but in many settings, such as for wildlife diseases or farm animal diseases, logistical and economic hurdles make it impractical to vaccinate large enough fractions of hosts to achieve herd immunity. Transmissible vaccines, defined as vaccines capable of disseminating from vaccinated to non-vaccinated hosts, offer one potential solution to these challenges by amplifying the impact of vaccination campaigns. However, transmissible vaccines are not without risk. Reversion to virulence or recombination with wildtype pathogens could cause transmissible vaccines to make matters worse or complicate elimination efforts. This proposed work will for the first time quantify the effects of transmissible vaccines on disease ecology and evolution using the example of an economically important, naturally transmissible vaccine currently in widespread use on poultry farms.

Marek's disease, a poultry-specific disease that is a threat to sustainable chicken and egg farming, is currently controlled by the "Rispens" vaccine, a live, attenuated vaccine that has been widely used for two decades. Recent experiments have found that this vaccine is capable of efficiently transmitting from vaccinated to non-vaccinated chickens. These results are consistent with recent field surveillance studies that have found vaccine isolates in chicken cohorts that have not been directly vaccinated. In addition, advances in whole genome sequencing has revealed the presence of recombination between the vaccine virus and wildtype virus, which is concerning given that the vaccine virus harbors highly virulent forms on the oncogenic meq gene. Together, these observations demonstrate that the Rispens vaccine is a transmissible vaccine capable of evolving and potentially facilitating adverse evolution of wildtype Marek's disease virus. Our primary objective is to use this study system to quantify the consequences of transmissible vaccine use. The project goals are as follows:

1) Develop a general model of transmissible vaccination to identify key knowledge gaps
2) Characterize vaccine transmission and its impact on wildtype virus transmission
3) Characterize the genetic evolution of wildtype virus and vaccine virus
4) Model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

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B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

Dissemination of this work on vaccine-driven changes to disease ecology and evolution has been critical during the COVID-19 pandemic, since so much is currently unknown regarding how pathogen evolution will alter the efficacy of current and future COVID-19 vaccines. I have taken three main approaches to disseminate relevant information to decision makers and to the public.

Previously, I have reported activity 1) serving on Penn State's vaccine preparedness committee, 2) posting messages to Twitter regarding the value of monitoring COVID for vaccine driven evolution and pathogen evolution that may undermine the protection affording by vaccination, 3) giving interviews to news agencies to provide a scientific perspective on the evolution of new virus variants, and 4) writing articles for The Conversation to use my voice to directly disseminate information to the public.

In the current project year I have additionally disseminated information through talks and participation in workshops. I presented my current research in an invited talk to the International Veterinary Vaccinology Network via a Zoom presentation entitled, "Epidemiology and vaccination against Marek's disease. I have also participated in a Zoom seminar panel on self-disseminating vaccines in which we explored the risks and opportunities that transmissible vaccine research creates. In addition I am attending a workshop on transmissible vaccines later this month (March 2023) to give an invited talk.

Lastly, I am currently developing a 4-part community-outreach event for the Osher LifeLong Learning Institute (OLLI) at Penn State that will be offered for the first time this summer (June 2023). These outreach events take the form of short courses that are opened to the public with the typical participant being community members in the State College area. The topic being discussed will be the effect of vaccines on the ecology and evolution of infectious diseases.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

In the next reporting period, we will continue to pursue the proposed research on multiple fronts.

For Aim 1, I will work with former postdoc Aniruddha Deka to (b)(4); (b)(6)

(b)(4); (b)(6)

For Aim 2, we will conduct additional experiments in the UK to measure the transmission potential of the Rispens vaccine and the benefits conferred by transmission of this vaccine. Our earlier experiments have demonstrated that the Rispens vaccine is capable of transmission between hosts, and we have shown that different vaccines differ in their ability to transmit. In the upcoming year, we will analyze this experimental data to quantify the precise amount of vaccine transmission that occurs. We will further hone a promising digital PCR method that we are using to distinguish between wildtype virus and vaccine virus to better resolve the degree to which vaccination protects against infection. Lastly, we will help to design the next round of experiments with collaborators Dr. Nair and Dr. Yao, which will be possible to conduct now that a new postdoc has been hired.

For Aim 3, we will continue to improve the quality of our "parental" virus assemblies using a combination of Illumina and PacBio sequence data. Once we are happy with these genomes, we will write up our results for publication. As previously discussed, the Rispens vaccine genome sequences that we have identified are substantially different from the Rispens genome that has been deposited on GenBank. We will also use use the assembled parental genomes to test for evidence of recombination in our experimental samples. Recombination would be marked by sequencing reads that look like a combination of two parental virus genomes rather than like either one alone. Using previously collected sequence and phenotype data on a batch of 63 virus isolates, we will also explore whether there are associations between Marek's disease virus genotype and virulence using a genome wide association study.

For Aim 4, we will (b)(4); (b)(6)
Following this submission, we will expand the model so that it allows for the transmissible element of the Rispens vaccine. This is a non-trivial task that will require refitting the model parameters to data, although we anticipate no issues since the methods have been developed in our previous work. Once this is performed, we will simulate the model to explore how disease dynamics and pathogen evolution have played out, and simulate it again assuming the vaccine cannot transmit, to ask

how things would have been different if the transmissiblity element of the vaccine were absent. In addition, we will finish writing up and submit the manuscript that uses contact tracing data to identify heterogeneity in susceptibility between hosts.

We have simultaneously progressed each of the four Aims:

Aim 1 of this grant involves developing general models of transmissible vaccines to identify the key knowledge gaps in understanding the ecological and evolutionary consequences of these vaccines. Previously, we identified that the costs and benefits of transmissible vaccines are a key knowledge gap and so we developed a simple framework for assessing these costs and benefits. Postdoc Aniruddha Deka worked to analyze this model to analytically derive the benefits and costs, in the form of changes to disease prevalence, recombination frequency, and vaccine reversion to virulence rates. (b)(4); (b)(6)

(b)(4); (b)(6)

Aim 2 of this grant involves animal experiments to measure key parameters in the mathematical models of Marek's disease virus and vaccine dynamics. This work is being conducted in collaboration with Dr. Nair and Dr. Yao at the Pirbright Institute in the UK. The BBSRC is funding this part of the research project and the start date of those funds was delayed on account of COVID-19. While the funding is now available, the postdoc initially selected to carry out the experiments developed health issues that further postponed progress. Regardless, one experiment was completed in the past year. In addition, a new postdoc has since been hired and planning is deep underway for the next experiment. The experiment that was conducted sought to characterize the transmissibility of three different vaccines -- two commercial vaccines and a less attenuated version of one of the commercial vaccines. The results of that experiment showed that the less attenuated vaccine was the most transmissible, the more attenuated commercial vaccine was still transmissible, but less so, and the other commercial vaccine did not show any evidence of transmissibility. Thus, in the context of Marek's disease, we have determined that there are two viable commercial vaccines that give similar protection against Marek's disease but that differ in their propensity to transmit beyond the primary vaccinated host. Moreover, the transmissibility of the transmissible commercial vaccine can likely be ramped up or down by altering the number of passages during development.

Notably, wild type Marek's disease virus was not included in the above study. This was by design because there is currently no suitably accurate assay that can distinguish between singly infected chickens and chickens simultaneously infected with both wildtype virus and vaccine virus. We are therefore developing an assay, which employs digital PCR and new statistical models, with the goal of being able to reliably distinguish between singly infected and co-infected hosts. This method builds on a probe-based qPCR assay that was previously developed and used by us. Preliminary results are promising but reagent concentrations and cycling conditions still need to be further optimized.

Aim 3 of this grant uses dust samples collected as part of a previous study and other types of samples (peripheral blood lympocyte samples, and feather tip samples) collected in Aim 2 to look at the genetic diversity of Marek's disease virus and the Rispens vaccine and the potential for recombination. In prior years, we have developed a process to enrich our samples for

Marek's disease virus and the Rispens vaccine using oligo enrichment, which was necessary since virus and vaccine DNA make up approximately 0.001% of the DNA isolated from these samples. Since the last reporting period, we have shown that this method enriches Marek's disease virus DNA to become approximately 1% of the total DNA, which is suitable for sequencing on a MiSeq. We have now generated sequence data for 20 experimental samples, as well as for 4 stocks of virus (hereafter referred to as the "parental viruses") that were used to infect chickens in a previous experiment. In work that is being led by graduate student Alejandro Ortigas-Vasquez, we have generated whole genomes de novo using the sequence data for the parental virus, and we are in the process of generating whole genomes for the experimental samples. We are also in the process of sequencing the parental virus using PacBio long read sequencing to improve confidence in our assemblies and to close gaps in repeat regions. The methods developed here with the parental viruses are being optimized for use with the experimental samples. From these data, we have so far learned that the Rispens vaccine sequence on GenBank is highly divergent from the Rispens vaccine sequences that we generated, even though we used two different stocks of Rispens for our analysis. Our sequence for the wildtype virus Md5 on the other hand was nearly identical to the GenBank Md5 sequence. We are currently (b)(4); (b)(6)

(b)(4); (b)(6)

Aim 4 of this project synthesizes the data from Aims 1-3 to understand the consequences of vaccines on vaccine and virus evolution. In prior reports, I have discussed an ongoing project in (b)(4); (b)(6) This project is being written up for publication. In the past year, I have also published a paper on the evolution of an emerging infectious disease, with a particular focus on vaccine-driven evolution. This paper, published in PLOS Biology, develops a framework for understanding how to classify vaccine-adapted variants of a pathogen should they arise. The framework establishes that there are two relevant axes: 1) whether the variant is a generalist or a specialist on vaccinated hosts, and 2) whether the variant is inhibited or facilitated by vaccination. We show that the direction of selection changes over time such that initially most emerging vaccine-escape variants will be generalist pathogens that are better at infecting both vaccinated and nonvaccinated hosts, but that over time, most new variants will be specialist variants that grow better on vaccinated than nonvaccinated hosts. In the last year, we have also been developing a method to detect and quantify heterogeneity in susceptibility for a newly arising pathogen. Typical methods rely on data that can only be collected after an epidemic has run its course. Our method, currently being led by graduate student I (b)(4); (b)(6)

(b)(4); (b)(6)

Individual Development Plans (IDP) are a mandatory requirement for postdoctoral fellows at Penn State University. This involves a yearly meeting between the postdoc and myself to discuss long and short term goals, opportunities for career development, and to discuss any obstacles that have been encountered and potential solutions. In addition to this live meeting, there are online entries by the mentor and trainee to reflect on goals, obstacles, and approaches. I typically have an additional informal IDP meeting with members of my lab so that we meet every 6 months instead of 12, since I find that these meetings provide a low-stakes opportunity to give and get feedback about how things can be improved. In addition to these meetings, I meet individually with each member of my lab weekly to discuss the progress of the last week and the plan for the next week. I often let the trainee guide these meetings to ensure that they are able to discuss what they feel they most need to discuss.

I also believe that reading, presenting, attending seminars, and discussing scientific ideas are important components of academic training. To facilitate these activities, I hold weekly lab meetings where every week a different person presents their own work or a published paper relevant to their work. I encourage all members of my lab to attend at least one and preferably two research seminars per week. I hold once weekly "tea breaks" in which members of the lab meet to discuss anything that is on their mind, science related or otherwise. The feedback that I have received from trainees has taught me that these opportunities are valuable for creating lab cohesion, for soliciting scientific feedback between lab members, and for starting conversations about mental health. The postdoc on this project, Aniruddha Deka, benefitted from these activities. As of October 2022, he has moved on to a new postdoc position at Texas A&M where he works with Martial Ndeffo. I also advise graduate student Beth Tuschhoff, and while we do not have a formal IDP through Penn State, we nevertheless complete an informal IDP at the end of each semester to again discuss past progress, current obstacles, and future goals.

Dr. Szpara, who oversees the work of two staff scientists on this project (Christopher Bowen, Daniel Renner) and one graduate student (Alejandro Ortigas-Vasquez), holds two-hour meetings every other week with members of her lab, in addition to a weekly group meeting. She also holds an annual lab retreat that focuses on professional development.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Day T, Kennedy DA, Read AF, McAdams D. The economics of managing evolution. PLoS biology. 2021 November;19(11):e3001409. PubMed PMID: 34784349; PubMed Central PMCID: PMC8594813; DOI: 10.1371/journal.pbio.3001409.
Complete	Day T, Kennedy DA, Read AF, Gandon S. Pathogen evolution during vaccination campaigns. PLoS biology. 2022 September;20(9):e3001804. PubMed PMID: 36149891; PubMed Central PMCID: PMC9553060; DOI: 10.1371/journal.pbio.3001804.

Non-compliant Publications Previously Reported for this Project

Public Access Compliance	Citation
Non-Compliant	Day T, Kennedy DA, Read AF, Gandon S. The evolutionary epidemiology of pathogens during vaccination campaigns. arXiv. 2021 September 28. DOI: 10.48550/arXiv.2109.13680.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	Kennedy, David	BS,PHD	PD/PI	(b)(6)					NA
	N	SZPARA, MORIAH	PHD	Co-Investigator						NA
	N	Deka, Aniruddha		Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA
	N	Renner, Daniel		Technician						NA
	N	Tuschhoff, Beth	BS,PHD	Graduate Student (research assistant)						NA
	N	Bowen, Christopher		Technician						NA
(b)(6)	N	Ortigas-Vasquez, Alejandro		Graduate Student (research assistant)						NA

Glossary of acronyms:
S/K - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

Yes

File Uploaded: Kennedy_other-support-format-page-rev-10-2021_2023_03_13.pdf

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

PHS OTHER SUPPORT
For All Application Types – DO NOT SUBMIT UNLESS REQUESTED

There is no "form page" for reporting Other Support. Information on Other Support should be provided in the format shown below.

*Name of Individual: David Kennedy
Commons ID: (b)(6)

Other Support – Project/Proposal

*Title: *US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study (THIS AWARD)*

*Major Goals: The major goals of this project are: 1) To develop a general model of transmissible vaccination to identify key knowledge gaps, 2) to characterize vaccine transmission and its impact on wildtype virus transmission, 3) to characterize the genetic evolution of wildtype virus and vaccine virus, and 4) to model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine.

*Status of Support: Active

Project Number: R01 GM140459

Name of PD/PI: Kennedy, David

*Source of Support: National Institutes of Health

*Primary Place of Performance: On campus

Project/Proposal Start and End Date: (MM/YYYY) (if available): 8/1/2020-7/31/2025

* Total Award Amount (including Indirect Costs): $1,849,255

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2021	(b)(6)
2. 2022	
3. 2023	
4. 2024	
5. 2025	

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual:
Commons ID:

*Title: *The impact of viral genomic variation on neonatal disease outcomes*

*Major Goals: We proposed to use viral comparative genomics and a murine model of infection to test how viral genetic differences influence the severity of HSV-1 and HSV-2 infection in humans, in cultured cells, and in animal models.

*Status of Support: Active

Project Number: 1 R01 AI163217-01A1

Name of PD/PI: Szpara, Moriah

Role: Key Personnel

*Source of Support: National Institutes of Health

*Primary Place of Performance: On campus

Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/2022-01/2027

* Total Award Amount (including Indirect Costs): $3,249,473

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	(b)(6)
2. 2024	
3. 2025	
4. 2026	
5. 2027	

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual:
Commons ID:

*Title: *Using experimental evolution to probe herpesvirus adaptation to neurons, fibroblasts, & interferon signaling*

*Major Goals: The major goals of this project are: 1) To determine the genetic changes that occur in HSV-1 during experimental evolution in neurons and fibroblast cells, and 2) to determine the genetic adaptation of HSV-1 to altered interferon pressure.

*Status of Support: Active

Project Number: R21 AI159480

Name of PD/PI: Szpara, Moriah

*Source of Support: National Institutes of Health

*Primary Place of Performance: On campus

Project/Proposal Start and End Date: (MM/YYYY) (if available): 9/1/2021-8/31/2023

* Total Award Amount (including Indirect Costs): $433,277

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	(b)(6)
2. 2024	
3. [enter year 3]	
4. [enter year 4]	
5. [enter year 5]	

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual:
Commons ID:

*Title: *Using Caenorhabditis viruses to identify the role of spillover outcomes on disease emergence (NEW AWARD)*

*Major Goals: The major goals of this project are to: 1) Characterize virus dynamics following exposure of Caenorhabditis hosts to their non-native viruses, 2) Characterize the evolution of pathogens following exposure of Caenorhabditis hosts to their non-native viruses, and 3) Develop mathematical models connecting virus dynamics to host jump success.

*Status of Support: Active

Project Number: NSF NPM2J7MSCF61

Name of PD/PI: Kennedy, David

*Source of Support: National Science Foundation

*Primary Place of Performance: On campus

Project/Proposal Start and End Date: (MM/YYYY) (if available): 7/1/2022-6/30/2025

* Total Award Amount (including Indirect Costs): $714,745

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	(b)(6)
2. 2024	
3. 2025	
4. [enter year 4]	
5. [enter year 5]	

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual:
Commons ID:

*Title: *Virulence Evolution After Viral Host Jump and Emergence*

*Major Goals: The major goals of this project are: 1) To define virulence spectrum of IHNV before, during, and after host jump and emergence, 2) to quantify virus transmission potential before, during, and after host jump and emergence, 3) to elucidate genetic correlates of virulence and transmission phenotypes, and 4) to develop mathematical models to infer the factors responsible for the evolution of viral virulence and transmission after host jump and emergence.

*Status of Support: Active

Project Number: 721653-712683

Name of PD/PI: Wargo, Andrew

*Source of Support: The Virginia Institutes of Marine Science

*Primary Place of Performance: On campus

Project/Proposal Start and End Date: (MM/YYYY) (if available): 8/1/2018-7/31/2021 (No cost extension to 7/31/2023)

* Total Award Amount (including Indirect Costs): $117,175 (subaward)

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	(b)(6)
2. 2020	
3. 2021	
4. 2022	
5. 2023	

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual:
Commons ID:

IN-KIND

*Summary of In-Kind Contribution:

*Status of Support:

*Primary Place of Performance:

Project/Proposal Start and End Date (MM/YYYY) (if available):

*Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. [enter year 1]	
2. [enter year 2]	
3. [enter year 3]	
4. [enter year 4]	
5. [enter year 5]	

*Estimated Dollar Value of In-Kind Information:

***Overlap** (summarized for each individual):

There is no overlap between any of these proposals or with R01AI163217.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: David Kennedy _____

Date: ____Mar 13, 2023_____

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?
Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?
NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?
Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

This is a collaborative grant with the Pirbright Institute in the UK. During the reporting period, the postdoc that was hired by Pirbright developed health issues that prevented them from being able to conduct their research. After a long delay, the postdoc acknowledged that they would not be able to carry out the work and they left the project. A new postdoc was recently hired and is currently being trained. This person will conduct experiments that will provide data integral to all four aims in the study.

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subject

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

No

G.8 PROJECT/PERFORMANCE SITES

Organization Name	UEI	Congressional District	Address
Primary: The Pennsylvania State University	NPM2J7MSCF61	PA-012	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK 110 Technology Center Building University Park, PA 16802
The Pennsylvania State	NPM2J7MSCF61	PA-012	PENNSYLVANIA STATE

University			UNIVERSITY-UNIV PARK 110 Technology Center Building University Park, PA 16802

G.9 FOREIGN COMPONENT

Organization Name: The Pirbright Institute
Country: UNITED KINGDOM
Description of Foreign Component:
This proposal is a US-UK Collab, meaning that it is a collaboration between Penn State and The Pirbright Institute. The experimental work from Aim 2 is being conducted at the Pirbright Institute.

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes

Estimated unobligated balance: $489,066

G.10.b Provide an explanation for unobligated balance:
Due to the COVID pandemic and the accompanying difficulties with hiring and recruiting postdocs and graduate students, there was a large carryover leading into year's reporting period. is

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent
The pace of spending in this reporting period has picked up substantially from the prior reporting period approximately matching the inflow from the prior year. This spending will increase substantially in the upcoming year since one graduate student recently began working on this grant, one graduate student has just committed to my lab and he too will work on this, and there is a pending offer to one more graduate student who would also be working on this grant. In addition, sequencing costs are going to increase in this upcoming year now that methods and pipelines have been optimized for analysis.

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period? No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

Biology (Eberly College of Science) / The Pennsylvania State University
US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study
National Institutes of Health
Project Dates: 05/01/2023 - 04/30/2024

	05/01/2023 - 04/30/2024	Total
Direct Costs		
Salaries (Category I)		
Kennedy, David A (Principal Investigator)	23,367	23,367
@(b)(6) of time 12 months ((b)(6) effort CY)		
Szpara, Moriah Louise (Co-PI)	26,621	26,621
@(b)(6) of time / 12 mos (b)(6) effort CY)		
Technician - Chris Bowen (Technician)	13,770	13,770
@(b)(6) of time / 12 mos (b)(6) effort CY)		
Technician - Daniel Renner (Technician)	19,136	19,136
@(b)(6) of time / 12 mos (b)(6) effort CY)		
Research Scientist - TBD (Research Associate)	72,334	72,334
@ 100% of time 12 months		
Total Salaries	155,228	155,228
Graduate Assistants (Category II)		
Grad Asst - Beth Tuschhoff - (b)(6)	25,124	25,124
@(b)(6) of time 9 AY months (b)(6) months)		
Grad Asst - David Romero - (b)(6)	25,124	25,124
@ (b)(6) of time 9 AY months (b)(6) months)		
Grad Asst - Alejandro Ortigas-Vasquez - (b)(6)	25,124	25,124
@(b)(6) of time 9 AY months (b)(6) months)		
Total Graduate Assistants	75,372	75,372
Wages (Category III)		
3 - Grad Assts - Summer Wages	24,138	24,138
@ 50% of time 3 SU months (1.5 months)		
Total Wages	24,138	24,138
Post Doctoral (Category V)		
Post Doctoral Scholar - TBN (Post Doctoral)	58,368	58,368
@ 100% of time 12 months		
Total Post Doctoral	58,368	58,368
Total Salaries and Wages	313,106	313,106
Fringe		
Category I @ 36.00%	55,882	55,882
Category II @ 10.40%	7,839	7,839
Category III @ 8.00%	1,932	1,932
Category V @ 25.40%	14,825	14,825
Total Fringe	80,478	80,478
Total Salaries, Wages and Fringe	393,584	393,584

Biology (Eberly College of Science) / The Pennsylvania State University
US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study
National Institutes of Health
Project Dates: 05/01/2023 - 04/30/2024

	05/01/2023 - 04/30/2024	Total
Modified Total Direct Costs		
Travel - Domestic	4,900	4,900
Travel - International	5,640	5,640
Materials and Supplies	17,300	17,300
Publication costs	3,000	3,000
Purchased Services	28,428	28,428
PacBio Sequencing		
NSF ICS-ACI Services	7,200	7,200
Total Modified Total Direct Costs	460,052	460,052
Other Direct Costs		
Participant support - scholarships	700	700
2 youth participants/year		
Tuition Remission	63,450	63,450
Total Other Direct Costs	64,150	64,150
Total Direct Costs	524,202	524,202
F&A Costs (MTDC basis)		
F&A Rate: 60.50%	278,331	278,331
Total Requested From Sponsor	802,533	802,533
Total Project Costs	802,533	802,533
Carry Forward and Current		

Budget Justification – Pennsylvania State University

A. Senior Personnel Salaries and Wages
Salary support is requested for PI David Kennedy and Co-PI Szpara. Dr. Kennedy is requesting (b)(6) of support ((b)(6) time). Dr. Szpara is also requesting (b)(6) of support per year ((b)(6) time). Dr. Kennedy will coordinate and oversee the work conducted for this project, including supervision of a two graduate students (Tuschhoff and Romero) and a postdoctoral researcher (to be hired). Dr. Szpara will oversee the work in Aim 3, including supervision of a research technician (Bowen), a bioinformatician (Renner), and a graduate student (Ortigas-Vasquez). Both Dr. Kennedy and Dr. Szpara will contribute to conference calls, experimental design, progress reports, and the dissemination and publication of results.

B. Other Personnel Salaries and Wages: Salary support is requested for a (b)(6) time lab technician (Bowen), a (b)(6) time bioinformatician (Renner), three (b)(6) -time graduate student (Tuschhoff, Romero, Ortigas-Vasquez), a 100%-time staff scientist, and a 100%-time postdoctoral scholar. These positions are justified by the scope of the work. The lab technician (Bowen) will conduct DNA extractions, sample preparation, and other molecular biology methods required in Aim 3. The bioinformatician (Renner) will process the sequencing reads for *de novo* genome assembly and contig reconstruction. The postdoctoral scholar will construct and analyze general models of the consequences of transmissible vaccines (Aims 1 and 2)). One graduate student (Ortigas-Vasquez) will develop methods for processing high throughput short and long read data to better resolved MDV genomes and to detect recombination (Aims 2 and 3). Another graduate student will develop phylogenetic methods to reconstruct MDV and vaccine phylogenies for the purposes of identifying recombination and reversion to virulence (Aims 3 and 4). The other graduate student (Tuschhoff) will develop statistical methods that can be used to better fit epidemiological models to data (Aim 4). The staff scientist will fit models to data to explore the effects of vaccine transmissibility on MDV dynamics and evolution.

C. Fringe Benefits
Fringe benefits are computed using the fixed rates of 36.0% applicable to Category I Salaries, 10.4% applicable to Category II Graduate Assistants, 8.0% applicable to Category III Wages, 0.4% applicable to Category IV Student Wages, and 25.4% for Category V, Postdoctoral Scholars and Fellows, for fiscal year 2023 (July 1, 2022, through June 30, 2023). If this proposal is funded, the rates quoted above shall, at the time of funding, be subject to adjustment for any period subsequent to June 30, 2023, if superseding Government approved rates have been established. Fringe benefit rates are negotiated and approved by the Office of Naval Research, Penn State's cognizant federal agency.

D. Equipment: None

E. Travel
Funds are requested for Dr. Kennedy and two trainees to travel to the International Symposium on Marek's Disease and Avian Herpesviruses (domestic). Registration in a typical year is $550 ($350 for graduate students). We estimate a cost of $300 per day per person for food and lodging, and an average of $500 per flight.

Lastly, funds are requested for Dr. Kennedy and one trainee to travel to Pirbright for four days during one of the experimental studies. Per diem and lodging and meal costs are based on Department of Defense rates for "other" cities in the United Kingdom ($330 per person per day). Flights are estimated at $1500 per person.

F. Participant support: We request $700 to fund scholarships for two youths to attend Penn State's Science-U summer program.

G. Other direct costs

G.1. Materials and supplies
Funds are requested for library prep and MiSeq sequencing of dust samples ($12,300). For consumables that will be used in prepping and handling samples, we request an additional $5000 per year in years 1 through 4.

G.2. Publications
We are requesting $3000 in each of years 2 through 5 for publication costs.

G.3. Consulting Services: None

G.4. Computer Services: To attain the computational requirements of Aims 1, 3, and 4, we are requesting funds for a subscription to PSU's high-performance computing infrastructure, ICS-ACI. This subscription is $25 per core per month, where the recommended minimum subscription being 20 cores ($6000 per year). We are additionally requesting funds to subscribe to the minimum storage allotment ($1200 per year).

G.5. Purchased Services: Funds are requested to cover PacBio sequencing at the Penn State Genomics Core. These expenses include $2200 for indexing materials, $1900 for indexing labor, $4784 for sixteen SMRTbell Express Template Preps, and $19,744 for Sequel Sequencing of 16 SMRTcells.

G.6. Subawards: None

G.7. Other: Tuition
Computed using the approved tuition charges for a one-half (1/2) time graduate assistant of $10,190 (pre-comprehensive) and $3,320 (post-comprehensive) for fall and spring semesters 2022/2023, and $5,095 for summer session 2023. The charges quoted above are increased by three percent (4%) for any project period occurring after summer session 2023, and each summer session thereafter.

H. Total direct costs

I. Indirect costs (F&A) Using current awards fixed rate of 60.50%.

J. Definition of a Year
The University defines the term "year" as the fiscal year (July – June).

From: Gregor, Garth A
To: Patchan, Lori (NIH/NIGMS) [C]
Cc: Kennedy, David A; Adkins, Ronald (NIH/NIGMS) [E]; VPR - Office of Sponsored Programs
Subject: [EXTERNAL] FW: Grant Number: 5R01GM140459 - 04 PI Name: Kennedy, David
Date: Wednesday, May 3, 2023 4:26:17 PM
Attachments: budgetjustification_2023Update.pdf
Budget.pdf

Dear Ms. Patchan,

Please find the attached requested budget and budget justification. These documents cover almost the entire unobligated balance and next year of funding.

If there are no unexpected additional expenses, we might have a small unobligated balance going into the next project year. I am a NIH Signing Official.

Please contact me with any question or if you need any additional information. Thank you.

Sincerely,

--
Garth Gregor, MBA, CRA, MPA
Eberly College of Science
513 Thomas Building
University Park, PA 16802
(b)(6) (p)
gag14@psu.edu

From: Patchan, Lori (NIH/NIGMS) [C] <lori.patchan@nih.gov>
Date: Tuesday, April 11, 2023 at 4:33 PM
To: Kennedy, David A <dak30@psu.edu>, VPR - Office of Sponsored Programs <osp@psu.edu>
Cc: Adkins, Ronald (NIH/NIGMS) [E] <ronald.adkins@nih.gov>
Subject: Grant Number: 5R01GM140459 - 04 PI Name: Kennedy, David

> Some people who received this message don't often get email from lori.patchan@nih.gov. Learn why this is important

Dear John and Dr. Kennedy,
Good day, during our staff review we noted on your RPPR/Q.G.10 an Estimated Unobligated Balance indicating a large balance of $489,066. Both preceding years an UOB was reported on the RPPR (year-03 and year-02). We will need to know how you intend to spend down both the balance (approximately $489,066 total cost, as reported on the RPPR) as well as the committed FY23 funds ($369,851 total cost) in the upcoming year (Year-04: 05/01/2023-04/30/2024). Kindly provide a detailed spending plan to include a budget and justification outlying your plan. Also please include the current UOB as of today.

As noted on your NoA: for awards under SNAP (see Administrative Requirements—Monitoring—Reporting—Streamlined Non-Competing Award Process for applicability), funds are automatically carried over to the subsequent budget period. However, the recipient will be required to indicate, as part of the grant's progress report, whether any estimated unobligated balance (including prior-year carryover) is expected to be greater than 25 percent of the current year's total approved budget. The total approved budget amount includes current year and any carryover from prior years of the project period. If the unobligated balance is greater than 25 percent of the total approved budget, the recipient must provide an explanation and indicate plans for expenditure of those funds within the current budget year.

Please have your AOR respond with this information no later than **Tuesday, April 18, 2023.** I can be reached by phone or email if you have any questions.

Kind regards,

Lori L. Patchan, MS
Grants Management Specialist (C)
NIH\NIGMS
45 Center Drive
Bethesda, MD 20892-6200
Email: lori.patchan@nih.gov
Telephone: (301) 594-5136

From: Gregor, Garth A
To: Patchan, Lori (NIH/NIGMS) [C]
Cc: Snyder, Jessica Jo; Chester, Margaret Mc Math
Subject: [EXTERNAL] FW: SAM inquiry: 5R01GM140459-04 (ExpLog#271317)
Date: Wednesday, May 17, 2023 9:16:26 AM

Dear Ms. Patchan:

My apologies for the delayed response.

Please find the following formal response related to our faculty member, Dr. David Kennedy from two years ago from our Export Compliance Unit(I have confirmed with Ms. Chester that this is all still correct):

"From: CHESTER, MARGARET MC MATH <mmc9@psu.edu>
Sent: Wednesday, January 13, 2021 9:50 AM
To: Wilson, Khadijah (NIH/NIAID) [C <khadijah.wilson@nih.gov>
Cc: CHESTER, MARGARET MC MATH <mmc9@psu.edu>; Gregor, Garth A <gag14@psu.edu>; VPR - Office of Sponsored Programs <osp@psu.edu>
Subject: RE: SAM inquiry: 5R01AI132692-04 (PSU Export Log #241003)

Ms. Wilson,

Your inquiry concerning the status of Dr. David Kennedy, a Penn State faculty member, who was listed as a participant in grant application 5-R01-AI132692-04 entitled "Forward genetic prediction and testing of virulence loci in herpes simplex virus 1)" which was submitted to the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), was forwarded to my attention for review and follow up. As the Interim University Export Compliance Officer for The Pennsylvania State University, I hereby certify that I have determined that this specific individual listed in our grant application submission is not the restricted individual(s) who appear in any of the GSA Excluded Parties List System listings in SAM or in other related government restricted party databases. (I note further that the individual listed in SAM is apparently not included in OIG List of Excluded Individuals/Entities.) I have reached this determination on the basis of verifiable information concerning this individual which is not a match for any of the individuals listed in the GSA Excluded Parties listings. Such distinguishing information includes information related to full name, academic background, location history, and other relevant personal and professional histories.

Based on the results of our review, I confirm that the individuals referenced in our for grant application 5-R01-AI132692-03 1, inclusive of Dr. David Kennedy, are not presently debarred, suspended or otherwise excluded from participating in Federally funded grant projects.

Should you have any remaining questions on this matter, please do not hesitate to contact our office.

Sincerely,

Margaret”

Please contact me with any questions or if you need any additional information. I am a NIH Signing Official. Thank you.

Sincerely,

--
Garth Gregor, MBA, CRA, MPA
Eberly College of Science
513 Thomas Building
University Park, PA 16802
(b)(6) (p)
gag14@psu.edu

From: Patchan, Lori (NIH/NIGMS) [C] <lori.patchan@nih.gov>
Sent: Tuesday, April 11, 2023 4:37 PM
To: VPR - Office of Sponsored Programs <osp@psu.edu>
Subject: SAM inquiry: 5R01GM140459-04

Dear John,

Good day, for the same RPPR/Dr. Kennedy, this recent grant application (5R01GM140459-04/US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study) submitted to the National Institutes of Health (NIH), National Institute of General Medical Sciences (NIGMS) includes the name of an individual, **David Kennedy**, who will be participating or has participated on the grant. An individual with this same name appears on the General Services Administration (GSA) System for Awards Management (SAM).

The SAM website provides a single comprehensive list of individuals and firms excluded by Federal government agencies from receiving Federal contracts or Federally approved subcontracts and from certain types of Federal financial and nonfinancial assistance and benefits.

Based on available information, we are not able to verify whether the individual named above is the same individual currently listed on the SAM. Therefore, rather than requesting private information, we ask that you review the SAM website and confirm to me by email whether this individual is presently debarred, suspended or otherwise excluded from participating in Federally funded grant projects. A response by **Tuesday, April 18, 2023** is appreciated. Until this information is received, we will be unable to complete our review.

As a reminder, we are providing you the following information on this regulation:

HHS regulations published in 2 CFR part 376 implement the government-wide debarment and

suspension system guidance (2 CFR part 180) for HHS' non-procurement programs and activities. "Non-procurement transactions" include, among other things, grants, cooperative agreements, scholarships, fellowships, and loans. NIH implements the HHS Debarment and Suspension regulations as a term and condition of award. Accordingly, recipients of NIH grants ("primary covered transactions"), including sponsoring institutions for Kirschstein-NRSA individual fellowships, are required to determine whether it or any of its principals (as defined in 2 CFR part 180.995 and 2 CFR part 376.995) is excluded or disqualified from participating in a covered transaction (i.e., grant or cooperative agreement) prior to entering into the covered transaction, i.e., prior to the drawdown of funds which signals acceptance of the grant award.

Prior to the drawdown of funds for each grant award, grantees must report to the funding IC if the grantee or any of its principals:

- Are presently excluded or disqualified;
- Have been convicted within the preceding three years of any of the offenses listed in 2 CFR part 180.800(a) or had a civil judgment for one of those offenses within that time period;
- Are presently indicted for or otherwise criminally or civilly charged by a governmental entity (Federal, State, or local) with commission of any of the offenses listed in 2 CFR part 180.800(a); or
- Have had one or more public transactions (Federal, State, or local) terminated within the preceding three years for cause or default.

Please see the NIH Grants Policy Statement, 4.1.6, Debarment and Suspension, for further information and notification requirements.

Thank you,

Lori L. Patchan, MS
Grants Management Specialist (C)
NIH\NIGMS
45 Center Drive
Bethesda, MD 20892-6200
Email: lori.patchan@nih.gov
Telephone: (301) 594-5136

From: Adkins, Ronald (NIH/NIGMS) [E]
To: Bourque, Jenny (NIH/NIGMS) [C]
Subject: RE: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David
Date: Wednesday, April 13, 2022 8:43:03 AM

Jenny,

Yes, this does look reasonable to me. I wonder if it really will be possible to get that number of graduate students and postdoctoral fellows working on the project, particularly when several are TBN, but the plan is nevertheless reasonable. Thank you for requesting it.

Ron

From: Bourque, Jenny (NIH/NIGMS) [C] <jenny.bourque@nih.gov>
Sent: Tuesday, April 12, 2022 3:41 PM
To: Adkins, Ronald (NIH/NIGMS) [E] <ronald.adkins@nih.gov>
Subject: FW: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David

Hi Ron,

The grantee has provided the attached spending plan for 5R01GM140459 – 03 (Kennedy). I have reviewed it and think it looks reasonable. Once you've had an opportunity to take a look, can you let me know if you agree?

Thanks!

Jenny Bourque
Grants Management Specialist (C)
NIH/National Institute of General Medical Sciences
Building 45
Bethesda, MD 20892
jenny.bourque@nih.gov

From: Gregor, Garth A <gag14@psu.edu>
Sent: Tuesday, April 12, 2022 3:25 PM
To: Bourque, Jenny (NIH/NIGMS) [C] <jenny.bourque@nih.gov>
Cc: Sergeant, Lisa <lus22@psu.edu>; Gensimore, Melissa T <msr9@psu.edu>; Kennedy, David A <dak30@psu.edu>
Subject: [EXTERNAL] RE: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David

Dear Ms. Bourque,

Please find the attached requested detailed budget for the next project year of funding. The anticipated carry forward will be significantly reduced as of 4/30/23 although not all of the $804,210 will be spent. We plan to have the budget balanced during the project year ending 4/30/24. Please let me know if you need anything additional to consider this request. I am a NIH signing official. Thanks and have a great evening,

--
Garth Gregor, MBA, CRA, MPA
Eberly College of Science
513 Thomas Building
University Park, PA 16802
(b)(6) (p)
gag14@psu.edu

From: Gregor, Garth A
Sent: Friday, April 8, 2022 8:14 AM
To: Bourque, Jenny (NIH/NIGMS) [C] <jenny.bourque@nih.gov>
Cc: Sergeant, Lisa <lus22@psu.edu>; Gensimore, Melissa T <msr9@psu.edu>; Kennedy, David A <dak30@psu.edu>
Subject: RE: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David

Dear Ms. Bourque,

I apologize for the delay, we will get this information to you shortly. Thanks and have a great day,

--
Garth Gregor, MBA, CRA, MPA
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513 Thomas Building
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(b)(6) (p)
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From: Bourque, Jenny (NIH/NIGMS) [C] <jenny.bourque@nih.gov>
Sent: Friday, April 8, 2022 7:58 AM
To: Gregor, Garth A <gag14@psu.edu>
Cc: Sergeant, Lisa <lus22@psu.edu>; Gensimore, Melissa T <msr9@psu.edu>; Kennedy, David A <dak30@psu.edu>
Subject: RE: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David

Good morning, Mr. Gregor,

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- We note that a large unobligated balance of 117% of total costs is reported in Q.G.10. The justification cited for the balance (delays and reduced expenses due to the pandemic) is reasonable. However, because the balance is so large and has increased from the 79% balance reported in year -02, additional information is needed before we can proceed with the issuance of the Notice of Award. To this end, please provide a detailed budget that demonstrates your institution's plans to expend the current balance, *plus the amount to be awarded in year -03*.

Thank you in advance for your time and attention. Please note all information must be submitted through an official authorized to sign for the applicant organization. If you have any questions about the content of this request, please contact me at the information below.

Best,

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Building 45
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Sent: Friday, March 25, 2022 8:17 AM
To: Gregor, Garth A <gag14@psu.edu>
Cc: Sergeant, Lisa <lus22@psu.edu>; Gensimore, Melissa T <msr9@psu.edu>; Kennedy, David A <dak30@psu.edu>
Subject: RE: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David

Good morning, Mr. Gregor,

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jenny.bourque@nih.gov

From: Gregor, Garth A <gag14@psu.edu>
Sent: Thursday, March 24, 2022 1:52 PM
To: Bourque, Jenny (NIH/NIGMS) [C] <jenny.bourque@nih.gov>
Cc: Sergeant, Lisa <lus22@psu.edu>; Gensimore, Melissa T <msr9@psu.edu>; Kennedy, David A <dak30@psu.edu>
Subject: [EXTERNAL] FW: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David

Dear Ms. Bourque,

Thanks for your email. I wanted to make sure that I am reading this correctly, you would like to see a detailed budget for the available funds of ~$434,359 and the anticipated Year -03 amount of $369,851 for a total of $804,210? The period of performance would be 5/1/22-4/30/23. Is that correct? Thanks again and have a great day,

--
Garth Gregor, MBA, CRA, MPA
Eberly College of Science
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Sent: Tuesday, March 22, 2022 12:47 PM
To: VPR - Office of Sponsored Programs <osp@psu.edu>
Cc: (b)(6) Adkins, Ronald (NIH/NIGMS) [E] <ronald.adkins@nih.gov>
Subject: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David

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awarded in year -03.

Thank you in advance for your time and attention. Please note all information must be submitted through an official authorized to sign for the applicant organization. If you have any questions about the content of this request, please contact me at the information below.

Regards,

Jenny Bourque
Grants Management Specialist (C)
NIH/National Institute of General Medical Sciences
Building 45
Bethesda, MD 20892
jenny.bourque@nih.gov

From: Adkins, Ronald (NIH/NIGMS) [E]
To: Bourque, Jenny (NIH/NIGMS) [C]
Subject: FW: Re:5R01GM140459-03 - Necessary to request spending plan?
Date: Tuesday, March 22, 2022 11:20:38 AM

Jenny,

You just emailed me about this award and its large UOB. Scientific progress is fine, but I agree that a spending plan would be totally appropriate. I apologize if I should have known to email you, but Michael is listed in the PO checklist as the assigned GMS.

Please let me know if you need any more information.

Ron

From: Adkins, Ronald (NIH/NIGMS) [E]
Sent: Tuesday, March 15, 2022 3:30 PM
To: macem@mail.nih.gov
Cc: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: Re:5R01GM140459-03 - Necessary to request spending plan?

Michael,

This RPPR reports a UOB of $434,564. This is up from $292,546 in the previous year. Do you think we need to request a spending plan? The explanation for the UOB is reasonable, but it has grown quite a bit in just two years.

Ron

Ronald Adkins
Health Science Administrator/Program Officer
NIGMS/NIH

From: Gregor, Garth A
To: Bourque, Jenny (NIH/NIGMS) [C]
Cc: Sergeant, Lisa; Gensimore, Melissa T; Kennedy, David A
Subject: [EXTERNAL] RE: Request for Additional Information for 5R01GM140459 - 03 PI Name: Kennedy, David
Date: Tuesday, April 12, 2022 3:25:50 PM
Attachments: NIH Kennedy Carry Forward Budget.pdf

Dear Ms. Bourque,

Please find the attached requested detailed budget for the next project year of funding. The anticipated carry forward will be significantly reduced as of 4/30/23 although not all of the $804,210 will be spent. We plan to have the budget balanced during the project year ending 4/30/24. Please let me know if you need anything additional to consider this request. I am a NIH signing official. Thanks and have a great evening,

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jenny.bourque@nih.gov

Biology (Eberly College of Science) / The Pennsylvania State University
US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study
National Institute of General Medical Sciences
Project Dates: 05/01/2022 - 04/30/2023

	05/01/2022 - 04/30/2023	Total
Direct Costs		
Salaries (Category I)		
Kennedy, David A (Principal Investigator)	22,612	22,612
@ (b)(6) of time / 12 mos (b)(6) effort CY)		
Szpara, Moriah Louise (Co-PI)	25,767	25,767
@ (b)(6) of time / 12 mos (b)(6) effort CY)		
Bowen, Christopher D (Technician)	16,176	16,176
@ (b)(6) of time / 12 mos (b)(6) effort CY)		
Renner, Daniel Wayne (Technician)	18,518	18,518
@ (b)(6) of time / 12 mos (b)(6) effort CY)		
Total Salaries	83,073	83,073
Graduate Assistants (Category II)		
Graduate Assistant - Beth Tuschhoff - (b)(6)	24,155	24,155
@ (b)(6) of time / 9 mos (b)(6) effort AY) pre-comp		
Graduate Assistant - Alejandro Ortigas-Vasquez	24,155	24,155
@ (b)(6) of time / 9 mos (b)(6) effort AY) pre-comp (b)(6)		
Total Graduate Assistants	48,310	48,310
Wages (Category III)		
Graduate Assistant - Beth Tuschhoff - (b)(6)	7,812	7,812
@ (b)(6) of time / 3 mos (b)(6) effort SU)		
Graduate Assistant - Alejandro Ortigas-Vasquez	7,812	7,812
@ (b)(6) of time / 3 mos (b)(6) effort SU) (b)(6)		
Total Wages	15,624	15,624
Post Doctoral (Category V)		
Post Doctoral Scholar - Aniruddha Deka (Post Doctoral)	18,350	18,350
@ (b)(6) of time / 12 mos (b)(6) effort CY)		
Post Doctoral Scholar - TBN (Post Doctoral)	36,754	36,754
@ (b)(6) of time / 12 mos (b)(6) effort CY)		
Post Doctoral Scholar - TBN (Post Doctoral)	36,754	36,754
@ (b)(6) of time / 12 mos (b)(6) effort CY)		
Total Post Doctoral	91,858	91,858
Total Salaries and Wages	238,865	238,865
Fringe		
Category I @ 35.31%	29,332	29,332
Category II @ 11.26%	5,440	5,440
Category III @ 7.98%	1,246	1,246
Category V @ 24.78%	22,764	22,764

Proposal: 81268
Generated by gag14 on: 04/12/2022
Created on 04/11/2022 and last updated on 04/12/2022

Biology (Eberly College of Science) / The Pennsylvania State University
US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study
National Institute of General Medical Sciences
Project Dates: 05/01/2022 - 04/30/2023

	05/01/2022 - 04/30/2023	Total
Total Fringe	58,782	58,782
Total Salaries, Wages and Fringe	297,647	297,647
Modified Total Direct Costs		
Travel - Domestic (CONUS)	2,600	2,600
Materials and Supplies	5,000	5,000
Publication costs	3,000	3,000
Purchased Services	31,040	31,040
PacBio Sequencing and MiSeq Sequencing		
Total Modified Total Direct Costs	339,287	339,287
Other Direct Costs		
Tuition Remission	39,528	39,528
Total Other Direct Costs	39,528	39,528
Total Direct Costs	378,815	378,815
F&A Costs (MTDC basis)		
F&A Rate: 58.19%	197,437	197,437
Total Requested From Sponsor	576,252	576,252
Total Project Costs	576,252	576,252

Proposal: 81268
Generated by gag14 on: 04/12/2022
Created on 04/11/2022 and last updated on 04/12/2022

From: Mace, Michael (NIH/NIGMS) [E]
To: Janes, Daniel (NIH/NIGMS) [E]
Subject: 5 R01 GM 140459-02 (David KENNEDY) -- RE: 5R01GM140459-02
Date: Tuesday, March 30, 2021 8:57:14 AM

Hello Dan,

Grant 5 R01 GM 140459-02 (David KENNEDY) is in my portfolio.

Thank you for providing the current unobligated balance.

Sincerely,
Michael Mace

Michael Mace | Grants Management Specialist
Telephone: 301-402-6431 | E-mail: macem@mail.nih.gov

From: Janes, Daniel (NIH/NIGMS) [E] <daniel.janes@nih.gov>
Sent: Monday, March 29, 2021 6:03 PM
To: Mace, Michael (NIH/NIGMS) [E] <macem@nigms.nih.gov>
Subject: FW: 5R01GM140459-02

Hi Michael,

Are you still the GM on David Kennedy's R01?

Please see below.

-Dan

From: Gregor, Garth A <gag14@psu.edu>
Sent: Monday, March 29, 2021 5:53 PM
To: Janes, Daniel (NIH/NIGMS) [E] <daniel.janes@nih.gov>
Cc: Kennedy, David A <dak30@psu.edu>
Subject: FW: 5R01GM140459-02

Hi Daniel,

Thanks for the email, I think something was overwritten when we entered in the justifications for our carryforward. I apologize for the confusion. Our best estimate for the carryforward amount as of 4/30/21 is $292,546 as explained in the RPPR. I am a NIH Signing Official. Please contact me with any questions or if you need any additional information. Thanks,

--

Garth Gregor, MBA, CRA, MPA
Eberly College of Science
513 Thomas Building
University Park, PA 16802
(b)(6) (p)
gag14@psu.edu

---------- Forwarded message ---------
From: **Janes, Daniel (NIH/NIGMS) [E]** <daniel.janes@nih.gov>
Date: Mon, Mar 29, 2021 at 2:10 PM
Subject: Re: 5R01GM140459-02
To: dak30@psu.edu <dak30@psu.edu>
Cc: osp@psu.edu <osp@psu.edu>, NIGMS GM eRA Notifications (NIH/NIGMS) <gmeranotifications@od.nih.gov>, Mace, Michael (NIH/NIGMS) [E] <macem@nigms.nih.gov>

Hi David,

In your recent R01 progress report, the unobligated balance is estimated as $80. I am assuming that this means $80,000 but we should confirm that is what was meant. Please have your business official revise the estimated unobligated balance and email it to me.

Thank you.

-Dan Janes

Altieri, Robert (NIH/NIGMS) [E]

From: Altieri, Robert (NIH/NIGMS) [E]
Sent: Thursday, July 23, 2020 2:51 PM
To: NIGMS Paylist Change
Cc: Janes, Daniel (NIH/NIGMS) [E]
Subject: RE: PAYLIST CHANGE: 1 R01 GM140459-01 (PI: David Kennedy) | Paylist: GMCDB-20-054-R01-EEID | G242DJ

Importance: High

Dear NIGMS Budget:

FYI…after the award was made, it was discovered that this PI does qualify as a New/Early Stage Investigator and was thus entitled to receive 5 years of funding as he requested in the application. Therefore, the award is being revised to add a 5th year of funding at the same total cost level as the other years. See below for additional details.

If you have any questions, let us know. Thanks!

-Rob

Robert Altieri
Grants Management Specialist
HHS/NIH/NIGMS
(301) 827-4926
Robert.Altieri@nih.gov

From: Janes, Daniel (NIH/NIGMS) [E] <daniel.janes@nih.gov>
Sent: Thursday, July 23, 2020 1:47 PM
To: Altieri, Robert (NIH/NIGMS) [E] <robert.altieri@nih.gov>
Subject: RE: 1 R01 GM140459-01

Thank you, Rob.

-Dan

From: Altieri, Robert (NIH/NIGMS) [E] <robert.altieri@nih.gov>
Sent: Thursday, July 23, 2020 1:38 PM
To: Janes, Daniel (NIH/NIGMS) [E] <daniel.janes@nih.gov>
Subject: RE: 1 R01 GM140459-01

Hi Dan,

Yeah, we should be able to revise the award to add a 5th year. -Rob

Robert Altieri
Grants Management Specialist

HHS/NIH/NIGMS
(301) 827-4926
Robert.Altieri@nih.gov

From: Janes, Daniel (NIH/NIGMS) [E] <daniel.janes@nih.gov>
Sent: Thursday, July 23, 2020 10:10 AM
To: Altieri, Robert (NIH/NIGMS) [E] <robert.altieri@nih.gov>
Subject: 1R01GM140459-01

Hi Rob,

David Kennedy called me this morning about his newly funded EEID award. Unfortunately, it somehow fell through the cracks during review that he is an early stage investigator. Is there any way we can restore the fifth year that should have been awarded to him?

Thanks,
Dan

NIGMS Pilot Payment Authorization

In accordance with NIH Grants Administration Manual 4204-204C, Notification of Funding, costs provided in the grant application, as described here, can vary from those awarded based on the outcome of negotiations of the final budget with the applicant institution. The official documentation of funding is the Notice of Award.

Authorization Date: 06/15/2020

Grant Number: 1R01GM140459-01 **Pay Plan Name:** GMCDB-20-054 R01 EEID

Project Title: US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study

Institution: PENNSYLVANIA STATE UNIVERSITY-UNIV PARK

PI: Kennedy, David

FOA: PAR20-001 **PCC:** G242DJ **Council Date:** 202005 **FY:** 2020

Project Period: 08/01/2020-07/31/2025 **Budget Period:** 08/01/2020-07/31/2021

Percentile: **Priority Score:** (b)(6) **Requested Years:** 5 **Authorized Years:** 4

Budget Authorization Information:

Year	FY	CAN	Task	Requested Direct Cost	Program Recommended Direct Cost	IC Admin Cut %	Authorized Direct Cost	Authorized F&A Cost	Authorized Total Cost
1	2020	8019957	2020.100	$284,961	$242,809	0.0	$242,809	$0	$242,809
2	2021	8019957		$329,760	$242,809	0.0	$242,809	$0	$242,809

** NO F&A COSTS IS AN ERROR

Year	FY	CAN	Task	Requested Direct Cost	Program Recommended Direct Cost	IC Admin Cut %	Authorized Direct Cost	Authorized F&A Cost	Authorized Total Cost
3	2022	8019957		$322,920	$242,809	0.0	$242,809	$0	$242,809
4	2023	8019957		$323,709	$242,809	0.0	$242,809	$0	$242,809

Review and Approval Information:

Approval	Approved By	Date	Comments
Division Director	ZUK, DORIT	Jun 8, 2020	
Budget Office	Tetter, Lisa	Jun 8, 2020	
Deputy Director	Greenberg, Judith H.	Jun 9, 2020	
DEA Director	Brown, Erica L.	Jun 9, 2020	
GMO	Olascoaga, Grace	Jun 15, 2020	

Additional Comments:
The US and UK parts of the project can each stand alone; although they do strengthen each other. The UK activities are in a separate application that was reviewed at NSF but not transferred to NIH. All NIGMS funds will be expended by US PI.

Grant Number	1R01GM140459-01	**Priority**	(b)(6)	**Budget Start**	08/01/2020		
Grantee Organization	PENNSYLVANIA STATE UNIVERSITY-U	**Percentile**		**Project Start**	08/01/2020		
Principal Investigator	David Kennedy	**PCC**	G242DJ	**Budget End**	07/31/2021		
Program Official	DANIEL JANES	**Council**	202005	**Project End**	07/31/2025		
Grants Management Speci	Robert Altieri	**FY**	2020				
Yrs Requested	5			**Yrs Authorized**	4		

SUMMARY	**CAN**	**PHS Org**	**Direct**	**Indirect (F&A)**	**Fee**	**Unoblig. Bal**	**Total/Award Amt**
Year 01			$ 242,809	$ 127,042	$ -	$ -	$ 369,851
Year 02			$ 242,809	$ 127,042	$ -		$ 369,851
Year 03			$ 242,809	$ 127,042	$ -		$ 369,851
Year 04			$ 242,809	$ 127,042	$ -		$ 369,851
			$ -	$ -	$ -		$ -
			$ -	$ -	$ -		$ -
			$ -	$ -	$ -		$ -
			$ -	$ -	$ -		$ -
			$ -	$ -	$ -		$ -
			$ -	$ -	$ -		$ -

BREAKDOWN	**CAN**	**PHS Org**	**Direct**	**Indirect (F&A)**	**Fee**	**Unoblig Bal**	**Total/Award Amt**
Year 01	8019957	GM	242,809	127,042	-	-	369,851
Year 01 Subtotal			$ 242,809	$ 127,042	$ -	$ -	$ 369,851
Year 02	8019957	GM	242,809	127,042	-		369,851
Year 02 Subtotal			$ 242,809	$ 127,042	$ -		$ 369,851
Year 03	8019957	GM	242,809	127,042	-		369,851
Year 03 Subtotal			$ 242,809	$ 127,042	$ -		$ 369,851
Year 04	8019957	GM	242,809	127,042	-		369,851
Year 04 Subtotal			$ 242,809	$ 127,042	$ -		$ 369,851

Grant Number	1R01GM140459-01	**Priority**	(b)(6)	**Budget Start**	08/01/20	
Grantee Organization	PENNSYLVANIA STATE UNIVER	**Percentile**		**Budget End**	07/31/21	
Principal Investigator	David Kennedy	**PCC**	G242DJ	**Project Start**	08/01/20	
Program Official	DANIEL JANES	**Council**	202005	**Project End**	07/31/25	
Grants Management Specialist	Robert Altieri	**FY**	2020	**EIN**		**Default Collapse to 1 F&A base**
Years Requested	5	**Years Recommended**	5	**Years Authorized**	4	**No**

Item/Category	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04		Grand Total
Salary & Wages	141,523	141,523	141,523	141,523		566,092
Fringe Benefits	37,099	37,099	37,099	37,099		148,396
Total Salary, Wages, & Fringe Benefits	178,622	178,622	178,622	178,622		714,488
Consultant Services						
Equipment						
Materials and Supplies	17,834	17,834	17,834	17,834		71,336
Travel	6,800	6,800	6,800	6,800		27,200
Patient Care						
Alterations and Renovations						
Other	6,731	6,731	6,731	6,731		26,924
Subaward/Consortium/Contractual Costs						
Publication Costs						
ADP/Computer Services						
Equipment or Facility Rental/User Fees						
SBIR/STTR Technical						
Tuition Remission	32,822	32,822	32,822	32,822		131,288
Participant Subsistence						
Participant Stipend						
Participant Travel						
Participant Tuition/Fee/Health Insurance						
Participant Other						
Total Direct Costs by Budget Period	242,809	242,809	242,809	242,809		971,236
Include for Consortia F&A Rollup	Yes	Yes	Yes	Yes	Yes	
Rate 1	60.50%	60.50%	60.50%	60.50%		
Base 1	209,987	209,987	209,987	209,987		
Subtotal Indirect (F&A)	127,042	127,042	127,042	127,042		508,168
Include for Consortia F&A Rollup	Yes	Yes	Yes	Yes	Yes	
Include Consortia Project						
Total Indirect (F&A) by Budget Period	127,042	127,042	127,042	127,042		508,168
Total Direct & Indirect (F&A) by Budget Period	369,851	369,851	369,851	369,851		1,479,404
Fee by Budget Period						
Total DC, F&A, & Fee by Budget Period	369,851	369,851	369,851	369,851		1,479,404
Offset (Unobligated Balance) Authorized						
Total DC, F&A, & Fee by Budget Period	369,851	369,851	369,851	369,851		1,479,404

** GRAD STUDENT COMPENSATION O.K.

** NOTE: PROGRAM RECOMMENDED FLAT-LINED BUDGET SO 1ST YEAR WAS REDUCED AND COPIED TO OUTYEARS.

Grant Number	1R01GM140459-01	**Priority**	(b)(6)	**Budget Start**	08/01/20
Grantee Organization	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	**Percentile**		**Project Start**	08/01/20
Principal Investigator	David Kennedy	**PCC**	G242DJ	**Budget End**	07/31/21
Program Official	DANIEL JANES	**Council**	202005	**Project End**	07/31/25
Grants Management Specialist	Robert Altieri	**FY**	2020	**EIN**	1246000376A1
Yrs Requested	5	**Yrs Recommend**	5	**Yrs Authorized**	4
Component Organization	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	**Component Name**	Project-001		

Number of Sub Awards

Component type (Project, Sub Award, Consortia Project): Project

Requested (424) Personnel

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04					Project				
Name/Project Role	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**
David Kennedy (PD/PI)		(b)(6)	11,065	4,187	15,252		(b)(6)	11,065	4,187	15,252		(b)(6)	11,065	4,187	15,252		(b)(6)	11,065	4,187	15,252		(b)(6)	11,065	4,187	15,252
Morjah Szpara (Co-Investigator)			25,375	9,604	34,979			25,375	9,604	34,979			25,375	9,604	34,979			25,375	9,604	34,979			25,375	9,604	34,979
Postdoc Assoc	1		51,361	12,081	63,442	1		51,361	12,081	63,442	1		51,361	12,081	63,442	1		51,361	12,081	63,442	1		51,361	12,081	63,442
Graduate Students	2		48,154	6,260	54,414	2		48,154	6,260	54,414	2		48,154	6,260	54,414	2		48,154	6,260	54,414	2		48,154	6,260	54,414
Undergrad Students																									
Secretarial/Clerical																									
Technician	1		11,907	4,507	16,414	1		11,907	4,507	16,414	1		11,907	4,507	16,414	1		11,907	4,507	16,414	1		11,907	4,507	16,414
Technician	1		18,230	6,900	25,130	1		18,230	6,900	25,130	1		18,230	6,900	25,130	1		18,230	6,900	25,130	1		18,230	6,900	25,130
Additional / Combined Personnel																									
Total Requested Personnel	**5**		**166,092**	**43,539**	**209,631**	**5**		**166,092**	**43,539**	**209,631**	**5**		**166,092**	**43,539**	**209,631**	**5**		**166,092**	**43,539**	**209,631**	**5**		**166,092**	**43,539**	**209,631**
Morjah Szpara (Co-Investigator)	37.85%																								
Technician	37.85%																								
Technician	37.85%																								

Allowable & IRG Recommended Personnel

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
Reduction Amount																									
Reduction Percentage																									
Name/Project Role	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**
David Kennedy (PD/PI)		(b)(6)	11,065	4,187	15,252		(b)(6)	11,065	4,187	15,252		(b)(6)	11,065	4,187	15,252		(b)(6)	11,065	4,187	15,252		(b)(6)			
Morjah Szpara (Co-Investigator)			25,375	9,604	34,979			25,375	9,604	34,979			25,375	9,604	34,979			25,375	9,604	34,979					
Postdoc Assoc	1		51,361	12,081	63,442	1		51,361	12,081	63,442	1		51,361	12,081	63,442	1		51,361	12,081	63,442	1				
Graduate Students	2		48,154	6,260	54,414	2		48,154	6,260	54,414	2		48,154	6,260	54,414	2		48,154	6,260	54,414	2				
Undergrad Students																									
Secretarial/Clerical																									
Technician	1		11,907	4,507	16,414	1		11,907	4,507	16,414	1		11,907	4,507	16,414	1		11,907	4,507	16,414	1				
Technician	1		18,230	6,900	25,130	1		18,230	6,900	25,130	1		18,230	6,900	25,130	1		18,230	6,900	25,130	1				
Additional / Combined Personnel																									
Total Allowable & IRG Recommended Personnel	**5**		**166,092**	**43,539**	**209,631**	**5**		**166,092**	**43,539**	**209,631**	**5**		**166,092**	**43,539**	**209,631**	**5**		**166,092**	**43,539**	**209,631**	**5**				

IC Funding/Awarded Personnel

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
Reduction Amount																									
Reduction Percentage					**14.79%**					**14.79%**					**14.79%**					**14.79%**					**14.79%**
Reduction Post T2 Target																									
Name/Project Role	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**
David Kennedy (PD/PI)		(b)(6)	9,428	3,568	12,996		(b)(6)	9,428	3,568	12,996		(b)(6)	9,428	3,568	12,996		(b)(6)	9,428	3,568	12,996		(b)(6)			
Morjah Szpara (Co-Investigator)			21,621	8,183	29,805			21,621	8,183	29,805			21,621	8,183	29,805			21,621	8,183	29,805					
Postdoc Assoc	1		43,764	10,294	54,058	1		43,764	10,294	54,058	1		43,764	10,294	54,058	1		43,764	10,294	54,058	1				
Graduate Students	2		41,031	5,334	46,365	2		41,031	5,334	46,365	2		41,031	5,334	46,365	2		41,031	5,334	46,365	2				
Undergrad Students																									
Secretarial/Clerical																									
Technician	1		10,146	3,840	13,986	1		10,146	3,840	13,986	1		10,146	3,840	13,986	1		10,146	3,840	13,986	1				
Technician	1		15,533	5,879	21,413	1		15,533	5,879	21,413	1		15,533	5,879	21,413	1		15,533	5,879	21,413	1				
Additional / Combined Personnel																									
Total IC Funding/Awarded Personnel	**5**		**141,523**	**37,099**	**178,622**	**5**		**141,523**	**37,099**	**178,622**	**5**		**141,523**	**37,099**	**178,622**	**5**		**141,523**	**37,099**	**178,622**	**5**				

Requested (424) Other Costs

	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	Project
Salaries	166,092	166,092	166,092	166,092	166,092

Fringe	43,539	43,539	43,539	43,539	43,539
Total Personnel	209,631	209,631	209,631	209,631	209,631
Equipment					
Travel	7,980	7,980	7,980	7,980	7,980
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					
Materials & Supplies	20,930	20,930	20,930	20,930	20,930
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual					
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1	7,900	7,900	7,900	7,900	7,900
Other 2	38,520	38,520	38,520	38,520	38,520
Other 3					
Total Requested (424) Other Costs	75,330	75,330	75,330	75,330	75,330
Total Requested (424) Costs	284,961	284,961	284,961	284,961	284,961
Allowable & IRG Recommended Other Costs	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Reduction Amount					
Reduction Percentage					
Salaries	166,092	166,092	166,092	[illegible]	
Fringe	43,539	43,539	43,539	43,539	
Total Personnel	209,631	209,631	209,631	209,631	
Equipment					
Travel	7,980	7,980	7,980	7,980	
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					
Materials & Supplies	20,930	20,930	20,930	20,930	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual					
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1 - please select Other type	7,900	7,900	7,900	7,900	
Tuition Remission Graduate	38,520	38,520	38,520	38,520	
Other 3 - please select Other type					
Total Allowable and IRG Recommended Other Costs	75,330	75,330	75,330	75,330	
Total Allowable and IRG Recommended Costs	284,961	284,961	284,961	284,961	
IC Funding/Awarded Other Costs	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Reduction Amount					
Reduction Percentage	14.79%	14.79%	14.79%	14.79%	14.79%
Reduction post T2 Target					
Salaries	141,523	141,523	141,523	[illegible]	
Fringe	37,099	37,099	37,099	37,099	
Total Personnel	178,622	178,622	178,622	178,622	
Equipment					
Travel	6,800	6,800	6,800	6,800	
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					
Materials & Supplies	17,834	17,834	17,834	17,834	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual					
Equipment or Facility Rental/User Fees					

Alterations/Renovations					
Other 1 - please select Other type	6,731	6,731	6,731	6,731	
Tuition Remission Graduate	32,822	32,822	32,822	32,822	
Other 3 - please select Other type					
Total IC Funding/Awarded Other Costs	**64,187**	**64,187**	**64,187**	**64,187**	
Total IC Funding/Awarded Costs	**242,809**	**242,809**	**242,809**	**242,809**	
Indirect (F&A) Costs Exclusions	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Equipment					
Subaward/Consortium/Contractual					
Patient Care					
Alterations/Renovations					
Tuition	32,822	32,822	32,822	32,822	
Other Exclusions					
Other Exclusions Less Staff Adjustment					
Total Exclusions	**32,822**	**32,822**	**32,822**	**32,822**	
Total Base	**209,987**	**209,987**	**209,987**	**209,987**	
Indirect (F&A) Costs Base Type	**MTDC**				
Indirect (F&A) Costs Breakdown	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Requested Base 1	246,441	246,441	246,441	246,441	
Requested Rate 1	58.05%	58.05%	58.05%	58.05%	58.05%
Requested Subtotal Indirect (F&A) 1	143,059	143,059	143,059	143,059	
Rate(s) 1 at Time of Award	**60.50%**	**60.50%**	**60.50%**	**60.50%**	
Months	**12**	**12**	**12**	**12**	**12**
Base 1 Less IRG/IC Reductions	**209,987**	**209,987**	**209,987**	**209,987**	
Subtotal Indirect (F&A) 1 Authorized	**127,042**	**127,042**	**127,042**	**127,042**	
Total Indirect (F&A) Costs Authorized	**127,042**	**127,042**	**127,042**	**127,042**	
PROJECT SUMMARY	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Total Direct Costs Authorized	**242,809**	**242,809**	**242,809**	**242,809**	
Total Indirect (F&A) Costs Authorized	**127,042**	**127,042**	**127,042**	**127,042**	
Total Direct & Indirect (F&A) Costs Authorized	**369,851**	**369,851**	**369,851**	**369,851**	
Fee Authorized					
Total Direct, Indirect (F&A) Costs, & Fee Authorized	**369,851**	**369,851**	**369,851**	**369,851**	
Subaward / Consortia Project Allowable in Base	25,000				

Altieri, Robert (NIH/NIGMS) [E]

From: Janes, Daniel (NIH/NIGMS) [E]
Sent: Tuesday, July 7, 2020 3:09 PM
To: Altieri, Robert (NIH/NIGMS) [E]
Subject: RE: Question about funding recommendation: 1 R01 GM140459-01 (PI: David Kennedy)

Looks good. Correct. Thank you.

-Dan

From: Altieri, Robert (NIH/NIGMS) [E] <robert.altieri@nih.gov>
Sent: Tuesday, July 7, 2020 2:45 PM
To: Janes, Daniel (NIH/NIGMS) [E] <daniel.janes@nih.gov>
Subject: Question about funding recommendation: 1 R01 GM140459-01 (PI: David Kennedy)
Importance: High

Hi Dan,

Just to confirm, we're flat-lining the budget at the paylist level of $242,809 DC/year, correct (requested budget is below)? If so, I'm just going to make the cut on the 1st year and copy the numbers to the outyears. Let me know. Thanks! -Rob

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	209631	232408	238214	244167	250270
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES	20930	16225	14225	5000	
TRAVEL	7980	26550	4500	21550	4500
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	46420	54577	65981	52992	54254
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	284961	329760	322920	323709	309024
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	284961	329760	322920	323709	309024

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	$ 1570374

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Salaries and Wages
Principal Investigator – David Kennedy (b)(6) month effort year 1 and (b)(6) months effort years 2-5): Dr. Kennedy will coordinate and oversee the work conducted for this project, including supervision of a graduate student and a postdoctoral researcher. He will also contribute to conference calls, experimental design, progress reports, and the dissemination and publication of results.

Co-Principal Investigator – Moriah Szpara (b)(6) months effort): Dr. Szpara will oversee the work in Aim 3, including supervision of a research technician and a bioinformatician. She will also contribute to conference calls, experimental design, progress reports, and the dissemination and publication of results.

Bio Technician – Chris Bowen (b)(6) months effort): This technician's role will be to conduct DNA extractions, sample preparation, and other molecular biology methods required in Aim 3.

Computational Technician – Daniel Renner (b)(6) months effort): This technician's role will be to process the sequencing reads for de novo genome assembly and contig reconstruction.

Robert Altieri
Grants Management Specialist
HHS/NIH/NIGMS
(301) 827-4926
Robert.Altieri@nih.gov

** PROVISIONAL RATE AGREEMENT **

DEPARTMENT OF THE NAVY
OFFICE OF NAVAL RESEARCH
875 NORTH RANDOLPH STREET
SUITE 1425
ARLINGTON, VA 22203-1995

IN REPLY REFER TO:

June 24, 2020

NEGOTIATION AGREEMENT

INSTITUTION: **THE PENNSYLVANIA STATE UNIVERSITY**
UNIVERSITY PARK, PA 16801-3857

The Facilities and Administrative (F&A) cost rates contained herein are for use on grants, contracts and/or other agreements issued or awarded to the Pennsylvania State University (PSU) by all Federal Agencies of the United States of America, in accordance with the provisions and cost principles mandated by 2 CFR Part 200. These rates shall be used for forward pricing and billing purposes for the PSU's Fiscal Year 2021. This rate agreement supersedes all previous rate agreements/determinations related to these rates for Fiscal Year 2021.

SECTION I – RATES – TYPE: PROVISIONAL (PROV)

UNIVERSITY PARK

TYPE	FROM	TO	RATE	BASE	APPLICABLE TO	LOCATION
PROV	07/01/20	06/30/21	60.50%	(a)	Organized Research	On-Campus
PROV	07/01/20	06/30/21	26.00%	(a)	Organized Research	Off-Campus
PROV	07/01/20	06/30/21	42.28%	(a)	Instruction	On-Campus
PROV	07/01/20	06/30/21	26.00%	(a)	Instruction	Off-Campus

APPLIED RESEARCH LABORATORY

TYPE	FROM	TO	RATE	BASE	APPLICABLE TO	LOCATION
PROV	07/01/20	06/30/21	8.87%	(a)	Organized Research - ARL[1]	On-Campus
PROV	07/01/20	06/30/21	6.35%	(a)	Organized Research - ARL	Off-Campus

HERSHEY COLLEGE OF MEDICINE

TYPE	FROM	TO	RATE	BASE	APPLICABALE TO	LOCATION
PROV	07/01/20	06/30/21	62.18%	(a)	Organized Research - HCM[2]	On-Campus
PROV	07/01/20	06/30/21	26.00%	(a)	Organized Research - HCM	Off-Campus

[1] Applied Research Laboratory
[2] Hershey College of Medicine

DISTRIBUTION BASE

(a) Modified Total Direct Cost (MTDC) means all direct salaries and wages, applicable fringe benefits, materials and supplies, services, travel, and up to the first $25,000 of each subaward (regardless of the period of performance of the subawards under the award). MTDC excludes equipment, capital expenditures, charges for patient care, rental costs, tuition remission, scholarships and fellowships, participant support costs, and the portion of each subaward in excess of $25,000.

SECTION II - GENERAL TERMS AND CONDITIONS

A. **LIMITATIONS**: Use of the rates set forth under Section I is subject to availability of funds and to any other statutory or administrative limitations. The rates are applicable to a given grant, contract or other agreement only to the extent that funds are available and consistent with any and all limitations of cost clauses or provisions, if any, contained therein. Acceptance of any or all of the rates agreed to herein is predicated upon the following conditions: (1) that no costs other than those incurred by the institution were included in this indirect cost pool as finally accepted and that such costs are legal obligations of the institution and allowable under governing cost principles; (2) that the same costs that have been treated as indirect costs are not claimed as direct costs; (3) that similar types of costs have been accorded consistent accounting treatment; and (4) that the information provided by the institution which was used as a basis for acceptance of the rates agreed to herein, and expressly relied upon by the Government in negotiating and accepting the said rates is not subsequently found to be materially incomplete or inaccurate.

B. **ACCOUNTING CHANGES**: The rates contained in Section I of this agreement are based on the accounting system in effect at the time the agreement was negotiated. Changes to the method(s) of accounting for costs, which affect the amount of reimbursement resulting from the use of these rates require the prior written approval of the authorized representative of the cognizant agency for indirect costs. Such changes include but are not limited to changes in the charging of a particular type of cost from indirect to direct. Failure to obtain such approval may result in subsequent cost disallowances.

C. **PROVISIONAL RATES**: The provisional rates contained in this agreement are subject to unilateral amendment by the Government or bilateral amendment by the contracting parties at any time.

D. **USE BY OTHER FEDERAL AGENCIES**: The rates set forth in Section I are negotiated in accordance with and under the authority set forth in 2 CFR Part 200. Accordingly, such rates shall be applied to the extent provided in such regulations to grants, contracts, and other agreements to which 2 CFR Part 200 applies, subject to any limitations in part A of this section. Copies of this document may be provided by either party to other federal agencies to provide such agencies with documentary notice of this agreement and its terms and conditions.

E. **SPECIAL REMARKS**:

1. The rates included in Section I are not intended to be applied to Intergovernmental Personnel Act (IPA) costs. If the Pennsylvania State University elects to seek reimbursement of F&A or internal overhead costs associated with IPA agreements, then the University and the Office of Naval Research shall establish special F&A and/or internal overhead rates for IPA agreements in accordance with the provisions of 2 CFR Part 200.

2. The Government's agreement with the rates set forth in Section I is not an acceptance of Pennsylvania State University's accounting practices or methodologies. Any reliance by the Government on cost data or methodologies submitted by Pennsylvania State University is on a non-precedence-setting basis and does not imply Government acceptance.

Accepted:

FOR PENNSYLVANIA STATE UNIVERSITY:

(b)(6)

Joseph J. Doncsecz
Associate Vice President for Finance and
Corporate Controller

6/26/2020
Date

FOR THE U.S. GOVERNMENT:

(b)(6)

Betty J. Tingle
Contracting Officer

June 26, 2020
Date

For information concerning this agreement contact:
Betty Tingle, Contracting Officer
Office of Naval Research

Phone: (703) 696-7742
E-mail: betty.tingle@navy.mil

David A Kennedy CURRENT AND PENDING

ACTIVE

721653-712683 (Kennedy) 8/1/2018-7/31/2021 Calendar: (b)(6)
Virginia Institute of Marine Science $26,774 annual direct costs
Virulence Evolution After Viral Host Jump and Emergence
The major goals of this project are:
1) To define virulence spectrum of IHNV before, during, and after host jump and emergence, 2) to quantify virus transmission potential before, during, and after host jump and emergence, 3) to elucidate genetic correlates of virulence and transmission phenotypes, and 4) to develop mathematical models to infer the factors responsible for the evolution of viral virulence and transmission after host jump and emergence.

R01 AI132692 (Szpara) 2/23/2018-1/31/2023 Calendar: (b)(6)
National Institutes of Health $277,666 annual direct costs
Forward genetic prediction and testing of virulence loci in herpes simplex virus 1
The major goals of this project are: To establish links between naturally occurring genetic variations of human herpesvirus HSV-1 isolates, and their virulence phenotypes, using a genetically and experimentally tractable murine model. I am not a PI or Co-PI on this project. The project was funded prior to my promotion to my current position, and I am funded on the project as a "Research Associate", which is most directly comparable to a postdoctoral scholar.

PENDING

(b)(4)

(b)(4)

OTHER RESEARCH RESOURCES

Collaboration with Venugopal Nair and Yongxiu Yao at the Pirbright Institute, United Kingdom, pending this proposal. This collaboration is a key component of the proposal, since all vertebrate animal work related to this proposal will take place at the Pirbright Institute.

Collaboration with Suresh Kuchipudi at Penn State University, Pennsylvania, USA. In this collaboration, we are attempting to quantify the burden of SARS-CoV-2 in the undergraduate student population at Penn State between January 2020 and March 2020, based on retrospective analysis of flu swabs collected from students presenting to Penn State's University Health Services with flu-like symptoms. No financial support is being directed to me or my lab.

**** TOTAL ACTIVE (INCLUDING THIS AWARD) =** (b)(6) **MONTHS**

Search Results

Entity: PENNSYLVANIA STATE UNIVERSITY, THE

DUNS: 003403953

CAGE: 7A720

Date FAPIIS search conducted: 06/02/2020 12:32:45

Back View Corporate Relationships

FAPIIS Data

Report Type	Records	Count
Administrative Agreement	No	0
Defective Pricing	No	0
DoD Determination of Contractor Fault	No	0
Information on Trafficking in Persons	No	0
Non-Responsibility Determination	No	0
Recipient Not-Qualified Determination	No	0
Subcontractor Payment Issues	No	0
Termination for Cause	No	0
Termination for Default	No	0
Termination for Material Failure to Comply	No	0

Details of Selected Extended System Source

Proceedings Information as Entered by the Entity in SAM.gov

Question: Does your business or organization (represented by the DUNS number on this specific Entity Management section of SAM record) have current active Federal contracts and/or grants with total value (including any exercised/unexercised options) greater than $10,000,000?

***Contractor Response: Yes

Question: Within the last five years, has your business or organization (represented by the DUNS number on this specific Entity Management section of SAM record) and/or any of its principals, in connection with the award to or performance by your business or organization of a Federal contract or grant, been the subject of a Federal or State (1) criminal proceeding resulting in a conviction or other acknowledgment of fault; (2) civil proceeding resulting in a finding of fault with a monetary fine, penalty, reimbursement, restitution, and/or damages greater than $5,000, or other acknowledgment of fault; and/or (3) administrative proceeding resulting in a finding of fault with either a monetary fine or penalty greater than $5,000 or reimbursement, restitution, or damages greater than $100,000, or other acknowledgment of fault?

***Contractor Response: No

Performance Evaluations

Awardee	DUNS	Status/Count
	003403953	48

SAM Exclusion Data

*** No matching Performance Information section of SAM records were found based on the search criteria information we have. You may want to search Performance Information section of SAM directly at https://www.sam.gov/ and use the 'Advanced Search' option to locate the entity of interest.

** NOTE: THIS RECORD DOES NOT PERTAIN TO THE PD/PI, WHO HAS NEVER RESIDED IN TN.

SAM SYSTEM FOR AWARD MANAGEMENT

A NEW WAY TO SIGN IN - If you already have a SAM account, use your **SAM email** for login.gov. **Log In**

Login.gov FAQs

ALERT: SAM.gov will be down for scheduled maintenance Saturday, 07/11/2020 from 8:00 AM to 1:00 PM

ALERT: CAGE is experiencing intermittent service interruptions. SAM registrants may encounter an error validating a CAGE Code. If this happens, please try again later.

Exclusion Summary

RETURN TO SEARCH

Exclusion Record

Exclusion Record Details

Page Description

This page contains the exclusion details for the record matching your search criteria. There may be instances when a Firm or Individual has the same name, or a similar name, as your search criteria but is actually a different party. Read the entire record to understand why this entity was excluded and what effect this exclusion has on your decision.

To verify a potential match or obtain additional information, contact the federal agency that created the exclusion record. Contact information for the designated Agency Point of Contact (POC) is linked to the Excluding Agency name within the record. You can also navigate to the Agency Exclusion POC page within SAM Help under Exclusions Information.

Agency users with an exclusion management role may update an exclusion record to deactivate it. From the Edit Exclusion Record options, select Update, then set the Termination Date on the Exclusion Details page. Once an exclusion is inactive, it cannot be modified.

View Exclusion History

Current Record **View Selected Record**

PRINT

Current Record Details

Identification Information:

Prefix:	
First Name:	David
Middle Name:	
Last Name:	Kennedy
Suffix:	
NPI:	

Exclusion Details:

Exclusion Program:	Reciprocal
Classification Type:	Individual
Exclusion Type:	Ineligible (Proceedings Pending)

Nature (Cause):

Preliminary ineligible based upon adequate evidence of conduct indicating a lack of business honesty or integrity, or a lack of business integrity, or regulation, statute, executive order or other legal authority, pending completion of an investigation and/or legal proceedings; or based upon initiation of proceedings to determine final ineligibility based upon regulation, statute, executive order or other legal authority or a lack of business integrity or a preponderance of the evidence of any other cause of a serious and compelling nature that it affects present responsibility.

Effect:

Procurement:
Agencies shall not solicit offers from, award contracts to renew, place new orders with, or otherwise extend the duration of current contracts, or consent to subcontracts in excess of $35,000 (other than commercially available off-the-shelf items (COTS)), with these contractors unless the agency head (or designee) determines in writing there is a compelling reason to do so.

Nonprocurement:
No agency in the Executive Branch shall enter into, renew, or extend primary or lower tier covered transactions to a participant or principal determined preliminarily ineligible unless the head of the awarding agency grants a compelling reasons exception in writing. Additionally, agencies shall not make awards under certain discretionary Federal assistance, loans, benefits (or contracts there under); nor shall an ineligible person participate as a principal, including but not limited to, agent, consultant, or other person in a position to handle, influence or control Federal funds, or occupying a technical or professional position capable of substantially influencing the development or outcome of a funded activity; nor act as an agent or representative of other participants in Federal assistance, loans and benefits programs. Contact the award agency for questions regarding the extent of Nonprocurement transaction award ineligibility. The termination date will be listed as "Indefinite" (Indef.) unless otherwise specified.

CT Code:	
Active Date:	06/20/2019
Termination Date:	Indefinite
Excluding Agency :	DEPT OF THE ARMY
Status :	Active
Create Date :	06/20/2019
Update Date :	06/20/2019
Additional Comments:	

Primary Address:

Verify Street Address

Street Address 1:	
Street Address 2:	
	Verify Address
City:	Old Hickory
State/Province:	TN
ZIP/Postal Code:	37138
Country:	UNITED STATES

Cross-References:

No Cross References

More Locations:

No Locations

EIN	Organization	Valid	FDP 3	FDP 4
1246000376A1	PENNSYLVANIA STATE UNIVERSITY	Y	Y	Y

IPF NUMBER: **1524202**	Organization Name PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	Long (Index) Name: PENNSYLVANIA STATE UNIVERSITY AT UNIVERSITY PARK
Cong Dist: 05 City: UNIVERSITY PARK State Code: PA ZIP: 168027000 Country Code/Name: 231/UNITED STATES County Code/Name: 27/CENTRE	NGA Email: osp@psu.edu Name as shown on NGA (If Diff): PENNSYLVANIA STATE UNIVERSITY	110 Technology Center Building Phone: 814-865-1372
Med School Flag: N Multi Campus Flag: Y Multi Campus Sys ID: C AA Institution Flag: N Woman Owned Flag: N	ORI Cert Mail Date: 10/01/91 ORI Cert Exp Date: 04/30/20 ORI Cert Grp Code: C ORI Cert Stat Code: 1	Ownership Code: 03 State Government Org Type Code: 10 Institution of higher education
Pub File Mark: P02 Initial Ref Doc: 6 0701(47) Initial Ref Date: 12/12/47	SMSA CODE: 8050 **Primary DUNS Number / Ext.** 003403953 **Other DUNS Number / Ext.**	First FY/GDS Data: Data V

** NO ADMINISTRATIVE CONCERNS

SUMMARY STATEMENT

PROGRAM CONTACT:
DANIEL JANES
daniel.janes@nih.gov

(Privileged Communication)

Release Date: **04/01/2020**
Revised Date:

Application Number: **1 R01 GM140459-01**

Principal Investigator

KENNEDY, DAVID

Applicant Organization: Pennsylvania State University

Review Group: **ZRG1 IDM-U (55)**
Center for Scientific Review Special Emphasis Panel
PAR Panel: Ecology and Evolution of Infectious Diseases

Meeting Date: **02/11/2020**
Council: **MAY 2020**
Requested Start: **08/01/2020**

RFA/PA: **PAR20-001**
PCC: **G242DJ**

Dual IC(s): **TW**

Project Title: **US-UK Collab: The consequences of transmissible vaccines on disease ecology and pathogen evolution: Marek's disease virus as a case study**

SRG Action: **Impact Score** (b)(6)

Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**

Human Subjects: **10-No human subjects involved**

~~**Animal Subjects:** **30-Vertebrate animals involved - no SRG concerns noted**~~

Project Year	Direct Costs Requested	Estimated Total Cost
1	284,961	428,469
2	329,760	495,830
3	322,920	485,545
4	323,709	486,731
5	309,024	464,651
TOTAL	1,570,374	2,361,226

1R01GM140459-01 KENNEDY, DAVID

RESUME AND SUMMARY OF DISCUSSION: This application on the Ecology and Evolution of Infectious Diseases was received and reviewed in accord with National Science Foundation Program Solicitation NSF 19-592 and National Institutes of Health Notice NOT-TW-19-007 (https://grants.nih.gov/grants/guide/notice-files/NOT-TW-19-007.html). (b)(6)

(b)(6)

(b)(6)

DESCRIPTION (provided by applicant): Vaccination can be one of the most efficient and effective tools for controlling infectious diseases, but in many settings, including wildlife and farm animal diseases, logistical and economic hurdles make it impractical to vaccinate large enough fractions of hosts to achieve herd immunity. Transmissible vaccines, defined as vaccines capable of disseminating from vaccinated to non-vaccinated hosts, offer one potential solution to these challenges by amplifying the impact of vaccination campaigns. However, transmissible vaccines are not without risk. Reversion to virulence or recombination with wildtype pathogens could cause transmissible vaccines to make matters worse or complicate elimination efforts. This proposed work will for the first time quantify the effects of transmissible vaccines on disease ecology and evolution using an economically important, naturally transmissible vaccine currently in widespread use on poultry farms. Marek's disease, a poultry-specific disease that is a threat to sustainable poultry production, is currently controlled by the "Rispens" vaccine, a live, attenuated vaccine that has been widely used for two decades. Recent experiments have found that this vaccine is capable of efficiently transmitting from vaccinated to non-vaccinated birds. These results are consistent with recent field surveillance studies that have found vaccine isolates in cohorts that have not been directly vaccinated. In addition, advances in whole genome sequencing have revealed recombination between the vaccine virus and the wildtype virus, which is concerning given that the vaccine virus harbors highly virulent forms of the oncogenic meq gene. Together, these observations demonstrate that the Rispens vaccine is a transmissible vaccine capable of evolving and potentially facilitating adverse evolution of wildtype Marek's disease virus. Our primary objective is to quantify the consequences of transmissible vaccine use. Specifically, we will: 1) Develop a general model of transmissible vaccination to identify key knowledge gaps, 2) Characterize vaccine transmission and its impact on wildtype virus transmission, 3) Characterize the genetic evolution of wildtype virus and vaccine virus, 4) Model the overall impact of Rispens vaccination on Marek's disease virus and its vaccine

PUBLIC HEALTH RELEVANCE: Transmissible vaccines are being widely considered to control zoonotic diseases in animal populations, including Ebola, Marburg, Sin Nombre hantavirus, and rabies. However, before transmissible vaccines are introduced, the benefits and risks must be considered. This study will provide the first empirical estimate of how well a transmissible vaccine spreads, and it will determine whether adverse evolution has occurred due to the widespread use of a transmissible vaccine, or if not, whether it is likely to occur.

CRITIQUE 1:

(b)(6)

(b)(6)

CRITIQUE 2:

(b)(6)

(b)(6)

CRITIQUE 3:

(b)(6)

CRITIQUE 4:

(b)(6)

(b)(6)

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTIONS FOR HUMAN SUBJECTS: Not Applicable: No human subjects are involved in the project.

VERTEBRATE ANIMAL: (b)(6)

BIOHAZARD COMMENT: (b)(6)

COMMITTEE BUDGET RECOMMENDATIONS: (b)(6)

MEETING ROSTER: The roster for this review meeting is displayed as an aggregated roster that includes reviewers from multiple National Science Foundation Review Panels and Center for Scientific Review Special Emphasis Panels for the 2018/05, 2019/05 and 2020/05 council rounds.

Footnotes for 1 R01 GM140459-01; PI Name: Kennedy, David

NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
PAR Panel: Ecology and Evolution of Infectious Diseases
ZRG1 IDM-U (55)
02/11/2020 - 02/13/2020

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

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DIRECTORATE OF BIOLOGICAL SCIENCES
NATIONAL SCIENCE FOUNDATION
ARLINGTON, VA 22230

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 07/26/2016

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 1R01GM122079-01
FAIN: R01GM122079

Principal Investigator(s):
SCOTT L NUISMER

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

STEVE KIRKHAM
SPONS PROGRAMS ADMIN
UNIVERSITY OF IDAHO
875 PERIMETER DRIVE
MS3020
MOSCOW, ID 838443020

Award e-mailed to: osp@uidaho.edu

Period Of Performance:
Budget Period: 08/01/2016 – 04/30/2017
Project Period: 08/01/2016 – 04/30/2020

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $251,392 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Lori Burge
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 1R01GM122079-01

Award Calculation (U.S. Dollars)

Salaries and Wages	$72,069
Fringe Benefits	$26,725
Personnel Costs (Subtotal)	$98,794
Equipment	$12,000
Materials & Supplies	$2,500
Travel	$3,150
Other	$2,000
Subawards/Consortium/Contractual Costs	$72,484
Federal Direct Costs	$190,928
Federal F&A Costs	$60,464
Approved Budget	$251,392
Total Amount of Federal Funds Obligated (Federal Share)	$251,392
TOTAL FEDERAL AWARD AMOUNT	$251,392
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$251,392

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$251,392	$251,392
2	$252,639	$252,639
3	$252,945	$252,945
4	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1826000945A1
Document Number:	RGM122079A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2016

IC	CAN	2016	2017	2018	2019
GM	8472185	$251,392	$252,639	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: B120VR / **OC**: 414A / **Released**: (b)(6) 07/19/2016
Award Processed: 07/26/2016 12:03:19 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R01GM122079-01

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1R01GM122079-01

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.

c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

SECTION IV – GM Special Terms and Conditions – 1R01GM122079-01

1. The Year 01 budget period is slightly less than 12 months in length (full 12-month level of funds provided) so that the anniversary date for future non-competing awards will be May 1. The Research Performance Progress Report (RPPR) will be due 45 days prior to this date (60 days for non-SNAP awards) each year. Guidance on RPPR submission is documented in the RPPR Instruction Guide found at: http://grants.nih.gov/grants/rppr/index.htm.

This anniversary date may change the receipt date for the next competing continuation (Type 2) application. Consult the submission dates/deadlines on the NIH Office of Extramural Research Grants (OER) Home page at http://grants.nih.gov/grants/dates.htm.

2. This award provides funding for an application submitted in response to the NSF/NIGMS Joint Program in Mathematical Biology Initiative. This grant should be administered in accordance with the guidelines described in this specific announcement. These guidelines are in addition to the standard "Terms and Conditions" referenced in Section III of this Notice of Grant Award.

3. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-16-046.

4. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at:
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

5. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap. Therefore, this award and/or future years are adjusted accordingly, if applicable.

Current salary cap levels can be found at the following URL:

http://grants.nih.gov/grants/policy/salcap_summary.htm

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Justin Rosenzweig
Email: rosenzwj@mail.nih.gov **Phone**: 301-594-0158 **Fax**: 301-480-2554

Program Official: Veerasamy Ravichandran
Email: veerasamy.ravichandra@nih.gov **Phone**: 301-451-9822 **Fax**: 301-480-0884

SPREADSHEET SUMMARY
GRANT NUMBER: 1R01GM122079-01

INSTITUTION: UNIVERSITY OF IDAHO

Budget	Year 1	Year 2	Year 3	Year 4
Salaries and Wages	$72,069	$86,419	$86,419	$86,419
Fringe Benefits	$26,725	$26,725	$26,725	$26,725
Personnel Costs (Subtotal)	$98,794	$113,144	$113,144	$113,144
Equipment	$12,000			
Materials & Supplies	$2,500	$1,500	$1,500	$1,500
Travel	$3,150	$3,150	$3,150	$3,150
Other	$2,000	$4,500	$4,500	$4,500
Subawards/Consortium/Contractual Costs	$72,484	$72,561	$72,561	$72,561
TOTAL FEDERAL DC	$190,928	$194,855	$194,855	$194,855
TOTAL FEDERAL F&A	$60,464	$57,784	$58,090	$58,090
TOTAL COST	$251,392	$252,639	$252,945	$252,945

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4
F&A Cost Rate 1	46%	46%	47.5%	47.5%
F&A Cost Base 1	$131,444	$20,382	$122,294	$122,294
F&A Costs 1	$60,464	$9,376	$58,090	$58,090
F&A Cost Rate 2		47.5%		
F&A Cost Base 2		$101,912		
F&A Costs 2		$48,408		

Form Approved Through 8/31/2015

PI: NUISMER, SCOTT L
1 R01 GM122079-01
Dual:
IRG: ZGM1 SRC(99)

Council: 05/2016
Received: 03/31/2016

Department of Health and Human Services
alth Services

12171227 **pplication** MAR 21 2016

length restrictions indicated.

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*

COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)

Number: RFA-GM-16-570 Title: Joint DMS/NIGMS Mathematical Biology Initiative

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Nuismer, Scott, L	PhD	nuismer

3c. POSITION TITLE
Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
875 Perimeter Drive, MS3051
Moscow, ID 83844-3051

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Biological Sciences

3f. MAJOR SUBDIVISION
College of Science

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 208-885-4096 FAX: 208-885-7905

E-MAIL ADDRESS:
snuismer@uidaho.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☒ No ☐ Yes	☐ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
	☐ No ☐ Yes	☐ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes — 5a. Animal Welfare Assurance No

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
08/01/16	07/31/20	$190,310	$249,854	$772,790	$998,532

9. APPLICANT ORGANIZATION
Name University of Idaho
Address
875 Perimeter Drive, MS3020
Moscow, ID 83844-3020

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
826000945
DUNS NO.075746271 Cong. District ID-001

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name Steve Kirkham
Title Sponsored Programs Administrator
Address 875 Perimeter Drive, MS3020
Moscow, ID 83844-3020
Tel: 208-885-4391 FAX: 208-885-5752
E-Mail: stevenk@uidaho.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name Deborah N. Shaver
Title Director, Office of Sponsored Programs
Address 875 Perimeter Drive, MS3020
Moscow, ID 83844-3020
Tel: 208-885-6651 FAX: 208-885-5752
E-Mail: osp@uidaho.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*
(b)(6)

DATE
03/11/16

PROJECT SUMMARY (See instructions):

Viral vaccines have had remarkable and long-lasting impacts on human health, resulting in the world wide eradication of smallpox, the elimination of polio within much of the developed world, and the effective control of many other diseases. Although great strides have been made in the development and production of vaccines since Edward Jenner's first vaccinations with cowpox in the early 1800's, little has changed in the way vaccines are delivered. Even today, virtually every vaccine must be given directly to the patient. Recent advances in molecular biology suggest that the centuries-old method of individual-based vaccine delivery could be on the cusp of a major revolution. Specifically, genetic engineering brings to life the possibility of a "transmissible vaccine." Rather than directly vaccinating every individual within a population, a transmissible vaccine would allow large swaths of the population to be vaccinated effortlessly by releasing an infectious agent that is genetically engineered to be benign yet infectious. In fact, some existing vaccines are transmissible to a limited extent, and transmissible vaccines have already been developed and deployed in wild animal populations. Remarkably enough, however, no theory exists to guide the safe and effective use of this revolutionary new type of vaccine. We will develop a mathematical framework for understanding the ecology and evolution of transmissible vaccines, and test the emerging mathematical results using an experimental viral system. Epidemiological efficacy will be assessed by calculating the gains in disease protection conferred by a transmissible vaccine relative to a traditional vaccine. Evolutionary robustness will be explored using models that predict the rate at which a genetically engineered vaccine will lose its efficacy or increase its virulence. In both cases, models will be analyzed using a combination of direct and asymptotic solutions, approximations, numerical solutions, and individual-based simulations. Key mathematical results will be tested experimentally using interactions between bacteria and viruses that infect them.

RELEVANCE (See instructions):

Recent advances in genetic engineering have created the possibility of transmissible vaccines – live vaccines that transmit between vaccinated individuals and their contacts. The proposed research will use mathematical models and laboratory experiments to guide the development of safe and effective transmissible vaccines that have the potential to greatly reduce the burden of infectious disease.

PROJECT/PERFORMANCE SITE(S) (If additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location			
Organizational Name: University of Idaho			
DUNS: 075746271			
Street 1: 875 Perimeter Drive, MS3020		Street 2:	
City: Moscow	County: Latah		State: Idaho
Province:	Country: United States		Zip/Postal Code: 83844-3020
Project/Performance Site Congressional Districts: ID-001			
Additional Project/Performance Site Location			
Organizational Name: University of Texas at Austin			
DUNS: 170230239			
Street 1: 101 E. 27th Street, Stop A9000		Street 2:	
City: Austin	County: Travis		State: TX
Province:	Country: United States		Zip/Postal Code: 78712-1532
Project/Performance Site Congressional Districts: TX-25			

Program Director/Principal Investigator (Last, First, Middle): Nuismer, Scott, L

SCIENTIFIC/KEY PERSONNEL. See Instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Nuismer, Scott	(b)(6)	University of Idaho	PD/PI
Bull, James		U. of Texas at Austin	Co-PI
Remien, Christopher	(b)(6)	University of Idaho	Co-PI

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☐ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Program Director/Principal Investigator (Last, First, Middle): Nuismer, Scott, L

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 08/01/16 THROUGH 07/31/17

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Scott L Nuismer	PD/PI			(b)(6)	(b)(6)	10,730	3,391	14,121
Christopher R Remien	Co-PI					9,339	2,951	12,290
	Postdoc	12.00				52,000	20,383	72,383
	Undergrads	0.00				0	0	
	SUBTOTALS →					72,069	26,725	98,794

CONSULTANT COSTS	
EQUIPMENT *(Itemize)* workstations	12,000
SUPPLIES *(Itemize by category)* computer software $1,000 research materials and supplies $1,500	2,500
TRAVEL domestic-for the research team to present research at annual meetings	3,150
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* annual meeting registration costs	2,000
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS 46,365
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*	$ 164,809
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS 25,501
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD	$ 190,310

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	98,794	113,144	113,144	113,144	
CONSULTANT COSTS					
EQUIPMENT	12,000				
SUPPLIES	2,500	1,500	1,500	1,500	
TRAVEL	3,150	3,150	3,150	3,150	
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	2,000	4,500	4,500	4,500	
DIRECT CONSORTIUM/ CONTRACTUAL COSTS	46,365	46,365	46,365	46,365	
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	164,809	168,659	168,659	168,659	
F&A CONSORTIUM/ CONTRACTUAL COSTS	25,501	25,501	25,501	25,501	
TOTAL DIRECT COSTS	190,310	194,160	194,160	194,160	

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$** 772,790

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Personnel

Scott Nuismer, Project Director/Principal Investigator, (b)(6) month per year

Nuismer will coordinate overall project implementation and facilitate interaction among individuals working on mathematical and empirical objectives of the project by organizing the annual meeting of project participants. Nuismer has an extensive background in developing and analyzing mathematical models of host-parasite interactions, and particular expertise with models focused on how these interactions evolve in spatially structured environments. Consistent with this expertise, Nuismer will be involved in the mathematical modeling that comprises the first two specific objectives and will lead efforts to model the evolution of transmissible vaccines in the second objective. In addition, Nuismer will coordinate recruitment of undergraduate researchers and postdoctoral researchers at the University of Idaho and will be involved in their training on a day to day basis.

Continued on next page

JUSTIFICATION CONTINUATION

Personnel (cont)
Chris Remien, Co-Principal Investigator, (b)(6) month per year
Remien will work with PI Nuismer on the mathematical modeling in the first two specific objectives and will lead modeling efforts in the first objective, developing a mathematical framework to predict the extent of protection provided by transmissible vaccines. Remien has extensive experience in mathematical biology, developing and analyzing mechanistic mathematical models to issues as diverse as acetaminophen overdose, incorporation of stable isotopes into animal tissues, and detoxification of ingested toxins in mammals. He has applied and developed a wide variety of mathematics including dynamical systems, bifurcation theory, probability, inverse methods, statistics, and simulations. Together with PI Nuismer, Remien will recruit undergraduate and postdoctoral researchers and train them on a day-to-day basis.
Postdoctoral Researcher, 12 calendar months per year
Postdoctoral researchers will develop and analyze mathematical models in collaboration with PI Nuismer and Co-PI Remien. Postdoctoral researchers will also work with the PI and Co-PI to write up results for publication and present these results at scientific meetings. Finally, postdoctoral researchers will participate in mentoring undergraduate researchers.
Undergraduate Students, years 2, 3 and 4 (other funding is being used for year 1)
Undergraduate students will work together as a team to develop and analyze a mathematical model that addresses a sub-goal within one of the first two specific aims. These undergraduate students will be mentored by a postdoctoral researcher, PI Nuismer and Co-PI Remien. These students will be involved in writing up the results of their research and submitting them for publication. Students will also be given the opportunity to present the results of their research at local meetings.
Equipment
$12,000 in year 1 for two workstations to facilitate efficient numerical solution and individual based simulation.
Supplies
$1,000 in year 1 for computer software and $1,500 in years 2, 3, and 4 for research materials and supplies.
Travel
$3,150 each year for domestic travel for the research team to present research at annual meetings. Destinations are yet to be determined.
Other
$2,000 per year for principal investigators annual meeting registration costs. $2,500 in years 2, 3, and 4 for publication costs to publish research findings.

Program Director/Principal Investigator (Last, First, Middle): Bull, James, J

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM 08/01/16	THROUGH 07/31/17

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Bull, James, J	PD/PI	(b)(6)			(b)(6)	7,200	2,160	9,360
	Technician	6.00				20,004	6,001	26,005
SUBTOTALS →						27,204	8,161	35,365

CONSULTANT COSTS

EQUIPMENT *(Itemize)*

SUPPLIES *(Itemize by category)*

Supplies: Includes standard microbiological supplies (petri dishes, pipette tips, media), PCR and cloning reagents, antibiotics, enzymes, gel reagents, plus services such as DNR sequencing (to confirm engineering) and gene synthesis. Core facilities will be used for the sequencing. 10,000

TRAVEL
domestic-for PI to travel to the University of Idaho to meet with project personnel 1,000

INPATIENT CARE COSTS

OUTPATIENT CARE COSTS

ALTERATIONS AND RENOVATIONS *(Itemize by category)*

OTHER EXPENSES *(Itemize by category)*

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 46,365
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	25,501
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 71,866

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	35,365	35,365	35,365	35,365	
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES	10,000	10,000	10,000	10,000	
TRAVEL	1,000	1,000	1,000	1,000	
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES					
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	46,365	46,365	46,365	46,365	
F&A CONSORTIUM/ CONTRACTUAL COSTS	25,501	25,501	25,501	25,501	
TOTAL DIRECT COSTS	71,866	71,866	71,866	71,866	

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	$ 287,464

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Personnel

James Bull, Principal Investigator, (b)(6) month per year

The first year will be spent refining assays, getting the CRISPR Cas-9 system functioning in E. coli, and cloning the guide RNA into filamentous phage. Bull will conduct some of the assays and make some constructs himself as well as work with Nuismer and Remein to help the guide the choice of models used to model the phage dynamics and advise on other models.

Technician, 6.00 calendar months per year

The half-time technician will conduct the bulk of the lab work.

Supplies: The materials needed for this work include standard microbiological supplies (petri dishes, pipette tips, media), PCR and cloning reagents, antibiotics, enzymes, gel reagents, plus services such as DNA sequencing (to confirm engineering) and gene synthesis. Core facilities will be used for the sequencing.

Travel: Bull will make 1-2 trips a year to Idaho to meet with the other personnel on this project.

Indirect Costs: modified total direct cost base rate of 55%.

02 INFORMATION ABOUT PRINCIPAL INVESTIGATORS/PROJECT DIRECTORS(PI/PD) and co-PRINCIPAL INVESTIGATORS/co-PROJECT DIRECTORS

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PI/PD Name: Scott L Nuismer

Gender:

Ethnicity: (Choose one response)

Race:
(Select one or more)

Disability Status:
(Select one or more)

Citizenship: (Choose one)

(b)(6)

Check here if you do not wish to provide any or all of the above information (excluding PI/PD name): ☐

REQUIRED: Check here if you are currently serving (or have previously served) as a PI, co-PI or PD on any federally funded project ☒

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Hispanic or Latino. A person of Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race.
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White. A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

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PI/PD Name: Christopher R Remlen

Gender:

Ethnicity: (Choose one response)

Race:
(Select one or more)

Disability Status:
(Select one or more)

Citizenship: (Choose one)

(b)(6)

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PI/PD Name: James J Bull

Gender:

Ethnicity: (Choose one response)

Race:
(Select one or more)

Disability Status:
(Select one or more)

Citizenship: (Choose one)

(b)(6)

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INTRODUCTION

The development of viral vaccines has had remarkable and long-lasting impacts on human health, resulting in the world wide eradication of smallpox, the elimination of polio within much of the developed world, and the effective control of many other diseases (Lauring *et al.* 2010; Nathanson & Kew 2010; Kew 2012; Sánchez-Sampedro *et al.* 2015, see also http://archive.hhs.gov/nvpo/concepts/intro6.htm for historical accounts) . Despite these impressive successes, many infectious diseases cannot yet be efficiently controlled or eradicated through vaccination programs, either because an effective vaccine has not yet been developed (as with HIV), or because it is impossible to vaccinate a sufficient proportion of the population to guarantee herd immunity (Anderson & May 1991). Indeed, although the World Health Assembly originally set a target date of 2000 for eradication of poliovirus, we are no closer today than we were over two decades ago, due to the difficulty of reaching remote populations.

Recent advances in molecular biology suggest that the centuries-old method of individual-based vaccine delivery could be on the cusp of a major revolution. Specifically, genetic engineering brings to life the possibility of a "transmissible vaccine" (Bull 2015b). Rather than directly vaccinating every individual within a population, a transmissible vaccine would allow large swaths of the population to be vaccinated effortlessly by releasing an infectious agent genetically engineered to be benign yet infectious. This concept may sound like science fiction, but some existing vaccines already do this to a limited extent, and transmissible vaccines have now been developed and deployed in wild animal populations (Bárcena *et al.* 2000; Hardy *et al.* 2006). Given the current pace of technological advance in genetic engineering, it is only a matter of time before transmissible vaccines can be easily developed for a wide range of diseases and we must begin to delineate the conditions under which their potentially large benefits outweigh their substantial risks.

A first step in this delineation is the development of mathematical theory that predicts the epidemiological gains we can expect to accrue through the use of a transmissible vaccine. Remarkably, even as we sit at the cusp of this major technological revolution in vaccine delivery, no mathematical theory exists that has been tailored to the specific questions posed by transmissible vaccines. We propose to fill this gap by developing the theoretical foundations for understanding the ecology and evolution of transmissible vaccines and testing the emerging theory using a viral model. Our work will build on preliminary results collected as part of a new collaboration between PI Nuismer (Biology and Mathematics) and Co-PI Bull (Biology) that has developed preliminary mathematical models and begun engineering an empirical system in which to test our emerging results. The recent addition of Co-PI Remien (Mathematics and Biology) to our collaboration adds mathematical strength and will help us to develop a more comprehensive theory. Specific objectives of the proposal are:

Objective 1. Develop a mathematical framework predicting the extent of protection provided by a transmissible vaccine. For a transmissible vaccine to be useful, it must be able to invade the target population and immunize a larger number of individuals than could be achieved using a traditional vaccine. We will develop mathematical models, novel approximations, and individual-based simulations that allow us to predict the fate of a transmissible vaccine.

Objective 2. Develop a mathematical framework predicting the evolution of a transmissible vaccine. Developing a transmissible vaccine requires that an infectious agent be manipulated, either by adding genes that confer immunity or by eliminating or altering genes that cause virulence. We will develop mathematical models, novel approximations, and

individual-based simulations to determine when these genetic modifications are evolutionarily robust and to study the epidemiological consequences when they are not.

Objective 3. Test model predictions using an experimental viral model. We have developed three laboratory model systems of transmissible vaccines. Each uses bacterial hosts and bacteriophage viruses. These systems will be used to test key predictions that emerge from the first two objectives.

BIOLOGICAL BACKGROUND

Many methods exist to develop vaccines, but all are based on the principle of exposing the host to antigens of the pathogen so that the host acquires immunity against the antigens, protecting against infection by the pathogen itself. Many vaccines cannot replicate; they consist of antigens in an agent that cannot replicate within the host such as a killed virus or bacterium, antigens expressed in yeast or plants that are injected or ingested, or simply the naked antigen itself (Lauring *et al.* 2010 and Table 1). In contrast, 'live' vaccines do possess the genetic machinery to replicate within the host. In fact, many of the most successful viral vaccines, such as the oral polio vaccine, FluMist, measles, mumps, and chicken pox (to name a few) use live virus to establish an infection (Lauring *et al.* 2010; Hanley 2011). In most of these applications, the virus is a genetically weakened (attenuated) version of the wild-type virus so that it does not cause disease. By establishing an otherwise normal infection, the attenuated virus generates an immune response that mimics the response to infection by the wild-type virus, and, as a result, typically leads to better immunity than from killed or inactivated vaccines.

Table 1. Types of vaccines and potential for transmission

Vaccine type	Vaccine	Transmission
Live, attenuated	Measles, mumps, rubella, Varicella (chicken pox), Influenza (FluMist), Rotavirus, oral Polio	Possible
Inactivated/Killed	Polio, Hepatitis A, Influenza (injection)	No
Inactivated toxin	Diptheria, tetanus	No
Subunit/conjugate	Hepatitis B, Influenza (injection), Pertussis, Pneumococcal, Meningococcal	No

http://www.historyofvaccines.org/content/articles/different-types-vaccines

A live virus is a prerequisite for transmission, and indeed, some live viral vaccines are transmissible although only minimally so (Mallory *et al.* 2011; Atrasheuskaya *et al.* 2012; Diaz-Ortega *et al.* 2012; Kew 2012). The attenuation process has typically reduced viral replication so much that the patient does not produce sufficient numbers of viral progeny to establish new infections, but there is no intrinsic reason why live viruses cannot transmit. Until now, however, there has been a major drawback of a transmissible vaccine: vaccine evolution back to high virulence.

The oral polio vaccine (OPV) is the most thoroughly studied in this respect. The vaccine establishes an infection of the gut that lasts for two to three weeks. During this time, virus is excreted, and secondary contacts of the vaccinee can become infected. Sabin (the 'father' of the OPV) considered this secondary transmission to be a positive attribute of the vaccine as it spreads the vaccine beyond the people who were directly vaccinated (Burns et al., 2014; Kew,

2012; Nathanson and Kew, 2010). With OPV, however, there are only two or three attenuating mutations in two of the serotypes, and vaccine transmission enables vaccine evolution to reverse those changes. Evolution of the OPV has consequently led to vaccine-derived epidemics and to circulating viruses derived from the vaccine (Kew 2012; Burns *et al.* 2014). Because the vaccine was not developed to avoid reversion, transmission creates an unwanted problem.

Evolutionary reversion of live viral vaccines would be the death knell of transmissible vaccines (developed through attenuation) if not for advances in genetic engineering that make reversion to high virulence less likely (Bull 2015b). With evolution to high virulence slowed or blocked, any transmission beyond the vaccinated individuals thus becomes the unconditional bonus that Sabin envisioned for OPV. However, these new engineering technologies merely solve the technical hurdle of making transmissible vaccines safer. They do not reveal what is needed for a transmissible vaccine to be effective, or to remain safe and effective in the face of viral evolution. Modeling is required for this latter goal.

Attenuation is not the only method suitable for transmissible vaccine construction. Recombinant vector vaccines can also be transmissible. This design consists of a harmless, but potentially transmissible live agent, engineered to carry part of a gene from the pathogen. The vaccine is thus a chimera of two viruses, and the pathogen component serves only to stimulate immunity; it does not perform any function important to the vaccine virus. An example of this type of vaccine is a form of the rabies vaccine that is commonly used on dogs and in baits given to wild animals in which a gene from the rabies virus is inserted into live *vaccinia* virus. Attempts to engineer contraceptive viruses for wildlife also use this strategy (Hardy *et al.* 2006; Hardy 2007), as have transmissible vaccines designed to curtail *Myxomatosis* infection in wild rabbits (Bárcena *et al.* 2000). A vaccine chimera of this type is unlikely to revert to virulence because it carries only a small part of the genome of the pathogen, but a different evolutionary issue raises its head: a chimeric virus that is transmissible may evolve to lose the cloned gene of the pathogen, which is needed to confer immunity, because the cloned gene offers no benefit to transmission. The likelihood of evolutionary loss of the cloned gene depends on details of the cloning and may not occur for some chimeric vaccines, but it is a commonly expected outcome (Gladstone *et al.* 2012; Schmerer *et al.* 2014a)

Box 1. Modeling a transmissible vaccine

Assuming large, homogenous, and well-mixed populations, the change in the quantities of susceptible individuals (S), individuals infected with the vaccine (I_V), individuals infected with the disease (I_D), and individuals that have recovered from infection and are now immune (R) can be described by the following system of differential equations:

$$\frac{dS}{dt} = rN - \beta_V S I_V - \beta_D S I_D - (\sigma + d)S \quad (1a)$$

$$\frac{dI_V}{dt} = \beta_V S I_V + \sigma S - (\delta_V + d) I_V \quad (1b)$$

$$\frac{dI_D}{dt} = \beta_D S I_D - (\delta_D + v + d) I_D \quad (1c)$$

$$\frac{dR}{dt} = \delta_V I_V + \delta_D I_D - dR \quad (1d)$$

where r is the growth rate of the host population, d is the background death rate of hosts, β_V is the transmission rate of the vaccine, β_D is the transmission rate of the infectious disease, δ_V and δ_D are the rates at which individuals infected with the vaccine or disease, respectively, recover and become immune, v is the virulence or rate at which the disease causes death, and σ is the supplementation rate for the vaccine.

These engineering methods no doubt represent just a small set of the possibilities for transmissible vaccines that will soon be realized. Whether transmissible vaccines become a

reality depends on several factors, but one of the first obvious steps is to develop a theoretical framework to understand their possible efficacy. A transmissible vaccine may not be desirable in all cases, but it could be useful in specific cases, including some human diseases, recalcitrant pockets of disease in just some human populations, and diseases of U.S. wildlife and agriculture. Indeed, the current method of curtailing rabies epidemics in wildlife involves air dropping vaccine-infused baits across broad geographic areas. A transmissible vaccine could vastly reduce the effort and cost associated with such programs.

OVERVIEW OF MODELING APPROACH

There is a long and rich history of mathematical modeling of infectious disease, tracing back to the classical epidemiological model of Kermack-McKendrick (1927). The result is a well-developed body of theory predicting the epidemiological and evolutionary dynamics of infectious disease as well as optimal vaccination strategies (e.g., May & Anderson 1979; vanBaalen & Sabelis 1995; Keeling 1999; Allen & Burgin 2000; Regoes *et al.* 2000; Antia *et al.* 2003; Day & Proulx 2004; Gandon 2004; Gomes *et al.* 2004; Wearing *et al.* 2005). Notably absent, however, are models of transmissible vaccines. The absence of such models is becoming increasingly critical as technological advances in genetic engineering make the widespread availability of transmissible vaccines virtually inevitable (Bárcena *et al.* 2000; Hardy *et al.* 2006).

Our approach to modeling a transmissible vaccine will build on existing models of traditional, directly administered vaccines. These models often divide the host population into four possible categories: 1) susceptible host individuals, 2) infected host individuals, 3) vaccinated individuals who are not yet immune, and 4) vaccinated individuals who have gained immunity. The novel mathematical twist that a transmissible vaccine adds to these well-studied models is the potential for the vaccine itself to transmit between hosts. Integrating vaccine transmission leads naturally to a model of the form shown in Box 1, which reduces to a standard vaccine model with delayed immunity when the potential for vaccine transmission is eliminated (e.g., $\beta_V = 0$). Utilizing transmissible vaccine models that reduce to standard vaccine models under particular sets of assumptions facilitates comparison with previous mathematical results, allows established mathematical tools and approximations to be re-purposed, and allows the benefits of transmissible vaccines to be clearly quantified using a standard vaccine as the reference point. Although the model in Box 1 is a reasonable starting point for analyses, we will consider variations of this basic model that capture the nuanced biology of different transmissible vaccines and the diseases they are designed to thwart (Table 1).

Table 1. Variations to the basic model

Variation	Rationale
Partial immunity	Not all vaccines will confer perfect immunity to the target disease
Transient immunity	In some cases, immunity may not be permanent
Indirect transmission	Some diseases and transmissible vaccines may be transmitted indirectly (e.g., water born)
Co-infection	Some diseases and vaccines may co-infect
Latent phases	There may be a delay before infected individuals can transmit disease or vaccine

In the following specific objectives we introduce the specific mathematical approaches we will use to quantify the potential benefits provided by transmissible vaccines. Mathematical analyses will focus on extensions and generalizations of the basic model developed in Box 1, and will rely on a complementary suite of analyses including asymptotic solutions, separation of time scales approximations, numerical solutions, and individual-based simulations.

SPECIFIC OBJECTIVES

Objective 1. Develop a mathematical framework predicting the extent of protection provided by a transmissible vaccine (Lead: Remien)

We will develop and analyze mathematical models of transmissible vaccines to determine the extent of protection provided across a wide range of assumptions. We will begin by analyzing relatively simple mass action differential equation models (Goal 1.1) before developing and analyzing more sophisticated models that account for stochasticity in transmission (Goal 1.2) and heterogeneity in hosts and environment (Goal 1.3). Where possible, we will obtain analytical solutions directly or through the use of approximations. When analytical solutions or approximations are unavailable, we will use numerical solutions and simulation to gain an understanding of model dynamics.

Goal 1.1 Predict the extent of vaccine protection in large, well-mixed populations

The advantage of transmissible vaccines over traditional vaccines is their potential to rapidly and efficiently immunize a large fraction of the population with minimal cost and effort. To quantify the potential gains achievable through the deployment of a transmissible vaccine, we will analyze the differential equation models described in Box 1 and Table 1, to determine the number of individuals immunized by time t^*, the number of individuals infected by the disease by time t^*, and the cumulative mortality caused by the disease over the epidemic, $M = \int_{t=0}^{t=\infty} vI_D(t)dt$. Preliminary work on this objective using numerical solutions of the ODEs described in Box 1 reveals that even small levels of vaccine transmission can greatly reduce the cumulative mortality of a disease (Figure 1). Using techniques similar to those used in analysis of the simple Kermack-McKendrick model (Anderson & May 1991; Heesterbeek & Roberts 1995; Hethcote 2000; Brauer & Castillo-Chavez 2010), we will develop analytical solutions that generalize these numerical results and extend them to other key quantities, such as the number of individuals immunized by time t^* and the number of individuals infected by the disease by time t^*.

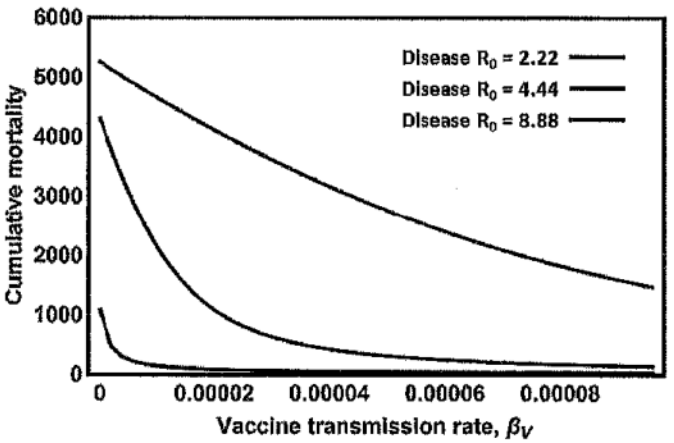

Figure 1. Consequences of vaccine transmission for cumulative mortality imposed by diseases with differing R_0

Goal 1.2: Predict the extent of vaccine protection in models with stochastic transmission

The models described in Goal 1.1 and Box 1 assume large population sizes and homogenous mixing among individuals. While these deterministic models often yield qualitatively general results and are analytically tractable, stochasticity in transmission of the vaccine and the disease may impact model results. For instance, when there is a small number of individuals in the vaccine infected class, such as at the beginning of a vaccination scheme, even a vaccine with a positive growth rate may die out. To accommodate stochasticity in transmission resulting from small numbers of infected or vaccinated individuals, we will develop and analyze continuous-time branching process models for transmissible vaccines (Figure 2). We will use these branching process models to identify the minimum number of initially

vaccinated individuals or the continual vaccination rate required to: 1) guarantee the initial spread of the vaccine, 2) meet target vaccine coverage and mortality reduction goals, and 3) eradicate the disease.

Following a similar approach to that used to study the spread of a disease with an initially small number of infective individuals (Whittle 1955; Daley 2001), vaccine transmission can be approximated by a simple birth-death process in the case where there is a small number of vaccinated individuals, no further vaccination ($\sigma = 0$), no individuals infected by the disease, and the number of secondary cases caused by an infectious individual is Poisson distributed. With these assumptions, the probability that the vaccine spreads from an initially small population size n is:

$$\begin{cases} 0 \text{ if } R_0 < 1 \\ 1 - \left(\frac{1}{R_0}\right)^n \text{ if } R_0 \geq 1 \end{cases}$$

For the branching process model where the transmissible vaccine is continually reintroduced ($\sigma > 0$), we will instead analyze the probability that the vaccine has spread to epidemic levels by time t^* and the number of vaccinated individuals by time t^*.

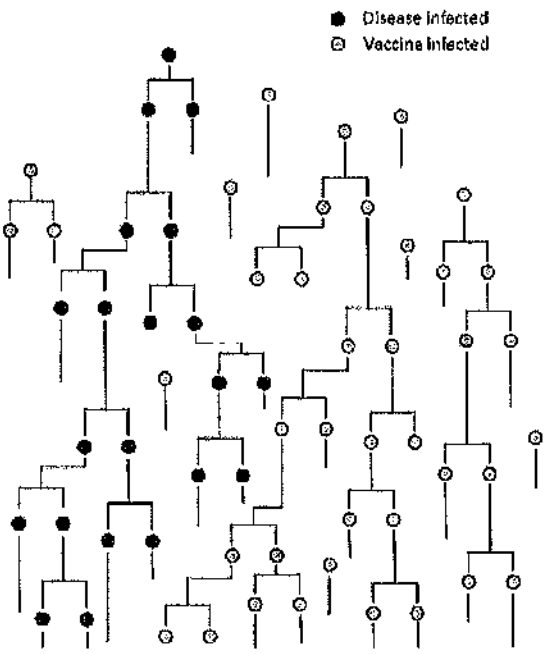

Figure 2. Schematic diagram of the stochastic race between infectious disease and transmissible vaccine. Disconnected blue circles represent continual supplementation of the transmissible vaccine.

After analyzing the conditions required for the spread of the vaccine, we will formulate Ito stochastic differential equations and Kolmogorov differential equations (Allen 2010) to study the extent of vaccine coverage and cumulative mortality in the context of the continuous time branching process models, with the number of susceptible, vaccinated, and infective individuals changing stochastically over time.

Goal 1.3: Predict the extent of vaccine protection in heterogeneous populations

Thus far, we have studied models that ignore individual variation in infectiousness. Individuals can, however, vary widely in infectiousness for a variety of reasons including effects of the host (e.g., age, occupation, behavior), pathogen (e.g., pathogen load, symptom severity) and environment (e.g., crowded setting, state of medical knowledge) (Lloyd-Smith *et al.* 2005). Indeed, it is well known that individual transmission potential is skewed such that 20% of the host population is typically responsible for 80% of the net transmission (Woolhouse *et al.* 1997). This heterogeneity in transmission poses a significant challenge for traditional vaccines, particularly when the most transmissive individuals tend to be outside the reach of public health systems, such as in the case of polio.

In contrast to standard vaccines, transmissible vaccines may be particularly adept at reaching highly transmissive individuals if they can be engineered to follow a similar transmission pathway as the target disease. We will develop and analyze mathematical models to evaluate whether this intuition is correct. If it is, far fewer individuals may need to be vaccinated to meet public health aims for disease reduction. To investigate how individual heterogeneity affects the dynamics of transmissible vaccines, we will begin by developing and

analyzing extensions of the ODE models described in Goal 1.1 and Box 1. Specifically, we will study models where two types of vaccine infected hosts and disease infected hosts exist, each characterized by a different transmission rate. By changing the degree to which transmission rates differ across host types, and the extent to which transmission rates of vaccine and disease are correlated across host types, we will be able to elucidate the conditions under which a transmissible vaccine outperforms a traditional vaccine, and by how much.

After analyzing the relatively simple ODE models, we will further investigate the effects of individual heterogeneity in transmission of vaccine and disease by developing and analyzing branching process models of transmissible vaccines with a range of distributions of the number of secondary cases caused by an infectious individual. The branching process models described in Goal 1.2 neglect individual variation, assuming that the expected number of secondary cases caused by an individual infected with the vaccine or disease is constant for all individuals, so that the number of secondary infections of an individual is Poisson distributed. If individuals vary in their expected number of secondary cases, the probability distribution of the number of secondary infections of an individual will be different from Poisson, leading to erroneous estimations of, for example, the probability that the vaccine or disease will spread (Callaway *et al.* 2000; Brauer & Castillo-Chavez 2010). We will extend the analyses described in Goal 1.2 to situations in which the expected number of secondary cases of the disease or vaccine varies with individual, with a range of correlation between the expected number secondary cases of the disease and of the vaccine for a given individual, corresponding to similarity of the transmission pathway of the disease and vaccine. As in the case without vaccines (Callaway *et al.* 2000), we will use probability generating functions to analyze the probability that the vaccine will spread for a range of distributions of expected number of secondary cases of an individual, such as gamma distributed, corresponding to a negative binomial distribution of the number of secondary infections of an individual of the vaccine or disease (Lloyd-Smith 2005). We will also study analogs of these models, where continual supplementation of the vaccine occurs, to gain insight into the effect of individual heterogeneity on the probability the vaccine has spread to epidemic levels by time t^* and to determine the effectiveness of the vaccination effort.

Objective 2. Develop a mathematical framework predicting the evolution of a transmissible vaccine (Lead: Nuismer)

Results from Objective 1 will elucidate the conditions under which a transmissible vaccine will be effective in reducing the impact of infectious disease. Those models will, however, assume that the transmissible vaccine is evolutionarily stable and thus that model parameters do not evolve. Yet, various attenuated vaccines are known to evolve when transmission occurs between hosts (Bull 2015b). For this reason, we must develop models that allow us to explore this potential "Achilles heel" of transmissible vaccines. Genetic engineering may be able to block this evolutionary reversion (Bull 2015b), but we are interested in knowing the consequences when it does occur. Furthermore, the models may suggest solutions that do not depend on genetic engineering. Work on Objective 2 will integrate vaccine evolution into our basic mathematical model (Box 1 and Table 1) using the framework of evolutionary population genetics.

Goal 2.1: Integrate vaccine evolution

A commonly used approach for modeling the evolution of infectious disease is adaptive dynamics (Dieckmann 2002; Kisdi & Geritz 2010; Allen *et al.* 2013). Models using this approach have developed a wide range of interesting predictions and been essential in developing our understanding of how infectious diseases evolve. Unfortunately, the adaptive dynamics approach is genetically implicit and thus cannot capitalize on the detailed genetic information

that is likely to be available for transmissible vaccines engineered within the laboratory. In cases where the genetic details matter, population genetics offers a powerful and versatile approach (Day & Gandon 2007). By developing population genetic models that predict the direction and rate of evolution for important vaccine traits, we can predict the durability of transmissible vaccines and facilitate the genetic engineering of safer and more evolutionarily robust designs.

We will begin with a very simple scenario where the genetically modified transmissible vaccine needs to accumulate *m* mutations to revert back to its wild type state, whether the wild type is a disease causing organism (in the case of an attenuated transmissible vaccine) or an innocuous infectious agent that no longer confers immunity to the target disease (in the case of a genetically engineered construct). By mapping vaccine genotypes to vectors of parameters (e.g., virulence, transmission rate), we can study the evolution of a transmissible vaccine for any possible mutational landscape. To make this approach concrete, imagine a simple scenario where only a single mutation is required to change the transmissible vaccine back into a wild type form that no longer confers immunity to the infectious disease. Using a simple extension of the model in Box 1 that integrates two possible vaccine strains, it is possible to show that the change in the frequency of the mutant vaccine is given by:

$$\frac{dp}{dt} = p(1-p)\left((\delta_V - \delta_V^*) + (\beta_V^* - \beta_V)S\right) + \mu(1-2p) - \frac{\sigma S p}{\widetilde{I_V}} \tag{2}$$

where p is the frequency of the mutant strain, β_V^* and δ_V^* are the transmission and recovery rates of the mutant vaccine, and $\widetilde{I_V}$ is the total number of hosts infected with the vaccine (mutant and wild type). This preliminary result reveals that an engineered vaccine will degrade most rapidly when the mutation rate (μ) is high and when the mutant has a greater transmission rate but slower recovery rate than the engineered vaccine. In addition, and less obviously, the rate at which the mutant vaccine spreads is slowed by the continual reintroduction of the wild type vaccine (σ) providing a glimpse of a potential strategy for managing vaccine evolution.

Further work on this Goal will focus on generalizing expression (2) to scenarios with multiple mutations (potentially co-segregating) and where population sizes are finite and evolution is a stochastic process (Figure 3). Fortunately, by utilizing a population genetic framework, we can capitalize on a well-established body of theory that predicts the probability of fixation for new mutations (Kimura 1962; Ewens 1967; Maruyama 1970), as long as we are willing to initially ignore feedbacks between vaccine evolution and epidemiological dynamics.

Although we will be able to develop a solid foundation of analytical results using a combination of novel approximations and existing theory, we will ultimately need to grapple with the complex interactions that are likely to occur between vaccine evolution and epidemiological dynamics. For instance, equation (2) shows that the rate of vaccine evolution depends on the number of susceptible hosts remaining within the population, and the number of individuals currently infected with the vaccine. From a practical standpoint, this means that understanding the full time-course of vaccine evolution, rather than just its initial evolution, requires studying the following system of coupled ODEs, even for the simplest evolutionary scenario where only two vaccine genotypes are possible:

$$\frac{dS}{dt} = rN - S\overline{\beta_V} - \beta_D S I_D - (\sigma + d)S \tag{3a}$$

$$\frac{dI_D}{dt} = \beta_D S I_D - (\delta_D + v + d)I_D \tag{3b}$$

$$\frac{d\widetilde{I_V}}{dt} = \widetilde{I_V}\left(\overline{\beta_V} + \overline{\delta_V} - d\right) + S\sigma \tag{3c}$$

$$\frac{dp}{dt} = p(1-p)\left((\delta_V - \delta_V^*) + (\beta_V^* - \beta_V)S\right) + \mu(1-2p) - \frac{\sigma S p}{\widetilde{I_V}} \tag{3d}$$

where $\overline{\beta_V}$ and $\overline{\delta_V}$ are the average transmission rate and recovery rate of the genetically heterogeneous vaccine population and thus evolve. Understanding the consequences of these feedbacks, and how they influence the evolutionary robustness of transmissible vaccines, will require entirely new mathematical approaches and tools. Even if we are unable to develop these over the course of the proposed work, we will be able to generate a predictive framework using numerical approaches and clearly identify and delineate an important mathematical problem of large biological relevance.

Goal 2.2: Predict when and how fast an attenuated vaccine will re-evolve virulence

One commonly used route to developing a transmissible vaccine is to attenuate (genetically weaken) the disease causing organism so that it no longer causes symptoms of disease but remains able to transmit (Table 1). For transmissible vaccines created in this way, a fundamental question is the likelihood of the vaccine re-evolving its prior level of virulence. Using the complementary approaches developed in Goal 2.1, we will work to answer this question as a function of the underlying genetic changes that produced the attenuated vaccine. In addition, we will explore potential strategies for managing and controlling evolution in attenuated transmissible vaccines. For instance, our preliminary results suggest it may be possible to slow evolution through the continual reintroduction of attenuated vaccine.

Goal 2.3: Predict when and for how long a genetically engineered vaccine will remain effective

An alternative route to developing a transmissible vaccine is to add a gene that stimulates host immunity to a transmissible but non-disease causing organism (Table 1). For example, the rabies vaccine administered to wildlife is a *vaccinia* virus engineered to carry a single rabies virus gene; the cytomegalovirus engineered to control vertebrate pests carries a foreign gene from the pest designed to induce autoimmunity. Transmissible vaccines created in this way face an evolutionary hurdle because, all else being equal, natural selection will favor viral genomes that eject the foreign gene and thus eliminate the metabolic costs the gene imposes at no benefit to the virus. As a consequence, we expect transmissible vaccines created in this way to generally be evolutionarily unstable, at least over long periods of evolutionary time. The key question, then, is not whether such a vaccine will persist indefinitely, but rather if it will immunize an epidemiologically relevant fraction of the host population prior to its evolutionary degradation. Using the approaches developed in the first goal of this objective, we will explore the rate at which evolution causes vaccine effectiveness to degrade, and evaluate the consequences of varying rates of evolution

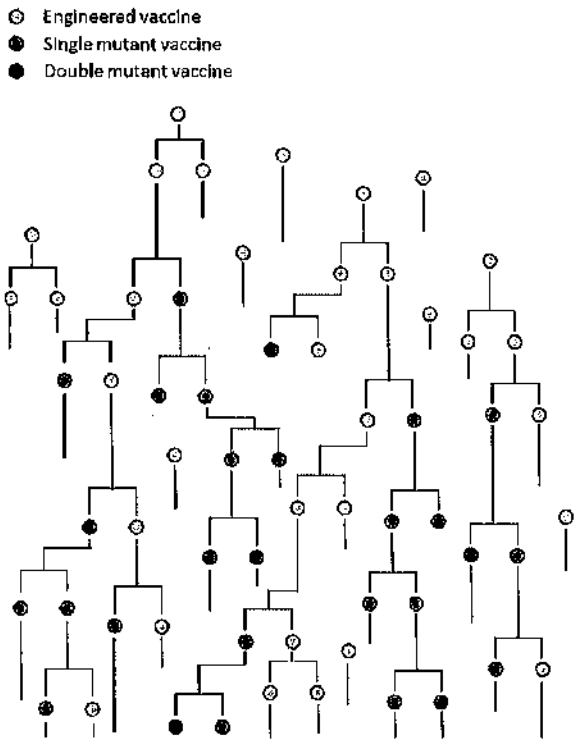

Figure 3. A schematic of transmissible vaccine evolution modeled as a stochastic process. Disconnected blue circles indicate continuous supplementation with the engineered vaccine

for the fraction of the host population that is immunized and the cumulative mortality caused by the disease.

Objective 3. Test predictions using experimental viral models (Lead: Bull)

The first two objectives will develop a theoretical framework for the ecology and evolution of transmissible vaccines. Work on Objective 3 will confront these models with the nuances of real organisms and evaluate their efficacy as predictive tools for the design and release of transmissible vaccines. All empirical work will use bacterial viruses (phages) and their bacterial hosts (*E. coli*). There are substantial differences between the life histories of phages and of human/animal viruses, but the phages pose unique advantages for experimental work: (i) their wild-type and genetically engineered strains are safe and pose no risk to plants or animals, (ii) their population densities and infection properties can be manipulated to a far greater degree than with any other viral system, (iii) model parameters can be estimated independently of model fit, and (iv) most of the systems we will use are already in hand. Indeed, there are thus far no alternative model systems that would allow experimental tests of the theory we propose to develop.

Goal 3.1: Develop attenuated and genetically engineered transmissible vaccines of bacteria against 'pathogenic' bacterial viruses.

The key to our empirical system lies in the unusual behavior of a small group of phages known as filamentous phages; this group includes the well-known, genetically similar phages M13, f1, and fd (we will work with f1). Although most phages escape their host by lysing them – dissolving the cell wall and causing the cell to rupture and die, filamentous phages do not kill their hosts. Instead, after infecting the host the progeny of filamentous phages are 'secreted' continuously though the bacterial cell wall and membranes. The non-killing behavior of filamentous phages opens the door to their use as a transmissible vaccine for the bacterial population. We will investigate three different types of phage vaccine, each of which serves as a model for the way in which transmissible vaccines, in general, can be designed.

Design 1 — Benign filamentous phages will be used as vaccines against other (harsh) filamentous phages, capitalizing on the fact that infection of a bacterial cell by one filamentous phage blocks infection by other filamentous phages. The only engineering needed for this work is to clone drug resistance genes into the phage, so that infection by different phages can be distinguished easily (the infected cells become resistant to the drug). These viruses are on hand from previous work (Bull *et al.* 1991; Bull & Molineux 1992; Messenger *et al.* 1999; Sachs & Bull 2005), but we can also create them anew as needed.

Design 2 — Filamentous phages will be used as vaccines against the lethal RNA phage Qβ, again taking advantage of a biological quirk that renders a bacterial cell infected by a filamentous phage immune to Qβ. No engineering is required for this work, but again, assays are facilitated if we have drug resistance encoded by the vaccine. These viruses are on hand, and the protection afforded by filamentous phages has been shown in preliminary studies.

Design 3 — Filamentous phages will be used as vaccines against various lethal DNA viruses (e.g., T4, T5, T7). This objective requires engineering the filamentous phage. One method already in hand is to engineer a 'targetron' into the filamentous phage (Yao *et al.* 2005); the targetron disrupts the gene encoding the receptor used by the lethal (DNA) virus. We have successfully cloned a targetron against the DNA phage T5 in a context similar to the one needed here. Another method is to engineer the filamentous phage with a 'guide' RNA used by the CRISPR *Cas-9* gene; the *Cas*-9 protein is encoded in the host, and when it receives the the guide RNA, it destroys the incoming phage DNA. We have not tested the *Cas-9* system, but it

is commercially available on a plasmid and has been easily engineered to function in *E. coli* against several DNA phages (Yaung *et al.* 2014). Year 1 will include developing this system.

Goal 3.2: Estimate model parameters and test model adequacy

Phages and host will be grown in liquid cultures. Because of mass action, the dynamics in liquid are characterized by few parameters, which we will estimate directly: host and phage densities, bacterial growth rates, adsorption rates, phage burst sizes (birth rates), and time between infection and phage reproduction (Bull *et al.* 2011). The primary challenge we must confront in this goal is to equate these experimental parameters with the more general parameters defining the model in Box 1, and its variations. We will take a twofold approach to this problem. Our first approach will be useful when model predictions rely on emergent parameters such as the basic reproductive number, R_0, that can be calculated for both types of models. In such cases, the parameter estimation problem is greatly simplified and we need only calculate the theoretically relevant emergent parameters from the experimental system. In other cases, however, our models may rely on the values of individual parameters that cannot be directly estimated in the experimental system. In cases like this, we will use a second approach. Specifically, we will develop a mathematical model tuned to the biology of the experimental system and for which all key parameters can be directly estimated. We will then analyze this more specific model, and attempt to re-create the key theoretical result we wish to test. If we cannot recreate the key result with this more specific and biologically detailed model, it is unlikely to be sufficiently general to warrant empirical testing; if we can re-create the key results, it can be easily tested experimentally using direct estimates of model parameters.

Goal 3.3: Test key predictions of the mathematical models developed in Objectives 1-2

This goal is the crux of the proposed experimental work in this proposal and will utilize the phage systems described above to test emerging mathematical predictions. The exact suite of experiments we ultimately perform will depend on the results of our mathematical analyses, but two basic experiments will be at the core.

Experiment 1. Estimating vaccine protection — Results of Objective 1 will predict the protection provided by vaccines with different properties (e.g., Figure 1). The theory will also elucidate how the extent of protection depends on stochastic effects and the rate at which the vaccine is directly applied to the population. Using the interaction between host and paired strains of filamentous phages (one vaccine strain and one nasty strain), we will be able to estimate the fraction of the host population that is vaccinated and protected against the disease for strains with various rates of transmission. This determination is made easy by filamentous phages with drug resistance markers – so that protected hosts can be scored by growth on antibiotic plates. In addition, by using sparse host populations, we can investigate stochastic effects. And by continually reintroducing the vaccine we can explore how the rate of supplementation influences cumulative protection. As noted in Goal 3.2, our tractable phage systems allow us both to predict vaccine behaviors from directly parameterized models and to observe them in the populations.

Experiment 2. Consequences of evolutionary vaccine decay — Objective 2 will predict the population consequences of a transmissible vaccine that gradually evolves immunogenicity loss (e.g., from having lost the engineered DNA insert). Using the CRISPR *Cas-9* system, we will engineer this situation directly. A filamentous phage engineered to carry a guide RNA protecting against a highly virulent DNA phage (T4, T5, or T7) will be competed with a mutant vaccine that lacks guide RNA and thus is transmissible but no longer acts as a vaccine. In addition to estimating the rate at which our genetically engineered vaccine degrades, we will be able to estimate the consequences of vaccine degradation on overall levels of vaccination and cumulative mortality in the host population. By using guide RNAs of different compositions we

can even manipulate the fitness consequences to the vaccine strain of carrying the immunogenic insert. Finally, we can explore the interaction between vaccine robustness and disease virulence by using different "disease" phages that vary in growth rate.

Project Timeline and management

Task	Year 1	Year 2	Year 3	Year 4
Objective 1 *Lead: Remien*	1.1 Mass action models			
	1.2 Stochastic models			
		1.3 Heterogeneous host models		
Objective 2 *Lead: Nuismer*	2.1 Developing mathematical tools for vaccine evolution			
			2.2 Evolution of virulence	
			2.3 Evolution of reduced immunogenicity	
Objective 3 *Lead: Bull*	3.1 Develop systems			
		3.2 Estimate key parameters		
			3.3 Test emerging mathematical results	
Broader Impacts	Recruit undergraduate cohort and develop research proposal	Mentor students through completion of their research project		Guide students through publication of their results
	Recruit and train first postdoctoral researcher		Recruit and train second postdoctoral researcher	

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Nuismer S.L. & Ridenhour B.J. (2008). The contribution of parasitism to selection on floral traits in Heuchera grossulariifolia. *Journal of Evolutionary Biology*, 21, 958-965.

Nuismer S.L., Ridenhour B.J. & Oswald B.P. (2007). Antagonistic coevolution mediated by phenotypic differences between quantitative traits. *Evolution*, 61, 1823-1834.

Oswald B.P. & Nuismer S.L. (2007). Neopolyploidy and pathogen resistance. *Proceedings of the Royal Society B*, 274, 2393-2397.

Oswald B.P. & Nuismer S.L. (2011a). Neopolyploidy and diversification in *Heuchera grossulariifolia Evolution*, 65, 1667-1679.

Oswald B.P. & Nuismer S.L. (2011b). A Unified Model of Autopolyploid Establishment and Evolution. *American Naturalist*, 178, 687-700.

Otto S.P., Servedio M.R. & Nuismer S.L. (2008). Frequency-dependent selection and the evolution of assortative mating. *Genetics*, 179, 2091-2112.

Paff M.L., Stolte S.P. & Bull J.J. (2014). Lethal mutagenesis failure may augment viral adaptation. *Mol. Biol. Evol.*, 31, 96-105.

Poullain V. & Nuismer S.L. (2012). Infection Genetics and the Likelihood of Host Shifts in Coevolving Host-Parasite Interactions. *American Naturalist*, 180, 618-628.

Regoes R.R., Nowak M.A. & Bonhoeffer S. (2000). Evolution of virulence in a heterogeneous host population. *Evolution*, 54, 64-71.

Ridenhour B.J. & Nuismer S.L. (2007). Polygenic traits and parasite local adaptation. *Evolution*, 61, 368-376.

Ridenhour B.J. & Nuismer S.L. (2014). A quantitative genetic approach for predicting ecological change in biological communities. *Theoretical Ecology*, 7, 137-148.

Sachs J.L. & Bull J.J. (2005). Experimental evolution of conflict mediation between genomes. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 390-395.

Sánchez-Sampedro L., Perdiguero B., Mejías-Pérez E., García-Arriaza J., Di Pilato M. & Esteban M. (2015). The Evolution of Poxvirus Vaccines. *Viruses*, 7, 1726-1803.

Schmerer M., Molineux I.J., Ally D., Tyerman J., Cecchini N. & Bull J.J. (2014a). Challenges in predicting the evolutionary maintenance of a phage transgene. *J Biol Eng*, 8, 21.

Schmerer M., Molineux I.J. & Bull J.J. (2014b). Synergy as a rationale for phage therapy using phage cocktails. *PeerJ*, 2, e590.

Springman R., Kapadia-Desai D.S., Molineux I.J. & Bull J.J. (2012a). Evolutionary recovery of a recombinant viral genome. *G3*, 2, 825-830.

Springman R., Keller T., Molineux I.J. & Bull J.J. (2010). Evolution at a high imposed mutation rate: adaptation obscures the load in phage T7. *Genetics*, 184, 221-232.

Springman R., Molineux I.J., Duong C., Bull R.J. & Bull J.J. (2012b). Evolutionary stability of a refactored phage genome. *ACS Synth Biol*, 1, 425-430.

vanBaalen M. & Sabelis M.W. (1995). The dynamics of multiple infection and the evolution of virulence. *American Naturalist*, 146, 881-910.

Wearing H.J., Rohani P. & Keeling M.J. (2005). Appropriate models for the management of infectious diseases. *Plos Medicine*, 2, 621-627.

Whittle P. (1955). The outcome of a stochastic epidemic-a note on Bailey's paper. *Biometrika*, 42, 116-122.

Woolhouse M.E.J., Dye C., Etard J.F., Smith T., Charlwood J.D., Garnett G.P., Hagan P., Hii J.L.K., Ndhlovu P.D., Quinnell R.J., Watts C.H., Chandiwana S.K. & Anderson R.M. (1997). Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. *Proceedings of the National Academy of Sciences of the United States of America*, 94, 338-342.

Yao J., Zhong J. & Lambowitz A.M. (2005). Gene targeting using randomly inserted group II introns (targetrons) recovered from an Escherichia coli gene disruption library. *Nucleic Acids Res.*, 33, 3351-3362.

Yaung S.J., Esvelt K.M. & Church G.M. (2014). CRISPR/Cas9-mediated phage resistance is not impeded by the DNA modifications of phage T4. *PLoS ONE*, 9, e98811.

Yoder J.B. & Nuismer S.L. (2010). When Does Coevolution Promote Diversification? *American Naturalist*, 176, 802-817.

Biographical sketch: Scott L. Nuismer

a. Professional Preparation

University of Utah	Biology	B.S. 1996
Washington St. University	Biology	Ph.D. 2000
University of Texas	Mathematical Genetics	2001-2003

b. Appointments

Professor, University of Idaho, Department of Mathematics. 2014-present (Affiliate)
Professor. University of Idaho. Department of Biological Sciences. 2013-present.
Associate Professor. University of Idaho. 2008-2013.
Assistant Professor. University of Idaho. 2003-2008.
NIH Postdoctoral Fellow. University of Texas. 2002-2003. Sponsor: Mark Kirkpatrick.
Postdoctoral Associate. University of Texas. 2001-2002. Sponsor: Mark Kirkpatrick.

c. Products

(i) Five products most closely related to the proposed work

Nuismer S.L., L.J. Harmon. 2015. Predicting rates of species interaction using phylogenetic trees. *Ecology Letters* 18:17-27.

Dybdahl, M.F., C.E. Jenkins, and S.L. Nuismer. 2014. Identifying the molecular basis of host-parasite coevolution: merging models and mechanisms. *The American Naturalist.* 184:1-13

Gilman, RT, and D.C. Jhwueng, and S.L. Nuismer. 2012. Coevolution in multidimensional trait space favors escape from parasites and pathogens. *Nature.* 483:328-330

Poullain, V, and S.L. Nuismer. 2012. Infection genetics and the likelihood of hosts shifts in coevolving host-parasite interactions. *The American Naturalist.* 180:618-628

Nuismer, S. L., R. Gomulkiewicz, and B. J. Ridenhour. 2010. When Is Correlation Coevolution? *The American Naturalist* 175:525-537.

(ii) Five other significant products

Jones, E., S.L. Nuismer, and R. Gomulkiewicz. 2013. Revisiting Darwin's conundrum reveals a twist on the relationship between phylogenetic distance and invasibility. *PNAS 110:* 20627–20632

Yoder, J.B. and S.L. Nuismer. 2010. When does coevolution promote diversification? *The American Naturalist* 176:802-81.

Nuismer, S.L., and S.P. Otto. 2005. Host-parasite interactions and the evolution of gene expression. *PLoS Biology* 3(7):1283-1288.

Otto, S.P. and S.L. Nuismer. 2004. Species interactions and the evolution of sex. *Science* 304:1018-1020.

Nuismer, S.L., and S.P. Otto. 2004. Host-parasite interactions and the evolution of Ploidy. *PNAS* 101:11036-11039.

d. Synergistic activities

2013-Present	Associate Editor for *The American Naturalist*
2008-2011	Associate Editor for *Evolution*.
2011	Organized Mathematical Biosciences workshop on coevolution (with Sharon Strauss)

2010	Organized Pacific Northwest Evolutionary Biology Meeting (EVO-WIBO)
2007	Mentor for the McNair program for underrepresented groups.

e. Collaborators & Other Affiliations

(i) Collaborators and Co-Editors (21)

Michael Alfaro	UCLA
Michael Barfield	Florida
Jordi Bascompte	Estacion Donana
John Byers	Idaho
Michael Doebeli	UBC.
Sylvain Gandon	CNRS
Robert Gilman	Liverpool
Richard Gomulkiewicz	WSU
Luke Harmon	Idaho
Katy Heath	Illinois
Robert Holt	Florida
D.C. Jhwueng	Feng-Chia University
Pedro Jordano	Estacion Donana
Oliver Kaltz	Montpelier
Sally Otto	UBC.
Ben Ridenhour	Notre Dame
Barrie Robison	Idaho
Maria Servedio	UNC
Jeremy Yoder	Minnesota
Bruce Anderson	University of Stellenbosch
Emily Jones	Rice

(ii) Graduate Advisors and Postdoctoral Sponsors (3)

John N. Thompson	UCSC
Richard Gomulkiewicz	WSU
Mark Kirkpatrick	UT-Austin

(iii) Thesis Advisor and Postgraduate-Scholar Sponsor

Graduate students (6 Total)

Benjamin Oswald. Ph.D. 2010
Virginie Poullain. Ph.D. 2011
Francois Blanquart. Ph.D. 2013
Ailene MacPherson. MS. 2015
Elizabeth Thornquist. Ph.D. Current
Bob Week. Ph.D. Current

Post-docs (3 Total)

Benjamin Ridenhour
Florence Debarre
Anahi Espindola

Role in Project

Nuismer will coordinate overall project implementation and facilitate interaction among individuals working on mathematical and empirical objectives of the project by organizing the annual meeting of project participants. Nuismer has an extensive background in developing and analyzing mathematical models of host-parasite interactions, and particular expertise with models focused on how these interactions evolve in spatially structured environments. Consistent with this expertise, Nuismer will be involved in the mathematical modeling that comprises the first two specific objectives and will lead efforts to model the evolution of transmissible vaccines in the second objective. In addition, Nuismer will coordinate recruitment of undergraduate researchers and postdoctoral researchers at the University of Idaho and will be involved in their training on a day to day basis.

Multiple PD/PI Leadership Plan

Rationale for multiple PIs

A co-PI structure was chosen to reflect the two disciplines being brought together in the proposal – Biology and mathematics. PI Nuismer has extensive experience and expertise developing and analyzing mathematical models but was formally trained as a biologist. Co-PI Remien provides complementary modeling expertise and a formal background in mathematics. Nuismer and Remien will use their combined mathematical expertise to develop the theory proposed in the first two objectives. Co-PI Bull has a long track record of developing insightful empirical tests of mathematical predictions and will lead the empirical studies that make up the third specific objective.

Leadership plan

Nuismer and Remien have offices in close proximity and will meet bi-weekly to discuss research objectives and all administrative responsibilities. Skype meetings will be held as needed to connect the Idaho and Texas arms of the project. In addition, Bull travels the Idaho regularly and during those visits we will conduct weekly meetings with all co-PIs. All co-PIs will share research results and discuss changes in research directions or reallocation of funds, if necessary. Co-authorship on publications will be established based on the relative scientific contributions of the co-PIs and key personnel.

Conflict resolution

If a conflict arises, the co-PIs will meet and attempt to resolve the dispute. If they fail to resolve the dispute, they will attempt to come to a mutual agreement with the aid of university ombudsman. Failing that, the disagreement shall be referred to an arbitration committee consisting of two impartial senior faculty to be appointed, one each, by the Deans of the College of Sciences at the University of Idaho and the University of Texas. No members of the arbitration committee will be directly involved in the research grant or disagreement.

Biographical Sketch: Christopher H. Remien

a. Professional Preparation

St. Olaf College	Northfield, MN	Mathematics, Russian	B.A.	2005
University of Utah	Salt Lake City, UT	Mathematics	M.Sc.	2008
University of Utah	Salt Lake City, UT	Mathematics	Ph.D.	2012
National Institute for Mathematical and Biological Synthesis	Knoxville, TN	Mathematical Biology	Postdoctoral Fellow	2012-2014

b. Appointments

University of Idaho	Affiliate Faculty	Statistics	2015-Present
University of Idaho	Assistant Professor	Mathematics	2014-Present
University of Idaho	Affiliate Faculty	Biology	2014-Present
University of Idaho	Affiliate Faculty	Center for Modeling Complex Interactions	2014-Present

c. Products

(i) Up to five products most closely related to the proposed work

- Remien CH, Adler FR, Waddoups L, Box TD, Sussman NL. Mathematical Modeling of Liver Injury After Acetaminophen Overdose: Early Discrimination Between Survival and Death. Hepatology. 56: 727-734. 2012.
- Remien CH, Sussman NL, Adler FR. Mathematical Modelling of Chronic Acetaminophen Metabolism and Liver Injury. Mathematical Medicine and Biology. 31(3): 302-317. 2014.
- Remien CH, Adler FR, Chesson LA, Valenzuela LO, Ehleringer JR, Cerling TE. Deconvolution of Isotope Signals from Bundles of Multiple Hairs. Oecologia. 175:781-789. 2014.
- Cerling TE, Wynn JG, Andanje SA, Bird MI, Korir DK, Levin NE, Mace WD, Macharia AN, Quade J, Remien CH. Woody Cover and Hominin Environments in the Past 6 Million Years. Nature. 476: 51-56. 2011.
- Remien CH. Modeling the dynamics of stable isotope tissue-diet enrichment. Journal of Theoretical Biology. 367: 14-20. 2015.

(ii) Up to five other significant products

- Cerling TE, Wittemyer G, Ehleringer JR, Remien CH, Douglas-Hamilton I. History of Animals Using Isotope Records (HAIR): A 6-year Dietary History of One Family of African Elephants. Proceedings of the National Academy of Sciences (USA). 106(20): 8093-8100. 2009.
- O'Grady SP, Valenzuela LO, Remien CH, Enright LE, Jorgensen M, Kaplan J, Wagner J, Cerling TE, Ehleringer JR. Hydrogen and Oxygen Isotope Ratios in Body Water and Hair: Modeling Isotope Dynamics in Non-Human Primates. American Journal of Primatology. 74: 651-660. 2012.

- O'Grady SP, Wende AR, Remien CH, Valenzuela LO, Enright LE, Chesson LA, Abel ED, Cerling TE, Ehleringer JR. Aberrant Water Homeostasis Detected by Stable Isotope Analysis. PLoS One. 5(7). 2010.
- Sussman NL, Remien CH, Kanwal F. The End of Hepatitis C. Clinical Gastroenterology and Hepatology. 12: 533-536. 2014.

d. Synergistic activities

- Led a year-long Research Experience for Undergraduates at University of Utah in which a diverse group of five undergraduate students developed mathematical models of melanoma formation and immunological control.
- Led a Mathematical Biology Journal Club at the University of Utah for first and second year graduate students.
- Served as a project mentor to a group of mathematics and biology graduate students in the Joint 2013 MBI-NIMBioS-CAMBAM Summer Graduate Workshop. The students simulated a stochastic epidemic and used Bayesian statistical techniques to estimate underlying parameters from simulated data.
- Visited, met with students, and gave applied math seminar at Tennessee State University, a historically black university and NIMBioS minority-serving partner institution.
- Recipient of NSF IGERT fellowship, RTG fellowship, and NIMBioS postdoctoral fellowship.

e. Collaborators and Other Affiliations

(i) Collaborators and Co-Editors (15 total)

Frederick Adler (University of Utah), Terry Box (University of Utah), Thure Cerling (University of Utah), Lesley Chesson (University of Utah), Denise Dearing (University of Utah), James Ehleringer (University of Utah), Steve Krone (University of Idaho), Chris Marx (University of Idaho), Aaron Miller (University of Utah), Tanya Miura (University of Idaho), Ben Ridenhour (University of Idaho), Norman Sussman (Baylor College of Medicine), Luciano Valenzuela (CONICET, University of Utah), Andreas Vasdekis (University of Idaho), Michelle Wiest (University of Idaho)

(ii) Graduate Advisors and Postdoctoral Sponsors (4 total)

Frederick Adler (University of Utah), Thure Cerling (University of Utah), Louis Gross (NIMBioS, University of Tennessee), Nathan Sanders (University of Copenhagen, University of Tennessee)

(iii) Thesis Advisor and Postgraduate-Scholar Sponsor (1 total)

Evan Martin (University of Idaho) M.Sc. Current

Role in Project

Remien will work with PI Nuismer on the mathematical modeling in the first two specific objectives and will lead modeling efforts in the first objective, developing a mathematical framework to predict the extent of protection provided by transmissible vaccines. Remien has extensive experience in mathematical biology, developing and analyzing mechanistic mathematical models to issues as diverse as acetaminophen overdose, incorporation of stable isotopes into animal tissues, and detoxification of ingested toxins in mammals. He has applied and developed a wide variety of mathematics including dynamical systems, bifurcation theory, probability, inverse methods, statistics, and simulations. Together with PI Nuismer, Remien will recruit undergraduate and postdoctoral researchers and train them on a day-to-day basis.

Multiple PD/PI Leadership Plan

Rationale for multiple PIs

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Biographical Sketch: James J. Bull

a. Professional Preparation

University of Sussex	(postdoc)	1980-1981	Biology
University of Wisconsin	(postdoc)	1977-1980	Genetics
University of Utah	Ph.D.	1971-1977	Biology
Texas Tech University	B.S.	1967-1971	Zoology

b. Appointments

1999-present	University of Texas, Austin	Professor (Integrative Biology, following reorganization)
1991-99	University of Texas, Austin	Professor (Zoology)
1986-91	University of Texas, Austin	Associate Professor (Zoology)
1983-86	University of Texas, Austin	Assistant Professor (Zoology)
1981-82	University of Utah	Research Assistant Professor (Biology)

c. Products

(i) Five publications most closely related to proposal project

Bull, J.J. 2015. Evolutionary reversion of live viral vaccines: Can genetic engineering subdue it? Virus Evolution 1(1): vev005

Cecchini N, Schmerer M, Molineux IJ, Springman R, Bull JJ. 2013. Evolutionarily stable attenuation by genome rearrangement in a virus. G3. 3(8):1389-97. doi: 10.1534/g3.113.006403.

Bull, J.J. and D. Ebert. 2008. Invasion thresholds and the evolution of nonequilibrium virulence. *Evolutionary Applications* **1**: 172-182.

Sachs, J.L., and J. J. Bull. 2005. Experimental evolution of conflict mediation between genomes. *Proceedings National Academy Sciences* **102**:390-395.

Bull, J.J., and I.J. Molineux. 1992. Molecular genetics of adaptation in an experimental model of cooperation. *Evolution* **46**:882-895.

(ii) Five other significant publications

Bull, J.J. 2015. Evolutionary decay and the prospects for long-term disease intervention using engineered insect vectors. Evol Med Public Health. 2015 Jul 8;2015(1):152-66.

Bull JJ, Lauring AS. 2014. Theory and empiricism in virulence evolution. PLoS Pathog. **2014** Oct 23;10(10):e1004387

Bull JJ, Turelli M. 2013. Wolbachia versus dengue: evolutionary forecasts. Evolution, Medicine and Public Health 2013 (1): 197-207. eot018doi: 10.1093/emph/eot018.

Bull JJ, Molineux IJ, Wilke CO. 2012. Slow fitness recovery in a codon-modified viral genome. Mol Biol Evol. 29(10):2997-3004.

Bull, J.J., and R. R. Regoes. 2006. Pharmacodynamics of non-replicating viruses, bacteriocins and lysins. Proc. Royal Soc. (B) **273**(1602):2703-12.

d. Synergistic Activities

NIH study section Genetic Variation & Evolution: member 2004-2006, chair 2006-2008
NIH Special study sections: chair on 2-3 meetings/year 2011, 2012, Ad Hoc on 2 in 2015.
Associate Editor, Genetics (2009-present)
Chair, 2011 Gordon Conference on Microbial Population Biology
Annually teach 500 non-science major undergrads critical thinking

e. Collaborators and other affiliations (previous 48 months) = 31

D. Ally (industry)	S. Krone (U. Idaho)
R. Antia (Emory U)	A. Lauring (U. Mich.)
N. Cecchini (tech at MD Anderson)	I. Molineux (U Texas)
R. Bull (son)	A. Nguyen (dental school)
S. Collins (Edinburgh U)	G. Otto (U Texas)
C. Crandall (undergrad, U. Idaho)	M. Paff (Grad student, U Texas)
A. Ellington (U. Texas)	A. Rodriguez (undergrad, U. Idaho)
J. Gill (Texas A&M)	M. Schmerer (U Texas)
E. Gladstone (med school)	R. Springman (tech in DC area)
W Harcombe (U Minnesota)	M. Turelli (UC Davis)
R. Heineman (Kutztown U)	J. Tyerman (industry)
T. Jessop (Massey U, Australia)	E. Vimr (U Illinois)
P. Joyce (U Idaho)	I-Nang Wang (SUNY Albany)
D. Kapadia-Desai (former undergrad, unknown)	M. Whiteley (U. Texas)
T. Keller (Ga. Tech as postdoc)	H. Wichman (U Idaho)
B. Kochin (Emory U)	C. Wilke (U Texas)
S. Krone (U. Idaho)	

Graduate and Postdoctoral advisors of Bull (4)

J. F. Crow (deceased)
E. Charnov (retired)
J. Legler (deceased)
J. Maynard Smith (deceased)

Thesis Advisor and Postgraduate Scholar Sponsorships (previous 5 years) **(5)**

Sam Brown (faculty, U. Edinburgh)
W. Harcombe (faculty, U. Minnesota)
R. Heineman (faculty, Kutztown U.)
T. Keller (postdoc Georgia Tech)
M. Paff (current grad student)

Role in Project

Bull will be responsible for the empirical side of the project, which will be carried out in his lab at the U. of Texas. This will involve supervising the (half-time) technician to carry out the lab work, but Bull will do some of the lab work himself. Bull will also advise on the models in all phases of the project and specifically the models tailored to the empirical work. The choice of which theoreticial results to test will be done in close collaboration by all 3 PIs/Co-PIs, with Bull specifically advising on the technical feasibility of various tests. Bull will also advise the modeling regarding which features of viral genome engineering are likely to become feasible.

Multiple PD/PI Leadership Plan

Rationale for multiple PIs

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Current and Pending Support

(See GPG Section II.D.8 for guidance on information to include on this form.)

The following information should be provided for each investigator and other senior personnel. Failure to provide this information may delay consideration of this proposal.

Investigator: Scott L Nuismer

Other agencies (including NSF) to which this proposal has been/will be submitted.

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

MPS BIO: Developing a multivariate theory of phenotypic coevolution

Source of Support: NSF

Total Award Amount: $246,717 Total Award Period Covered: September 2011-August 2016

Location of Project: University of Idaho

Person-Months Per Year Committed to the Project. Cal: Acad: (b)(6) Sumr: (b)(6)

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

A Bayesian approach to inferring the strength of coevolution

Source of Support: NSF

Total Award Amount: $251,014 Total Award Period Covered: July 2015-June 2018

Location of Project: University of Idaho

Person-Months Per Year Committed to the Project. Cal: Acad: Sumr: (b)(6)

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

Predicting the evolution of synthetic genomes: transmissible viral defense

Source of Support: NSF (Michigan State University; BEACON)

Total Award Amount: $95,311 ($34,279 to Nuismer) Total Award Period Covered: May 2014 -- September 2016

Location of Project: University of Idaho

Person-Months Per Year Committed to the Project. Cal: Acad: Sumr:

(b)(4)

(b)(4)

*If this project has previously been funded by another agency, please list and furnish information for immediately preceding funding period.

Current and Pending Support

(See GPG Section II.D.8 for guidance on information to include on this form.)

The following information should be provided for each investigator and other senior personnel. Failure to provide this information may delay consideration of this proposal.

Investigator: Christopher H. Remien	Other agencies (including NSF) to which this proposal has been/will be submitted.

(b)(4)

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

Mathematical Modeling of Acetaminophen-Induced Liver Injury to Assess Outcome

PI: Christopher H. Remien

Source of Support: (b)(4); (b)(6)

Total Award Amount: $68,153 Total Award Period Covered: Jul 1, 2015- Jun 30, 2016

Location of Project: University of Idaho

Person-Months Per Year Committed to the Project. Cal: Acad: (b)(6) Sumr: (b)(6)

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

Modeling variability in persistence induced from within by a toxic metabolite

PI: Christopher Marx, Co-PI: Andreas Vasdekis, Collaborator: Christopher H. Remien

Source of Support: CMCI Pilot Grant, NIH COBRE

Total Award Amount: $66,962 Total Award Period Covered: 1 year

Location of Project: University of Idaho

Person-Months Per Year Committed to the Project. Cal: Acad: (b)(6) Sumr:

(b)(4)

(b)(4)

*If this project has previously been funded by another agency, please list and furnish information for immediately preceding funding period.

Current and Pending Support

(See GPG Section II.D.8 for guidance on information to include on this form.)

The following information should be provided for each investigator and other senior personnel. Failure to provide this information may delay consideration of this proposal.

Investigator: Bull, JJ

Other agencies (including NSF) to which this proposal has been/will be submit-

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

Persistent viral attenuation by transcriptional and translational deoptimization

PIs: C O Wilke, JJ Bull, D. Boutz

Source of Support: NIH 2R01GM088344-05

Total Award Amount: $1,240,000 Total Award Period Covered: 05/01/2015–04/30/2019

Location of Project: University of Texas at Austin

Person-Months Per Year Committed to the Pro- Cal: (b)(6) Acad: Sumr:

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

Experimental Models of Viral Evolution at High Mutation Rate (in second no-cost extension)

PI: J. J. Bull

Source of Support: NIH GM 57756-(13-16)

Total Award Amount: $818,129 Total Award Period Covered: 09/01/2010–08/31/2016

Location of Project: University of Texas at Austin

Person-Months Per Year Committed to the Pro- Cal: (b)(6) Acad: Sumr:

Support: ☒ Current ☐ Pending ☐ Submission Planned in Near Future ☐ *Transfer of Support

Project/Proposal Title:

Predicting the evolution of synthetic genomes: transmissible viral defense

PIs: JJ Bull, S Nuismer

Source of Support: NSF (Michigan state U., BEACON)

Total Award Amount: $95,311 ($61,032 to Bull) Total Award Period Covered: 05/2014-09/2016

Location of Project: University of Texas at Austin, University of Idaho

Person-Months Per Year Committed to the Pro- Cal: (b)(6) Acad: Sumr:

(b)(4)

(b)(4)

*If this project has previously been funded by another agency, please list and furnish information for immediately preceding funding period.

Current and Pending Support-2

(See GPG Section II.D.8 for guidance on information to include on this form.)

The following information should be provided for each invest gator and other senior personnel. Failure to provide this information may delay consideration of this proposal.

Investigator: Bull, JJ	Other agencies (including NSF) to which this proposal has been/will be submitted.
(b)(4)	

FACILITIES, EQUIPMENT & OTHER RESOURCES

FACILITIES: Identify the facilities to be used at each performance site listed and, as appropriate, indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Use "Other" to describe the facilities at any other performance sites listed and at sites for field studies. USE additional pages as necessary.

Laboratory: NA

Clinical: NA

Animal: NA

Computer: PI Nuismer has access to a multi-core workstation in his office and a recently renovated lab equipped with one multi-core workstation and several modern computers. All computers are equipped with Mathematica, C++, statistical analysis software, and standard office productivity software packages. Co-PI Remien has a multi-core workstation in his office with equipped with modern mathematical, statistics, and office software.

Office: Both PI's have offices and access to shared office space for postdoctoral and undergraduate researchers.

Other:
IBEST Bioinformatics Core: The core includes several computer clusters including a 512 core AMD64 primary production system, a 96 processor Intel Xeon secondary production system, a 96 processor PowerPC G5 tertiary production system, a 44 processor Intel Xeon development system. The facility has dedicated personal, and the machines are loaded with a wide arrangement of software for mathematical modeling. The facility is housed in close proximity to the offices of PI Nuismer and Co-PI Remien.

Center for Modeling Complex Interactions: An NIH-funded Center for Biomedical Research Excellence (COBRE) to bring together mathematical, statistical, and molecular modeler, the center is housed in Mines 323 and will provide a critical mass of knowledge, space, and culture for collaborative modeling at the University of Idaho.

MAJOR EQUIPMENT: List the most important items available for this project and, as appropriate identifying the location and pertinent capabilities of each.

OTHER RESOURCES: Provide any information describing the other resources available for the project. Identify support services such as consultant, secretarial, machine shop, and electronics shop, and the extent to which they will be available for the project. Include an explanation of any consortium/contractual arrangements with other organizations.

Facilities, Equipment and Other Resources (J Bull)

Laboratory: Bull's lab space is located on the first floor of Patterson Labs (PAT 131) and consists of 2 large, main labs and 5 small labs, united through a common, short hallway with controlled access to the remainder of the building. All space and equipment are shared freely with David Hillis. The main labs provide the usual amenities of benchs, sinks, gel photography, waterbaths, and small equipment. Other rooms provide space for special functions and large equipment. The lab is rated for BL2 bacterial work.

Clinical: N/A
Animal: N/A

Computer: Bull's lab has a variety of (chiefly Mac) laptop and desktop computers. As a member of the Center for Computational Biology and Bioinformatics, Bull also has access to their several high performance computing (HPC) clusters, extensive and secure data storage systems, web servers, and a wide array of software packages (552 cores, 1.4TB memory, and 12TB storage). It is not expected that the Texas contribution to this project will be computationally intensive, but if the need arises, Bull also has access to the Texas Advanced Computing Center (TACC).

Office: Bull's office is located in PAT 131, across the hall from his lab area. Adjacent offices provide space for 6-8 group members.

MAJOR EQUIPMENT

The proposed work uses standard microbiological methods, and Bull's lab is equipped accordingly. The lab is authorized for BL2 work (biosafety level 2 allows for common infectious agents), although this project only requires BL1). Major equipment consists of an autoclave, large centrifuges, PCR machines, -80C freezers, -20C freezers, refrigerators, computers, hoods, microscopes, water baths, incubators and ovens.

OTHER RESOURCES

The **Genomic Sequencing and Analysis Facility (GSAF)** is an experienced NGS facility and currently processes over 7,000 NGS samples per year. Their equipment and capabilities include: (i) Two Illumina HiSeq 2500 next-generation DNA sequencers (one V3, one V4) and associated peripherals. The HiSeq can generate over one terabase of sequence in a 6-day run or 120 gigabases in a ~1 day rapid run. The GSAF has experience generating small RNA, mRNA, genomic DNA fragment, RAD (including ddRAD), bacterial and fungal metagenomics, and genomic DNA large-insert mate-pair libraries for the Illumina platform. (ii) Two Illumina MiSeq version 2 next-generation DNA sequencer and associated peripherals. The MiSeq is intended for lower data output, faster turn-around time projects, or for projects requiring longer read lengths (up to 600 bp per template, as two 300 bp sequences). (iii) One Illumina NextSeq 500 next-generation DNA sequencer and associated peripherals. The NextSeq is ideal for intermediate scale projects, requiring more read depth than is feasible on the MiSeq platform but with faster turn-around time than the HiSeq platform. (iv) Informatic tools and hardware sufficient for analysis of next-generation DNA sequencing data.

Data Management Plan

Because the first two objectives of the proposed work are mathematical and computational in nature, they will not generate data in the traditional sense. They will, however, result in the development of *Mathematica* notebooks that will be shared from the PI's website, C++ code that will also be shared from the PI's website and on GitHub, and in the development of new mathematical models that will be disseminated through publication in peer-reviewed journals. In contrast, the third objective will generate conventional data as part of experiments testing key theoretical results using bacteria and bacteriophage. In the following sections, we describe the type of data that will be collected and our plans for managing, storing, disseminating, and sharing this data are described

The phage experiments will acquire data in the form of frequencies and abundances across time. Those data will be presented directly in publications, with raw data provided in supplementary materials. They are not so numerous as to require special storage. Some genetic constructs will be created during the study (e.g., filamentous phages with drug resistances), and although these are not likely to be widely sought, will be made available to anyone requesting. Indeed, many of them have been available for years, and they have been sent out when requested. The primary products of the phage work will be publications describing tests of the emerging mathematical theory using studies of phage experimental dynamics. The publications and supplementary material will contain all relevant data from the experimental work. We do not propose, expect or intend any confidentiality or IP protection of our work; indeed, we will encourage others to use it and be happy to send them strains. Co-PI Bull will be responsible for maintenance of phage and bacterial strains for dissemination.

Postdoctoral Researcher Mentoring Plan

At least two postdoctoral researchers will be supported over the course of the proposed work. These individuals will play an integral role in the scientific and educational goals of the research and will receive extensive mentoring. Specific mentoring goals are described in the following sections.

Career planning — We will develop a career plan with each postdoc, beginning with discussions between the post-doc and PIs about possible career options and goals during the first few months of their tenure. After these initial discussions, we will help each postdoc develop a written plan for achieving their career goals including identification of key benchmarks. As part of this plan, and along with the obvious goal of publishing high profile papers, the PIs will set up visits and possible collaborations between the postdoc and appropriate colleagues (known by the PIs) at UI and other institutions. If teaching is part of the plan, we will help the postdoc obtain experience developing and delivering lectures and developing and running tutorials. In addition, the University of Idaho is now home to a Center for Modeling Complex Interactions (funded by NIH through 2020), and the postdoc will be encouraged to take part in some of the working groups that fit with his/her career goals. These efforts will be complementary to and augment the work on transmissible vaccines.

Publications — The postdoctoral researchers will receive extensive mentoring in the publication process through preparation and submission of manuscripts resulting from the proposed research. These manuscripts will be prepared in close collaboration with PI's Nuismer, Remien, and Bull, with weekly meetings during the initial planning stages of each manuscript. All PI's will read and revise multiple drafts of each manuscript and provide extensive feedback.

Presentations — Because the postdoctoral researchers will be expected to present their results at national meetings, multiple opportunities will be available for training these individuals to present their results successfully and with the greatest impact. During preparation of each presentation, all PI's will work with the postdocs to identify the key results that should be emphasized in the presentation and to identify the critical aspects of methodology that should be included. Once the presentation slides are complete, the PI's will review the slides and make detailed suggestions for improvement. Finally, the postdocs will give a practice presentation to the PI's lab groups and receive feedback from all individuals.

Mentoring — The proposed work will offer multiple opportunities for the postdoctoral researchers to gain valuable experience aiding the PI's in mentoring undergraduate students. Specifically, the postdocs will be integrated into the undergraduate research team as a junior adviser, with the PI's facilitating trouble shooting and helping the postdocs to learn how to effectively teach mathematical modeling to not only undergraduate mathematics students, but also undergraduate biology students. The PI's will provide written and verbal feedback to the postdocs on the positive and negative aspects of their mentoring approach, and will provide concrete suggestions for improvement.

Collaboration with researchers from diverse disciplinary areas — The PI's represent a diverse range of disciplinary backgrounds, providing real opportunities for interdisciplinary training. Specifically, the postdocs will work directly with PI's Nuismer and Remien and thus will work with a quantitative biologist (Nuismer) and mathematician (Remien) on a daily basis. In addition, the postdocs will be intimately involved in testing model predictions using experimental data collected by PI Bull through the Texas arm of the project.

Center for Modeling Complex Interactions

University of Idaho, 875 Perimeter Drive MS 3025, Moscow ID 83844-3025
http://www.cmciuidaho.org

Scott Nuismer
University of Idaho
875 Perimeter Drive, MS3051
Moscow, ID 83844-3051

Dear Dr. Nuismer:

I was excited to learn about your new project on transmissible vaccines. I invite you to form a working group with our Center for Modeling Complex Interactions (CMCI); it is entirely your decision who to include in the group.

CMCI provides an environment for collaborative work on problems such as yours. The environment is well-suited for including undergraduate and graduate students, postdocs, and faculty from across the university. CMCI should provide you with a platform for advertising your work, and recruiting University of Idaho students and faculty who might not otherwise be aware of it.

The potential for training students is excellent, and interactions with faculty and postdocs should both excite undergraduates, and give them a head start on careers in biology or mathematics.

Sincerely yours,

(b)(6)

Holly Wichman, Director

Program Director/Principal Investigator (Last, First, Middle): Nuismer, Scott, L

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.
Name of former program director/principal investigator: _____

☐ CHANGE of Grantee Institution. Name of former institution: _____

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☐ No ☐ Yes
If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See Instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 6/17/2015 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	131,444	x Rate applied	45.30%	% = F&A costs	$ 59,544
b. 02 year	Amount of base $	122,294	x Rate applied	45.30%	% = F&A costs	$ 55,399
c. 03 year	Amount of base $	122,294	x Rate applied	45.30%	% = F&A costs	$ 55,399
d. 04 year	Amount of base $	122,294	x Rate applied	45.30%	% = F&A costs	$ 55,399
e. 05 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$
					TOTAL F&A Costs	$ 225,742

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.)*:

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☒ Yes ☐ No

Program Director/Principal Investigator (Last, First, Middle): Bull, James, J

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☒ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number:
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number:
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number:
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator:

☐ CHANGE of Grantee Institution. Name of former institution:

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☐ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: September 1, 2014 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with Regional Office.

☐ No DHHS Agreement, but rate established with Date

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	46,365	x Rate applied	55.00%	% = F&A costs	$ 25,501
b. 02 year	Amount of base $	46,365	x Rate applied	55.00%	% = F&A costs	$ 25,501
c. 03 year	Amount of base $	46,365	x Rate applied	55.00%	% = F&A costs	$ 25,501
d. 04 year	Amount of base $	46,365	x Rate applied	55.00%	% = F&A costs	$ 25,501
e. 05 year	Amount of base $		x Rate applied	0.00%	% = F&A costs	$
					TOTAL F&A Costs	$ 102,003

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☒ Yes ☐ No

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 11/08/2017

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 5R01GM122079-02 REVISED
FAIN: R01GM122079

Principal Investigator(s):
SCOTT L NUISMER, PHD

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

STEVE KIRKHAM
SPONS PROGRAMS ADMIN
UNIVERSITY OF IDAHO
875 PERIMETER DRIVE
MS3020
MOSCOW, ID 838443020

Award e-mailed to: osp@uidaho.edu

Period Of Performance:
Budget Period: 05/01/2017 – 04/30/2018
Project Period: 08/01/2016 – 04/30/2020

Dear Business Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Lori Burge
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 5R01GM122079-02 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$86,419
Fringe Benefits	$26,725
Personnel Costs (Subtotal)	$113,144
Materials & Supplies	$1,500
Travel	$3,150
Other	$4,500
Subawards/Consortium/Contractual Costs	$72,561
Federal Direct Costs	$194,855
Federal F&A Costs	$57,784
Approved Budget	$252,639
Total Amount of Federal Funds Obligated (Federal Share)	$252,639
TOTAL FEDERAL AWARD AMOUNT	$252,639
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$252,639	$252,639
3	$252,945	$252,945
4	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1826000945A1
Document Number:	RGM122079A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2017

IC	CAN	2017	2018	2019
GM	8020220	$252,639	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: B120VR / **OC**: 414E / **Released**: (b)(6) 11/07/2017
Award Processed: 11/08/2017 12:01:33 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM122079-02 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5R01GM122079-02 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

This revised award reflects approval of the addition of vertebrate animal research as described in the grantee's submitted document of 10/06/17.

TERMS AND CONDITIONS FROM PREVIOUS AWARD:

In accordance with NIH's fiscal year 2017 policies, this award is being revised to 100% of the amount previously committed from last year's Notice of Award.

TERMS AND CONDITIONS FROM PREVIOUS AWARD:

1. NIH is currently operating under a Continuing Resolution (See NIH Guide Notice NOT-OD-17-048: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-048.html). Therefore, this non-competing award has been made at a level below that committed for FY2017 in the previous Notice of Award. If the final appropriation permits, adjustments may be made up to the FY2017 funding plan level.

2. This award provides funding for an application submitted in response to the NSF/NIGMS Joint Program in Mathematical Biology Initiative. This grant should be administered in accordance with the guidelines described in this specific announcement. These guidelines are in addition to the standard "Terms and Conditions" referenced in Section III of this Notice of Grant Award.

3. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at:
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

4. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL:

http://grants1.nih.gov/grants/policy/salcap_summary.htm

5. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Justin Rosenzweig
Email: rosenzwj@mail.nih.gov **Phone**: 301-594-0158 **Fax**: 301-480-2554

Program Official: Veerasamy Ravichandran
Email: veerasamy.ravichandra@nih.gov **Phone**: 301-451-9822 **Fax**: 301-480-0884

SPREADSHEET SUMMARY
GRANT NUMBER: 5R01GM122079-02 REVISED

Budget	Year 2	Year 3	Year 4
Salaries and Wages	$86,419	$86,419	$86,419
Fringe Benefits	$26,725	$26,725	$26,725
Personnel Costs (Subtotal)	$113,144	$113,144	$113,144
Materials & Supplies	$1,500	$1,500	$1,500
Travel	$3,150	$3,150	$3,150
Other	$4,500	$4,500	$4,500
Subawards/Consortium/Contractual Costs	$72,561	$72,561	$72,561
TOTAL FEDERAL DC	$194,855	$194,855	$194,855
TOTAL FEDERAL F&A	$57,784	$58,090	$58,090
TOTAL COST	$252,639	$252,945	$252,945

Facilities and Administrative Costs	Year 2	Year 3	Year 4
F&A Cost Rate 1	46%	47.5%	47.5%
F&A Cost Base 1	$20,382	$122,294	$122,294
F&A Costs 1	$9,376	$58,090	$58,090
F&A Cost Rate 2	47.5%		
F&A Cost Base 2	$101,912		
F&A Costs 2	$48,408		

Notice of Award

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 06/06/2017

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 5R01GM122079-02 REVISED
FAIN: R01GM122079

Principal Investigator(s):
SCOTT L NUISMER, PHD

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

STEVE KIRKHAM
SPONS PROGRAMS ADMIN
UNIVERSITY OF IDAHO
875 PERIMETER DRIVE
MS3020
MOSCOW, ID 838443020

Award e-mailed to: osp@uidaho.edu

Period Of Performance:
Budget Period: 05/01/2017 – 04/30/2018
Project Period: 08/01/2016 – 04/30/2020

Dear Business Official:

The National Institutes of Health hereby revises this award to reflect an increase in the amount of $25,264 (see “Award Calculation” in Section I and “Terms and Conditions” in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the “Terms and Conditions” is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as “Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.” Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator’s Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Robert Altieri
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 5R01GM122079-02 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$86,419
Fringe Benefits	$26,725
Personnel Costs (Subtotal)	$113,144
Materials & Supplies	$1,500
Travel	$3,150
Other	$4,500
Subawards/Consortium/Contractual Costs	$72,561
Federal Direct Costs	$194,855
Federal F&A Costs	$57,784
Approved Budget	$252,639
Total Amount of Federal Funds Obligated (Federal Share)	$252,639
TOTAL FEDERAL AWARD AMOUNT	$252,639
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$25,264

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$252,639	$252,639
3	$252,945	$252,945
4	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1826000945A1
Document Number:	RGM122079A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2017

IC	CAN	2017	2018	2019
GM	8020220	$252,639	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: B120VR / **OC**: 414E / **Released**: (b)(6) 06/02/2017
Award Processed: 06/06/2017 12:03:07 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM122079-02 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5R01GM122079-02 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

REVISED:

In accordance with NIH's fiscal year 2017 policies, this award is being revised to 100% of the amount previously committed from last year's Notice of Award.

TERMS AND CONDITIONS FROM PREVIOUS AWARD:

1. NIH is currently operating under a Continuing Resolution (See NIH Guide Notice NOT-OD-17-048: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-048.html). Therefore, this non-competing award has been made at a level below that committed for FY2017 in the previous Notice of Award. If the final appropriation permits, adjustments may be made up to the FY2017 funding plan level.

2. This award provides funding for an application submitted in response to the NSF/NIGMS Joint Program in Mathematical Biology Initiative. This grant should be administered in accordance with the guidelines described in this specific announcement. These guidelines are in addition to the standard "Terms and Conditions" referenced in Section III of this Notice of Grant Award.

3. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at:
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

4. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL:

http://grants1.nih.gov/grants/policy/salcap_summary.htm

5. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Justin Rosenzweig
Email: rosenzwj@mail.nih.gov **Phone**: 301-594-0158 **Fax**: 301-480-2554

Program Official: Veerasamy Ravichandran
Email: veerasamy.ravichandra@nih.gov **Phone**: 301-451-9822 **Fax**: 301-480-0884

SPREADSHEET SUMMARY
GRANT NUMBER: 5R01GM122079-02 REVISED

INSTITUTION: UNIVERSITY OF IDAHO

Budget	Year 2	Year 3	Year 4
Salaries and Wages	$86,419	$86,419	$86,419
Fringe Benefits	$26,725	$26,725	$26,725
Personnel Costs (Subtotal)	$113,144	$113,144	$113,144
Materials & Supplies	$1,500	$1,500	$1,500
Travel	$3,150	$3,150	$3,150
Other	$4,500	$4,500	$4,500
Subawards/Consortium/Contractual Costs	$72,561	$72,561	$72,561
TOTAL FEDERAL DC	$194,855	$194,855	$194,855
TOTAL FEDERAL F&A	$57,784	$58,090	$58,090
TOTAL COST	$252,639	$252,945	$252,945

Facilities and Administrative Costs	Year 2	Year 3	Year 4
F&A Cost Rate 1	46%	47.5%	47.5%
F&A Cost Base 1	$20,382	$122,294	$122,294
F&A Costs 1	$9,376	$58,090	$58,090
F&A Cost Rate 2	47.5%		
F&A Cost Base 2	$101,912		
F&A Costs 2	$48,408		

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 04/14/2017

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 5R01GM122079-02
FAIN: R01GM122079

Principal Investigator(s):
SCOTT L NUISMER, PHD

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

STEVE KIRKHAM
SPONS PROGRAMS ADMIN
UNIVERSITY OF IDAHO
875 PERIMETER DRIVE
MS3020
MOSCOW, ID 838443020

Award e-mailed to: osp@uidaho.edu

Period Of Performance:
Budget Period: 05/01/2017 – 04/30/2018
Project Period: 08/01/2016 – 04/30/2020

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $227,375 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Lori Burge
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 5R01GM122079-02

Award Calculation (U.S. Dollars)

Salaries and Wages	$77,777
Fringe Benefits	$24,053
Personnel Costs (Subtotal)	$101,830
Materials & Supplies	$1,350
Travel	$2,835
Other	$4,050
Subawards/Consortium/Contractual Costs	$65,305
Federal Direct Costs	$175,370
Federal F&A Costs	$52,005
Approved Budget	$227,375
Total Amount of Federal Funds Obligated (Federal Share)	$227,375
TOTAL FEDERAL AWARD AMOUNT	$227,375
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$227,375

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$227,375	$227,375
3	$252,945	$252,945
4	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1826000945A1
Document Number:	RGM122079A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2017

IC	CAN	2017	2018	2019
GM	8472185	$227,375	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: B120VR / **OC**: 414E / **Released**: (b)(6) 04/12/2017
Award Processed: 04/14/2017 12:09:20 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM122079-02

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5R01GM122079-02

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

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An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

1. NIH is currently operating under a Continuing Resolution (See NIH Guide Notice NOT-OD-17-048: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-048.html). Therefore, this non-competing award has been made at a level below that committed for FY2017 in the previous Notice of Award. If the final appropriation permits, adjustments may be made up to the FY2017 funding plan level.

2. This award provides funding for an application submitted in response to the NSF/NIGMS Joint Program in Mathematical Biology Initiative. This grant should be administered in accordance with the guidelines described in this specific announcement. These guidelines are in addition to the standard "Terms and Conditions" referenced in Section III of this Notice of Grant Award.

3. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at:
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

4. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL:

http://grants1.nih.gov/grants/policy/salcap_summary.htm

5. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Justin Rosenzweig
Email: rosenzwj@mail.nih.gov **Phone**: 301-594-0158 **Fax**: 301-480-2554

Program Official: Veerasamy Ravichandran
Email: veerasamy.ravichandra@nih.gov **Phone**: 301-451-9822 **Fax**: 301-480-0884

SPREADSHEET SUMMARY
GRANT NUMBER: 5R01GM122079-02

INSTITUTION: UNIVERSITY OF IDAHO

Budget	Year 2	Year 3	Year 4
Salaries and Wages	$77,777	$86,419	$86,419
Fringe Benefits	$24,053	$26,725	$26,725
Personnel Costs (Subtotal)	$101,830	$113,144	$113,144
Materials & Supplies	$1,350	$1,500	$1,500
Travel	$2,835	$3,150	$3,150
Other	$4,050	$4,500	$4,500

Subawards/Consortium/Contractual Costs	$65,305	$72,561	$72,561
TOTAL FEDERAL DC	$175,370	$194,855	$194,855
TOTAL FEDERAL F&A	$52,005	$58,090	$58,090
TOTAL COST	$227,375	$252,945	$252,945

Facilities and Administrative Costs	Year 2	Year 3	Year 4
F&A Cost Rate 1	46%	47.5%	47.5%
F&A Cost Base 1	$18,344	$122,294	$122,294
F&A Costs 1	$8,438	$58,090	$58,090
F&A Cost Rate 2	47.5%		
F&A Cost Base 2	$91,721		
F&A Costs 2	$43,567		

A. COVER PAGE

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES	
Grant Number: 5R01GM122079-02	**Project/Grant Period:** 08/01/2016 - 04/30/2020
Reporting Period: 08/01/2016 - 04/30/2017	**Requested Budget Period:** 05/01/2017 - 04/30/2018
Report Term Frequency: Annual	**Date Submitted:** 03/16/2017
Program Director/Principal Investigator Information: SCOTT L NUISMER , PHD **Phone number:** (208) 885-4096 **Email:** snuismer@uidaho.edu	**Recipient Organization:** UNIVERSITY OF IDAHO UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW, ID 838443020 **DUNS:** 075746271 **EIN:** 1826000945A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: STEVE KIRKHAM MORRILL HALL, RM 112 MOSCOW, ID 838443010 **Phone number:** 2088852259 **Email:** stevenk@uidaho.edu	**Signing Official:** STEVE KIRKHAM MORRILL HALL, RM 112 MOSCOW, ID 838443010 **Phone number:** 2088852259 **Email:** stevenk@uidaho.edu
Human Subjects: No	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1. Develop a mathematical framework predicting the extent of protection provided by a transmissible vaccine. For a transmissible vaccine to be useful, it must be able to invade the target population and immunize a larger number of individuals than could be achieved using a traditional vaccine. We will develop mathematical models, novel approximations, and individual-based simulations that allow us to predict the fate of a transmissible vaccine.

Aim 2. Develop a mathematical framework predicting the evolution of a transmissible vaccine. Developing a transmissible vaccine requires that an infectious agent be manipulated, either by adding genes that confer immunity or by eliminating or altering genes that cause virulence. We will develop mathematical models, novel approximations, and individual-based simulations to determine when these genetic modifications are evolutionarily robust and to study the epidemiological consequences when they are not.

Aim 3. Test model predictions using an experimental viral model. We have developed three laboratory model systems of transmissible vaccines. Each uses bacterial hosts and bacteriophage viruses. These systems will be used to test key predictions that emerge from the first two objectives.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Accomplishments Text March 2017.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: Professional Development Text March 2017.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Aim 1. Our top priority for the next reporting period is to finish developing and analyzing a mathematical model of a recombinant vectored transmissible vaccine. Completing analysis of this model, and disseminating the results rapidly is important because some recombinant vectored vaccines are already being tested and others are in development. Our mathematical results will help to predict whether such vaccines are likely to work, and what key quantities must be measured empirically to predict their performance at the population level. During this second reporting period, we will also begin development of mathematical models that include host heterogeneity and population structure.

Aim 2. Work on this aim in the next reporting period will continue development of mathematical models studying the consequences of reversion for transmissible vaccines. This work will develop models of attenuated vaccines (where reversion leads to wild type virulence) and recombinant vectored vaccines (where reversion leads to an empty vaccine vector). In both cases, efforts over the next reporting period will focus on predicting the consequences of reversion as a function of the number of genetic substitutions required.

Aim 3. With the constructs in hand, we will now begin the empirical validation and intensive dynamics studies. The money for the empirical part of the project is not sufficient for a full-time technician with supplies, so this first phase has used a technician at half time. With the design and construction behind us, and with the moderate use of funds in the first phase, we will now be able to support a full time effort on the lab work in the coming year.

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

Aim 1. Work on the first specific aim has made rapid progress. Specifically, we have completed and published a mathematical model predicting the extent of coverage gained by using an attenuated transmissible vaccine (Nuismer et al 2016). The results of this work suggest that even weak vaccine transmission can have surprisingly large benefits. Follow up work has begun developing and analyzing mathematical models evaluating the efficacy of an alternative form of transmissible vaccine: recombinant vectored transmissible vaccines.

Aim 2. We have only recently begun work on this aim. Work so far has focused on developing two different models. The first model explores the basic problem of reversion in attenuated transmissible vaccines. Preliminary results from analyses of this model suggest that as long as reversion does not occur too frequently, and depends on only a single genetic substitution, it has very little impact on the efficacy of a transmissible vaccine. We are now extending these results to cases where reversion depends on multiple genetic substitutions and working to tie empirical estimates of reversion rates in the Oral Polio Vaccine to model parameters. The second model we are just now beginning to develop investigates the role of host heterogeneity, with a specific focus on the consequences of immunocompromised hosts for rates of reversion.

Aim 3. A 2-component CRISPR anti-phage system been designed, and the engineered plasmids have now been received. They will be tested shortly. (2) Work has also been done on a new design of attenuation by genome engineering: protein fragmentation (engineering a protein to be encoded in two polypeptides instead of one). This design was implemented in a bacteriophage and had a profound initial effect on fitness. Extended growth of the phage resulted in an unexpectedly large increase in fitness. Genomic analysis is underway. (3) A perspective on different vaccine designs is written and in the final stages before submission.

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

Work on the project during the first year has provided training for a postdoctoral researcher (Andrew Basinski), a graduate student (Tanner Varrelman), and an undergraduate student (Ryan May). Specifically, each of these individuals is being trained by PI Nuismer and Co-PI Remien to develop and analyze mathematical models of infectious disease. In addition, Nuismer and Remien have worked extensively with Postdoctoral researcher Basinski to develop his writing skills and to help him formulate a strategic plan for moving into a faculty position at the end of his postdoctoral position.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Nuismer SL, Althouse BM, May R, Bull JJ, Stromberg SP, Antia R. Eradicating infectious disease using weakly transmissible vaccines. Proceedings. Biological sciences. 2016 October 26;283(1841). PubMed PMID: 27798311; PubMed Central PMCID: PMC5095390.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period?

No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	NUISMER, SCOTT L	PHD	PD/PI	(b)(6)					NA
	N	Varrelman, Tanner	BS	Graduate Student (research assistant)						NA
	Y	BULL, James Jeffrey	PHD,BS	Co-Investigator						NA
	N	May, Ryan		Undergraduate Student						NA
	N	Basinski, Andreew	PHD	Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA
	Y	Remien, Christopher Haskell	PhD	Co-Investigator						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

No

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

No

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

No

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes

Estimated unobligated balance: 102072

G.10.b Provide an explanation for unobligated balance:
The first year of the grant was only nine months, starting on August 1 and ending April 30. Money has been spent approximately in proportion to the fraction of a year that the account has been active. In addition, recruiting and hiring a qualified postdoctoral researcher required several months and developing the experimental viral system was slowed by the need to recruit a part time technician to perform the work. Together, the shortened first year and the time required to recruit and hire a post-doc and technician resulted in significant carryover from the first year.

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent
Carryover funds will be used to: 1) Support a graduate student RA working on the project, 2) Support travel to meetings, 3) Support the postdoctoral researcher, and 4) Support a part time technician working on developing the viral test system.

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 04/25/2018

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 5R01GM122079-03
FAIN: R01GM122079

Principal Investigator(s):
SCOTT L NUISMER, PHD

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

Sarah Martonick
UNIVERSITY OF IDAHO
875 PERIMETER DRIVE
MS3020
MOSCOW, ID 838443020

Award e-mailed to: osp@uidaho.edu

Period Of Performance:
Budget Period: 05/01/2018 – 04/30/2019
Project Period: 08/01/2016 – 04/30/2020

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $252,945 (see “Award Calculation” in Section I and “Terms and Conditions” in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the “Terms and Conditions” is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as “Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.” Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator’s Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Lori Burge
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 5R01GM122079-03

Award Calculation (U.S. Dollars)

Salaries and Wages	$86,419
Fringe Benefits	$26,725
Personnel Costs (Subtotal)	$113,144
Materials & Supplies	$1,500
Travel	$3,150
Other	$4,500
Subawards/Consortium/Contractual Costs	$72,561
Federal Direct Costs	$194,855
Federal F&A Costs	$58,090
Approved Budget	$252,945
Total Amount of Federal Funds Obligated (Federal Share)	$252,945
TOTAL FEDERAL AWARD AMOUNT	$252,945
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$252,945

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
3	$252,945	$252,945
4	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1826000945A1
Document Number:	RGM122079A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2018

IC	CAN	2018	2019
GM	8472185	$252,945	$252,945

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: B120VR / **OC**: 414E / **Released**: (b)(6) 04/20/2018
Award Processed: 04/25/2018 12:11:15 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM122079-03

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5R01GM122079-03

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget

period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

1. This award provides funding for an application submitted in response to the NSF/NIGMS Joint Program in Mathematical Biology Initiative. This grant should be administered in accordance with the guidelines described in this specific announcement. These guidelines are in addition to the standard "Terms and Conditions" referenced in Section III of this Notice of Grant Award.

2. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at:
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

3. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

4. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL:
http://grants1.nih.gov/grants/policy/salcap_summary.htm

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Justin Rosenzweig
Email: rosenzwj@mail.nih.gov **Phone**: 301-594-0158 **Fax**: 301-480-2554

Program Official: Veerasamy Ravichandran
Email: veerasamy.ravichandra@nih.gov **Phone**: 301-451-9822 **Fax**: 301-480-0884

SPREADSHEET SUMMARY
GRANT NUMBER: 5R01GM122079-03

INSTITUTION: UNIVERSITY OF IDAHO

Budget	Year 3	Year 4
Salaries and Wages	$86,419	
Fringe Benefits	$26,725	
Personnel Costs (Subtotal)	$113,144	
Materials & Supplies	$1,500	
Travel	$3,150	
Other	$4,500	
Subawards/Consortium/Contractual Costs	$72,561	
TOTAL FEDERAL DC	$194,855	$194,855

TOTAL FEDERAL F&A	$58,090	$58,090
TOTAL COST	$252,945	$252,945

Facilities and Administrative Costs	Year 3	Year 4
F&A Cost Rate 1	47.5%	47.5%
F&A Cost Base 1	$122,294	$122,294
F&A Costs 1	$58,090	$58,090

A. COVER PAGE

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES	
Grant Number: 5R01GM122079-03	**Project/Grant Period:** 08/01/2016 - 04/30/2020
Reporting Period: 05/01/2017 - 04/30/2018	**Requested Budget Period:** 05/01/2018 - 04/30/2019
Report Term Frequency: Annual	**Date Submitted:** 03/14/2018
Program Director/Principal Investigator Information: SCOTT L NUISMER , PHD **Phone number:** (208) 885-4096 **Email:** snuismer@uidaho.edu	**Recipient Organization:** UNIVERSITY OF IDAHO UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW, ID 838443020 **DUNS:** 075746271 **EIN:** 1826000945A1 **RECIPIENT ID:**
Change of Contact PD/PI: No	
Administrative Official: SARAH SIMONE MARTONICK 875 Perimeter Drive MS 3020 Moscow, ID 838443020 **Phone number:** 2088852145 **Email:** smartonick@uidaho.edu	**Signing Official:** SARAH SIMONE MARTONICK 875 Perimeter Drive MS 3020 Moscow, ID 838443020 **Phone number:** 2088852145 **Email:** smartonick@uidaho.edu
Human Subjects: No	**Vertebrate Animals:** Yes
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1. Develop a mathematical framework predicting the extent of protection provided by a transmissible vaccine. For a transmissible vaccine to be useful, it must be able to invade the target population and immunize a larger number of individuals than could be achieved using a traditional vaccine. We will develop mathematical models, novel approximations, and individual-based simulations that allow us to predict the fate of a transmissible vaccine.

Aim 2. Develop a mathematical framework predicting the evolution of a transmissible vaccine. Developing a transmissible vaccine requires that an infectious agent be manipulated, either by adding genes that confer immunity or by eliminating or altering genes that cause virulence. We will develop mathematical models, novel approximations, and individual-based simulations to determine when these genetic modifications are evolutionarily robust and to study the epidemiological consequences when they are not.

Aim 3. Test model predictions using an experimental viral model. We have developed three laboratory model systems of transmissible vaccines. Each uses bacterial hosts and bacteriophage viruses. These systems will be used to test key predictions that emerge from the first two objectives.

B.1.a Have the major goals changed since the initial competing award or previous report?

Yes

Revised goals:

Aim 1. Develop a mathematical framework predicting the extent of protection provided by a transmissible vaccine. For a transmissible vaccine to be useful, it must be able to invade the target population and immunize a larger number of individuals than could be achieved using a traditional vaccine. We will develop mathematical models, novel approximations, and individual-based simulations that allow us to predict the fate of a transmissible vaccine.

Aim 2. Develop a mathematical framework predicting the evolution of a transmissible vaccine. Developing a transmissible vaccine requires that an infectious agent be manipulated, either by adding genes that confer immunity or by eliminating or altering genes that cause virulence. We will develop mathematical models, novel approximations, and individual-based simulations to determine when these genetic modifications are evolutionarily robust and to study the epidemiological consequences when they are not.

Aim 3. Test model predictions using an experimental viral model. A recombinant vector vaccine is a type of engineered vaccine that is being tested in many contexts — against Ebola, HIV, and in wild-life. We will test whether a recombinant Murine cytomegalovirus will evolve within the host to lose expression of its antigenic insert.

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Accomplishments Text March 2018.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: Professional Development Text March 2018.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

PI Nuismer presented results at the University of Toronto and the University of Tennessee. Nuismer also presented results to the MIDAS group through the monthly call. Postdoctoral researcher Andrew Basinski presented a poster on results of recombinant vector vaccine modeling at the Society for Mathematical Biology meeting.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Aim 1. Our top priority for the next reporting period is to finish developing and analyzing mathematical models of transmissible vaccines that integrate explicit spatial structure and within population heterogeneity. Specifically, postdoctoral researcher Andrew Basinski is currently developing and analyzing diffusion models to understand how vaccine transmission enhances the spatial coverage of vaccination. These models are being parameterized using data from Rabies vaccination campaigns that distribute vaccines using aerial bait drops. PhD student Tanner Varrelman is developing models that integrate risk heterogeneity. These models break the population

down into groups that transmit the infectious disease (and transmissible vaccine) at high rates and groups that transmit at lower rates. The goal is to evaluate whether the benefits of vaccine transmission are increased in the presence of risk heterogeneity.

Aim 2. Work on this aim in the next reporting period is focused on integrating multiple strains into our models of transmissible vaccines. Specifically, we are working on development of a multi-strain model tuned to the biology of CMV, which includes recurrent latency. Our focus on modeling CMV is driven by its apparent suitability as a vector for transmissible vaccines and the availability of data for strain prevalence in several semi-natural systems. In addition, we are working on developing a family of models where evolution is implicit and included as changes in rates of transmission, recovery, and immunity as a function of the length of the transmission chain. These models are motivated by the observation that transmissible vaccines often transmit better, and confer greater immunity, in individuals vaccinated directly than in individuals that contract the vaccine infectiously from a directly vaccinated individual.

Aim 3. We have constructed a murine CMV (mCMV) to carry ovalbumin (a model antigen), thus representing any CMV that carries a vaccine cargo. Over the next reporting period, we will infect mice with the ‘vaccine’ and calculate the rate at which the antigenic region is lost or downregulated.

Aim 1. Work on the first specific aim continues to make rapid progress. Specifically, we have completed and published a new mathematical model studying the efficacy of recombinant vectored transmissible vaccines (Basinski et al. 2017). This work demonstrated that RVV's can be powerful tools, but only when cross-immunity between the vector and naturally circulating vector strains is minimal. In addition to this work on RVV's we develop mathematical models studying the efficacy of transmissible vaccines when used against an emerging epidemic or pandemic. These models differed from our previous research by focusing on temporal dynamics rather than just steady states and thus captured the potential benefits vaccine transmission provides with respect to the speed of vaccine delivery. Together, the results of

(b)(4); (b)(6)

(b)(4); (b)(6) Finally, we synthesized our modeling work and existing experimental studies of transmissible vaccines in an opinion article (Bull et al. 2017).

Aim 2. Previous work on this aim established that vaccine reversion within attenuated transmissible vaccines posed little problem for their efficacy at the population level unless rates of reversion are extremely high (Nuismer et al. 2016). In contrast, recent work we have completed demonstrates that vaccine reversion can cause a recombinant vector vaccine to fail even if rates of reversion are tiny (Basinski et al. 2017). The reason this occurs, is that when a recombinant vector vaccine reverts, the result is a free vector (now lacking the antigenic insert) that may have a competitive advantage due to its reduced immune profile and reduced costs of expressing the antigenic insert. These model results suggest that the fate of a recombinant vector vaccine may rest on two key parameters: 1) at what rate is the antigenic insert deleted or its expression suppressed, and 2) what are the consequences of deletion or reduced expression for competition with intact vaccine. The identification of these key parameters led us to reshape specific aim 3 to focus on their estimation in a mouse model.

Aim 3. A leading vector candidate for use in recombinant vector transmissible vaccines is cytomegalovirus (CMV). CMV is a promising vector candidate because of its high species specificity, its large genome size and stability, and its apparent ability to reinfect. Because our mathematical models demonstrate that the success of a recombinant vector vaccine depends on the rate at which it ejects or downregulates its antigenic insert, we constructure a murine CMV (mCMV) to carry ovalbumin (a model antigen), thus representing any CMV that carries a vaccine cargo. The initial question for us is the simple but important one of whether the insert is evolutionarily stable, or instead, whether the replicating virus will evolve within the host to lose or downregulate the ovalbumin gene. Stability of the antigen is obviously critical to vaccine success. The design is to infect mice with the 'vaccine' and observe its evolution over time and in different tissues. As vertebrate animal work was not approved in the original application, we applied for permission for the mouse studies, and obtained final approval in December. IACUC protocols are in place, and the engineered virus has been confirmed and is being grown. Mouse studies are expected to commence shortly.

Work on the project during the second year has provided continued training for a postdoctoral researcher (Andrew Basinski), a graduate student (Tanner Varrelman), and an undergraduate student (Ryan May). Each of these individuals is being trained by PI Nuismer and Co-PI Remien to develop and analyze mathematical models of infectious disease. Nuismer and Remien have worked extensively with Postdoctoral researcher Basinski to develop his writing and presentation skills and to help him formulate a strategic plan for moving into a faculty position at the end of his postdoctoral position.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Bull JJ, Smithson MW, Nuismer SL. Transmissible Viral Vaccines. Trends in microbiology. 2018 January;26(1):6-15. PubMed PMID: 29033339; PubMed Central PMCID: PMC5777272.
Complete	Basinski AJ, Varrelman TJ, Smithson MW, May RH, Remien CH, Nuismer SL. Evaluating the promise of recombinant transmissible vaccines. Vaccine. 2018 January 29;36(5):675-682. PubMed PMID: 29279283; PubMed Central PMCID: PMC5811206.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	NUISMER, SCOTT L	PHD	PD/PI	(b)(6)					NA
	N	Basinski, Andreew	PHD	Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA
	N	BULL, James Jeffrey	PHD,BS	Co-Investigator						NA
	N	Remien, Christopher Haskell	PhD	Co-Investigator						NA
	N	Varrelman, Tanner	BS	Graduate Student (research assistant)						NA
	N	May, Ryan		Undergraduate Student						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

No

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

No

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

Yes

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020

UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
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UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes

Estimated unobligated balance: 118352

G.10.b Provide an explanation for unobligated balance:
We have significant carryover for two reasons. First. the initial year of the award was shortened by NIH. Thus, we had substantial carryover from year 1 to year 2, which was compounded by a delay in getting a postdoctoral researcher hired and on payroll. Second, switching our third specific aim from a bacteriophage system to a mammalian virus model resulted in significant delays while waiting for vertebrate animal approvals. These approvals are now in place, and our rate of spending will increase substantially as a result.

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent
The carryover balance will be used to support the viral evolution studies now central to our third specific aim. These experiments are now up and running and we anticipate our spending rate will increase substantially as a result. Additional carryover funds will be used to support PhD student Tanner Varrelman as an Research Assistant, facilitating his research on risk structured populations.

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

Recipient Information

1. Recipient Name
REGENTS OF THE UNIVERSITY OF IDAHO
875 PERIMETER DRIVE MS 3020

MOSCOW, ID 83844

2. Congressional District of Recipient
01

3. Payment System Identifier (ID)
1826000945A1

4. Employer Identification Number (EIN)
826000945

5. Data Universal Numbering System (DUNS)
075746271

6. Recipient's Unique Entity Identifier

7. Project Director or Principal Investigator
SCOTT L NUISMER, PHD

SNUISMER@UIDAHO.EDU
(208) 885-4096

8. Authorized Official
Sarah Martonick
smartonick@uidaho.edu
(208) 885-2145

Federal Agency Information

9. Awarding Agency Contact Information
Maricela Trujillo
Grants Management Specialists
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
maricela.trujillo@nih.gov
301-594-3927

10. Program Official Contact Information
Veerasamy Ravichandran

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
veerasamy.ravichandra@nih.gov

Federal Award Information

11. Award Number
5R01GM122079-04

12. Unique Federal Award Identification Number (FAIN)
R01GM122079

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

15. Assistance Listing Number
93.859

16. Assistance Listing Program Title
Biomedical Research and Research Training

17. Award Action Type
Non-Competing Continuation (REVISED)

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 05/01/2019 **– End Date** 04/30/2022	
20. Total Amount of Federal Funds Obligated by this Action	$0
20 a. Direct Cost Amount	$0
20 b. Indirect Cost Amount	$0
21. Authorized Carryover	$0
22. Offset	$0
23. Total Amount of Federal Funds Obligated this budget period	$252,945
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$252,945
26. Project Period Start Date 08/01/2016 **– End Date** 04/30/2022	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$1,009,921

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Tiffany Walker

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

SECTION I – AWARD DATA – 5R01GM122079-04 REVISED

Principal Investigator(s):
SCOTT L NUISMER, PHD

Award e-mailed to: osp@uidaho.edu

Dear Authorized Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Tiffany Walker
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Federal Direct Costs	$194,855
Federal F&A Costs	$58,090
Approved Budget	$252,945
Total Amount of Federal Funds Authorized (Federal Share)	$252,945
TOTAL FEDERAL AWARD AMOUNT	$252,945

AMOUNT OF THIS ACTION (FEDERAL SHARE) $0

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
4	$252,945	$252,945

Fiscal Information:

Payment System Identifier:	1826000945A1
Document Number:	RGM122079A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2019

IC	CAN	2019
GM	8472185	$252,945

NIH Administrative Data:
PCC: B120VR / **OC**: 41025 / **Released**: Walker, Tiffany 03/09/2021
Award Processed: 03/10/2021 12:01:43 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM122079-04 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

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SECTION III – STANDARD TERMS AND CONDITIONS – 5R01GM122079-04 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate

purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: http://grants.nih.gov/grants/policy/policy.htm#gps.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the eRA Commons (Commons) within 120 days of the period of performance end date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, http://grants.nih.gov/grants/policy/policy.htm#gps, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the Payment Management System's (PMS) quarterly cash transaction data. A final quarterly federal cash transaction report is not required for awards in PMS B subaccounts (i.e., awards to foreign entities and to Federal agencies). NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures or quarterly federal cash transaction reporting. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level. If the grantee submits a final expenditure FFR but does not reconcile any discrepancies between expenditures reported on the final expenditure FFR and the last cash report to PMS, NIH will close the award at the lower amount. This could be considered a debt or result in disallowed costs.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: http://grants.nih.gov/grants/forms.htm. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, D42, D43, D71, DP7, G07, G08, G11, K12, K16, K30, P09, P40, P41, P51, R13, R25, R28, R30, R90, RL5, RL9, S10, S14, S15, U13, U14, U41, U42, U45, UC6, UC7, UR2, X01, X02.

Unless an application for competitive renewal is submitted, a Final Research Performance Progress Report (Final RPPR) must also be submitted within 120 days of the period of performance end date. If a competitive renewal application is submitted prior to that date, then an Interim RPPR must be submitted by that date as well. Instructions for preparing an Interim or Final RPPR are at: https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the Interim or Final RPPR. *Note that data reported within Section I of the Interim and Final RPPR forms will be made public and should be written for a lay person audience*.

NIH strongly encourages electronic submission of the final invention statement through the Closeout feature in the Commons, but will accept an email or hard copy submission as indicated below.

Email: The final invention statement may be e-mailed as PDF attachments to: NIHCloseoutCenter@mail.nih.gov.

Hard copy: Paper submissions of the final invention statement may be faxed to the NIH Division of Central Grants Processing, Grants Closeout Center, at 301-480-2304, or mailed to:

National Institutes of Health
Office of Extramural Research
Division of Central Grants Processing
Grants Closeout Center
6705 Rockledge Drive
Suite 5016, MSC 7986
Bethesda, MD 20892-7986 (for regular or U.S. Postal Service Express mail)
Bethesda, MD 20817 (for other courier/express deliveries only)

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final RPPR is not required. However, a final expenditure FFR is required and should be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

SECTION IV – GM SPECIFIC AWARD CONDITIONS – 5R01GM122079-04 REVISED

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

This revision approves the grantee's request dated 03/02/2021 to extend the budget/project period for 12 months. The new budget and project period end date is 04/30/2022.

TERMS AND CONDITIONS FROM PREVIOUS AWARD

1. This award provides funding for an application submitted in response to the NSF/NIGMS Joint Program in Mathematical Biology Initiative. This grant should be administered in accordance with

the guidelines described in this specific announcement. These guidelines are in addition to the standard “Terms and Conditions” referenced in Section III of this Notice of Grant Award.

2. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-19-031.

3. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at:
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

4. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL: http://grants1.nih.gov/grants/policy/salcap_summary.htm

5. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

SPREADSHEET SUMMARY
AWARD NUMBER: 5R01GM122079-04 REVISED

INSTITUTION: UNIVERSITY OF IDAHO

Budget	Year 4
TOTAL FEDERAL DC	$194,855
TOTAL FEDERAL F&A	$58,090
TOTAL COST	$252,945

Facilities and Administrative Costs	Year 4
F&A Cost Rate 1	47.5%
F&A Cost Base 1	$122,294
F&A Costs 1	$58,090

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 04/29/2019

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Grant Number: 5R01GM122079-04
FAIN: R01GM122079

Principal Investigator(s):
SCOTT L NUISMER, PHD

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES

Deborah Shaver
UNIVERSITY OF IDAHO
875 PERIMETER DRIVE
MS3020
MOSCOW, ID 838443020

Award e-mailed to: osp@uidaho.edu

Period Of Performance:
Budget Period: 05/01/2019 – 04/30/2020
Project Period: 08/01/2016 – 04/30/2020

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $252,945 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Jennifer Billington
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 5R01GM122079-04

Award Calculation (U.S. Dollars)

Federal Direct Costs	$194,855
Federal F&A Costs	$58,090
Approved Budget	$252,945
Total Amount of Federal Funds Obligated (Federal Share)	$252,945
TOTAL FEDERAL AWARD AMOUNT	$252,945
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$252,945

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
4	$252,945	$252,945

Fiscal Information:

CFDA Name:	Biomedical Research and Research Training
CFDA Number:	93.859
EIN:	1826000945A1
Document Number:	RGM122079A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2019

IC	CAN	2019
GM	8472185	$252,945

NIH Administrative Data:
PCC: B120VR / **OC**: 414E / **Released**: (b)(6) 04/26/2019
Award Processed: 04/29/2019 12:05:48 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01GM122079-04

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5R01GM122079-04

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal

Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: http://grants.nih.gov/grants/policy/policy.htm#gps.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the eRA Commons (Commons) within 120 days of the period of performance end date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, http://grants.nih.gov/grants/policy/policy.htm#gps, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the Payment Management System's (PMS) quarterly cash transaction data. A final quarterly federal cash transaction report is not required for awards in PMS B subaccounts (i.e., awards to foreign entities and to Federal agencies). NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures or quarterly federal cash transaction reporting. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level. If the grantee submits a final expenditure FFR but does not reconcile any discrepancies between expenditures reported on the final expenditure FFR and the last cash report to PMS, NIH will close the award at the lower amount. This could be considered a debt or result in disallowed costs.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: http://grants.nih.gov/grants/forms.htm. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, D42, D43, D71, DP7, G07, G08, G11, K12, K16, K30, P09, P40, P41, P51,

R13, R25, R28, R30, R90, RL5, RL9, S10, S14, S15, U13, U14, U41, U42, U45, UC6, UC7, UR2, X01, X02.

Unless an application for competitive renewal is submitted, a Final Research Performance Progress Report (Final RPPR) must also be submitted within 120 days of the period of performance end date. If a competitive renewal application is submitted prior to that date, then an Interim RPPR must be submitted by that date as well. Instructions for preparing an Interim or Final RPPR are at: https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the Interim or Final RPPR. *Note that data reported within Section I of the Interim and Final RPPR forms will be made public and should be written for a lay person audience*.

NIH strongly encourages electronic submission of the final invention statement through the Closeout feature in the Commons, but will accept an email or hard copy submission as indicated below.

Email: The final invention statement may be e-mailed as PDF attachments to: NIHCloseoutCenter@mail.nih.gov.

Hard copy: Paper submissions of the final invention statement may be faxed to the NIH Division of Central Grants Processing, Grants Closeout Center, at 301-480-2304, or mailed to:

National Institutes of Health
Office of Extramural Research
Division of Central Grants Processing
Grants Closeout Center
6705 Rockledge Drive
Suite 5016, MSC 7986
Bethesda, MD 20892-7986 (for regular or U.S. Postal Service Express mail)
Bethesda, MD 20817 (for other courier/express deliveries only)

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final RPPR is not required. However, a final expenditure FFR is required and should be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.
Treatment of Program Income:
Additional Costs

SECTION IV – GM Special Terms and Conditions – 5R01GM122079-04

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

1. This award provides funding for an application submitted in response to the NSF/NIGMS Joint Program in Mathematical Biology Initiative. This grant should be administered in accordance with the guidelines described in this specific announcement. These guidelines are in addition to the standard “Terms and Conditions” referenced in Section III of this Notice of Grant Award.

2. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-19-031.

3. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at:
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

4. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Current salary cap levels can be found at the following URL: http://grants1.nih.gov/grants/policy/salcap_summary.htm

5. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Maricela Trujillo
Email: maricela.trujillo@nih.gov **Phone**: 301-594-3927

Program Official: Veerasamy Ravichandran
Email: veerasamy.ravichandra@nih.gov **Phone**: 301-451-9822 **Fax**: 301-480-0884

SPREADSHEET SUMMARY
GRANT NUMBER: 5R01GM122079-04

INSTITUTION: UNIVERSITY OF IDAHO

Budget	Year 4
TOTAL FEDERAL DC	$194,855
TOTAL FEDERAL F&A	$58,090
TOTAL COST	$252,945

Facilities and Administrative Costs	Year 4
F&A Cost Rate 1	47.5%
F&A Cost Base 1	$122,294
F&A Costs 1	$58,090

A. COVER PAGE

Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES	
Grant Number: 5R01GM122079-04	**Project/Grant Period:** 08/01/2016 - 04/30/2020
Reporting Period: 05/01/2018 - 04/30/2019	**Requested Budget Period:** 05/01/2019 - 04/30/2020
Report Term Frequency: Annual	**Date Submitted:** 03/11/2019
Program Director/Principal Investigator Information: SCOTT L NUISMER , PHD **Phone number:** (208) 885-4096 **Email:** snuismer@uidaho.edu	**Recipient Organization:** UNIVERSITY OF IDAHO UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW, ID 838443020 **DUNS:** 075746271 **EIN:** 1826000945A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: DEBORAH N SHAVER 875 Perimeter Dr. MS 3020 Moscow, ID 838443020 **Phone number:** 2088856651 **Email:** osp@uidaho.edu	**Signing Official:** DEBORAH N SHAVER 875 Perimeter Dr. MS 3020 Moscow, ID 838443020 **Phone number:** 2088856651 **Email:** osp@uidaho.edu
Human Subjects: No	**Vertebrate Animals:** Yes
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1. Develop a mathematical framework predicting the extent of protection provided by a transmissible vaccine. For a transmissible vaccine to be useful, it must be able to invade the target population and immunize a larger number of individuals than could be achieved using a traditional vaccine. We will develop mathematical models, novel approximations, and individual-based simulations that allow us to predict the fate of a transmissible vaccine.

Aim 2. Develop a mathematical framework predicting the evolution of a transmissible vaccine. Developing a transmissible vaccine requires that an infectious agent be manipulated, either by adding genes that confer immunity or by eliminating or altering genes that cause virulence. We will develop mathematical models, novel approximations, and individual-based simulations to determine when these genetic modifications are evolutionarily robust and to study the epidemiological consequences when they are not.

Aim 3. Test model predictions using an experimental viral model. A recombinant vector vaccine is a type of engineered vaccine that is being tested in many contexts — against Ebola, HIV, and in wild-life. We will test whether a recombinant Murine cytomegalovirus will evolve within the host to lose expression of its antigenic insert.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Accomplishments Text March 2019.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: Professional Development Text March 2019.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

Postdoctoral researcher Andrew Basinski presented a talk on recombinant vector transmissible vaccines at the annual MIDAS meeting. PI Nuismer presented a talk on transmissible vaccines at a DARPA proposers day meeting. Multiple papers were published during this reporting period.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Aim 1. The first specific aim is essentially complete. During the next reporting period, work on this objective will focus on wrapping up remaining publications and disseminating key results.

Aim 2. Work on this aim in the next reporting period will focus on integrating multiple vaccine strains. Specifically, we are working on development of a multi-strain model that allows vaccine reversion to be a multi-step process. Integrating multi-step reversion will allow us to develop predictions for the evolutionary stability of transmissible vaccines as a function of their underlying genetic engineering. We anticipate these results will help guide efforts to engineer recombinant vector and attenuated transmissible vaccines that are more evolutionarily robust and less likely to revert.

Aim 3. Our priority is analyzing the sequences of PCR products to determine the state of the virus at late time points. If the answer is simple, we move on. If the PCR sequences are not simple, we will need to take a more targeted approach to the sequencing. In either case, we will extend the viral growth studies to tissue culture for comparison to in vivo growth. If we get the same answer from tissue culture as from mouse growth, the results will suggest that tissue culture growth of a vaccine can be used as a proxy for in vivo growth – offering reduced effort in vaccine design.

Aim 1. Work on the first specific aim is essentially complete. During this reporting period, we completed and published models quantifying the scope for transmissible vaccines (TV's) to facilitate control of epidemics (Nuismer et al., 2018), exploring how heterogeneity in host populations influences transmissible vaccine efficacy (Varrelman et al. 2019), and (b)(4); (b)(6)

(b)(4); (b)(6)

Combined with previous work accomplished on this aim in previous reporting periods, our results clearly show that TV's can be powerful tools for controlling infectious disease, but only when cross-immunity between the vector and naturally circulating vector strains is minimal. In addition to developing a robust theoretical framework for understanding the likely epidemiological impacts of transmissible vaccines, our work provides clear recommendations for developing transmissible vaccines with properties that maximize their efficacy. Finally, work on this aim has quantified the cost savings that could accrue if transmissible vaccines were substituted for conventional vaccines in long-running efforts to control and isolate rabies infections in wild raccoon populations in North America (Basinski et al. 2019).

Aim 2. Previous work on this aim established that vaccine reversion within attenuated transmissible vaccines posed little problem for their efficacy at the population level unless rates of reversion are extremely high (Nuismer et al. 2016). In contrast, subsequent work focuses on recombinant vector transmissible vaccines demonstrated that vaccine reversion can result in failure even if rates of reversion are tiny (Basinski et al. 2017). The reason this occurs, is that when a recombinant vector vaccine reverts, the result is a free vector (now lacking the antigenic insert) that may have a competitive advantage due to its reduced immune profile and reduced costs of expressing the antigenic insert. These model results suggest that the fate of a recombinant vector vaccine may rest on two key parameters: 1) at what rate is the antigenic insert deleted or its expression suppressed, and 2) what are the consequences of deletion or reduced expression for competition with intact vaccine. Work during this reporting period followed up on these initial results with a more integrative modeling approach that allowed deletion or downregulation of the antigenic insert to occur at an arbitrary rate. This new modeling framework allowed us to identify critical rates of antigenic deletion or downregulation above which a recombinant vector vaccine will perform no better than a conventional vaccine. In addition, work on this aim developed a maximum likelihood approach for estimating this critical rate of deletion or downregulation from serial passage experiments conducted in vivo or in vitro. This work provides the statistical and conceptual tools for interpreting results of experiments like those being conducted in Aim 3 and is now under review. Additional work conducted on this aim developed and analyzed models where evolution reduces the transmissibility of a vaccine as it moves from host to host (Bull et al. 2019). This work was inspired by empirical studies demonstrating a decline in vaccine transmission from hosts that were directly inoculated to those that received the vaccine via transmission. The results of this work demonstrate that even if vaccine transmission occurs only from directly vaccinated individuals, its benefits can be quite large, particularly when directly vaccinated individuals are highly contagious.

Aim 3. A leading vector candidate for use in recombinant vector transmissible vaccines (and indeed, for any recombinant vector vaccine) is cytomegalovirus (CMV). CMV is a promising vector candidate because of its high species specificity, its large genome size and stability, and its apparent ability to reinfect hosts that already carry CMV. Because our mathematical models demonstrate that the success of a recombinant vector vaccine depends on the rate at which it ejects or downregulates its antigenic insert, we constructed a model vaccine: murine CMV engineered to express ovalbumin as a model antigen. The goal was to test stability of the virus in mice, but as animal work was not requested in the

original application, we had to await NIH permission and IACUC approvals at the University of Texas before for implementing the mouse studies.

Our initial question is the simple but important one of whether the insert is evolutionarily stable, or instead, whether the replicating virus will evolve within the host to lose or downregulate the ovalbumin gene. Stability of antigen expression is obviously required for vaccine success. The design introduced the engineered CMV into mice; tissues were sampled over time; viral titers from those tissues were obtained; PCR analysis of CMV from those tissues has been conducted to determine relative amounts of virus with and without ovalbumin insert. The PCR products from late in the infection often did not obey expected sizes, and indeed, sometimes exhibited multiple bands, so sequences are necessary to confirm what was amplified. Those sequences have just arrived and await analysis; they are shotgun sequences, intended to merely to tell us whether the PCR products are virus or mouse, and if virus, from what part of the genome.

Work on the project has continued to provide training for a postdoctoral researcher (Andrew Basinski) and graduate student (Tanner Varrelman). In addition, training opportunities have been provided for a new postdoctoral researcher (Nathan Layman) and a new undergraduate student (Courtney Schreiner). Each of these individuals is being trained by PI Nuismer and Co-PI Remien to develop and analyze mathematical models of infectious disease. Nuismer and Remien have worked extensively with Postdoctoral researchers Basinski and Layman to develop their writing and presentation skills and to help them formulate a strategic plan for moving into scientific careers at the end of their postdoctoral positions. PI Nuismer and postdoctoral researcher Basinski have also worked extensively with undergraduate Courtney Schreiner as she has developed and analyzed a mathematical model identifying the optimal time to vaccinate fluctuating wildlife populations. This work, on which Courtney is the lead author, is now being prepared for publication and should be submitted within the next several months.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Nuismer SL, May R, Basinski A, Remien CH. Controlling epidemics with transmissible vaccines. PloS one. 2018 May 10;13(5):e0196978. PubMed PMID: 29746504; PubMed Central PMCID: PMC5945036.
Complete	Tom EF, Molineux IJ, Paff ML, Bull JJ. Experimental evolution of UV resistance in a phage. PeerJ. 2018 July 9;6:e5190. PubMed PMID: 30013847; PubMed Central PMCID: PMC6042481.
PMC Journal - In process	Basinski AJ, Nuismer SL, Remien CH. A little goes a long way: Weak vaccine transmission facilitates oral vaccination campaigns against zoonotic pathogens. PLoS neglected tropical diseases. 2019 March 08.
PMC Journal - In process	Varrelman TJ, Andrew BJ, Chris RH, Scott NL. Transmissible vaccines in heterogeneous populations: Implications for vaccine design. One health (Amsterdam, Netherlands). 2019 June;7.
In Process at NIHMS	Smithson MW, Basinki AJ, Nuismer SL, Bull JJ. Transmissible vaccines whose dissemination rates vary through time, with applications to wildlife. Vaccine. 2019 February 21;37(9):1153-1159. PubMed PMID: 30686635.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	NUISMER, SCOTT L	PHD	PD/PI	(b)(6)					NA
	N	Remien, Christopher Haskell	PhD	Co-Investigator						NA
	N	Varrelman, Tanner	BS	Graduate Student (research assistant)						NA
	N	Layman, Nathan	PhD	Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA
	N	Schreiver, Courtney		Undergraduate Student						NA
	N	Basinski, Andreew	PHD	Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA
	N	BULL, James Jeffrey	PHD,BS	Co-Investigator						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

No

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

No

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

Yes

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020
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UNIVERSITY OF IDAHO	075746271		UNIVERSITY OF IDAHO MORRILL HALL, RM 114 MOSCOW ID 838443020

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes

Estimated unobligated balance: 148000

G.10.b Provide an explanation for unobligated balance:
Our project had a substantially shortened first year which resulted in an initial year carryover that has continued to propagate, even though, once the award was made, we have been spending at a rate close to what was planned in our original budget. Unexpended funds also resulted from a change of study system in Aim 3 that required approvals for work on vertebrate animals (the proposal was to work on bacteriophages, we changed it to work on cytomegalovirus).

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent

Funds carried over will be used as described in our original budget for the theory component (Aims 1, 2). With preliminary empirical work done on the revised Aim 3, using mice and cytomegalovirus, we will now expand that work into tissue culture growth of virus. The unused funds allocated for empirical work will be used for tissue culture, technician time and sequencing viral genomes.

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

Recipient Information

1. Recipient Name
REGENTS OF THE UNIVERSITY OF IDAHO
875 PERIMETER DR MS 3020
MOSCOW, ID 83844

2. Congressional District of Recipient
01

3. Payment System Identifier (ID)
1826000945A1

4. Employer Identification Number (EIN)
826000945

5. Data Universal Numbering System (DUNS)
075746271

6. Recipient's Unique Entity Identifier
QWYKRJH5NNJ3

7. Project Director or Principal Investigator
SCOTT L NUISMER, PHD
Professor
snuismer@uidaho.edu
208-885-6280

8. Authorized Official
Deborah Shaver
osp@uidaho.edu
208-885-6651

Federal Agency Information

9. Awarding Agency Contact Information
Parvathy Rajeev Panakal
Grants Management Specialist
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
parvathy.panakal@nih.gov
(301) 480-1240

10. Program Official Contact Information
Jean Yuan
Scientific Review Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
xin.yuan@nih.gov

Federal Award Information

11. Award Number
2R01GM122079-05A1

12. Unique Federal Award Identification Number (FAIN)
R01GM122079

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
A Mathematical Theory of Transmissible Vaccines

15. Assistance Listing Number
93.859

16. Assistance Listing Program Title
Biomedical Research and Research Training

17. Award Action Type
Competing Continuation

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 09/20/2023 **– End Date** 08/31/2024	
20. Total Amount of Federal Funds Obligated by this Action	$367,126
20 a. Direct Cost Amount	$291,000
20 b. Indirect Cost Amount	$76,126
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$367,126
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$367,126
26. Project Period Start Date 08/01/2016 **– End Date** 08/31/2027	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$367,126

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Tiffany Walker

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

SECTION I – AWARD DATA – 2R01GM122079-05A1

Principal Investigator(s):
SCOTT L NUISMER, PHD

Award e-mailed to: postaward@uidaho.edu

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $367,126 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF IDAHO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM122079. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Tiffany Walker
Grants Management Officer
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$82,743
Fringe Benefits	$30,591
Personnel Costs (Subtotal)	$113,334
Equipment	$7,964
Travel	$7,116
Other	$5,208
Subawards/Consortium/Contractual Costs	$155,785
Publication Costs	$1,593
Federal Direct Costs	$291,000
Federal F&A Costs	$76,126
Approved Budget	$367,126
Total Amount of Federal Funds Authorized (Federal Share)	$367,126
TOTAL FEDERAL AWARD AMOUNT	$367,126
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$367,126

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
5	$367,126	$367,126
6	$335,075	$335,075
7	$359,092	$359,092
8	$239,682	$239,682

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1826000945A1
Document Number:	RGM122079B
PMS Account Type:	P (Subaccount)
Fiscal Year:	2023

IC	CAN	2023	2024	2025	2026
GM	8472185	$367,126	$335,075	$359,092	$239,682

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: B120YJ / **OC**: 41022 / **Released**: Walker, Tiffany 09/11/2023
Award Processed: 09/18/2023 12:02:39 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 2R01GM122079-05A1

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 2R01GM122079-05A1

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01GM122079. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by

persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights laws enforced by HHS. See https://www.hhs.gov/civil-rights/for-providers/provider-obligations/index.html and https://www.hhs.gov/.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html and https://www.lep.gov.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html.
- HHS funded health and education programs must be administered in an environment free of sexual harassment; see https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html. For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see https://grants.nih.gov/grants/policy/harassment.htm.
- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see https://www.hhs.gov/conscience/conscience-protections/index.html and https://www.hhs.gov/conscience/religious-freedom/index.html.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – GM SPECIFIC AWARD CONDITIONS – 2R01GM122079-05A1

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

RESTRICTIONS:

1. Funds included in this award for research involving live vertebrate animals are restricted and may not be used for any other purpose without NIGMS' approval. Under governing PHS Policy no funds may be drawn down from the payment system and no obligations may be made against federal funds for research involving live vertebrate animals prior to OLAW approval of an Animal Welfare Assurance (Assurance) in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals. This restriction applies to the recipient organization and all performance sites (e.g., collaborating institutions, subawardees) lacking OLAW-approved Assurances, whether domestic, foreign, or interinstitutional. If the recipient organization does not have an Assurance and the animal research will be conducted at an institution with an Assurance, the recipient must obtain an Interinstitutional Assurance from OLAW. Only activities that do not involve live vertebrate animals may be conducted at any performance site until OLAW has approved an

Assurance for that site. The Assurance documents must be submitted to OLAW no later than **90 days** prior to the involvement of animals, and the Assurance must be approved by OLAW before conducting the animal activity. Failure to submit the Assurance to OLAW within the required timeframe or to otherwise comply with the above requirements can result in suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action.

When the appropriate Assurance(s) has been received and approved, OLAW will change the code to 30, enter “R” (Resolved) in IMPAC II and notify the IC through e-mail that the restriction may be lifted.

2. Funds included in this award for research involving live vertebrate animals are restricted and may not be used for any other purpose without NIGMS' approval. Under governing PHS Policy no funds may be drawn down from the payment system and no obligations may be made against federal funds for research involving live vertebrate animals prior to submission of valid Institutional Animal Care and Use Committee (IACUC) approval in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals. The present award is made without currently valid verification of IACUC approval for this project. Only activities that do not involve live vertebrate animals may be conducted pending [Insert IC abbreviation, e.g., NIAID]’s acceptance of verification of IACUC approval. The verification of IACUC approval must be submitted to the Grants Management contact identified on the Notice of Award. Failure to submit the verification of IACUC approval or to otherwise comply with the above requirements can result in suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action.

ICs are responsible for ensuring that verification of IACUC approval is received and entered into IMPAC II. Upon notification by the IC, OLAW will change the code to 30, enter “R” (Resolved) in IMPAC II and notify the IC through e-mail that the restriction may be lifted.

3. This award is issued in accordance with the NIH fiscal policies described in NIH Guide Notice NOT-OD-23-071.

4. Unobligated Balances: As indicated in Section III of this Notice of Award, an unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval. In accordance with section 8.1.1.1 of the NIH GPS, NIGMS staff reserve the right to make budgetary reductions to award commitments in cases where recipients have accrued excessively large unobligated balances.

5. As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of General Medical Sciences.

6. None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap. Therefore, this award and/or future years are adjusted accordingly, if applicable.
Current salary cap levels can be found at the following URL:

http://grants.nih.gov/grants/policy/salcap_summary.htm

7. The Year-01 budget period is slightly less than 12 months in length (full 12-month level of funds provided) so that the anniversary date for future non-competing awards will be September 1st. The Research Performance Progress Report (RPPR) will be due 45 days prior to this date (60 days for non-SNAP awards) each year. Guidance on RPPR submission is documented in the RPPR Instruction Guide found at: http://grants.nih.gov/grants/rppr/index.htm
.
This anniversary date may change the receipt date for the next competing continuation (Type 2)

application. Consult the submission dates/deadlines on the NIH Office of Extramural Research Grants (OER) Home page at http://grants.nih.gov/grants/dates.htm.

8. This award includes funds awarded for consortium activity. Recommended levels in future years also include costs for this purpose. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at: http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm

SECTION V - NIGMS CONTACTS

The NIGMS WWW home page is at http://www.nigms.nih.gov

SPREADSHEET SUMMARY
AWARD NUMBER: 2R01GM122079-05A1

INSTITUTION: UNIVERSITY OF IDAHO

Budget	Year 5	Year 6	Year 7	Year 8
Salaries and Wages	$82,743	$70,322	$101,557	$103,899
Fringe Benefits	$30,591	$25,999	$37,547	$38,413
Personnel Costs (Subtotal)	$113,334	$96,321	$139,104	$142,312
Equipment	$7,964			
Travel	$7,116	$6,048	$8,735	$8,936
Other	$5,208	$4,426	$6,392	$6,540
Subawards/Consortium/Contractual Costs	$155,785	$172,851	$124,813	
Publication Costs	$1,593	$1,354	$1,955	$2,000
TOTAL FEDERAL DC	$291,000	$281,000	$280,999	$159,788
TOTAL FEDERAL F&A	$76,126	$54,075	$78,093	$79,894
TOTAL COST	$367,126	$335,075	$359,092	$239,682

Facilities and Administrative Costs	Year 5	Year 6	Year 7	Year 8
F&A Cost Rate 1	50%	50%	50%	50%
F&A Cost Base 1	$152,251	$108,149	$156,186	$159,788
F&A Costs 1	$76,126	$54,075	$78,093	$79,894

PI: **NUISMER, SCOTT L**	Title: A Mathematical Theory of Transmissible Vaccines	
Received: 03/02/2022	Opportunity: PA-20-185	Council: 10/2022
Competition ID: FORMS-G	FOA Title: NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed)	
2R01GM122079-05A1	Dual: AI	Accession Number: 4688554
IPF: 3543501	Organization: UNIVERSITY OF IDAHO	
Former Number: 2R01GM122079-05	Department:	
IRG/SRG: MABS	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 5: 350,914 Year 6: 402,905 Year 7: 286,333 Year 8: 167,788	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N HFT: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Alec Redwood	University of Western Australia	Co-Investigator
Chan Baca	University of Western Australia	Co-Investigator
Scott Nuismer	Regents of the University of Idaho	PD/PI
James Bull	Regents of the University of Idaho	Co-Investigator
Christopher Remien	Regents of the University of Idaho	Co-Investigator

OMB Number: 4040-0001
Expiration Date: 12/31/2022

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
GM122079

b. Agency Routing Number

2. DATE SUBMITTED
2022-03-02

Application Identifier
V220109

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **UEI*:** QWYKRJH5NNJ3

Legal Name*: Regents of the University of Idaho
Department:
Division:
Street1*: 875 Perimeter Dr., MS 3020
Street2:
City*: Moscow
County: Idaho
State*: ID: Idaho
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 83844-4244

Person to be contacted on matters involving this application
Prefix: First Name*: Deborah Middle Name: Last Name*: Shaver Suffix:
Position/Title: AVP, Research Admin
Street1*: 875 Perimeter Drive, MS 3020
Street2:
City*: Moscow
County: Idaho
State*: ID: Idaho
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 83844-4244
Phone Number*: 208-885-6651 Fax Number: Email: osp@uidaho.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 826000945

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*
❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
A Mathematical Theory of Transmissible Vaccines

12. PROPOSED PROJECT
Start Date* Ending Date*
10/01/2022 09/30/2026

13. CONGRESSIONAL DISTRICTS OF APPLICANT
ID-001

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Scott Middle Name: Landis Last Name*: Nuismer Suffix:
Position/Title:
Organization Name*: Regents of the University of Idaho
Department:
Division:
Street1*: 875 Perimeter Drive
Street2: MS 4244
City*: Moscow
County: ID057
State*: ID: Idaho
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 83844-3051
Phone Number*: 208-885-6280 Fax Number: Email*: snuismer@uidaho.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$1,589,339.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$1,589,339.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Sarah Middle Name: Simone Last Name*: Martonick Suffix:
Position/Title*: Post Award Manager
Organization Name*: Regents of the University of Idaho
Department: Office of Sponsored Programs
Division:
Street1*: 875 Perimeter Dr, MS3020
Street2:
City*: Moscow
County: Latah
State*: ID: Idaho
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 83844-3020
Phone Number*: 208-885-2145 Fax Number: Email*: smartonick@uidaho.edu

Signature of Authorized Representative*
Sarah Simone Martonick

Date Signed*
03/02/2022

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_Letter.pdf

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 12/31/2022

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Regents of the University of Idaho
UEI:	QWYKRJH5NNJ3
Street1*:	875 Perimeter Drive
Street2:	MS 3051
City*:	Moscow
County:	Idaho
State*:	ID: Idaho
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	83844-3051
Project/Performance Site Congressional District*:	ID-001

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Western Australia
UEI:	CPLPM5RWMX26
Street1*:	35 Stirling Highway
Street2:	
City*:	Crawley
County:	
State*:	
Province:	
Country*:	AUS: AUSTRALIA
Zip / Postal Code*:	WA 6009
Project/Performance Site Congressional District*:	00-000

Additional Location(s) File Name:

Funding Opportunity Number: PA-20-185. Received Date: 2022-03-02T18:46:20.000-05:00

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ○ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ○ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ○ **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ● **Yes** ○ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ● Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number A3852-01

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ● **Yes** ○ **No**

6.a. If yes, identify countries: Australia

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary.pdf
8. Project Narrative*	Project_Narrative.pdf
9. Bibliography & References Cited	Nuismer_References.pdf
10.Facilities & Other Resources	Facilities_Resources.pdf
11.Equipment	Equipment.pdf
12. Other Attachments	Foreign_Justification.pdf

Funding Opportunity Number: PA-20-185. Received Date: 2022-03-02T18:46:20.000-05:00

Each year, millions of people are harmed or killed by pathogens that spill over from wild or domestic animal reservoirs. A new approach to reducing the threat of spillover is to eliminate the pathogen from its animal reservoir using transmissible vaccines that move from animal to animal providing immunity to the pathogen as they go. Transmissible vaccines reduce the vaccination effort required for pathogen control within animal reservoirs and allow the vaccine to penetrate remote reservoir habitats where direct vaccination is impossible. Bringing this revolutionary idea to fruition requires that we engineer vaccines that simultaneously: 1) transmit efficiently from animal to animal, 2) stimulate a robust immune response to the target pathogen, and 3) maintain their integrity in the face of evolutionary pressures. This project will develop mathematical models that predict how these traits of the vaccine emerge from the interplay between vaccine replication and the animal's immune response. These models will be parameterized and validated using laboratory studies of prototype transmissible vaccines that use murine cytomegalovirus (MCMV) as a vector backbone. We focus on MCMV as a vector because it is highly species specific, capable of superinfection, and provides a model for vaccine development across murine rodents that serve as important reservoirs for a wide range of human pathogens. The models will be validated using experiments with immune depleted mice that challenge their ability to explain both pattern and process. Work on this project capitalizes on an existing collaboration between experts in mathematical modeling, viral evolution, and murine cytomegalovirus.

Each year, millions of people are harmed or killed by viruses that spill over from wild or domestic animal reservoirs, and in some cases these spillovers result in devastating pandemics. One new avenue for suppressing these animal pathogens is to develop self-disseminating animal vaccines that block the viruses at their source and prevent them from spilling over into the human population. This project uses a combination of mathematical models and laboratory studies to develop a framework for designing self-disseminating vaccines and optimizing their performance.

Facilities and Resources

University of Idaho

The University of Idaho provides an ideal environment for the proposed work. Key strengths of the environment include a rich culture of inter-disciplinary research at the interface of mathematics, computer science, and biology and resource cores that provide access to high performance computing and technical support. Each of these aspects is detailed in the subsequent sections.

Interdisciplinary research culture

The Institute for Interdisciplinary Data Sciences (IIDS) and Institute for Modeling Collaboration and Innovation (IMCI) have created an intellectual, cultural, and physical environment that fosters synergy in interdisciplinary biomedical research. Both provide a range of spaces, support staff, and events that encourage internal collaboration and facilitate external collaboration including a vibrant seminar series highlighting research using mathematical and computational tools to answer challenging biological problems.

Research Computing

Research Computing and Data Services (RCDS) within IIDS manages one large computer cluster for research and data analysis and modeling. The main cluster provides over 2,500 processor cores and over 8 terabytes (TB) of system memory. The servers that comprise the cluster are interconnected with 40Gb/sec QDR (Quad Data Rate) Infiniband for inter-node communication and 1Gb/sec ethernet for management. The modular design of this cluster, primarily enclosures (blade chassis) and blade servers, makes it possible to service or upgrade components without interrupting end users. Removable and redundant fans and power supplies located at the back of the enclosures provide easy access and replacement without powering down individual systems, and each enclosure contains its own network components to maximize inter-enclosure server communication. Components include Dell M1000e blade enclosures with various blade servers, Dell rack servers, and various Supermicro servers. We have 16 cluster nodes with various NVIDIA GPU accelerators.

Work in the investigator's lab will capitalize on the main cluster within RCDS for large-scale simulation modeling and Bayesian analysis.

Investigator Lab and Office Suite

The investigator's group occupies a newly renovated lab (1700 sq. feet) optimized for mathematical and computational research. This space provides semi-private office space for six postdoctoral fellows and graduate students and a large open space designed to facilitate collaborative research and the generation of new ideas. All office spaces are equipped with modern high-performance workstations.

University of Western Australia

A/Prof Alec Redwood and Dr Baca Chan are located within the Harry Perkins Institute for Medical Research building which was newly completed in 2014. The Perkins building is situated within the Queen Elizabeth II (QEII) medical center, which is a focal point for medical health research in Western Australia. Sharing this site is the Sir Charles Gardner Hospital, the Perth

Children's Hospital, as well as numerous research institutions including the Telethon Kids Institute, the Perron Institute for Neurological and Translational Science, the Ear Science Institute Australia and Keogh Institute for Medical Research. The medical school and research arms of the University of Western Australia is likewise located at the QEII Medical Centre and spread throughout several buildings.

The Perkins building is purpose built for medical research with laboratories, clinical facilities and a state-of-the-art animal care facility. Housed within the building includes the Harry Perkins Institute for Medical Research, the Institute for Respiratory Health, the WA Health Translation Network, the National Centre for Asbestos Related Diseases (NCARD) and the Lions Eye Institute. For the purpose of this project, research laboratories are certified physical containment 2 (PC2) facilities with Biological Safety Cabinets required for the infectious work outlined in this proposal. The Centre for Microscopy, Characterization and Analysis (CMCA) is the in-house flow cytometry core. The Perkins Monoclonal Antibody Facility will provide the neutralizing antibodies required for the depletion experiments outlined in Goal 2c. All the equipment and resources for this project are readily available within the Perkins building.

Our scientific environment benefits from being the focal hub of medical research, with scientists from multiple institutions working from one sprawling site. Advanced technology is accessible due to the concentration of research institutes located on site. We have absolute institutional support from the Institute for Respiratory Health and the University of Western Australia

Equipment

University of Idaho

IIDS Research Computing and Data Services

Research Computing and Data Services (RCDS) is the computational backbone for research at the University of Idaho. It provides investigators with access to reliable, state-of-the-art high performance computing (HPC) and data storage infrastructure for use in analyzing and managing large volumes of multidisciplinary research data. RCDS provides the expertise and computational tools required for processing data across all stages of the scientific data lifecycle, including raw data acquisition, modeling and analysis, sharing, dissemination, and archival. RCDS technical staff include systems administrators, scientific programmers, web developers, and data managers that collaborate with researchers to transform scientific questions into meaningful results with broader impact. Users may run jobs that use hundreds of parallel processors or require large amounts of memory and can take weeks to complete. Typical high-end projects include mathematical/computational modeling, machine learning, phylogenetic analyses, interactive data dashboards and visualizations, genome assembly, protein structure modeling, and computational physics simulations.

Overview of Facilities

RCDS infrastructure is explicitly designed to manage the complex computational and storage requirements for UI researchers with very high performance and reliability. RCDS contains an advanced mix of high-performance computing clusters, powerful servers, and reliable data storage components as well as the knowledge and technical skills required to compress years of analysis into days. Funding for RCDS infrastructure was provided from a variety of sources, including the National Institutes of Health (NIH), the National Science Foundation (NSF), the U.S. Department of Agriculture (USDA), the U.S. Department of Energy (DOE), and (b)(4); (b)(6) (b)(4); (b)(6) RCDS equipment is housed in a modern data center provided by the University of Idaho, a second campus data center in the basement of the UI Library, and in the Collaborative Computing Center (C3) data center at the Idaho National Laboratory (INL).

Data Centers

McClure Data Center: The primary IIDS Research Computing and Data Services data center is a redesigned and renovated 1400 square-foot facility in Room 124 in McClure Hall on the University of Idaho campus. Optical fiber and copper interconnections provide 1-25 Gb/s data transfer rates within the data center, which is connected to the multi-path 10Gb/s university backbone and from there to the Idaho Regional Optical Network (IRON) and Internet2. The McClure data center has a dedicated 80KVa UPS with three-phase power and four-forced air handlers attached to redundant university chilled water systems.

UI Library Data Center: The secondary RCDS data center resides within the basement of the UI Library. This facility is also used as the primary production data center for the central campus Information Technology Services (ITS) unit and provides the most direct uplink from the UI campus to IRON/Internet2. RCDS currently maintains several equipment racks within this shared center which houses additional RCDS data storage, virtualization, and data backup infrastructure. RCDS maintains in-rack UPS units within these Library racks, while an attached diesel generator provides indefinite emergency backup power.

INL Collaborative Computing Center (C3): RCDS also manages server and storage infrastructure within the C3 facility in Idaho Falls. The C3 is a 64,000 sq. ft state-of-the-art facility with a 200- person occupancy and a large 7,000 sq. ft data center capable of supporting up to 200 watercooled server racks with a maximum power load of 8.5MW. RCDS manages 5 equipment racks within the C3, housing servers, storage, and network hardware. The C3 currently hosts two large DOE supercomputers: Sawtooth and Falcon, with Falcon scheduled to be transferred to academic co-management in early 2022, initially led by IIDS RCDS staff.

All three RCDS data centers have rigorous physical security and access controls. RCDS facility staff have office space in room 123 McClure Hall, 441D Life Sciences South, and room 416 in the UI Library.

Computing Systems

RCDS manages one large computer cluster for research and data analysis and modeling. Our main cluster provides over 2,500 processor cores and over 8 terabytes (TB) of system memory. The servers that comprise the cluster are interconnected with 40Gb/sec QDR (Quad Data Rate) Infiniband for inter-node communication and 1Gb/sec ethernet for management. The modular design of this cluster, primarily enclosures (blade chassis) and blade servers, makes it possible to service or upgrade components without interrupting end users. Removable and redundant fans and power supplies located at the back of the enclosures provide easy access and replacement without powering down individual systems, and each enclosure contains its own network components to maximize inter-enclosure server communication. Components include Dell M1000e blade enclosures with various blade servers, Dell rack servers, and various Supermicro servers. We have 16 cluster nodes with various NVIDIA GPU accelerators.

RCDS also maintains 12 servers (various Dell and Supermicro rack servers) that are not connected to the cluster systems for jobs that require very large, shared memory machines (such as distance-based phylogenetic analyses, genome assembly, and molecular simulations), for software development, and for investigators who are unfamiliar with or do not require a cluster environment. The most powerful servers in this group each contain 64 cores and 1 TB (1000GB) of system memory. These powerful servers are used heavily for applications such as hybrid sequence assembly of Illumina data.

RCDS manages a rich virtualization environment for hosting 100+ virtual machines (VMs) dedicated to specific applications or research projects. These VMs run web servers, applications, databases, GIS services, models-as-a-service (MaaS), custom web Application Programming Interfaces (APIs), and more. We use VMWare ESXi 6.7 and OpenNebula hypervisors. The main VMWare environment is run on a Dell VRTX converged chassis with 4x M640 Dell PowerEdge blade servers, each with 512GB of RAM and 28/56 physical/hyperthreaded Xeon cores.

Because this scale of operation falls well outside typical University of Idaho information technology and computing services, we maintain our own support infrastructure. These include several servers for storage and authentication of user accounts (LDAP), domain name resolution (DNS), internet address assignment (DHCP) and secure connections to private networks (VPN). We also provide web and database services for online documentation and training.

Data Storage Systems

We have four distinct classes of data storage. The first group is our high-performance storage (290TB available). This storage comprises faster but more expensive disk drives and multiple control systems that are linked together through a distributed file system (Lustre) that allows us to group storage components into logical units. This makes it possible to access portions of data from multiple storage devices and aggregates data reading and writing across multiple disk drives and network connections, thereby increasing overall performance. Metadata servers contain typical file system information such as ownership permissions, and physical location. We have multiple metadata servers working in parallel to recognize failures and automate device control to minimize staff intervention and disruption of services. Each individual disk storage system (array) combines multiple disks into a single logical unit (RAID), which provides redundancy on a disk level. Components currently include Dell MD3420 storage arrays, Dell R515, R510, R630 servers, and various Supermicro servers.

The second group is our commodity storage (1.9PB gross). This storage group uses cheaper, but slower, disks to house most user data. We currently run a Ceph distributed file system, which offers increased performance and reliability. Components currently include various Dell and Supermicro rack servers.

The third storage group comprises our backup storage systems (898TB gross, 630TB of which is off-site). We back up user data regularly to an offsite location on HDDs using ZFS snapshots. Components include Storinator Storage Pods and a Supermicro rack server.

Finally, our main virtualization and hosting infrastructure currently uses a 30TB ultra-highperformance, in-chassis SSD RAID-5 array to host the virtual disks for production VMs. 500TB of slower production data storage is provided by a NetApp FAS 2554 server connected to the VRTX chassis at 10Gbps. A second 500TB NetApp FAS 2554 is located within the C3 data center in Idaho Falls, primarily for the purposes of off-site backup and Disaster Recovery (DR) for our virtualization services.

Data Management and Scientific Programming Services

RCDS provides research data management infrastructure and services that enable UI investigators to store, catalog, disseminate, and archive their research data outputs. RCDS helps researchers write comprehensive Data Management Plans (DMPs) to include in their funding proposals. RCDS operates the UI's official research data repository and is actively engaged with related national initiatives such as the Data Observation Network for Earth (DataONE) and the Earth Science Information Partners (ESIP). Through our involvement with DataONE, RCDS is part of a federation of similar repositories at a global scale, thereby increasing the exposure, resiliency, and discoverability of RCDS-published research data. We can also provision Digital Object Identifiers (DOIs) for datasets through our institutional DataCite membership.

RCDS provides custom scientific programming services to help investigators design, develop, and host custom research applications and tools. These tools often include databases, web applications, and interactive geospatial mapping and data visualization. RCDS is increasingly involved in helping researchers with computational modeling, machine learning, and mobile application development.

Science DMZ

Working with the UI ITS Networking team, we have set up a Science DMZ network to allow for unfettered, high-throughput access to research data. This Science DMZ network hosts a Globus Data Transfer Node (DTN) and perfSONAR servers. Globus allows for reliable, high-speed data transfers across the Internet2 backbone, making it possible to connect safely and efficiently to computational cores at collaborators' institutions to share data. The perfSONAR servers provide a managed mechanism to test and improve latency and network throughput to other institutions

University of Western Australia

The QuantStudio™ 7 Flex Real-Time PCR System housed within the Harry Perkins Institute for Medical Research. This equipment is essential for our research as it enables multiplexing and sensitive quantification of target DNA.

Foreign Justification

Work on this project focuses on developing a mathematical framework for developing effective transmissible pathogens that circulate within wild animal populations. We will parameterize and validate these models using prototype transmissible vaccines ultimately suitable for application to rodent populations that harbor important human pathogens such as arenaviruses and hantaviruses. The prototype transmissible vaccines will be developed and tested by Dr. Alec Redwood and Dr. Baca Chan at the University of Western Australia. Vaccine prototype testing will be performed in tissue culture and in BALB/c mice at the University of Western Australia and the resulting data used to parameterize and validate the mathematical models developed at the University of Idaho.

Dr. Redwood and Dr. Chan are essential for this work. Dr Chan is the senior post-doctoral scientist in Dr. Redwood's laboratory. She has the essential molecular virology skills required to undertake this work and has constructed numerous recombinant cytomegalovirus viruses. She has extensive experience in the MCMV model of infection in mice and has described new interactions between herpesviruses and host immunity. Dr Redwood is a recognized expert in the biology of murine cytomegalovirus (MCMV). He created the reagents used for these studies, notably the bacterial artificial chromosome of MCMV, ARK25. He is the lead Australian PI in the DARPA funded PREEMPT project applying his molecular virology skills to the production of MCMV vaccines for the control of zoonotic infections in wild-life populations. This PREEMPT project was the catalyst for the existing collaboration with Prof. Nuismer. Dr Redwood was also heavily involved in pioneering work that sought to use MCMV as a biological control agent for pest animal species. No other group has such a long history in the production of CMV based vaccines coupled with the requisite molecular virology skills.

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Scott Middle Name Landis Last Name*: Nuismer Suffix:

Position/Title*:
Organization Name*: Regents of the University of Idaho
Department:
Division:
Street1*: 875 Perimeter Drive
Street2: MS 4244
City*: Moscow
County: ID057
State*: ID: Idaho
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 83844-3051

Phone Number*: 208-885-6280 Fax Number:

E-Mail*: snuismer@uidaho.edu

Credential, e.g., agency login: (b)(6)

Project Role*: PD/PI Other Project Role Category:

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Nuismer_Biosketch.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT13564479 Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

PROFILE - Senior/Key Person

Prefix: First Name*: James Middle Name Last Name*: Bull Suffix:

Position/Title*:
Organization Name*: Regents of the University of Idaho
Department:
Division:
Street1*: 875 Perimeter Drive
Street2: MS 4244
City*: Moscow
County: Idaho
State*: ID: Idaho
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 83844-4244

Phone Number*: 208-885-6280 Fax Number:

E-Mail*: jbull@uidaho.edu

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Bull_Biosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Christopher Middle Name Last Name*: Remien Suffix:

Position/Title*:
Organization Name*: Regents of the University of Idaho
Department:
Division:
Street1*: 875 Perimeter Drive
Street2: MS 4244
City*: Moscow
County: Idaho
State*: ID: Idaho
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 83844-4244

Phone Number*: 2088855901 Fax Number:

E-Mail*: cremien@uidaho.edu

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Remien_Biosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Alec Middle Name Last Name*: Redwood Suffix:

Position/Title*:
Organization Name*: University of Western Australia
Department:
Division:
Street1*: 35 Stirling Highway
Street2:
City*: Crawley
County:
State*:
Province:
Country*: AUS: AUSTRALIA
Zip / Postal Code*: WA 6009

Phone Number*: 608410334743 Fax Number:

E-Mail*: alec.redwood@uwa.edu.au

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Biosketch_Redwood.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Chan Middle Name Last Name*: Baca Suffix:

Position/Title*:
Organization Name*: University of Western Australia
Department:
Division:
Street1*: 35 Stirling Highway
Street2:
City*: Crawley
County:
State*:
Province:
Country*: AUS: AUSTRALIA
Zip / Postal Code*: WA 6009

Phone Number*: 608410334743 Fax Number:

E-Mail*: baca.chan@uwa.edu.au

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Biosketch_Chan.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Scott L. Nuismer

eRA COMMONS USER NAME (credential, e.g., agency login): (b)(6)

POSITION TITLE: Professor, Biological Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Utah	B.S.	06/1996	Biology
Washington St. University	Ph.D.	12/1999	Zoology
University of Texas, Austin	Postdoctoral	05/2003	Evolutionary genetics

A. Personal Statement

My research has long focused on interactions between pathogens and their hosts and has developed a firm mathematical foundation for understanding how these interactions evolve and coevolve. Currently, this work emphasizes the development of new computational and statistical tools for predicting the risk of pathogen spillover and emergence and identifying promising new technologies for reducing this risk. Recognizing the revolutionary opportunities transmissible vaccines offer for vaccinating wildlife populations and reducing spillover risk has made this a central focus of my research. This work has developed a mathematical framework for quantifying the benefits of vaccine transmission and has identified key challenges that must be overcome for transmissible vaccines to realize their full potential. Recently, this work has accelerated due to the involvement of an empirical collaborator, Dr. Alec J. Redwood, with the expertise required to begin developing and studying prototype transmissible vaccines within a mouse model system. My expertise modeling the evolutionary epidemiology of transmissible vaccines positions me well to pursue the proposed work focused on developing and analyzing mathematical models that integrate the within and between host dynamics of recombinant vector transmissible vaccines. When combined with the expertise of my collaborators in genetic engineering (Bull, Redwood, and Chan), mathematics (Remien), and cytomegalovirus vectored vaccines (Redwood), we are well-prepared to advance our overall understanding of the biology of recombinant vector transmissible vaccines and identify innovative solutions to the challenges posed by rapid evolution.

1. Varrelman, T.J., C.H. Remien, A.J. Basinski, S. Gorman, A. Redwood, S.L. Nuismer. 2022. Quantifying the effectiveness of betaherpesvirus-vectored transmissible vaccines. *PNAS* 119 (4) e2108610119.
2. Nuismer, S.L., N.C. Layman, A.J. Redwood, B. Chan, J.J. Bull. 2022. Methods for measuring the evolutionary stability of engineered genomes to improve their longevity. *Synthetic Biology* 6 (1), ysab018.
3. Nuismer, S.L. and J.J. Bull. 2020. Self-disseminating vaccines to suppress zoonoses. *Nature Ecology & Evolution* 4 (9), 1168-1173
4. Nuismer. S.L. et al. 2020. Bayesian estimation of Lassa virus epidemiological parameters: Implications for spillover prevention using wildlife vaccination. *PLoS Neglected Tropical Diseases* 14 (9), e0007920.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2013- Professor, Bioinformatics and Computational Biology, University of Idaho
2013- Professor, Biological Sciences, University of Idaho
2008-2013 Associate Professor, Biological Sciences, University of Idaho
2003-2008 Assistant Professor, Biological Sciences, University of Idaho

Other Experience

2013-2021 Associate Editor, *The American Naturalist*
2009-2012 Associate Editor, *Evolution*

Honors

2016 Research and creative activity excellence award. University of Idaho.
2008 Early career faculty award. College of Science. University of Idaho.

C. Contributions to Science

1. *Establishing a mathematical framework for transmissible vaccines*

   Vaccines have proven to be one of the most successful methods available for curbing the impact of infectious disease. Unfortunately, however, conventional vaccines are often ineffective tools for reducing or eliminating the risk of emerging pathogens that spill over from animal reservoirs. The reason traditional vaccines are ineffective in this scenario is the inherent challenge of delivering vaccine to free living wildlife populations. Vaccines capable of transmitting from one host to the next have the potential to overcome these challenges and revolutionize prevention of emerging infectious diseases. I am currently leading efforts to develop a mathematical framework for predicting how well transmissible vaccines will work and how their engineering can be optimized to meet the dual challenges of efficacy and safety. This work has quantified the benefits of vaccine transmission over a range of scenarios and highlighted the important challenges imposed by pre-existing vector immunity and vaccine evolution. Representative publications from this research include:

   a. Layman, N.C., B.M. Tuschhoff, S.L. Nuismer. 2021. Designing transmissible viral vaccines for evolutionary robustness and maximum efficiency. *Virus Evolution* 7 (1), veab002
   b. Nuismer, S.L. A. Basinski, J.J. Bull. 2019. Evolution and containment of transmissible recombinant vector vaccines. *Evolutionary Applications* 12:8 1595-1609.
   c. Basinski, A.J., T.J. Varrelman, M.W. Smithson, R.H. May, C.H. Remien, and S.L. Nuismer. 2017. Evaluating the promise of recombinant transmissible vaccines. *Vaccine*. 36:675-682.
   d. Bull, J.J., M.W. Smithson, and S.L. Nuismer. 2017. Transmissible viral vaccines. *Trends in Microbiology*. 26:6-15.

2. *Developing mathematical tools for studying multi-locus evolution in interacting species*

   Developing and analyzing mathematical models of complex, multi-locus genetic systems is a formidable challenge. This challenge is magnified in cases where we must study the simultaneous evolution of interacting species, such as a pathogen and the host it infects. My work has developed foundational mathematical tools and approximations that allow evolution in complex genetic systems to be studied for interacting species pairs.

   a. Nuismer, S. L., S. P. Otto, and F. Blanquart. 2008. When do host-parasite interactions drive the evolution of non-random mating? *Ecology Letters* 11:937-946.

b. Nuismer, S. L., B. J. Ridenhour, and B. P. Oswald. 2007. Antagonistic coevolution mediated by phenotypic differences between quantitative traits. *Evolution* 61:1823-1834.
c. Nuismer, S. L., M. Doebeli, and D. Browning. 2005. The coevolutionary dynamics of antagonistic interactions mediated by quantitative traits with evolving variances. *Evolution* 59:2073-2082.
d. Nuismer, S. L., and S. P. Otto. 2004. Host-parasite interactions and the evolution of ploidy. *PNAS* 101:11036-11039.

3. *Statistical methods for detecting selection and identifying the genetic basis of pathogen resistance*

Methods for detecting natural selection or identifying genetic loci responsible for pathogen resistance have historically ignored functional and statistical interactions between host and parasite genomes. Working with various collaborators, I have led efforts to develop the first robust and general techniques for integrating these functional and statistical interactions between genomes into methods for detecting natural selection and identifying genes responsible for pathogen resistance. We have used these new techniques to quantify the strength of reciprocal selection acting on pairs of interacting species and to demonstrate why traditional genome wide association studies focused on pathogen resistance are commonly unrepeatable.

a. Week, B. and S.L. Nuismer. 2019. The measurement of coevolution in the wild. *Ecology Letters*. 22: 717-725.
b. Nuismer, S.L. and B. Week. 2019. Approximate Bayesian Estimation of Coevolutionary Arms Races. *PLoS Computational Biology*. 15(4): e1006988.
c. MacPherson, A., S.P. Otto, and S.L. Nuismer. 2018. Keeping pace with the Red Queen: identifying the genetic basis of susceptibility to infectious disease. *Genetics*. 208:779-789.
d. Nuismer S.L., C.E. Jenkins, and M.F. Dybdahl. 2017. Identifying coevolving loci using interspecific genetic correlations. *Ecology and Evolution*. 7:6894-6903.

4. *Synthesizing models of species interactions and coevolution*

Coevolution is the process of reciprocal evolution between interacting species. Since formalization of coevolution as a well-defined process in 1980, a large body of theory has been developed to understand and predict how coevolution influences the dynamics and outcomes of species interactions. Although this body of theory is elegant and insightful, it is also mathematically complex and scattered throughout the primary literature making it challenging for students and empiricists to understand the models and predictions, let alone develop models of their own. Recently, I completed a book, *Introduction to Coevolutionary Theory*, that develops the mathematical framework of coevolution by starting with the simplest of models and gradually moving toward some of the most complex. By motivating each chapter with a concrete biological example and important biological question, the book demonstrates how mathematical models can be used to formalize hypotheses and generate empirically testable predictions. To date, this book has been used in multiple graduate seminar courses and used as a basis for two workshops I have led targeting empirical researchers interested in developing coevolutionary models of their own.

a. Nuismer S.L. 2017. Introduction to Coevolutionary Theory. WH Freeman. New York.

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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: James J. Bull

eRA COMMONS USER NAME (credential, e.g., agency login): (b)(6)

POSITION TITLE: Professor (U. Idaho), Emeritus Professor (U. Texas)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Texas Tech University, Lubbock, TX	BS	1971	Zoology
University of Utah, Salt Lake City, UT	PhD	1977	Biology
University of Wisconsin, Madison, WI	Postdoc	1980	Genetics
University of Sussex, Sussex, UK	Postdoc	1981	Biology

A. Personal Statement

My research over four decades spans modeling/theory and empirical work in genetics and evolution, the latter ranging from organismal field work to microbiology and molecular genetics. I worked at the University of Texas for 36 years and moved to the University of Idaho in 2019. A large part of my effort has been training undergraduates, both in research and in the classroom. In the 1990s, I developed a scientific reasoning course for non-science majors to help them understand how to apply the scientific method in daily life (materials now on cors236.com); I taught this course for almost 30 years and had a cumulative audience of over 6,000 students (as an approximation). In the lab, I personally trained 13 undergrads in all stages of the work, from the experimental design and conduct to publication; the work mostly involved evolution of bacteriophages so was safe, fast and suitable for individual control. Many of these students went on to medical or dental school. More recently, I have mentored 4 undergrads in computational work and theory, resulting in authorships for them. Seven of these undergrads were women, one Latina, and several Asians. As I develop my program at the University of Idaho, I want to actively engage underrepresented groups in both research and science education, as it has become clear that our society is highly polarized over basic scientific issues.

B. Positions, Scientific Appointments, and Honors

1981 - 1982 Research Assistant Professor, Department of Biology, University of Utah, Salt Lake City, UT
1983 - 1986 Assistant Professor, Department of Zoology, University of Texas, Austin, TX
1986 - 1991 Associate Professor, Department of Zoology, University of Texas, Austin, TX
1991 - 1999 Professor, Department of Zoology, University of Texas, Austin, TX
1999 - 2019 Professor, Department of Integrative Biology, University of Texas, Austin, TX
2019 - Professor, Department of Biological Sciences, University of Idaho, Moscow, ID

Professional Service
Science Board of Reviewing Editors, 1987 - 2001
Associate Editor, Genetics, 2011 - 2016

Associate Editor, Evolution, Medicine, and Public Health, 2001 - present
NIH Genetics Study Section and Evolution of Infectious Disease study section, ad hoc member 1999 - 2004
NIH GVE Study Section, 2005 - 2008 (Chair 10/06 - 06/08); ad hoc member 2009, 2010
NIH ad hoc Study Sections, 2015 - 2021, approximately 1-2 per year
Honors
1993-2019 Lagowski Regents Professor (University of Texas)
2003- American Academy of Arts and Sciences
2016- National Academy of Sciences

C. Contributions to Science

1. *Experimental genome evolution of viruses and vaccine design.* From 1990 to the present, my major effort has been to study experimental molecular evolution using phages as model viral systems. The emphases were sometimes to understand how a wild-type virus evolves (*e.g.*, evolution of host range or drug resistance), how an engineered genome evolves in response to the engineering, and often how to create evolutionarily stable viral attenuation for vaccine design. I have found that (i) a few attenuation designs appear not to revert, (ii) engineered genomes are usually unstable, but not always, and (iii) viral evolution sometimes has a limited capacity – evolution is not assured. Approximately 35 of my papers fall under this realm, nearly all empirical.

    a. Bull JJ, Nuismer SL, Antia R. 2019. Recombinant vector vaccine evolution. PLoS Comp. Biol. 15(7):e1006857.
    b. Garry DJ, Ellington AD, Molineux IJ, Bull JJ. 2018. Viral attenuation by engineered protein fragmentation. Virus Evol. 4(1):vey017. PMC6009699
    c. Bull JJ, Molineux IJ, Wilke CO. 2012. Slow fitness recovery in a codon-modified viral genome. Mol Biol Evol. 29(10):2997-3004 PMC3457771
    d. Wichman HA, Badgett MR, Scott LA, Boulianne CM, Bull JJ. 1999. Different trajectories of parallel evolution during viral adaptation. Science 285:422-425.

2. *Phage therapy*. What started as an offshoot to my interest in phages as models for evolution became one of major interests. Phage therapy is the use of phages as antibiotics, an idea that is now ~100 years old. For various reasons, it has a checkered history, but probably largely because phage therapy is idiosyncratic – useful in some cases but not others. My main contributions are (i) developing the first mathematical models for phage therapy, (ii) resolving why one class of phages works and another class largely fails in a classic experimental system of phage therapy, and (iii) helping develop the use of phage enzymes for therapy. Thirteen of my papers apply to this topic.

    a. Lin H, Paff ML, Molineux IJ, Bull JJ. 2018. Antibiotic Therapy Using Phage Depolymerases: Robustness Across a Range of Conditions. Viruses. 2018 Nov 12;10(11). pii: E622.
    b. Lin H, Paff ML, Molineux IJ, Bull JJ. 2017. Therapeutic application of phage capsule depolymerases against K1, K5, and K30 capsulated *E. coli* in mice. Front Microbiol. 2017 8:2257. PMC5696595
    c. Bull JJ, Otto G, Molineux IJ. 2012. *In vivo* growth rates are poorly correlated with phage therapy success in a mouse infection model. Antimicrob Agents Chemother. 56(2):949-54. PMC3264239
    d. Bull JJ, Vimr ER, Molineux IJ. 2010. A tale of tails: Sialidase is key to success in a model of phage therapy against K1-capsulated *Escherichia coli*. Virology 398:79-86.

3. *Lethal mutagenesis of viruses.* This is a rather focused topic that centers on possible ways to treat viral infections and to understand the role of mutations in viral evolution. Lethal mutagenesis is simply the idea of boosting mutation rate so high that every individual in a population dies out. It gained popularity in virology because of Eigen's theoretical concept of an 'error catastrophe' (ironically NOT the same as lethal mutagenesis) and the discovery that the antiviral drug ribavirin causes an elevated mutation rate. My work developed the first population genetic theory of lethal mutagenesis. My subsequent empirical work has questioned whether lethal mutagenesis is a practical form of treatment – it seems to defy expectations. I have ten papers that broadly center on lethal mutagenesis and evolution at high mutation rate.

a. Paff ML, Stolte SP, Bull JJ. 2014. Lethal mutagenesis failure may augment viral adaptation. Molecular Biology and Evolution 31(1):96-105. PMC3879444
b. Bull JJ, Joyce P, Gladstone E, Molineux IJ. 2013. Empirical complexities in the genetic foundations of lethal mutagenesis. Genetics 195(2):541-52. PMC3781979
c. Springman R, Keller T, Molineux IJ, Bull JJ. 2010. Evolution at a high imposed mutation rate: adaptation obscures the load in phage T7. Genetics 184:221-232. PMC2815918
d. Bull JJ, Sanjuan R, Wilke C. 2007. Theory of lethal mutagenesis for viruses. J. Virol. 81(6):2930-2939. PMC1865999

4. *Evolution of cooperation and virulence*. From 1990 to the present, I have studied the evolutionary foundations of cooperation – how individuals of one species can evolve to help individuals of another. A compelling application of this topic is the evolution of disease virulence -- 'why should a parasite evolve to harm its host?' My main discoveries have been experimentally evolved realizations of higher and lower virulence and their consequent challenges to a large body of theory arguing that virulence evolution is predictable. About a third of my 16 papers in this area have been experiments that use phages, the others are theory and syntheses.

a. Bull JJ, Rice W. 1991. Distinguishing mechanisms for the evolution of cooperation. Journal of Theoretical Biology 149:63-74.
b. Bull JJ, Molineux IJ, Rice WR. 1991. Selection of benevolence in a host-parasite system. Evolution 45:875-882.
c. Bull JJ.1994. Virulence. Evolution 48:1423-1437.
d. Sachs JL, Bull JJ. 2005. Experimental evolution of conflict mediation between genomes. Proceedings National Academy Sciences 102:390-395. PMC544279

5. *Evolution of sex determination and sex ratios*. From the 1970s to ~1990, I discovered how major transitions in sex determination can occur: how a population can change from male heterogamety (XX/XY as in mammals) to female heterogamety (ZZ/ZW as in birds) to environmental sex determination (as in many reptiles), and a few others. I also came to understand how environmental sex determination operates in reptiles. This work involved population genetics theory plus field work on reptiles (the latter largely to understand the then-surprising discovery that egg incubation temperature determined the sex of many turtles). In this area, I have approximately 50 papers and one book (Bull 1983).

a. Bull JJ.1983. *Evolution of Sex Determining Mechanisms*. Benjamin/Cummings Publ. Co., Menlo Park, California. 316 pp.
b. Bull JJ, Vogt RC. 1979. Temperature-dependent sex determination in turtles. Science 206:1186-1188.
c. Bulmer, M. G., and J.J. Bull. 1982. Models of polygenic sex determination and sex ratio evolution. Evolution 36:13-26.
d. Bull JJ, Hillis DM, O'Steen S. 1988. Mammalian ZFY sequences exist in reptiles regardless of sex determining mechanism. Science 242:567-569.

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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Remien, Christopher

eRA COMMONS USER NAME (credential, e.g., agency login): (b)(6)

POSITION TITLE: Associate Professor, Department of Mathematics and Statistical Science

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
St. Olaf College, Northfield, MN	BA	05/2005	Mathematics and Russian
University of Utah, Salt Lake City, UT	MS	05/2008	Mathematics
University of Utah, Salt Lake City, UT	PHD	12/2012	Mathematics
National Institute for Mathematical and Biological Synthesis, Knoxville, TN	Postdoctoral Fellow	08/2014	Mathematical Biology

A. Personal Statement

The goal of this project is to develop and analyze models to guide the development of a transmissible vaccine platform in rodents. The first Specific Aim involves developing and analyzing within-host models of vaccine dynamics, including growth, immunogenicity, and evolution. The second Specific Aim involves parameterizing and validating the within-host models with in vitro and in vivo experimental data. The third Specific Aim will perform model validation using immune depleted mice. My training and experience in mathematical modeling of biological interactions, and specific background modeling within-host, epidemiological, and dynamics, makes me uniquely suited for this project. I have broad experience and training in mathematical biology, and specific expertise developing and analyzing models with complex temporal dynamics related to health and disease. I have developed epidemiological models to assess the impact of transmissible vaccines, and connected epidemiological models to data to study the dynamics of Lassa Fever in West Africa. In these projects and others, I have successfully collaborated with other researchers and have produced peer-reviewed publications and conference presentations. As a mathematical biologist, I am keenly aware of the challenges of interdisciplinary research and have successfully collaborated with a wide range of scientists, including mathematicians, molecular biologists, microbiologists, ecologists, and medical doctors. I have experience successfully mentoring undergraduates, graduate students, and postdocs in developing and analyzing mathematical models of biomedical systems. My demonstrated success in interdisciplinary research and expertise in mathematical biology will allow this project to be successful.

1. Varrelman TJ, Remien CH, Basinski AJ, Gorman S, Redwood A, Nuismer SL. Quantifying the effectiveness of betaherpesvirus-vectored transmissible vaccines. Proc Natl Acad Sci U S A. 2022 Jan 25;119(4) PubMed Central PMCID: PMC8794881.
2. Nuismer SL, Remien CH, Basinski AJ, Varrelman T, Layman N, Rosenke K, Bird B, Jarvis M, Barry P, Hanley PW, Fichet-Calvet E. Bayesian estimation of Lassa virus epidemiological parameters: Implications for spillover prevention using wildlife vaccination. PLoS Negl Trop Dis. 2020 Sep;14(9):e0007920. PubMed Central PMCID: PMC7529244.
3. Basinski AJ, Nuismer SL, Remien CH. A little goes a long way: Weak vaccine transmission facilitates oral vaccination campaigns against zoonotic pathogens. PLoS Negl Trop Dis. 2019 Mar;13(3):e0007251. PubMed Central PMCID: PMC6426267.
4. Basinski AJ, Varrelman TJ, Smithson MW, May RH, Remien CH, Nuismer SL. Evaluating the promise of recombinant transmissible vaccines. Vaccine. 2018 Jan 29;36(5):675-682. PubMed Central PMCID: PMC5811206.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2020 -	Associate Professor, Department of Mathematics and Statistical Science, University of Idaho, Moscow, ID
2014 -	Affiliate Faculty, Department of Biology, University of Idaho, Moscow, ID
2014 - 2020	Assistant Professor, Department of Mathematics, University of Idaho, Moscow, ID
2012 - 2014	Postdoctoral Fellow, National Institute for Mathematical and Biological Synthesis, Knoxville, TN

Honors

2019	College of Science Early Career Award, University of Idaho
2013	Travel Grant, Society for Mathematical Biology
2012	National Institute for Mathematical and Biological Synthesis Postdoctoral Fellowship, NSF
2012	Research Training Group in Mathematical Biology Fellowship, NSF
2011	Graduate Training Fellowship, University of Utah
2011	Research Training Group in Mathematical Biology Fellowship, NSF
2010	Research Training Group in Mathematical Biology Fellowship, NSF
2009	Research Training Group in Mathematical Biology Fellowship, NSF
2008	Graduate Teaching Fellowship, University of Utah
2007	Integrative Graduate Education and Research Traineeship, NSF
2006	Integrative Graduate Education and Research Traineeship, NSF

C. Contribution to Science

1. I have developed and analyzed mathematical models to determine the extent to which vaccine transmission reduces the vaccination effort required to control infectious diseases in human and wildlife populations. Transmissible vaccines are capable of spreading from one individual to another and are currently being developed for a range of diseases. We have found that even small amounts of vaccine transmission can greatly reduce the vaccination effort required to control a pathogen. Our work has also identified key factors, such as the extent of cross immunity between a recombinant vector vaccine and its viral vector, that are important for effective transmissible vaccine design.

    a. Varrelman TJ, Remien CH, Basinski AJ, Gorman S, Redwood A, Nuismer SL. Quantifying the effectiveness of betaherpesvirus-vectored transmissible vaccines. Proc Natl Acad Sci U S A. 2022 Jan 25;119(4) PubMed Central PMCID: PMC8794881.

    b. Basinski AJ, Fichet-Calvet E, Sjodin AR, Varrelman TJ, Remien CH, Layman NC, Bird BH, Wolking DJ, Monagin C, Ghersi BM, Barry PA, Jarvis MA, Gessler PE, Nuismer SL. Bridging the gap: Using reservoir ecology and human serosurveys to estimate Lassa virus spillover in West Africa. PLoS Comput Biol. 2021 Mar;17(3):e1008811. PubMed Central PMCID: PMC7959400.

    c. Varrelman TJ, Basinski AJ, Remien CH, Nuismer SL. Transmissible vaccines in heterogeneous populations: Implications for vaccine design. One Health. 2019 Jun;7:100084. PubMed Central PMCID: PMC6395884.

    d. Nuismer SL, May R, Basinski A, Remien CH. Controlling epidemics with transmissible vaccines. PLoS One. 2018;13(5):e0196978. PubMed Central PMCID: PMC5945036.

2. I have developed and analyzed mathematical models that couple population dynamics and population genetics, with specific application towards gene drives. Gene drives are a new technology that allow an allele to be spread preferentially to offspring. In theory, a gene drive system can be engineered to effortlessly eradicate a species or to alter the genome of an entire species. I have developed and analyzed mathematical models to predict resistance evolution to gene drives.

    a. Yuksel MK, Remien CH, Karki B, Bull JJ, Krone SM. Vector dynamics influence spatially imperfect genetic interventions against disease. Evol Med Public Health. 2021;9(1):1-10. PubMed Central PMCID: PMC7910803.

b. Bull JJ, Remien CH, Gomulkiewicz R, Krone SM. Spatial structure undermines parasite suppression by gene drive cargo. PeerJ. 2019;7:e7921. PubMed Central PMCID: PMC6824332.
c. Bull JJ, Remien CH, Krone SM. Gene-drive-mediated extinction is thwarted by population structure and evolution of sib mating. Evol Med Public Health. 2019;2019(1):66-81. PubMed Central PMCID: PMC6556056.
d. Gomulkiewicz R, Krone SM, Remien CH. Evolution and the duration of a doomed population. Evol Appl. 2017 Jun;10(5):471-484. PubMed Central PMCID: PMC5427677.

3. While safe in small doses, overdose of acetaminophen (APAP, Tylenol) is the leading cause of acute liver injury in the United States, accounting for about 56,000 emergency room visits, 26,000 hospital admissions, and 500 deaths annually. A small fraction of APAP is converted within hepatocytes to the toxic metabolite N-acetyl-p-benzoquinoneimine. The liver has significant regenerative capacity so that survival is dependent on the APAP dosage, which must be above a critical lethal threshold, and the time to administration of the antidote N-acetylcysteine. Unfortunately, APAP dosage and time to administration of N-acetylcysteine are not typically known when a patient arrives in the emergency room. I developed a system of differential equations to describe the cellular, intracellular, and marker dynamics associated with APAP overdose. The dynamics of the model only depend on the overdose amount and time since overdose, the two parameters critical for survival. I obtained biomarker and outcome data for 53 patients with APAP-induced acute liver injury from the University of Utah Hospital and fit patient data to the model using trajectory matching to estimate overdose amount, time since overdose, and outcome. The model does a good job of discriminating patients who eventually recover from those who eventually die without liver transplant, using only measurements taken at hospital admission. The model predictions of the time courses of the biomarkers following treatment also fit well to patient data. I have extended the model to analyze the role of chronic APAP use on liver injury.

a. Ghosh A, Berger I, Remien CH, Mubayi A. The role of alcohol consumption on acetaminophen induced liver injury: Implications from a mathematical model. J Theor Biol. 2021 Jun 21;519:110559. PubMed PMID: 33333080.
b. Sussman NL, Remien CH. The Headache of Acetaminophen Overdose: Getting the NAC. Clin Gastroenterol Hepatol. 2017 Apr;15(4):563-564. PubMed PMID: 28017841.
c. Remien CH, Sussman NL, Adler FR. Mathematical modelling of chronic acetaminophen metabolism and liver injury. Math Med Biol. 2014 Sep;31(3):302-17. PubMed PMID: 23788256.
d. Remien CH, Adler FR, Waddoups L, Box TD, Sussman NL. Mathematical modeling of liver injury and dysfunction after acetaminophen overdose: early discrimination between survival and death. Hepatology. 2012 Aug;56(2):727-34. PubMed PMID: 22331703.

4. I have developed new methods to analyze microbial time-series data. New sequencing technologies have provided a large amount of information regarding the composition of microbial communities, and time-series data from 16S rDNA amplicon sequencing are becoming increasingly common. We developed a method of analysis that uses an elastic-net regularized ARIMA model with Poisson errors to estimate predictive models of microbiome dynamics and to uncover key interactions that drive these dynamics. The model utilizes regularization to prevent overfitting and to select among the many possible interactions those that most likely explain the data, and is scalable enough to handle data consisting of thousands of taxa. We applied this method to microbiome data from Neotoma albigula that were fed varying amounts of oxalate over a 22 day period. One major hurdle in adapting population dynamic theory for microbial systems is that data obtained from DNA sequencing yield estimates of relative not absolute abundances, while population dynamic models track absolute abundances or densities. We have bridged this gap by using structural identifiability analyses to determine the extent to which time series of relative abundances can be used to parameterize the generalized Lotka-Volterra model. While phenomenological models such as autoregressive models and the generalized Lotka-Volterra are quite useful for data analysis, I have also developed mechanistic mathematical models of microbial population dynamics of specific systems. One example is in modeling the phenotypic diversity in tolerance to a metabolic toxin in the bacteria Methylobacterium extorquens. Though cells are genetically identical, they vary dramatically in their ability to grow in formaldehyde, and this tolerance distribution changes systematically over time in different

growth conditions. We developed a partial differential equation model that mimics the experimental design and used maximum likelihood to fit the model to data.

a. Remien CH, Eckwright MJ, Ridenhour BJ. Structural identifiability of the generalized Lotka-Volterra model for microbiome studies. R Soc Open Sci. 2021 Jul;8(7):201378. PubMed Central PMCID: PMC8292772.
b. Chiarelli TJ, Grieshaber NA, Omsland A, Remien CH, Grieshaber SS. Single-Inclusion Kinetics of *Chlamydia trachomatis* Development. mSystems. 2020 Oct 13;5(5) PubMed Central PMCID: PMC7567582.
c. Lee JA, Riazi S, Nemati SH, Vasdekis AE, Ridenhour BJ, Remien CH, Marx CJ. Microbial phenotypic heterogeneity in response to a metabolic toxin: continuous, dynamically shifting distribution of formaldehyde tolerance in Methylobacterium extorquens populations. BioRxiv. 2019 January 23.
d. Ridenhour BJ, Brooker SL, Williams JE, Van Leuven JT, Miller AW, Dearing MD, Remien CH. Modeling time-series data from microbial communities. ISME J. 2017 Nov;11(11):2526-2537. PubMed Central PMCID: PMC5649163.

5. I have developed mathematical models to further our understanding of stable isotope ratios of animal tissues. Stable isotopes can be used as a powerful indirect method to estimate an animal's diet and migration history. Molecules in an animal's diet and drinking water are incorporated into tissues, recording and integrating carbon, nitrogen, hydrogen, oxygen, and sulfer stable isotope ratios of dietary sources, allowing the calculation of diet from measurements of consumer tissue. Diet and drinking water are the primary determinants of stable isotope ratios of measured animal tissues, but stable isotopes do not act as pure tracers. Physiological and metabolic processes lead to the partial separation of light isotopes from heavy isotopes and isotope signatures of tissue can also be distorted from sampling. My work has focused on building mechanistic mathematical models to better understand and interpret stable isotope ratios of animal tissues. I have developed forward and inverse models that use dierential equations, integral equations, and regularization to interpret measurements in light of the mixing of isotope signals during tissue formation and sampling. I have also applied stable isotope techniques to natural systems. I developed a modern reference to better estimate the fraction woody cover from stable carbon isotope ratios of paleosols, which has implications for interpreting paleoenvironments important to human evolution.

a. Remien CH. Modeling the dynamics of stable isotope tissue-diet enrichment. J Theor Biol. 2015 Feb 21;367:14-20. PubMed PMID: 25457228.
b. Remien CH, Adler FR, Chesson LA, Valenzuela LO, Ehleringer JR, Cerling TE. Deconvolution of isotope signals from bundles of multiple hairs. Oecologia. 2014 Jul;175(3):781-9. PubMed PMID: 24793936.
c. Cerling TE, Wynn JG, Andanje SA, Bird MI, Korir DK, Levin NE, Mace W, Macharia AN, Quade J, Remien CH. Woody cover and hominin environments in the past 6 million years. Nature. 2011 Aug 3;476(7358):51-6. PubMed PMID: 21814275.
d. Cerling TE, Wittemyer G, Ehleringer JR, Remien CH, Douglas-Hamilton I. History of Animals using Isotope Records (HAIR): a 6-year dietary history of one family of African elephants. Proc Natl Acad Sci U S A. 2009 May 19;106(20):8093-100. PubMed Central PMCID: PMC2688856.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Redwood, Alec James

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Principal Research Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Curtin University – Perth, WA. Australia	PhD	12/1997	Immunology
Curtin University – Perth, WA. Australia	Honours (1st Class)	08/1990	Biomedical Sciences
Curtin University – Perth, WA. Australia	B.Sc. (Distinction	08/1989	Biomedical Sciences

A. Personal Statement

I am a Principal Research Fellow (Associate Professor Equivalent) and head of the vaccine and viral immunity laboratory at UWA. For most of my career I have focused on vaccine design and viral mechanisms of immunomodulation. Relevant to this application, I was laboratory lead in world fist studies investigating the use cytomegaloviruses (CMV) as a disseminating vaccine vector. Presently, my laboratory is collaborating on a multinational, DARPA funded, project investigating the potential use of cytomegalovirus (CMV) as a disseminating vaccine for the control of emerging infectious diseases. Specifically, the program seeks to vaccinate zoonotic reservoir species thereby preventing spillover into human populations and short-circuiting potential pandemic/s.

1. Scott L. Nuismer, Nathan Layman, Alec J. Redwood, Baca Chan and James J. Bull. 2021. Methods for measuring the evolutionary stability of engineered genomes to improve their longevity. Synthetic Biology.
2. Varrelman TJ, Remien CH, Basinski AJ, Gorman S., Redwood, A. and Nuismer, S. Quantifying the effectiveness of betaherpesvirus-vectored transmissible vaccines. 2022. In PNAS. 2022 119 (4)
3. Murphy, A., Redwood, A.J. and Jarvis, M. (2016). Self-disseminating vaccines for emerging infectious diseases. Expert Review of Vaccines. 15(1):31-9. Review
4. Nikolovski. S., Lloyd. M.L., Harvey, N., Hardy. C.M, Shellam. G. R. and Redwood. A.J. 2009. Overcoming innate host resistance to vaccination: employing a genetically distinct strain of murine cytomegalovirus avoids vector-mediated resistance to virally vectored immunocontraception. Vaccine. 27, 5226-5232

B. Positions, Scientific Appointments, and Honors

Positions and Employment:

2018- Principal Research Fellow (Associate Professor) Institute for Respiratory Health
2014-18 Associate Professor in Immunology, Institute for Immunology and Infectious Diseases.
2001-14. Research Fellow, Microbiology, the University of Western Australia

Other experience and Professional Memberships:

2019-20 National Health and Medical Research Council, Ideas Grant Panel Member.
2015- Chair, Medical Sciences Course Consultative Committee, School of Medical Sciences, ECU

2010-11 State Councilor Australasian Society for Immunology
Honors
1998-00 Athelstan and Amy Saw Medical Research Fellowship, UWA
1989 Gold Medal, Most Outstanding Graduate-AIMLS

C. Contributions to Science

Vaccine design. Vaccine antigens must do two things to promote immunity. They must gain entry into an antigen presenting cell so they can be presented to T cells (or B cells) and they must induce a "danger signal" that kick starts the immune response. Viral vectors do both of these tasks, naturally delivering antigenic cargo into cells and inducing powerful danger signals invoking strong immunity. My work on murine cytomegalovirus (MCMV) and my molecular virology skills has meant that I have collaborated on a number of traditional viral vectored vaccine approaches. Vaccine vectors can also be harnessed as disseminating vaccines. I was involved with, and was eventually the laboratory lead, in a world first viral vectored mouse immunocontraception program funded by the Australian Government, through the Cooperative Research Centers program. Currently my laboratory is focused on the use of viral vectors for the preventative control of zoonotic infections in wildlife populations. Representative publications from this research include:

1. Yunis, J., Redwood, A., Belz, G, and Stevenson, P. 2020. Membrane association of a model CD4+ T cell vaccine antigen confers enhanced yet incomplete protection against Murid Herpesvirus-4 infection. Immunology and Cell Biology. 98(4):332-343.
2. Kaitlyn M. Morabito, Tracy J. Ruckwardt, Erez Bar-Haim, Deepika Nair, Syed M. Moin, Alec J. Redwood, David A. Price and Barney S. Graham. 2018. Memory inflation drives tissue-resident memory CD8+ T cell maintenance in the lung after intranasal vaccination with MCMV. Frontiers in Immunology. 9 (1861).
3. Morabito, K.M., Ruckwardt, T.R., Redwood, A.J., Moin, S.M., Price, D.A. and Graham, B.S. (2016). Intranasal administration of RSV antigen-expressing MCMV elicits robust tissue-resident effector and effector memory CD8+ T cells in the lung. Mucosal Immunology. 10(2):545-554.
4. Redwood, A.J., Messerle, M., Harvey, N.L., Hardy, C.M., Koszinowski, U.H., Lawson, M. A. and Shellam, G.R. 2005. Use of a murine cytomegalovirus, K181-derived, bacterial artificial chromosome as a vaccine vector for immunocontraception. Journal of Virology. 79, 2998-3008.

Immunological manipulation and the evolution cytomegaloviruses. RNA viruses mutate rapidly allowing them to adapt quickly to individual host genetics as well as that of the host population. DNA viruses do not have the capacity for rapid mutation and must adopt alternative strategies to respond to allelic variation in the host. My research has shown that CMVs encode a series of allelic immune evasion genes that are functionally diverse and exist to modulate allelic host responses. The primary tool used for these studies is the natural sequence variation found within low passage strains of MCMV that we have isolated from wild caught mice. In this area, my research can be broadly defined as viral evolution, host immune manipulation and multi-strain infection. The development of these strains and models has allowed me to produce a research stream that is entirely unique. Representative publications from this research include:

1. Baca Chan, Maja Mitrovic, Laura L. Masters, Stipan Jonjic, Lee M. Smith and Alec J. Redwood. 2021. The m15 locus of MCMV modulates natural killer cell responses and promotes dissemination of virus to the salivary glands. *Pathogens*. 10, 866
2. Redwood, A. J., Masters, L. L., Chan, B., Leary, S., Forbes, C., Jonjić, S., Juranić Lisnić, V., Lisnić, B. and Smith, L. M. 2020. Repair of an attenuated low passage murine cytomegalovirus bacterial artificial chromosome identifies a novel spliced gene essential for salivary gland tropism. J. Virol. 22. e01456-20
3. Smith, L. M., McWhorter, A.R., Masters, L.L., Shellam, G.R., and Redwood, A.J. 2008. Laboratory strains of murine cytomegalovirus are genetically similar but phenotypically distinct from wild strains of virus. Journal of Virology. 82, 6689-6696.
4. McWhorter, A.R., Smith L.M., Chan, B., Masters, L.L., Shellam, G.R., Redwood, A.J. 2013. Natural killer cell dependent within-host competition arises during multiple MCMV infection: Consequences for Viral Transmission and Evolution. PLoS Pathogens, 9, e1003111.

T-cell immunity. My focus on immune evasion and vaccine design has also led to the development of an alternative stream of research investigating T cell immunity to a range of antigens. T cells have a remarkable ability to recognize highly diverse antigens. Current studies focus on mapping T-cell responses to herpesviruses

(HSV and EBV), tumors (tumor immunology) and small drug molecules (drug hypersensitivity). Representative publications from this research include:

1. (b)(4); (b)(6)
2. Shamin Li, Yannick Simoni, Summer Zhuang, Austin Gabel, Shaokang Ma, Jonathan Chee, Jenette Creaney, Robert K Bradley, Alec Redwood, Bruce W. Robinson and Evan W Newell. 2021. Characterization of neoantigen-specific T cells in cancer resistant to immune checkpoint therapies. PNAS. 118(30), e2025570118.
3. Redwood, A.J., Rwandamuriye, R., Chopra, A., Leary, S., Ram, R., McDonnell, W., Konvinse, K., White, K., Pavlos, R., Koelle, D.M., Mallal, S and Phillips, E. 2019. Single cell transcriptomics reveal polyclonal memory T-cell responses in abacavir patch test positive skin. Journal of Allergy Clinical Immunology. 144(5). 1413-1416.e7.
4. Jing L., Laing, KJ · Dong, L., Russell R.M., Barlow, R.S, Haas, J.G. Ramchandani, M.S., Johnston, C., Buss, S., Redwood, A.J., White, K. D., Mallal, S.A., Phillips, E.J., Posavad, C.M., Wald, A and Koelle, D.M (2016). Extensive CD4 and CD8 T cell cross-reactivity between alphaherpesviruses. The Journal of Immunology. 196(5):2205-18.

Complete List of Published Work in NCBI:
https://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography/

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Baca Chan

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Research Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Western Australia	B.Sc. (Hons) B.Comm.	11/2006	Microbiology and Biochemistry Accounting and Managerial Accounting
University of Western Australia	Ph.D.	10/2012	Microbiology

A. Personal Statement

My research focusses on the interaction between herpesviruses and the host immune response. My PhD work identified a novel murine cytomegalovirus (MCMV) gene locus which targets Natural Killer cells to promote MCMV infection in the mouse host. My postdoc work examined the impact of herpesvirus escape from host innate immune responses. I identified and characterized multiple genes in MCMV which inhibit type I interferon signalling, for example by delaying adaptor trafficking or preventing transcription factor binding to interferon promoters. I also contributed to the better understanding of host factors involved in innate immune responses to gammaherpesviruses, such as murine gammaherpesvirus-68 (MHV-68) and Kaposi's sarcoma-associated herpesvirus (KSHV). In my current position, I am optimising a transmissible vaccine that seeks to prevent zoonotic spillover from wildlife to human populations. Zoonotic infections pose a significant pandemic threat, as seen currently with SARS-CoV-2, but also with Lassa Fever Virus (LASV), Ebola, SARS-CoV-1 and MERS-CoV. This project aims to vaccinate the reservoir animals, thereby preventing animal to human transmission. A key regulatory concern for disseminating vaccines is recalling the engineered virus following release. We have designed a vaccine expressing a LASV antigen engineered into the MCMV genome. We have developed an in-built mechanism which utilises homologous recombination between flanking repeat sequences to self-excise the transgene following several rounds of transmission. This results in reversion to wild type virus naturally found in the animals. We are now fine-tuning the system to identify the optimal balance between the strength of LASV-specific T cell responses elicited and the rate of antigen decay within the vaccinated population. We are transferring the system to the newly identified Mastomys cytomegalovirus (MasCMV), to be applied in Mastomys, which are the reservoir hosts of LASV.

(b)(6)

B. Positions, Scientific Appointments, and Honors

2018- Research Fellow, Institute for Respiratory Health, Australia
2013-2016 Postdoctoral researcher, Helmholtz Centre for Infection Research, Germany

C. Contributions to Science

1. Identifying and describing new mechanisms of viral escape from host immunity
Herpesviruses are well known to establish life-long infections in their hosts, even in the face of strong host immune responses. Our understanding of how these viruses evade the initial detection of infection by hosts is still incomplete. I developed a quantitative screen to identify herpesviral proteins that inhibit innate immune responses as exemplified by the production of key signalling molecules, type I interferons. This led to the characterisation of new genes in both human and murine cytomegalovirus (HCMV and MCMV respectively) and the demonstration of new mechanisms in how these viruses manipulate host innate immune response to promote infection in the host. I have also described host responses to gammaherpesviruses, as well as the characterisation of innate immune evasion genes in this family of viruses.

Publications from this research include:

a. **Chan B**, Arapović M, Masters LL, Rwandamuiye F, Jonjić S, Smith LM, Redwood, A.J. The m15 locus of murine cytomegalovirus modulates natural killer cell responses to promote dissemination to the salivary glands and viral shedding. Pathogens 2021;10(7).

b. Stempel M, **Chan B**, Juranić Lisnić V, Krmpotić A, Hartung J, Paludan SR, Füllbrunn N, Lemmermann NAW, Brinkmann MM. The herpesviral antagonist m152 reveals differential activation of STING-dependent IRF and NF-kappaB signaling and STING's dual role during MCMV infection. EMBO J. 2019;38(5).

c. **Chan B**, Gonçalves Magalhães V, Lemmermann NAW, Juranić Lisnić V, Stempel M, Bussey KA, Reimer KA, Reimer E, Podlech J, Lienenklaus S, Reddehase MJ, Jonjić S, Brinkmann MM. The murine cytomegalovirus M35 protein antagonizes type I IFN induction downstream of pattern recognition receptors by targeting NF-kappaB mediated transcription. PLoS Pathog. 2017;13(5):e1006382.

d. Zhang G, **Chan B**, Samarina N, Abere B, Weidner-Glunde M, Buch A, Pich A, Brinkmann MM, Schulz T. Cytoplasmic isoforms of Kaposi sarcoma herpesvirus LANA recruit and antagonize the innate immune DNA sensor cGAS. Proc Natl Acad Sci U S A. 2016;113(8):E1034-43.

2. Enhancing the model of MCMV infection in mice by characterizing wild strains of MCMV
Due to the strict host species specificity of cytomegaloviruses (CMV), MCMV infection of mice represents the best described animal model of human CMV (HCMV) infection. However, our understanding of MCMV pathogenesis has relied on two laboratory strains of MCMV, Smith and K181, which have been extensively passaged in tissue culture and which may not reflect the strains circulating in wild mice. Our group has isolated and sequenced multiple wild strains in MCMV, demonstrating significant genetic variability in key immune evasion genes. I have been involved in the understanding of the interaction between multiple genetically distinct wild strains identified in a single mouse and how this impact viral transmission. Our work has also led to the cloning of a wild strain of MCMV, G4, as a bacterial artificial chromosome (BAC), which enables rapid manipulation of this viral genome.

Publications from this research include:

a. Redwood AJ, Masters LL, **Chan B**, Leary S, Forbes C, Jonjić S, Juranić Lisnić V, Lisnić B, Smith LM. Repair of an attenuated low-passage murine cytomegalovirus bacterial artificial chromosome identifies a novel spliced gene essential for salivary gland tropism. J Virol. 2020; 94(22).

b. McWhorter AR, Smith LM, Masters LL, **Chan B**, Shellam GR, Redwood AJ. Natural killer cell dependent within-host competition arises during multiple MCMV infection: consequences for viral transmission and evolution. PLoS Pathog. 2013;9(1):e1003111.

3. Developing transmissible vaccines to target zoonoses
I am currently involved in a multi-centre project aimed at developing transmissible vaccines to eradicate zoonotic spillover into human populations. This work utilizes the cytomegalovirus (CMV) genome as the vaccine vector to express LASV antigens leading to the induction of LASV-specific immunity. Our studies so far have demonstrated proof-of-principle of a self-excisable system that returns genetically modified MCMV genomes to wild type. This work contribute to our understanding of the selective pressures exerted upon foreign transgenes within a transmissible vaccine vector and how this impacts the propagation potential of these vaccines.

Publication from this work:

a. Nuismer SL, Layman NC, Redwood AJ, **Chan B**, Bull JJ. Methods for measuring the evolutionary stability of engineered genomes to improve their longevity. Synth Biol (Oxf). 2021;6(1):ysab018.

Full list of publications:
https://orcid.org/0000-0003-0788-9503

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: QWYKRJH5NNJ3

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Regents of the University of Idaho

Start Date*: 10-01-2022 **End Date*:** 09-30-2023 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Scott		Nuismer		PD/PI	(b)(6)	(b)(6)			25,412.00	7,649.00	33,061.00
2 .		James		Bull		Co-I					7,006.25	2,108.00	9,114.25
3 .		Christopher		Remien		Co-I					11,481.00	3,456.00	14,937.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **57,112.25**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			60,000.00	25,200.00	85,200.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**85,200.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**142,312.25**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: QWYKRJH5NNJ3
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: Regents of the University of Idaho

Start Date*: 10-01-2022 **End Date*:** 09-30-2023 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
1 . Computer Workstations	10,000.00
Total funds requested for all equipment listed in the attached file	
Total Equipment	**10,000.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,000.00
2. Foreign Travel Costs	4,936.00
Total Travel Cost	**8,936.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: QWYKRJH5NNJ3
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Regents of the University of Idaho

Start Date*: 10-01-2022 **End Date*:** 09-30-2023 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	2,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	195,616.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Software	1,983.00
9. Conference Registration	1,000.00
10. University of Western Australia Investigator Travel	3,557.00
Total Other Direct Costs	**204,156.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**365,404.25**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	50.00	184,788.00	92,394.00
		Total Indirect Costs	**92,394.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**457,798.25**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	457,798.25

L. Budget Justification* File Name: Budget_Justification_FINAL.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: QWYKRJH5NNJ3

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Regents of the University of Idaho

Start Date*: 10-01-2023 **End Date*:** 09-30-2024 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Scott		Nuismer		PD/PI	(b)(6)	(b)(6)			25,412.00	7,649.00	33,061.00
2 .		James		Bull		Co-I					7,006.25	2,108.00	9,114.25
3 .		Christopher		Remien		Co-I					11,481.00	3,456.00	14,937.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **57,112.25**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			60,000.00	25,200.00	85,200.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**85,200.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**142,312.25**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: QWYKRJH5NNJ3

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Regents of the University of Idaho

Start Date*: 10-01-2023 **End Date*:** 09-30-2024 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,000.00
2. Foreign Travel Costs	4,936.00
Total Travel Cost	**8,936.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: QWYKRJH5NNJ3
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Regents of the University of Idaho

Start Date*: 10-01-2023 **End Date*:** 09-30-2024 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	2,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	262,566.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Software	1,983.00
9. Conference Registration	1,000.00
10. University of Western Australia Investigator Travel	3,557.00
Total Other Direct Costs	**271,106.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**422,354.25**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	50.00	159,788.00	79,894.00
		Total Indirect Costs	**79,894.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**502,248.25**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	502,248.25

L. Budget Justification* File Name: Budget_Justification_FINAL.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: QWYKRJH5NNJ3

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Regents of the University of Idaho

Start Date*: 10-01-2024 **End Date*:** 09-30-2025 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Scott		Nuismer		PD/PI	(b)(6)	(b)(6)			25,412.00	7,649.00	33,061.00
2 .		James		Bull		Co-I					7,006.25	2,108.00	9,114.25
3 .		Christoper		Remien		Co-I					11,481.00	3,456.00	14,937.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **57,112.25**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			60,000.00	25,200.00	85,200.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**85,200.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**142,312.25**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: QWYKRJH5NNJ3

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Regents of the University of Idaho

Start Date*: 10-01-2024 **End Date*:** 09-30-2025 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,000.00
2. Foreign Travel Costs	4,936.00
Total Travel Cost	**8,936.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: QWYKRJH5NNJ3
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Regents of the University of Idaho

Start Date*: 10-01-2024 **End Date*:** 09-30-2025 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	5,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	133,428.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Software	1,983.00
9. Conference Registration	1,000.00
10. University of Western Australia Investigator Travel	3,557.00
Total Other Direct Costs	**144,968.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**296,216.25**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	50.00	162,788.00	81,394.00
		Total Indirect Costs	**81,394.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**377,610.25**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	377,610.25

L. Budget Justification* File Name: Budget_Justification_FINAL.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: QWYKRJH5NNJ3

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Regents of the University of Idaho

Start Date*: 10-01-2025 **End Date*:** 09-30-2026 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Scott		Nuismer		PD/PI	(b)(6)	(b)(6)			25,412.00	7,649.00	33,061.00
2 .		James		Bull		Co-I					7,006.25	2,108.00	9,114.25
3 .		Christopher		Remien		Co-I					11,481.00	3,456.00	14,937.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **57,112.25**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			60,000.00	25,200.00	85,200.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**85,200.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**142,312.25**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: QWYKRJH5NNJ3
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: Regents of the University of Idaho

Start Date*: 10-01-2025 **End Date*:** 09-30-2026 **Budget Period:** 4

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,000.00
2. Foreign Travel Costs	4,936.00
Total Travel Cost	**8,936.00**

E. Participant/Trainee Support Costs	Funds Requested ($)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: QWYKRJH5NNJ3
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Regents of the University of Idaho

Start Date*: 10-01-2025 **End Date*:** 09-30-2026 **Budget Period:** 4

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	10,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Software	1,983.00
9. Conference Registration	1,000.00
10. University of Western Australia Investigator Travel	3,557.00
Total Other Direct Costs	**16,540.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**167,788.25**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	50.00	167,788.00	83,894.00
		Total Indirect Costs	**83,894.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**251,682.25**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	251,682.25

L. Budget Justification* File Name: Budget_Justification_FINAL.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

University of Idaho Budget Justification

Senior Personnel

Scott L. Nuismer, PI ((b)(6) months) Professor, Biological Sciences, will coordinate work on the project, lead model development and analysis, and guide development and application of statistical methods for model parameterization. Dr. Nuismer will also supervise and mentor the postdoctoral researcher. We request $25,412 per year in salary.

James J. Bull, Co-I ((b)(6) months) Professor, Biological Sciences, will assist in the development and analysis of mathematical models and in mentoring the postdoctoral researcher. We request $7,005 per year in salary.

Christopher H. Remien, Co-I ((b)(6) months) Associate Professor, Mathematics and Statistical Science, will assist in the development and analysis of mathematical models and statistical methods and in mentoring the postdoctoral researcher. We request $11,481 per year in salary.

Other Personnel

TBD, Postdoctoral Fellow (12.0 calendar months). The project Postdoc will develop and analyze mathematical models and develop, test, and implement statistical methods for parameter estimation. We request $60,000 per year in salary.

Fringe Benefits

University of Idaho FY23 consolidated fringe rates applied. 30.1% for faculty and 42.0% for staff.

Equipment

$10,000 in year 1 is requested for two workstation computers at $5,000 each. Workstations will facilitate development and analysis of mathematical models and speed development and testing of Approximate Bayesian statistical methodologies prior to deployment on the RCDS computational core.

Travel

Domestic

We request $4,000 per year for travel to conferences by the University of Idaho research team.

Foreign

$4,936 per year is requested for one individual from the University of Idaho research team to travel to Australia for in-person collaborator meetings. This estimate is based on roundtrip airfare of $2,500 and the federal per diem of $348 per day for Perth for a visit of seven days.

Other Direct Costs

Publication Fees

$2,000 in years 1 and 2, $5,000 in year 3, and $10,000 in year 4 is requested to defray the cost of publishing the project's research.

Software

$1,983 per year is requested for three Mathematica licenses to be used for model development and analysis.

Conference Registration

We request $1,000 per year for meeting registrations for the University of Idaho research team.

Subaward

A total of $591,610 is requested for a University of Western Australia subaward. This subaward supports the collection of data critical for model parameterization and validation by a team of researchers who has pioneered the development herpesvirus vectored vaccines.

UWA Travel

$3,557 per year is requested for one individual from the University of Western Australia research team to travel to the U.S. for in-person collaborator meetings. This estimate is based on roundtrip airfare of $2,500 and the federal per diem of $151 per day for Moscow, Idaho for a visit of seven days.

Indirect Costs

Calculated at the University of Idaho Federally Negotiated Indirect Cost Rate as Modified Total Direct Cost excluding participant support costs, equipment > $5,000, tuition, and those amounts of sub awards exceeding $25,000. 50% rate applied to the entire project period for a total of $337,576.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		228,449.00
Section B, Other Personnel		340,800.00
Total Number Other Personnel	4	
Total Salary, Wages and Fringe Benefits (A+B)		569,249.00
Section C, Equipment		10,000.00
Section D, Travel		35,744.00
1. Domestic	16,000.00	
2. Foreign	19,744.00	
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		636,770.00
1. Materials and Supplies		
2. Publication Costs	19,000.00	
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	591,610.00	
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	7,932.00	
9. Other 2	4,000.00	
10. Other 3	14,228.00	
11. Other 4		
12. Other 5		
13. Other 6		
14. Other 7		
15. Other 8		
16. Other 9		
17. Other 10		
Section G, Direct Costs (A thru F)		1,251,763.00
Section H, Indirect Costs		337,576.00

Section I, Total Direct and Indirect Costs (G + H)	1,589,339.00
Section J, Fee	
Section K, Total Costs and Fee (I + J)	1,589,339.00

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Western Australia

Start Date*: 10-01-2022 **End Date*:** 09-30-2023 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Alec		Redwood		Co-I	(b)(4); (b)(6)	(b)(6)			12,527.64	4,447.31	16,974.95
2 .		Baca		Chan		Co-I					80,302.00	28,508.00	108,810.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **125,784.95**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**125,784.95**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Western Australia

Start Date*: 10-01-2022 **End Date*:** 09-30-2023 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: CPLPM5RWMX26
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: The University of Western Australia

Start Date*: 10-01-2022 **End Date*:** 09-30-2023 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	55,340.73
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**55,340.73**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**181,125.68**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . NIH	8.00	181,125.68	14,490.00
		Total Indirect Costs	**14,490.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**195,615.68**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	195,615.68

L. Budget Justification* File Name: UWA_Budget_Justification.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Western Australia

Start Date*: 10-01-2023 **End Date*:** 09-30-2024 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Alec		Redwood		Co-I	(b)(4); (b)(6)	(b)(6)			12,903.48	4,580.74	17,484.22
2 .		Baca		Chan		Co-I					84,835.00	30,116.00	114,951.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **132,435.22**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
					Total Salary, Wages and Fringe Benefits (A+B)		**132,435.22**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Western Australia

Start Date*: 10-01-2023 **End Date*:** 09-30-2024 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: CPLPM5RWMX26
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: The University of Western Australia

Start Date*: 10-01-2023 **End Date*:** 09-30-2024 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	110,681.46
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**110,681.46**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**243,116.68**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . NIH	8.00	243,116.68	19,449.33
		Total Indirect Costs	**19,449.33**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**262,566.01**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	262,566.01

L. Budget Justification* File Name: UWA_Budget_Justification.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Western Australia

Start Date*: 10-01-2024 **End Date*:** 09-30-2025 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Alec		Redwood		Co-I	(b)(4); (b)(6)	(b)(6)			6,645.28	2,359.07	9,004.35
2 .		Baca		Chan		Co-I					43,689.60	15,509.81	59,199.41

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **68,203.76**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**68,203.76**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Western Australia

Start Date*: 10-01-2024 **End Date*:** 09-30-2025 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: CPLPM5RWMX26
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: The University of Western Australia

Start Date*: 10-01-2024 **End Date*:** 09-30-2025 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	55,340.73
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**55,340.73**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**123,544.49**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . NIH	8.00	123,544.49	9,883.55
		Total Indirect Costs	**9,883.55**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**133,428.04**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	133,428.04

L. Budget Justification* File Name: UWA_Budget_Justification.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Western Australia

Start Date*: 10-01-2025 **End Date*:** 09-30-2026 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Alec		Redwood		Co-I		(b)(6)			0.00	0.00	0.00
2 .		Baca		Chan		Co-I					0.00	0.00	0.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*

Total Number Other Personnel **Total Other Personnel**

Total Salary, Wages and Fringe Benefits (A+B) **0.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2022-03-02T18:46:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: CPLPM5RWMX26

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Western Australia

Start Date*: 10-01-2025 **End Date*:** 09-30-2026 **Budget Period:** 4

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: CPLPM5RWMX26
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: The University of Western Australia

Start Date*: 10-01-2025 **End Date*:** 09-30-2026 **Budget Period:** 4

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**0.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . NIH	8.00	0.00	0.00
		Total Indirect Costs	**0.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**0.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	0.00

L. Budget Justification* File Name: UWA_Budget_Justification.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

University of Western Australia Budget Justification

All items in this budget have been costed in Australian dollars and 10% GST applied when necessary, then converted into United States dollars using the exchange rate of $1AUS = $0.72 USD (www.xe.com 10th February 2022).

Final values are calculated in $USD.

Total Direct Costs = $547,787 USD

Salaries / Personnel:
Dr Baca Chan – IRH Academic Salary scale ((b)(4); (b)(6)).
Salary support is requested for Dr Chan at (b)(6) for the duration of the project. She will manage the proposed studies and provide day-to-day supervision for the Research Assistants and any postgraduate students. She has extensive molecular biology, virology and immunology expertise, as well as many years of experience in working with animal models of infection. She will also be responsible for protocol development and ethics submissions. Requested salary is based on projections and includes direct and indirect costs and a level increase from (b)(6) in year 2 and an increase of 3% for year 3.

Salary Calculation for Baca Chan

Year base salary	**Rates**	1 (b)(4); (b)(6)	2	3
Percentage of time working		(b)(4); (b)(6) (b)(6)		
Workers' compensation (ELA)	1.96%	$2,186	$2,309	$1,189
Annual Leave and Leave loading	9.04%	$10,082	$10,651	$5,486
Long service leave	2.5%	$2,788	$2,946	$1,517
Superannuation				
Statutory	17%	$18,960	$20,030	$10,316
Admin expense	5%	$5,577	$5,891	$3,034
Total		**$151,125**	**$159,654**	**$82, 222**

Assoc. Prof. Alec Redwood – IRH Academic Salary scale ((b)(4); (b)(6)).
Salary support is requested for A/Prof Redwood at (b)(6) for the duration of the project. This work will be performed within Dr Redwood's research group. Dr Redwood has more than 20 years' experience in the use of MCMV as a vaccine vector. He will have overall responsibility for the works being carried out at UWA, including the supervision of staff and reporting to relevant bodies, such as the Office of Gene Technology Regulator (OGTR). Dr Redwood will meet regularly with all investigators to interpret data, to ensure that the project remains on-track, and to direct change as required. Requested salary is based on projections and includes direct and indirect costs and a certified agreed cumulative increase of 3% pa.

Salary Calculation for Alec Redwood

Year base salary	Rates	1 (b)(4); (b)(6)	2	3
Certified Agreement increase (Cumulative)	3.00%			
Base Salary with 3% increase		(b)(4); (b)(6)		
Percentage of time working		(b)(6)		
Workers' compensation (ELA)	1.96%	$341	$351	$181
Annual Leave and Leave loading	9.04%	$1,573	$1,620	$834
Long service leave	2.5%	$435	$448	$231
Superannuation				
Statutory	17.00%	$2,958	$3,047	$1,569
Admin expense	5%	$870	$896	$461
Total		$23,576	$24,284	$12,506

Goal 2a: Determine transgene stability in tissue culture
Construction of MCMV vaccines including whole genome sequencing to verify genomes: $1198.63/virus.

Passaging MCMV vaccines in tissue culture including cell culture, plaque assays: $24/sample.

qPCR DNA extraction, probes, plates and reagents: $23/sample.

	Year 1	Year 2	Year 3
Virus Construction	$5,760		
Passaging and consumables	$5,520		
ddPCR	$4,795		
SUBTOTAL	$16,075		

Goal 2b: Determine vaccine dynamics within the host

Infection experiments including mouse costs, agistment and shipping:
Purchase costs $40/mouse; agistment 45c/mouse/day (for acute infection 1 week settling + 18 days experiment and for chronic infection 1 week settling + 20 weeks experiment); shipping $80/large shipper.

qPCR DNA extraction, probes, plates and reagents:
DNA extraction kits $2000/250 samples; qPCR $22/sample.

Sanger sequencing
Sequencing costs $11/sample

ELISpot assays including peptides, plates, antibodies and reagents:
Antibodies, reagents peptides $1600/plate (estimate 5.76 plates); plates $500/plate

Consumables and General including plastic ware, tips, pipettes, tubes, tissue culture flasks, buffers, media required for the study: $24/sample

	Year 1	Year 2	Year 3
Animal infection	$ 17,973	$ 17,973	
Sequencing	$ 8,448	$ 8,448	
qPCR	$ 13,306	$ 32,774	
ELISpot	$ 9,828	$ 9,828	
General Consumables	$ 11,232	$ 11,232	
SUBTOTAL	$ 60,787	$ 80,255	

Goal 3a: Validation of models of vaccine evolution

Infection experiments including mouse costs, agistment, shipping and depletion antibodies:
Purchase costs $40/mouse; agistment 40c/mouse/day (for acute infection 1 week settling + 1 week depletion + 18 days experiment and for chronic infection 1 week settling + 1 week depletion + 20 weeks experiment) depletion antibodies $3000/25mg

qPCR DNA extraction, probes, plates and reagents:
DNA extraction kits $2000/250 samples; qPCR $22/sample.

Sanger sequencing
Sequencing costs $11/sample

ELISpot assays including peptides, plates, antibodies and reagents:
Antibodies, reagents peptides $1600/plate (estimate 0.96 plates); plates $500/plate

Consumables and General including plastic ware, tips, pipettes, tubes, tissue culture flasks, buffers, media required for the study: $24/sample

	Year 1	Year 2	Year 3
Animal infection		$ 31,438	$ 31,437
Sequencing		$ 8,448	$ 8,448
qPCR		$ 21,343	$ 24,737
ELISpot		$ 1,008	$ 1,008
General Consumables		$ 11,232	$ 11,232
SUBTOTAL		$ 73,469	$ 76,862

	Year 1	Year 2	Year 3
TOTAL	$76,862	$153,724	$76,862

Indirect Costs:
Calculated at the standard Indirect Cost Rate of 8% for non-US institutions as Modified Total Direct Cost excluding participant support costs, equipment > $5,000, tuition, and those amounts of sub awards in excess of $25,000.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		326,423.93
Section B, Other Personnel		
Total Number Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)		326,423.93
Section C, Equipment		
Section D, Travel		
1. Domestic		
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		221,362.92
1. Materials and Supplies	221,362.92	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1		
9. Other 2		
10. Other 3		
11. Other 4		
12. Other 5		
13. Other 6		
14. Other 7		
15. Other 8		
16. Other 9		
17. Other 10		
Section G, Direct Costs (A thru F)		547,786.85
Section H, Indirect Costs		43,822.88

Section I, Total Direct and Indirect Costs (G + H)	591,609.73
Section J, Fee	
Section K, Total Costs and Fee (I + J)	591,609.73

Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	350,914	402,905	286,333	167,788	0	**1,207,940**

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 09/30/2024

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ● Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

● Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ○ Yes ● No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ● No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

6. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 09/30/2024

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	Nuismer_Introduction.pdf
Research Plan Section	
2. Specific Aims	Aims_Page.pdf
3. Research Strategy*	Research_Strategy.pdf
4. Progress Report Publication List	Progress_Publication_List.pdf
Other Research Plan Section	
5. Vertebrate Animals	Vertebrate_Animals.pdf
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	Consortium_Arrangements.pdf
9. Letters of Support	Letters_of_Support.pdf
10. Resource Sharing Plan(s)	Data_Sharing_Plan.pdf
11. Authentication of Key Biological and/or Chemical Resources	Key_Biological_Resources.pdf
Appendix	
12. Appendix	

Tracking Number: GRANT13564479

Funding Opportunity Number: PA-20-185. Received Date: 2022-03-02T18:46:20.000-05:00

A Mathematical Theory of Transmissible Vaccines: Introduction

(b)(4); (b)(6)

Specific Aims

Spillover of pathogens from wild and domestic animal populations has seeded recent epidemics and pandemics including SARS, influenza H1N1, Ebola, and SARS-CoV-2. These epidemics and pandemics have occurred against a backdrop of sustained human infection caused by pathogens such as rabies, Brucella, and Lassa virus that reliably spillover and sicken millions of people each year. Remarkably, even in cases where spillover is chronic and predictable we have made only modest progress in reducing or eliminating spillover and thus the burden of human disease. In those cases where progress has been made, it has generally been through the use of intensive, costly, and logistically demanding animal vaccination programs. The key limitation of these programs is the need to vaccinate each individual, whether by direct injection or distribution of vaccine-laden baits. Genetic engineering now offers a fresh approach to overcoming this long-standing challenge: animal vaccines designed to self-disseminate through infectious transmission. These transmissible vaccines reduce the vaccination effort required for pathogen control within animal reservoirs and allow the vaccine to penetrate remote reservoir habitats where direct vaccination is impossible.

Our previous work established a theoretical foundation for the potential benefit of transmissible vaccines and demonstrated how they might revolutionize the prevention of zoonotic disease. Our work also demonstrated that bringing this technology to fruition faces a triple challenge: engineering vaccines that are (i) immunogenic, (ii) capable of spreading through the reservoir population and (iii) not prone to evolve loss of their engineered immunogenecity. Here, we propose to tackle this triad of challenges by developing and analyzing mathematical models that guide development of a general platform for transmissible vaccines applicable to a wide range of important reservoir species. This effort uses novel, within-host models of transmissible vaccines that combine the within-host processes of vaccine replication, host immune response, and vaccine evolution. These models are parameterized for three prototype transmissible vaccines using a combination of *in vitro* and *in vivo* experiments and validated using experimental infection of immunocompsomised mice.

Our specific aims are:

Specific Aim 1. Develop within-host models of vaccine growth, immunogenicity and evolution. An optimal transmissible vaccine replicates rapidly within a host, stimulates a robust immune response to the target pathogen, and avoids unwanted evolution. Work on this aim will develop within-host models of transmissible vaccines that quantify how these properties interact and identify constraints on vaccine design. These models will enable the statistical methodologies for screening vaccine candidates developed in the second aim.

Specific Aim 2. Parameterize within-host models using prototype transmissible vaccines. Using the ubiquitous murine cytomegalovirus as a vaccine backbone, we will engineer transmissible vaccine prototypes to carry immunogenic transgenes. We will use a combination of *in vitro* and *in vivo* experiments to parameterize the models developed in Aim 1. The parameterized models will quantify the key properties of each vaccine prototype and illuminate general constraints on the design of cytomegalovirus-vectored transmissible vaccines.

Specific Aim 3. Model validation using immune-depleted mice. We will validate the models parameterized in Aim 2 using experimental innoculation of immune depleted mice. This validation procedure will challenge our models ability to accurately predict vaccine dynamics and isolate the role the host immune response plays in driving vaccine evolution.

Accomplishing these specific aims will allow the effectiveness of transmissible vaccines to be predicted *a priori*, and guide the long-term development of this new technology for preventing pathogen spillover into the human population. The proposed work capitalizes on an existing collaboration between experts in mathematical modeling, viral evolution, and murine cytomegalovirus to pioneer a framework for developing transmissible vaccines.

A. Significance

Spillover of zoonotic pathogens has proven difficult to control and virtually impossible to eliminate. As a consequence, each year approximately 50,000 people die from rabies, 800,000 are sickened by Lassa virus, and more than 500,000 are sickened by brucellosis—all acquired from animals [5, 42, 22]. More broadly, the World Health Organization estimates there are currently more than 200 zoonotic pathogens that regularly spill over from wild and domestic animals into the human population. Beyond the burden imposed by this chronic, predictable, and pervasive spillover of zoonotic pathogens is the enormous public health impact of recent epidemics and pandemics seeded by zoonotic pathogens such as Ebola, MERS, SARS-CoV-1, and of course, SARS-CoV-2. Although animal vaccination programs using standard methods have reduced the burden of spillover in some cases (e.g., rabies, brucellosis) [32], other regions endure continued spillover because of the logistical and financial challenges associated with delivering large quantities of vaccine to hard to reach wild and domestic animal populations [3].

A novel solution to this problem is the development of vaccines that are capable of self dissemination—transmissible vaccines [10, 34, 38]. Such vaccines are still nascent, and this project will develop and parameterize models that guide their development. Despite the novelty and uncertainties, we pursue a transmissible vaccine because of its enormous potential. A transmissible vaccine makes it possible to reduce, if not eliminate, the risk of spillover from hard to reach and difficult to vaccinate populations of wild and domestic animals.

Progress Report

Work on our current R01 established a mathematical foundation for transmissible vaccines and quantified their potential for reducing the risk of pathogen spillover [36, 10, 38, 54]. This research has produced 24 publications. A fundamental result to emerge from this work is that the benefits of a transmissible vaccine depend on its basic reproductive number R_0—the expected number of new vaccine infections resulting from a single vaccine-infected individual in a vaccine naive population—relative to the R_0 of the target pathogen [36]. Specifically, if the basic reproductive number of the vaccine, $R_{0,V}$, exceeds the basic reproductive number of the target pathogen $R_{0,P}$, the pathogen can be eliminated from the reservoir population using only a single vaccine introduction. Even when the vaccine reproductive number is less than that of the pathogen, vaccine transmission reduces the number of vaccine doses that must be directly administered to eliminate the pathogen by an amount equal to $R_{0,V}/R_{0,P}$. Thus, even a limited ability to transmit within the reservoir population can substantially decrease the vaccination effort required to suppress the pathogen. Additional results derived as part of this work clarify the benefits of vaccine transmission in the face of prior immunity to the vaccine [4], spatial structure within the reservoir population [6], reservoir host heterogeneity [53], and vaccine evolution [27, 37, 26].

Beyond quantifying the potential benefits of vaccine transmission, our work has identified three critical properties of transmissible vaccines that determine their success: 1) transmission among hosts, 2) stimulation of a robust immune response against the target pathogen, and 3) evolutionary stability of the vaccine [27, 37]. An ideal transmissible vaccine maximizes each of these properties simultaneously, but biological constraints are likely to conspire to limit what is possible in practice (Figure 1).

Understanding the biological constraints that define the scope of possibilities requires that we understand the dynamics of transmissible vaccines within the host itself. Thus, the next critical step in our long-term goal of establishing a theoretical framework for transmissible vaccine development is constructing mathematical models that describe the interplay between vaccine replication and evolution within the host and the host immune response stimulated by vaccine infection. The central contribution of our work will be an integrated mathematical and statistical framework for discriminating among vaccine candidates using routinely collected data from *in vitro* and *in vivo* studies. This project will lay the foundation for developing a range of transmissible vaccines for use in murid rodents, and by extension, for use in other wildlife reservoirs.

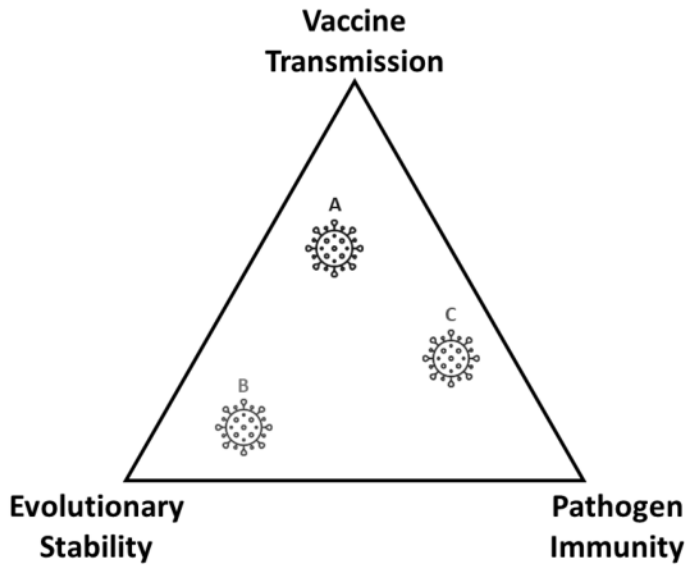

Figure 1: Properties of transmissible vaccines that must be balanced to optimize their performance as tools for spillover prevention. Vaccine candidates (e.g., A, B, and C) are characterized by different combinations of vaccine transmission within the reservoir, evolutionary stability of the vaccine itself, and the ability of the vaccine to stimulate an immune response to the target pathogen. Existing theory and data are insufficient to identify the optimal vaccine candidate.

B. Innovation

The primary challenge in designing effective transmissible vaccines is striking the optimal balance between three essential properties: 1) transmission among hosts, 2) stimulation of a robust immune response against the target pathogen, and 3) evolutionary stability of the vaccine (Figure 1). How these properties interact with one another to generate constraints on vaccine design remains almost entirely unknown. The proposed work will formalize these constraints and identify optimal solutions by developing and analyzing the first within-host models of transmissible vaccines. These models will describe the process of viral replication within the host, the resulting host immune response, and how these opposing forces influence the quantity and composition of vaccine shed from the host and thus available for onward transmission. Within-host models will be parameterized using laboratory studies of prototype transmissible vaccines conducted *in vitro* and *in vivo*. Within-host models will be validated using *in vivo* experiments with immune-depleted mice. These validation experiments will challenge our model's ability to accurately predict vaccine dynamics in a novel environment where selection by CD8+ T cells has been suppressed. ***The key innovation of our work is the development of a model-based method for screening prototype transmissible vaccines and optimizing their performance.***

C. Approach

Overview of approach

The models and statistical methods we develop here focus on recombinant vector transmissible vaccines. These vaccines are constructed by inserting a portion of the pathogen genome with immunogenic properties (the transgene) into a benign vector virus. We focus our work on recombinant vector vaccines for several reasons. (1) Safety. The vector can be chosen to be harmless and specific to the desired reservoir species. Vaccine evolution is likely to follow a predictable path toward elimination of the transgene and a return to the benign vector virus. These features minimize safety concerns that confront other transmissible vaccine designs [46, 28]. (2) Versatility. The recombinant vector method is flexible, allowing for insertion of a wide range of immunogenic transgenes. Thus, once established, the vector platform can be engineered to target different pathogens or pathogen strains by altering the identity of the transgene. (3) Transmission. The transmission rate of the vaccine can, in principle, be tuned by choosing an appropriate vector or vector strain.

Although the mathematical and statistical framework we will develop for screening transmissible vaccine can-

didates is quite general, model parameterization and validation will focus on murine cytomegalovirus (MCMV) as the vaccine vector. Betaherpesviruses in general, and cytomegaloviruses like MCMV in particular, have been long recognized as promising vaccine vectors because of several key biological features [48]. First, they are broadly distributed across reservoir species [14, 51, 21]. Thus, our results are likely to inform and guide the future development of transmissible vaccines for a range of zoonotic pathogens with rodents and bats as reservoirs. Second, co-infection by multiple strains is common for betaherpesviruses [19, 21], including MCMV [8, 50, 12], suggesting that superinfection is common [20, 18]. Thus, the spread of an MCMV-vectored vaccine is not expected to be blocked when MCMV already exists in the wild population. Third, MCMV and other betaherpesviruses are species-specific, reducing the risk of off-target infection [49]. Fourth, we have well-established collaborations with Australian scientists [54, 39] who have decades of experience with the natural history of MCMV [52, 50, 31] and the use of this virus as a vaccine vector [44, 49, 45, 33].

Specific Aim 1. Develop within-host models of vaccine growth, immunogenicity and evolution

The eventual success or failure of any transmissible recombinant vector vaccine depends on the interplay of three fundamental properties: 1) transmission rate, 2) the immune response elicited against the target pathogen, and 3) evolutionary stability of the transgene [27]. We do not yet know, however, how these various properties of transmissible vaccines interact with one another to create constraints on transmissible vaccine design (Figure 1). Understanding these constraints, and the biological mechanisms through which they arise within the host, is the central goal of the modeling in Aim 1.

We will develop mathematical models describing the growth and evolution of recombinant vector transmissible vaccines within the host. These models will allow us to understand how the selective pressures imposed by competition for host cells and by the host immune response drive evolutionary loss of immunogenic transgenes and thus eliminate vaccine function. These models will also predict the dynamics of vaccine shedding and host immune response to the transgene(s), quantities critical for advancing population-level models of transmissible vaccines. We will initially focus on the dynamics of the vaccine within the salivary gland, the organ most closely associated with shedding of MCMV [47] and thus of greatest relevance to the epidemiological dynamics of a transmissible vaccine. Our models will also integrate one of the hallmarks of MCMV infection: life-long infection characterized by periods of latency and sporadic reactivation [15]. Latency is the persistence of silent viral genomes without the production of infectious viral particles and may have significant consequences for vaccine evolution.

These considerations lead us to an initial model of the form:

$$\frac{dC}{dt} = b - \left(\beta A_W + \beta(1-c)A_V\right) C - dC \tag{1a}$$

$$\frac{dA_W}{dt} = \beta A_W C - \gamma A_W + \rho L_W + \mu A_V - \kappa_W T_W A_W - d A_W \tag{1b}$$

$$\frac{dA_V}{dt} = \beta(1-c) A_V C - \gamma A_V + \rho L_V - \mu A_V - \kappa_W T_W A_V - \kappa_V T_V A_V - d A_V \tag{1c}$$

$$\frac{dL_W}{dt} = \gamma A_W - \rho L_W - d L_W \tag{1d}$$

$$\frac{dL_V}{dt} = \gamma A_V - \rho L_V - d L_V \tag{1e}$$

$$\frac{dT_W}{dt} = \theta_W \frac{A_W + A_V}{A_W + A_V + \tau_W} - \delta T_W \tag{1f}$$

$$\frac{dT_V}{dt} = \theta_V \frac{A_V}{A_V + \tau_V} - \delta T_V \tag{1g}$$

where t is the time since infection and all parameters and variables are defined in Table 1. Throughout, we use the subscript V to indicate functional vaccine and the subscript W to indicate dysfunctional vaccine that no longer stimulates pathogen immunity due to mutations that eliminate or disable the immunogenic transgene. We refer to this dysfunctional vaccine as mutant throughout. This system of equations describes the epidemiological and

Symbol	Biological interpretation
C	Density of uninfected host cells
A_W and A_V	Density of cells actively infected with mutant vaccine (W) or intact vaccine (V)
L_W and L_V	Density of cells latently infected with mutant vaccine (W) or intact vaccine (V)
T_W and T_V	CD8+ T cells targeting antigens of the vaccine vector (W) or targeting antigens encoded by the transgene (V)
b	Birth rate of host cells
d	Natural death rate of host cells
β	Rate of viral transmission between cells
c	The reduction in viral transmission attributable to carrying the transgene, independent of host immunity
γ	Rate at which active virus becomes latent
ρ	Rate at which latent virus becomes active
μ	Rate of spontaneous transgene loss through mutation
κ_W and κ_V	CD8+ T cell mediated death rate targeting the vaccine vector (W) or antigens encoded by the transgene (V)
θ_W and θ_V	The maximum rate of increase for CD8+ T cells stimulated by the vaccine vector (W) or antigens encoded by the transgene (V)
τ_W	Density of cells actively infected with virus (mutant vaccine and vaccine) that yields half the maximal growth rate of CD8+ T cells
τ_V	Density of cells actively infected with vaccine that yields half the maximal growth rate of CD8+ T cells
δ	Death/decay rate of CD8+ T cells
σ_W	Shedding rate of mutant vaccine
σ_V	Shedding rate of vaccine

Table 1: Model variables and parameters. The variables C, A_W, A_V, L_W, L_V, T_W, and T_V are all functions of the time since infection. Estimates for parameters b, d, and δ will be drawn from the literature. Remaining parameters will be estimated using data collected as part of the proposed work.

evolutionary dynamics of the vaccine within a host as well as the host's immune response. To link this model to our existing population-level models and to the data collected in Aim 2, we assume viral shedding into the saliva is a function of the density of actively infected cells within the salivary gland such that:

$$\sigma_W = f(A_W) \tag{2a}$$

$$\sigma_V = f(A_V) \tag{2b}$$

where the mathematical form of the functions $f(A_W)$ and $f(A_V)$ (e.g., linear or Hill functions) will be determined using data collected in Aim 2. Specifically, experiments conducted in Aim 2 will measure viral loads in saliva (σ_W and σ_V) and in the salivary gland (A_W and A_V) allowing us to fit this function using conventional statistical methods such as least squares.

Because well-established and validated models for the within-host dynamics of MCMV do not yet exist, this model builds from within-host models of other viral infections [e.g., 1, 2, 9, 43, 30] and thus represents a logical starting point for analysis. If, when confronted with data in Aim 2, this model fails to provide an adequate fit, we will pursue two structural modifications. First, we will integrate the lung into the model, an organ demonstrated to be involved in murine infection by MCMV [17, 33]. Although inclusion of the lung adds complexity and parameters to the model, data from lung involvement will have already been gathered in our experiments and will offset this gain in model complexity (see Aim 2). Second, we will explore alternative forms for the CD8+ T cell response (e.g., virus-independent CD8+ T cell expansion at a fixed rate, CD8+ T cell expansion rate proportional to viral

load) which have precedent in modeling an adaptive immune response [35, 55, 23].

Goal 1a. Establish basic principles of vaccine design using analytical approximations

Although numerically solving the system of equations (1) to predict the temporal dynamics of vaccine infection is straightforward, greater insight can be gained by identifying approximations that allow closed form solutions. Such solutions will allow us to formalize constraints on transmissible vaccine design (Figure 1) and identify strategies that maximize the host immune response to the target antigen (e.g., peak values of T_V) without compromising vaccine replication and evolutionary stability.

Our basic approach to developing approximate solutions will rely on a change of variables that disentangles the dynamics of viral growth from the dynamics of evolution. Specifically, we will pursue a change of variables of the form:

$$A = A_V + A_W \tag{3a}$$

$$L = L_V + L_W \tag{3b}$$

$$T = T_V + T_W \tag{3c}$$

$$p_A = \frac{A_V}{A_V + A_W} \tag{3d}$$

$$p_L = \frac{L_V}{L_V + L_W} \tag{3e}$$

$$\omega = \frac{T_V}{T_V + T_W} \tag{3f}$$

where A, L, and T are the total densities of actively infected cells, latently infected cells, and CD8+ T cells, respectively. The quantities p_A and p_L are the frequencies of the intact vaccine within actively infected and latently infected cells, respectively. Finally, ω quantifies the proportion of CD8+ T cells targeting the transgene carried by the vaccine. Although this change of variables does not simplify the mathematical challenge on its own, it does clarify the problem and suggest avenues to possible approximations. Preliminary analyses demonstrate the power of this approach. Specifically, assuming transitions between active and latent infection are rapid, the evolutionary dynamics of the immunogenic transgene can be approximated as:

$$\frac{dp_A}{dt} \approx -p_A(1-p_A)(c\beta C + \kappa_V \omega T) - \mu p_A \tag{4}$$

This simple expression demonstrates that transmissible vaccine evolution is driven by three forces: 1) selection based on reduced transmission among cells associated with transgene carriage ($c\beta C$), 2) selection based on CD8+ T cell attack of the transgene ($\kappa_V \omega T$), and 3) mutation (μp_A). Work on this goal will push such approximations further to better understand the feedbacks between vaccine replication, CD8+ T cell response, and vaccine evolution. All analytical approximations will be verified using numerical solutions.

Goal 1b. Develop numerical procedures for optimizing vaccine prototypes

The analytical approximations developed in the previous goal will identify general design principles for transmissible vaccines that maximize vaccine replication and transgene-specific immune response while minimizing vaccine evolution. Work on this goal will take a more applied approach to the problem and develop numerical methods that guide re-engineering of vaccine prototypes to increase their performance. These numerical methods will be applied to our prototype transmissible vaccines following model parameterization and validation in Aims 2-3.

Work on this goal will focus on optimizing the performance of transmissible vaccines by maximizing the following objective function:

$$\mathcal{O} = \int_{t=0}^{\psi} \sigma_V dt \times \int_{t=0}^{\psi} T_V dt \tag{5}$$

where the integrals are taken from the time an animal is inoculated with vaccine until the infection is cleared or the animal dies, ψ. The first integral of $\mathcal{O}$ quantifies the amount of intact vaccine that is shed by the animal over the course of the infection. This serves as a proxy for the vaccine's ability to infect other animals and thus spread

through the population. The second integral quantifies the extent to which the vaccine stimulates CD8+ T cell mediated immunity to the target pathogen and thus its ability to act as an effective vaccine. Both quantities are essential and yet both are reduced by unwanted vaccine evolution that eliminates the immunogenic transgene. The quantities σ_V and T_V are both functions of time and thus require that the system of equations (1) and (2) be solved numerically prior to numerical evaluation of the objective function.

Optimization of our vaccine prototypes will rely on parameters estimated for each vaccine prototype in Aim 2. Note that the objective function in equation (5) is a function of model parameters. We will first place each prototype vaccine onto the surface of the objective function at the position defined by its vector of parameter estimates. Next we will numerically calculate the gradient at this point to identify the multivariate direction of change in parameters that yields the most rapid ascent of the objective surface. This analysis informs re-engineering in cases where it is feasible to make small changes to multiple parameters simultaneously. We will also numerically calculate partial derivatives for each parameter to inform fine-scale adjustment and tinkering in cases where small changes can be made to only one or two model parameters due to biological or financial limitations. Applying these methods to our prototype transmissible vaccines will guide the next design steps in the development of transmissible vaccines for murine populations.

Challenges and planned resolution

Although we have used similar approaches to those in Goal 1a to derive analytical approximations to equations such as model 1 previously, there is no guarantee that in this case such approximations will be tractable and accurate. If this is the case, we are prepared to rely on numerical simulations. By numerically simulating over a wide variety of parameter values, we will be able to identify vaccine properties that minimize within-host evolution while still having high transmission potential and generating a robust immune response. An additional challenge we are prepared to confront is the possibility that the surface defined by the objective function $\mathcal{O}$ is characterized by multiple peaks. This is not a problem if re-engineering is limited to small adjustments of model parameters—in such cases the methods developed in Goal 1b will be both accurate and numerically efficient. If, however, large-scale changes of model parameters are practical, re-engineering may benefit from algorithms that scan the objective function more broadly. For this reason, we will complement the gradient based methods of Goal 1b with approaches based on a direct search.

Specific Aim 2. Parameterize within-host models using prototype transmissible vaccines

The within-host models developed in Aim 1 will be parameterized using experiments with prototype transmissible vaccines (Figure 2). These prototype transmissible vaccines will be constructed by engineering MCMV to carry defined CD8+ T cell targets that are presented by two different major histocompatibility complex class I molecules (MHC-I) encoded by BALB/c mice. The antigens to be used will be derived from the Lassa virus nucleoprotein (LV-NP118-126, RPLSAGVYM, H2-L^d restricted) and the Influenza A virus nucleoprotein (Flu-NP147-155, TYQRTRALV, H2-K^d restricted). We will also construct a third vaccine which will express both antigens. These antigens were chosen because they induce strong CD8+ T cell responses and the responses are readily quantified. Combining two antigens in one of the vaccine prototypes guarantees variation in the intensity of the CD8+ T cell response, allowing us to clearly understand its relationship to vaccine evolution. Similar vaccine prototypes have been produced by the assembled research team for other projects [56, 33, 44].

Our basic approach to model parameterization will be Bayesian and build up from simple experiments conducted in cell culture to more complex experiments conducted in mice (see Figure 2 and Table 2 for details of experimental design). The advantage of this two-step approach to model parameterization is that it allows us to estimate the spontaneous rate of transgene loss, μ, and the fitness cost of transgene carriage, c, using clean and cost efficient *in vitro* experiments. These estimates will then be used to anchor prior distributions for these parameters when models are fit using more complex *in vivo* data. The details of experimental procedures, preliminary results supporting the likely success of our approach, and explicit links between models and data are provided in the goals that follow.

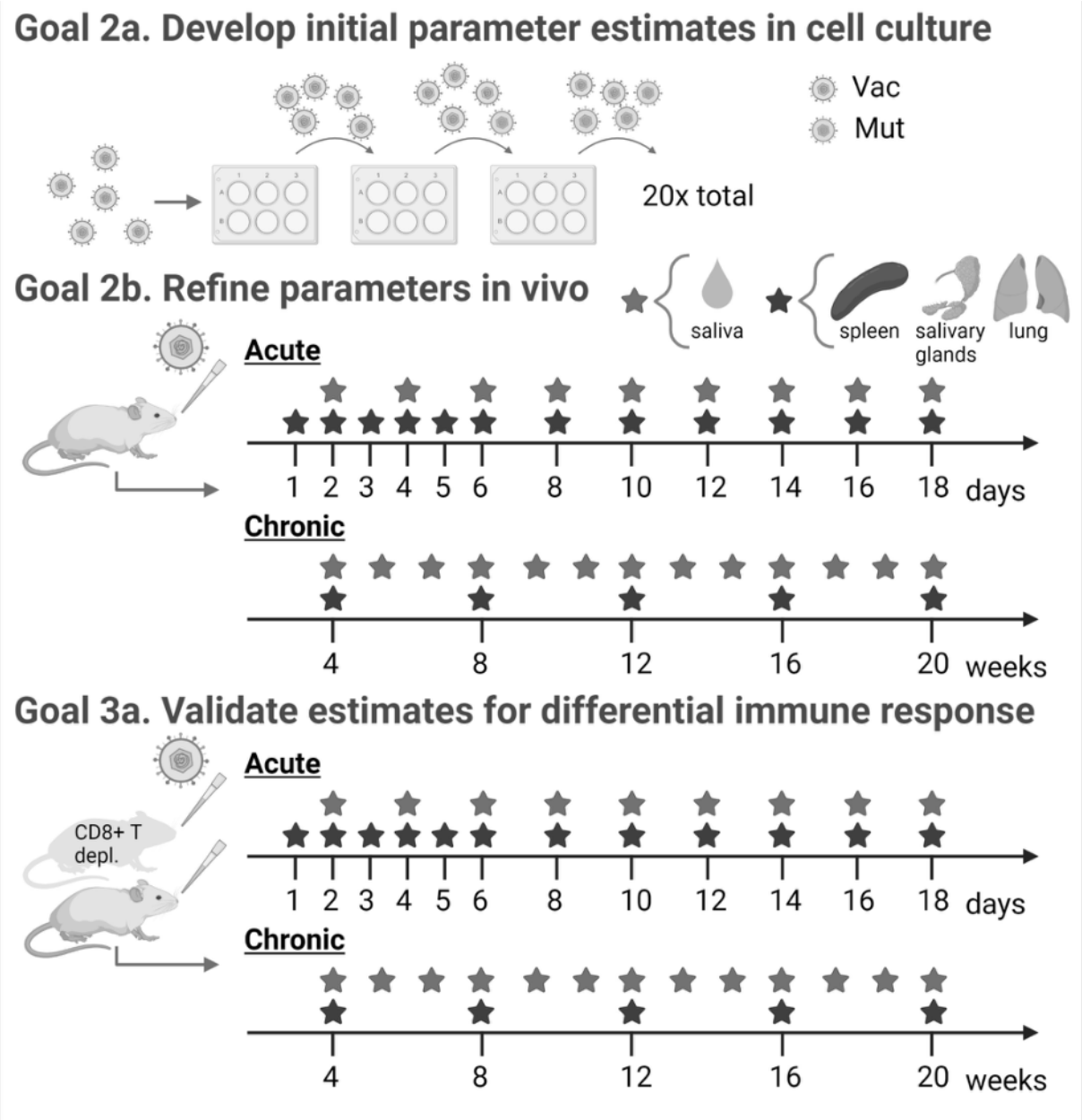

Figure 2: Experimental overview. In Goal 2a, vaccine strains of MCMV (Vac) will undergo 20 rounds of infection in tissue culture. Virus in which the transgene has been lost is referred to as the mutant (Mut). DNA will be extracted from infected cells for real-time polymerase chain reaction (RT-PCR) to monitor transgene loss. For *in vivo* experiments outlined in Goal 2b and 3a, mice will be infected by intranasal inoculation with 1×10^5 plaque forming units (PFU) of MCMV. In 3a, mice will be additionally treated with neutralizing antibodies to deplete CD8+ T cells. For analysis, during acute phases (days 1-18), salivary glands and lungs will be processed to determine viral titres by plaque assay, the proportion of vaccine and mutant genomes will be determined by RT-PCR. CD8+ T cell responses to the antigen encoded by the transgene will be determined, using splenocytes, by enzyme-linked immune absorbent spot (ELISpot) assay. CD8+ T cell responses to the MCMV vector will be determined at the same time by assessing responses to the immunodominant antigen IE1. For chronic timepoints (4-20 weeks), spleens will be processed for ELISpot. Active versus latent genomes in the lungs and salivary glands will be assessed by plaque assay and quantification of genome copies and viral transcription by RT-PCR. Saliva will be collected at indicated timepoints for assay by RT-PCR to measure viral shedding. In all experiments, mice infected with the wild type MCMV vector virus will be used as controls for mice infected with vaccine virus.

Environment	Innoculum (V:WT)	Rationale	Parameters Estimated
Cell culture	100:0	Quantify mutation rate and cost of carriage for vaccine prototypes	μ and c
BALB/c Mice	0:100	Parameterize model for wild type MCMV *in vivo*	β, γ, ρ, θ_W, τ_W, and κ_W
BALB/c Mice	100:0	Parameterize model for vaccine prototypes *in vivo*	μ, c, θ_V, τ_V, and κ_V
CD8+ T cell depleted mice	0:100	Validate model for wild type MCMV	NA
CD8+ T cell depleted mice	100:0	Validate model for vaccine prototypes	NA

Table 2: Experimental overview. All experiments will be repeated for each of the three prototype vaccines

Goal 2a. Estimate spontaneous rate of transgene loss and selective cost of transgene carriage

Cell culture offers a relatively simple environment in which to study the evolutionary dynamics of prototype transmissible vaccines in the absence of tissue heterogeneity and immunity. Our primary objectives will be to estimate: 1) the rate at which each transgene construct is lost through spontaneous mutation μ and 2) the reduction in replication/transmission associated with carrying and expressing each of the transgene constructs c. Although the precise values of both parameters may differ *in vivo*, the estimates derived here will anchor prior distributions from which to start the estimation process in the more complex *in vivo* environment.

Cell culture will consist of 500,000 murine cells per well of a 6-well plate. Vaccine virus will be added to this plate in triplicate and grown for 72 or 96 hours before being transferred to fresh cells on a new plate. At each transfer, the population density of intact vaccine and virus lacking the transgene (mutant) will be estimated using real time (quantitative) polymerase chain reaction (RT-PCR) on DNA extracted from infected cells. Transfers will be continued until the frequency of intact vaccine expressing the transgene falls below 10% or until 20 transfers have been completed. Experiments will be performed for each of the three prototype vaccines. The time series of intact vaccine frequency will be used to develop maximum likelihood estimates for the mutation rate, μ, and selective cost of carrying the transgene construct, c. We have recently validated this approach using simulated data sets [39], and demonstrated its feasibility using preliminary studies of transgene stability in MCMV (Figure 3). Work on this goal will apply this approach to each of our three prototype vaccines yielding estimates for the mutation rate, μ, and selective cost of transgene carriage, c, for each.

Goal 2b. Parameterize the within-host model in vivo

The experiments in goal 2a will yield initial estimates for the rate of spontaneous transgene loss through mutation, μ, and the selective cost of carrying and expressing the transgenic construct, c, for each of the three vaccine prototypes. In goal 2b, we will use experimental inoculations of BALB/c mice to refine these initial *in vitro* estimates and estimate the values of model parameters that define the dynamics of viral latency and the host immune response.

Experimental inoculations of mice will be administered intranasally to mimic the pathway of natural infection within wild rodent populations following protocols established by Helen Farrell and Philip Stevenson [16, 17]. Animals will be inoculated with wild type or vaccine virus and followed for 20 weeks with six mice sampled at each timepoint. Viral organ loads and CD8+ T cell responses will be quantified daily in the first 6 days of infection and every second day thereafter within the acute phase of infection (Days 0-18). Lytic virus in the lung and salivary glands will be quantified by standard plaque assay. Splenic CD8 T cell response to the viral vector and transgene will be assayed by IFNγ enzyme-linked immune absorbent spot (ELISpot) assay. Viral shedding into the saliva will be monitored every 2 days during the acute phase. CD8+ T cell responses and latency will be quantified every 4 weeks, with viral shedding monitored weekly during chronic infection (Weeks 4-20). Viral shedding will be

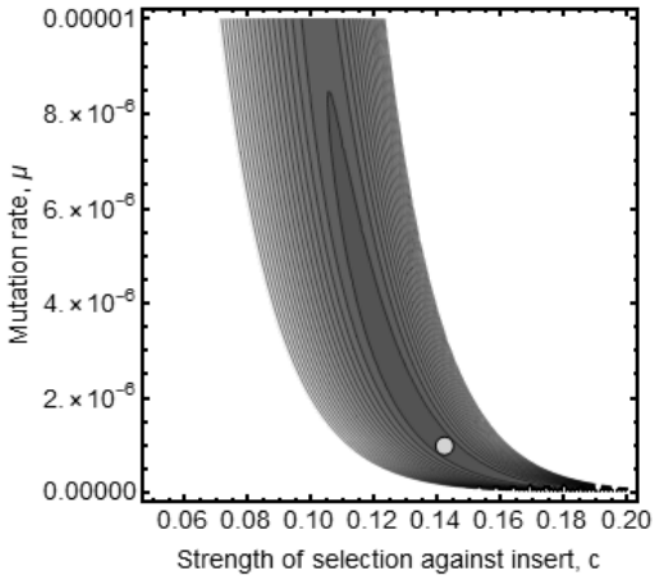

Figure 3: Maximum likelihood surface and estimate (yellow circle) for mutation rate μ and selective cost c for a preliminary study of transgene stability in MCMV using a β-galactosidase insert. The maximimum likelihood surface was constructed by applying the method developed in [39] to data on transgene frequency from a preliminary *in vitro* experiment.

sampled via collection of saliva on FTA filter paper [31]. Virus in the organs and saliva-saturated filter paper will be quantified using RT-PCR, which enables quantification of total virus and the differentiation between vaccine and mutant MCMV. Sampling in the saliva allows us to assess the impact of latency and periodic reactivation on the rate of transgene loss. Latency will be defined as the presence of MCMV genomes in conjunction with the lack of transcription of lytic genes M55 and ie3 as detected by RT-PCR. Latency may shield vaccine from immune pressure, slowing evolution and providing a reservoir for intact vaccine upon reactivation. Our work will be the first explore this possibility. The experimental design is summarized in Figure 2.

The composition of the initial viral inoculum will differ across two independent experiments. In the first, we will inoculate 102 mice (allowing 6 mice to be sampled per timepoint) with wild type MCMV. Data from this first experiment will be used to estimate baseline parameters defining the infection dynamics and immune response to the wild type MCMV vector. In a second experiment, 102 mice will be inoculated with each of the three prototype vaccines allowing us to study their evolution *in vivo*.

In contrast to the *in vitro* experiments conducted in Goal 2a, the involvement of the immune system in the *in vivo* experiments will preclude development of closed form solutions for likelihoods. As a consequence, work in goal 2b will use Approximate Bayesian Computation (ABC) to derive posterior distributions for model parameters [25, 7, 13]. Important advantages of ABC are that: 1) it requires only that the model can be simulated and 2) it does not become trapped on local optima for appropriately defined priors [29]. Although these advantages come at a significant computational cost, the ABC algorithm is easily parallelized allowing us to make full use of the University of Idaho's computational resources, including the 34,000 core Falcon super computer which will be managed by the University of Idaho beginning in Fall of 2022. The investigators have extensive experience using ABC to parameterize evolutionary and epidemiological models [e.g., 41, 40] and application of this method to preliminary *in vivo* data demonstrates that it yields good fits to temporal patterns of viral shedding in saliva (Figure 4).

Although the fit of our model to the preliminary data in Figure 4 is encouraging, verifying that individual parameters can be accurately estimated requires knowing their true values. We have conducted preliminary investigations using simulated data sets to demonstrate the feasibility of our approach and the likelihood of success. Specifically, we simulated experimental infections of mice using model (1-2) with parameters set to biologically informed values or to the values estimated from preliminary data (e.g., Figures 3 and 4). We then used our proposed ABC method to generate the posterior distribution. The results of this initial investigation demonstrate that key model parameters are identifiable when applied to simulated data of the form we propose to collect (Figure 5). The proposed work will refine our ABC approach using more extensive analyses of simulated data sets. Systematic investigation of relationships between true parameter values and those estimated by our ABC algorithm will allow

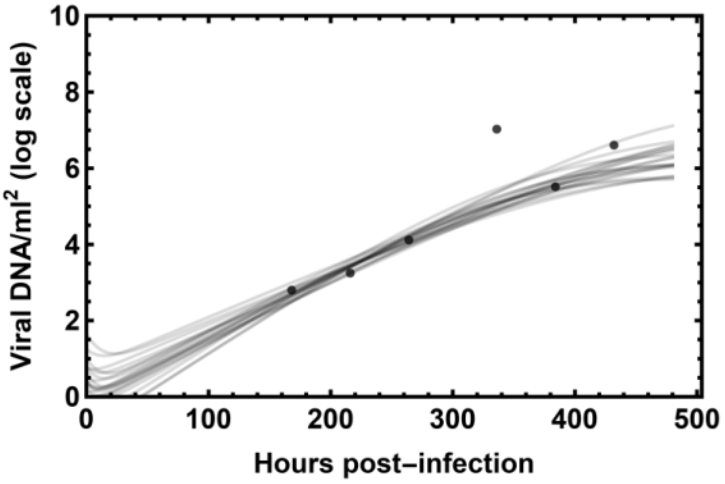

Figure 4: Model fit (gray lines) to preliminary *in vivo* data (red dots). Preliminary data comes from inoculation of five mice with wild type MCMV [11]. Saliva was collected every other day from day 7 to day 18 post-infection and viral loads determined by qPCR. Our model was fit to the data using ABC with uniform priors informed only by biological plausibility. Each gray line shows the timecourse of viral shedding in saliva predicted by our model when parameters were drawn at random from the posterior distribution.

us to optimize the summary statistics and acceptance threshold [e.g., 40].

Once the summary statistics and acceptance threshold used by our ABC method are optimized using simulated data sets, we will apply the method to the real data. We will first estimate parameters for wild type virus using the experimental measures of viral shedding in saliva, viral load in the salivary gland, proportion of virus currently latent, and magnitude of the CD8+ T cell response to MCMV. Model adequacy will be verified by repeatedly simulating data using parameters drawn at random from the posterior distributions allowing construction of 95% prediction intervals. Model fit will be considered adequate if 95% of the data lie within the 95% prediction interval. Next, we will estimate parameters for the three prototype vaccines using the same type of data described for the wild type, plus measurements of transgene frequency within the viral population and the CD8+ T cell response specific to the transgene(s). Here, too, model adequacy will be evaluated by repeatedly simulating data using parameters drawn at random from the posterior distribution and comparing the distribution of simulated data to the real data.

Challenges and planned resolution

Although the ability of our model to fit preliminary data is encouraging, it is possible that the basic model (1-2) will be unable to adequately fit the more complex *in vivo* data we propose to collect. In this event, we will begin the troubleshooting process by fitting and evaluating alternative models. First, we will replace the functional CD8+ T cell response in model (1-2) with alternative forms well-established in the literature [e.g., 23, 55, 35]. Second, we will extend the model (1-2) to include the lung, which, in addition to the salivary gland, is an important organ in MCMV infection [16]. Each alternative model will then be fit to the data. We will then take two approaches to reconciling data and models. In the first, we will select the single model that best fits the data using well-established methods [e.g., 7]. In the second, we will use Bayesian model averaging to combine models using weights determined by the posterior distributions [e.g., 24]. The relative utility of both approaches for our application will be evaluated using simulated data.

Specific Aim 3. Model validation using immune depleted mice

Work on the previous aim will yield parameterized models for the within-host epidemiological and evolutionary dynamics of three prototype vaccines. This aim will challenge those models to predict vaccine dynamics in the absence of a CD8+ T cell response, and thus evaluate how well the models capture the mechanisms responsible for vaccine replication, shedding, and evolution. Our basic approach will capitalize on our ability to easily turn the CD8+ T cell response off within the models, allowing us to repeatedly simulate data in its absence. We will use CD8+ T cell depleted mice to achieve the same thing experimentally. Model validation will assess the fit between the distribution of model predictions and the data. The details of our validation approach are described the goals that follow.

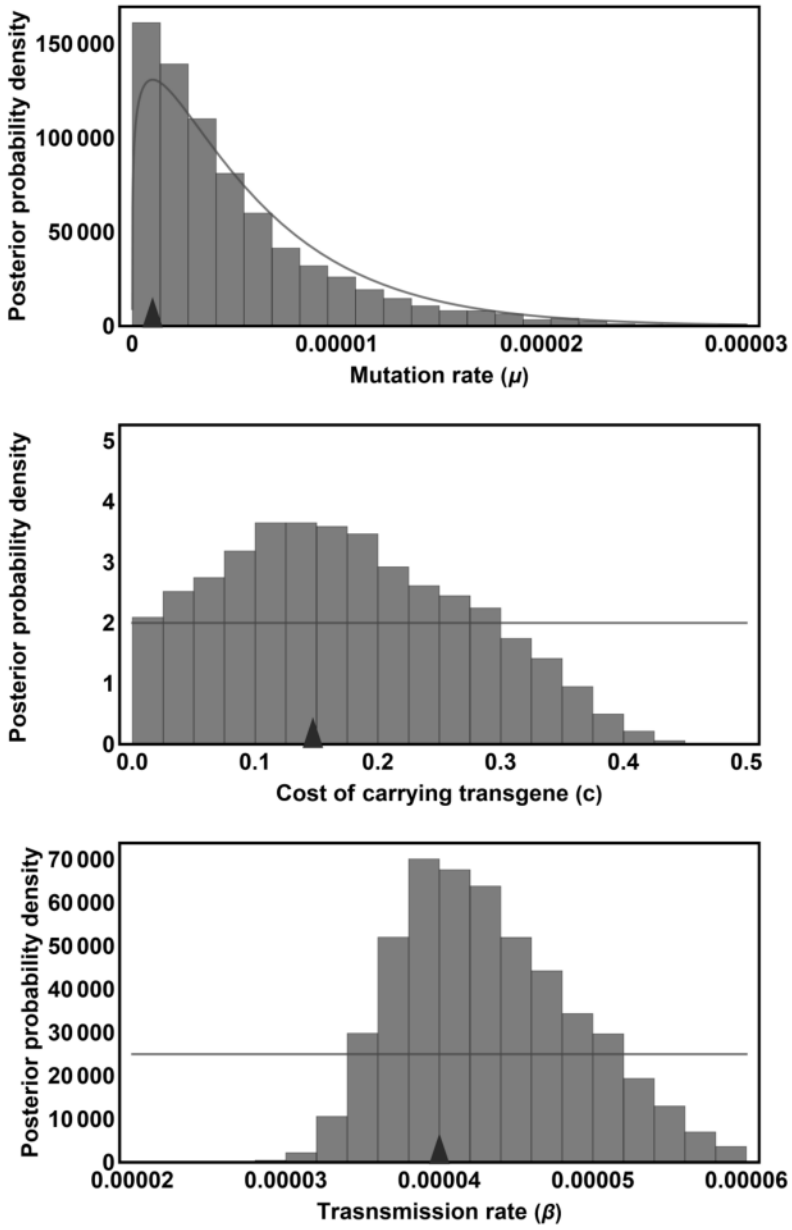

Figure 5: Univariate posterior distributions for mutation rate (μ), selective cost of transgene carriage (c), and rate of viral transmission between cells (β) constructed by applying our ABC approach to simulated data. Simulated data were generated using model (1-2) and the experimental design and sampling protocol shown in Figure 2. The true value of each parameter is indicated by the red triangle and the red line shows the prior distribution. We use an informative prior for the mutation rate because reliable estimates will be available from our *in vitro* studies. Our ABC procedure used summary statistics describing viral shedding in saliva, the proportion of virus currently latent, and the magnitude of the CD8+ T cell response to MCMV and to the antigenic insert; each can be calculated from the data we propose to collect. Posterior distributions for other key model parameters are similarly encouraging but not shown due to space limitations.

Goal 3a. Quantify vaccine dynamics in immune depleted mice in vivo

Experiments conducted as part of this aim will repeat the experimental inoculations with pure vaccine described in the previous goal, but using CD8+ T cell depleted mice. Depletion will be accomplished by intraperitoneal injection of 100μg of mouse adapted anti-CD8 (clone YTS169.4) at -3, -1 and 0 days post infection. Depletion will be maintained by intraperitoneal injections of anti-CD8 every 5th day and confirmed by flow cytometry. CD8+ T cell depleted and control immunocompetent mice will be inoculated by the intranasal route with the vaccine prototype expressing dual antigens and tracked for the same timepoints outlined in Goal 2b. Virus in the lungs and salivary glands will be assayed by plaque assay and by RT-PCR to quantify the proportion of vaccine and mutant strains. CD8+ T cell responses will be measured by ELISpot, although we expect CD8+ T cell responses to be evident only in the immunocompetent control mice.

Goal 3b. Validate the within-host model in vivo

Immune depleted mice offer a unique opportunity to validate our model and probe its ability to accurately quantify the importance of the CD8+ T cell response for the epidemiological and evolutionary dynamics of the vaccine within the host. Model validation will proceed by repeatedly simulating data from the posterior distribution to construct a 95% prediction interval as described in the previous aim. The key difference here is that these simulations

will be conducted with the CD8+ T cell response zeroed out (by setting parameters κ_W and κ_V to zero) to mimic the biology of the immune-depleted mice. If our model has accurately captured the role the CD8+ T cell response plays in driving the epidemiology and evolution of the prototype vaccines, 95% of the data from immune depleted mice should fall within the 95% prediction interval constructed from the simulations.

Challenges and planned resolution

One challenge we may encounter is the development of resistance to immune depletion in the mice over time. In this case, we will truncate the experiment at the timepoint where CD8+ T cells first rebound. This will be assessed by flow cytometry. Because our studies will employ a mouse-adapted clone of anti-CD8 (available from Absolute Antibody) that minimizes resistance to treatment, we are confident we can accrue sufficient data for model validation through the acute and early chronic stage.

An additional challenge we could encounter is a mismatch between model predictions and experimental data produced by the validation procedure. Specifically, it is possible that eliminating the CD8+ T cell response from the models will not yield predictions that match those in the CD8+ T cell depleted mice. The most likely reason for such a mismatch to arise is the presence of an additional form of adaptive immunity that modulates the dynamics of our prototype vaccines. For example, the creation of a novel CD4 antigen from the C-terminal extension of M78 by the CD8+ T cell antigens. Although this would be a significant obstacle to overcome, it would also be highly informative from the perspective of understanding the within-host dynamics of transmissible vaccines. If this occurs, we would repeat the entire model-fitting and validation procedure using models that integrate these alternative immune responses. Although time-consuming, we are well-prepared to modify and re-fit the models in this way if the need arises.

Closing summary

Spillover of zoonotic pathogens has proven to be an intractable problem with broad repercussions for human health. The proposed work will establish a theoretical framework for optimizing the development of betaherpesvirus-vectored transmissible vaccines. This framework will enable statistical methods for screening vaccine candidates and numerical methods that guide changes to these vaccine candidates to optimize their performance. Collectively, the proposed work paves the way for development of betaherpesviruses as a broadly applicable platform for development of transmissible vaccines for wild and domestic animal populations.

Project timeline

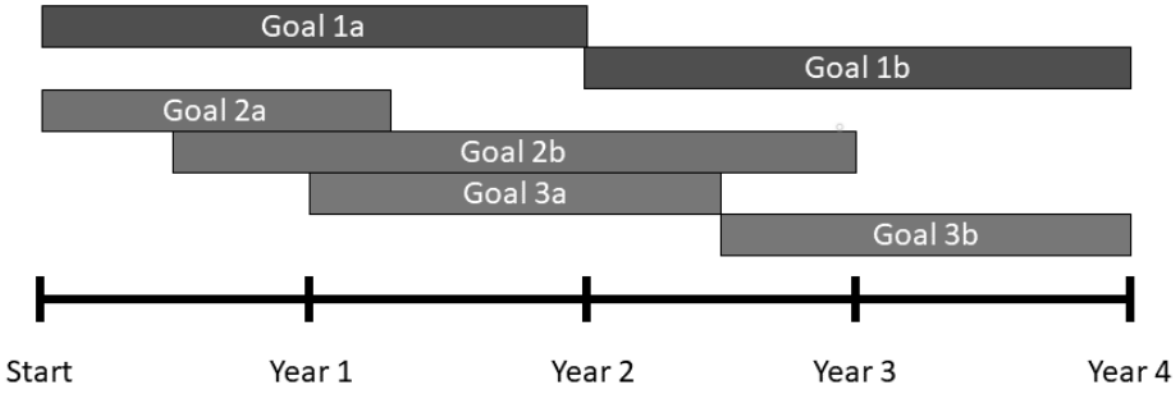

Figure 6: Project Timeline

Progress Report Publication List

1. Varrelman, T.J., C.H. Remien, A.J. Basinski, S. Gorman, A.J. Redwood, S.L. Nuismer. 2022. Quantifying the effectiveness of betaherpesvirus-vectored transmissible vaccines. PNAS 119 (4) e2108610119. PMCID8794881

2. Nuismer, S.L., N.C. Layman, A.J. Redwood, B. Chan, J.J. Bull. 2022. Methods for measuring the evolutionary stability of engineered genomes to improve their longevity. Synthetic Biology 6 (1), ysab018 PMCID8546616

3. Layman, N.C., B.M. Tuschhoff, and S.L. Nuismer. 2021. Designing transmissible viral vaccines for evolutionary robustness and maximum efficiency. *Virus Evolution*. 7 (1), veab002. PMCID33680502

4. Basinski, A.J., E. Fichet-Calvet, A.R. Sjodin, T.J. Varrelman, C.H. Remien, N.C. Layman, B.H. Bird, D.J. Wolking, C. Monagin, B.M. Ghersi, P.A. Barry, M.A. Jarvis, P.E. Gessler, and S.L. Nuismer. 2021. Bridging the gap: Using reservoir ecology and human serosurveys to estimate Lassa virus spillover in West Africa. *PLoS Computational Biology*. 17:3 e1008811. PMCID33657095

5. Layman, N.C., B.M. Tuschhoff, A.J. Basinski, C.H. Remien, J.J. Bull, S.L. Nuismer 2021. Suppressing evolution in genetically engineered systems through repeated supplementation. *Evolutionary Applications*. 14 (2), 348-359. PMCID33664781

6. Gomulkiewicz, R., M.L. Thies, J.J. Bull. 2021. Evading evolution of resistance to gene drives. *Genetics* 217(2):iyaa040 PMCID8045728

7. Antia, R., H Ahmed, J.J. Bull. 2021. Directed attenuation to enhance vaccine immunity. *PLoS Computational Biology* 17(2):e1008602. PMCID7877766

8. Nuismer S.L., C.H. Remien, A.J. Basinski, T. Varrelman, N. Layman, K. Rosenke, B. Bird, M. Jarvis, P. Barry, P.W. Hanley, and E. Fichet-Calvet. 2020. Bayesian estimation of Lassa virus epidemiological parameters: Implications for spillover prevention using wildlife vaccination. *PLoS Neglected Tropical Diseases*. 14: e0007920. PMCID32956349

9. Nuismer S.L., J.J. Bull. 2020. Self-disseminating vaccines to suppress zoonoses. *Nature Ecology and Evolution*. 4 (9), 1168-1173. PMCID32719452

10. Schreiner, C., S.L. Nuismer, A.J. Basinski. 2020. When to vaccinate a fluctuating wildlife population: is timing everything? *Journal of Applied Ecology*. 57 (2), 307-319. PMCID32139945

11. Yuksel, M.K., C.H. Remien, B. Karki, J.J. Bull, S.M. Krone. 2020. Vector dynamics influence spatially imperfect genetic interventions against disease. *Evolution, Medicine, and Public Health* 9(1):1-10. PMCID7910803

12. Nuismer, S.L., A.J. Basinski, J.J. Bull. 2019. Evolution and containment of transmissible recombinant vector vaccines. *Evolutionary Applications* 12 (8), 1595-1609. PMCID31462917

13. Bull, J.J., S.L. Nuismer, R. Antia. 2019. Recombinant vector vaccine evolution. *PLoS Computational Biology* 15 (7), e1006857. PMCID 31323032

14. Varrelman, T.J., A.J. Basinski, C.H. Remien, S.L. Nuismer. 2019. Transmissible vaccines in heterogeneous populations: Implications for vaccine design. *One Health* 7, 100084. PMCID30859117

15. Basinski, A.J., SL Nuismer, CH Remien. 2019. A little goes a long way: Weak vaccine transmission facilitates oral vaccination campaigns against zoonotic pathogens. *PLoS Neglected Tropical Diseases* 13 (3), e0007251. PMCID30849126

16. Smithson, M.W., A.J. Basinski, S.L. Nuismer and J.J. Bull. 2019. Transmissible vaccines whose dissemination rates vary through time, with applications to wildlife. *Vaccine* 37 (9), 1153-1159. PMCID30686635

17. Bull, J.J., C.H. Remien, S.M. Krone. 2019. Gene-drive-mediated extinction is thwarted by population structure and evolution of sib mating. *Evolution, Medicine, and Public Health* 2019 (1), 66-81. PMCID6556056

18. Bull, J.J., B.R. Levin, I.J. Molineux. 2019. Promises and pitfalls of in vivo evolution to improve phage therapy. *Viruses* 11 (12), 1083. PMCID6950294

19. Bull, J.J., C.H. Remien, R. Gomulkiewicz, S.M. Krone. 2019. Spatial structure undermines parasite suppression by gene drive cargo. *PeerJ* 7, e7921. PMCID6824332

20. Nuismer, S.L., May R, Basinski A, Remien C.H. 2018. Controlling epidemics with transmissible vaccines. *PLoS ONE* 13(5): e0196978. PMCID29746504

21. Tom E.F., I.J. Molineux, M.L. Paff, J.J. Bull. 2018. Experimental evolution of UV resistance in a phage. *PeerJ*. 6:e5190. PMCID6042481

22. Basinski, A.J. T.J. Varrelman, M.W. Smithson, R.H. May, C.H. Remien, and S.L. Nuismer. 2017. Evaluating the promise of recombinant transmissible vaccines. *Vaccine*. 36:675-682. PMCID29279283

23. Bull, J.J., M.W. Smithson, and S.L. Nuismer. 2017. Transmissible viral vaccines. *Trends in Microbiology*. 26:6-15. PMCID29033339

24. Nuismer S.L. 2016. Eradicating infectious disease using weakly transmissible vaccines. *Proceedings of the Royal Society of London Series B-Biological Sciences.* 283:20161903. PMCID27798311

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 09/30/2024

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *	❍ Yes ● No
Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.	
Are Human Subjects Involved	❍ Yes ● No
Is the Project Exempt from Federal regulations?	❍ Yes ❍ No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

These studies will be performed at the Harry Perkins Institute of Medical Research under the review of the Animal Ethics Committee. The Animal Ethics Committee and researchers are governed by the Australian Code for the Care and use of Animals for Scientific Purposes ("the Code"), 8th edition 2013, which is regulated via The Animal Welfare Act 2002 (especially sections 6, 49 & 50).

1. Description of Procedures (Vertebrate Animals Section)

A total of 936, 6-8 week old female Mus musculus (BALB/c strain) will be used in this project. All mice will be infected with murine cytomegalovirus (MCMV) by the intranasal route of inoculation (1×10^5 PFU in 4 µl). 468 mice will also receive either anti-CD8 depletion antibodies or PBS control by the intraperitoneal route on days -3, -1, 0 and every 5^{th} day thereafter post MCMV infection. All mice will be routinely (every 2 days for 3 weeks and weekly thereafter for up to 20 weeks) swabbed with thin strips of filter paper by the oral route to collect saliva. At the termination of the experimental period mice will be euthanised and lungs, spleen and salivary glands collected for virological and molecular analysis.

2. Justifications (Vertebrate Animals Section)

This project seeks to develop models of transmissible vaccines for the control of zoonotic pathogens in reservoir species. The goal being to prevent disease spill-over and break the infectious cycle before widespread human-to-human transmission. Mathematical modelling of disseminating vaccines have been developed, however these typically treat *in vivo* replication in the target animal as a "black box".

Here, for the first time we will include the complicated dynamics of *in vivo* replication, including viral dissemination, latency and host immunity, into our models of vaccine transmission. *In vivo* studies are absolutely required to parameterise these models because it remains impossible to re-capitulate the complexity of these interactions in tissue culture. For instance, the immune system responds to both antigenic stimulation as well as a series of additional signals that are context dependent and must occur in the setting of normal tissue architecture in organs such as the spleen and lymph nodes. Likewise *in vivo* viral replication and dissemination to the salivary glands for transmission cannot be modelled *in vitro*. However, it is worth noting that the development of our models, using real-world *in vivo* data, will reduce the reliance on animal studies in the future.

We have chosen mice and MCMV as our model systems because many of the key target species that harbour zoonotic infections are rodents. MCMV is a species-specific virus that only infects mice. We have specifically chosen BALB/c mice as these mice are known to make T cell responses to the target antigens included in this study. Female mice are more tractable than male mice, sex will play no role in the scientific questions being addressed in this study.

Therefore, the use of *in vivo* experiments is scientifically and ethically appropriate. Control of zoonotic infection benefits both humans and wildlife reservoir species.

3. Minimization of Pain and Distress (Vertebrate Animals Section)

This study falls under the procedural code #5 (Minor infection) – the Descriptor for this code is, "Minor Physiological Challenge - Animal remains conscious all of the procedure. There is interference with the animal's physiological or psychological processes. The challenge may

cause only a small degree of pain/distress or any pain/distress is quickly and effectively alleviated."

Mice will receive an intranasal inoculation of MCMV. MCMV infection is self-limiting and asymptomatic in this model. Mice are housed in the Tecniplast IVC system and cages are changed every 1 to 2 weeks depending on housing density. Feed and water is replenished if required at health checks. Animals will be provided with appropriate environmental enrichment. Mice are monitored for signs of distress, including weight loss, coat condition, body condition, body posture, movement, grimace scale and activity (proximity to others). An intervention score is provided for each mouse at the time of inspection and if appropriate mice are subjected to euthanasia.

At experimental endpoints mice will be euthanized using cervical dislocation (standard operating procedure (SOP) #1.08.01) under methoxyflurane inhalation anaesthetic (SOP #1.03.01). Death is confirmed by; i) physical separation of cervical vertebra (between thumb and forefinger), (ii) lack of response to light pressure stimuli and (iii) lack of heartbeat and urine release. All applications and SOPs are approved by the Animal Ethics Committee at the Perkins Institute of Medical Research.

4. Method of Euthanasia (Cover Page Supplement / PHS Fellowship Supplemental Form)

The method of euthanasia is consistent with AVMA guidelines.

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CONSORTIUM/CONTRACTUAL ARRANGEMENTS

The awardee organization (Regents of the University of Idaho) and the subaward organization (The University of Western Australia) will enter into a contractual agreement to carry out the tasks related to the proposed research.

Personnel from both entities will perform a substantive role in the conduct of the planned research. A formalized agreement whereby the specific level of effort from both consortium organizations and a categorical breakdown of costs such as personnel, supplies, and other allowable expenses including F&A will be executed. Both organizations have experience in the coordination of multiple collaborators.

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the NIH consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy. The Notice of Grant Award will further outline the consortium lead investigator responsible for ensuring proper conduct of the project or program at the consortium site. Further, we understand and acknowledge that NIH may request additional information before the award and may place a special condition(s) on the award.

Dr. Scott Nuismer, is the consortium Principal Investigator responsible for ensuring proper conduct of the project at the research site of the University of Idaho. Dr. Alec Redwood is the consortium site PI responsible for ensuring proper conduct of the project at the consortium site of the University of Western Australia.

The terms and conditions of the agreement will stipulate ownership of all data, reports, materials, inventions and if applicable, future use, developed under the subcontract agreement in accordance with *NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (15 Consortium Agreements).*

February 26, 2022

Deborah Shaver,

Director Office of Sponsored Programs

University of Idaho

Dear Ms. Shaver,

This letter confirms my enthusiastic support and assistance for the project entitled "A mathematical theory of transmissible vaccines" This proposal will be submitted to the National Institutes of Health. The appropriate University of Western Australia program and administrative personnel have reviewed and approved this proposal and budget.

This project is very well aligned with my expertise and interest in viral vectored vaccines. I was heavily involved in the first use of the virus, murine cytomegalovirus, as a disseminating immunocontraceptive vaccine. Currently, I am a co-principal investigator on the UC Davis-led PREEMPT project. The PREEMPT project seeks to use cytomegalovirus as disseminating vaccine vectors for the prevention of zoonotic spillover into the human population. This project led to the development of a productive collaboration with Professor Nuismer. I will engage with the University of Idaho team via teleconferences and data sharing to provide intellectual input and expertise central to the development of the program as proposed.

In conclusion, I look forward to continuing my collaborating with Professor Scott Nuismer and the team at the University of Idaho on this project, the results of which should provide important insight into the use of disseminating vaccines with specific reference to the stability of antigens within vaccine vectors.

Sincerely,

(b)(6)

Associate Professor Alec Redwood

Level 2/6 Verdun Street, Nedlands WA 6009
t. +61 8 6151 0877• e. admin@resphealth.uwa.edu.au
resphealth.org.au
ABN 78 098 197 636

institute for
RESPIRATORY HEALTH

Saturday, February 26, 2022

Deborah Shaver, Director
Office of Sponsored Programs
University of Idaho

Ms. Shaver,

This letter is an endorsement of my unreserved support and participation in the project entitled "A mathematical theory of transmissible vaccines". This proposal will be submitted to the National Institutes of Health. I am committed to serving as a subcontractor to the University of Idaho on this project.

This project is well aligned to my expertise and interest in harnessing the vaccine potential of viruses. I have 10+ years of experience in bioengineering cytomegalovirus genomes. I have been involved in the discovery of herpesviral genes involved in modulating host immune responses. Currently, I am overseeing the vaccine development in the UC Davis-led PREEMPT project. The PREEMPT project seeks to use cytomegalovirus as disseminating vaccine vectors for the prevention of zoonotic spillover into the human population. This project led to the development of a productive collaboration with Professor Nuismer. I will engage with the University of Idaho team via teleconferences and data sharing to provide intellectual input and expertise central to the development of the program as proposed.

I look forward to continuing my collaborating with Professor Scott Nuismer and the team at the University of Idaho on this project, the results of which should provide important insight into the use of disseminating vaccines with specific reference to the stability of antigens within vaccine vectors.

Sincerely,

(b)(6)

Dr Baca Chan

Level 2/6 Verdun Street, Nedlands WA 6009
t. +61 8 6151 0877• e. admin@resphealth.uwa.edu.au
resphealth.org.au
ABN 78 098 197 636

THE UNIVERSITY OF WESTERN AUSTRALIA

Office of Research

Our ref: 2022/GR000102

8 February 2022

Deborah Shaver
Director
Office of Sponsored Programs
University of Idaho
875 Perimeter Dr
Moscow, ID 83844
USA

Dear Ms Shaver

Collaborative Research: A mathematical theory of transmissible vaccines

The University of Western Australia (UWA) is pleased to be participating in this National Institutes of Health proposal. The UWA PI is Dr Alec Redwood. The appropriate UWA program and administrative personnel have reviewed and approved Dr Redwood's participation, along with the statement of work and the budget and budget justification. UWA is prepared to enter into a subaward with the University of Idaho should the grant be awarded. The budget requests $US591,609.73 ($547,786.85 Direct Costs & $43,822.88 Indirect Costs). The project period is October 1, 2022 to September 30, 2025.

Please contact me if any additional information or clarification is required.

Yours sincerely

(b)(6)

Caroline Chapman (Dr)
Manager, Research Grants

The University of Western Australia
M459, Perth WA 6009 Australia

T +61 8 6488 3027

E caroline.chapman@uwa.edu.au
CRICOS Provider Code 00126G

Resource Sharing Plan

This research will generate multiple products including source code, infection and immune data, simulation data, mathematical analyses, and publications. We will ensure that these products are: (i) secure and protected from loss; and, (ii) available to fellow researchers and the interested public in both the immediate and distant future. We will achieve these goals in the following ways.

Data Sharing Plan:

All data will be saved both on local researcher computers to secure storage provided by the IIDS-RCDS computational core. Mathematical modeling will be done in *Mathematica*, and all notebooks will be shared on the investigator's website. Bayesian computational approaches and simulation models will be written in C++ and shared through the investigator's website and GitHub. Each research paper we publish supported by this grant will include, as supplemental files, any Mathematica notebooks or C++ source code that feed into it. The investigators will disseminate the results widely through presentations at meetings and invited seminars. Viral infection and immune data will be stored as MS Excel files and as standard .csv files. In addition to publications and scientific presentations, key findings, mathematical and computational resources, and viral infection and immune data will be made available to the public through the investigator's website and on GitHub within one year of project completion.

Computer code:

All source code will be shared on the investigator's website and deposited in GitHub.

MCMV bacterial artificial chromosome (BAC)

The ARK25 BAC was created in Dr. Redwood's laboratory (PMID: 15709020). The BAC is retained as a glycerol stock. Virus rescued from ARK25 is routinely sequenced to ensure integrity. All mutant virus derived from ARK25 will also be fully sequenced.

Cell lines

The immortal murine bone marrow-derived stromal cell line M210B4 was obtained from the American Type Culture Collection (CRL-1972). Low passage stocks of these cells were frozen in liquid nitrogen. A new vial of cells is resuscitated every 3 months and therefore we are routinely reverting back to the low passage stocks.

BALB/c mice

Mice are obtained from the Animal Resource Centre (ARC), Murdoch University. The ARC is International Organization for Standardization (ISO) 9001 accredited; all Standard Operating Procedures and Work Instructions are audited annually. The ARC is an authorized breeder of select, pedigreed mouse strains from The Jackson Laboratory. All mice will be 6-8 week old female mice.

Anti-CD8+ T cell antibody

Anti-CD8+ T cell antibody (clone YTS169.4) for in vivo depletion studies is obtained from Absolute Antibody (Redcar, UK). The antibody manufacturing facility is certified under International Organization for Standardization (ISO) 9001:2015.

From:	OLAW Restricted Awards (NIH/OD)
To:	Panakal, Parvathy (NIH/NIGMS) [E]; OLAW Restricted Awards (NIH/OD)
Cc:	Carrasco, T. Maritza (NIH/OD) [E]
Subject:	Approved-#227-RA-No AWA-2R01GM122079-05A1-#1-NIGMS (Prime Institution University of Idaho - Restriction term Provided for University of Western Australia) Need Foreign Assurance
Date:	Thursday, August 24, 2023 8:19:12 PM
Attachments:	image001.png image002.png

Dear Parvathy,

You may issue a restricted award for the above-mentioned grant using circumstance #1 from the May 31, 2023 EOY memo.

1. Institutions lacking an Animal Welfare Assurance

In such cases, IC grants staff are responsible for monitoring awards to ensure that the prime recipient and all performance sites meet Assurance requirements prior to removal of the restriction.

The following restriction is required on the Notice of Award when the recipient organization or performance site(s) lacks an applicable Assurance:

Restriction: Funds included in this award for research involving live vertebrate animals are restricted and may not be used for any other purpose without [Insert IC abbreviation, e.g., NIAID] approval. Under governing PHS Policy no funds may be drawn down from the payment system and no obligations may be made against federal funds for research involving live vertebrate animals prior to OLAW approval of an Animal Welfare Assurance (Assurance) in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals. This restriction applies to the recipient organization and all performance sites (e.g., collaborating institutions, subawardees) lacking OLAW-approved Assurances, whether domestic, foreign, or interinstitutional. If the recipient organization does not have an Assurance and the animal research will be conducted at an institution with an Assurance, the recipient must obtain an Interinstitutional Assurance from OLAW. Only activities that do not involve live vertebrate animals may be conducted at any performance site until OLAW has approved an Assurance for that site. The Assurance documents must be submitted to OLAW no later than **90 days** prior to the involvement of animals, and the Assurance must be approved by OLAW before conducting the animal activity. Failure to submit the Assurance to OLAW within the required timeframe or to otherwise comply with the above requirements can result in suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action.

When the appropriate Assurance(s) has been received and approved, OLAW will change the code to 30, enter "R" (Resolved) in IMPAC II and notify the IC through e-mail that the restriction may be lifted.

Term to be used when removing a restriction applicable to pending Assurances:
This revised award reflects the Office of Laboratory Animal Welfare (OLAW) approval of an Animal Welfare Assurance for the recipient and/or all performance sites and removes the restrictive term

on the Notice of Award issued on (date).

Warmest Regards,

T. Maritza Carrasco
Lead Program Analyst, Division of Assurances
Office of Laboratory Animal Welfare, NIH
6700B Rockledge Drive, Suite 2500 - MSC 6910
Bethesda, Maryland 20892
Phone: (301) 402-5913
Email: carrascot@mail.nih.gov
Division of Assurances
E-Fax: (301) 451-5672
Email: olawdoa@mail.nih.gov

From: Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>
Sent: Thursday, August 24, 2023 4:40 PM
To: Carrasco, T. Maritza (NIH/OD) [E] <carrascot@od.nih.gov>; OLAW Restricted Awards (NIH/OD) <olawra@od.nih.gov>
Subject: RE: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Good Afternoon,

I believe we will need to place a restriction on the whole grant since the animal work is only being done by the foreign collaborator. UWA is currently in the process of getting the IACUC approval based on their recent correspondence.

Thank you,
Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

From: Carrasco, T. Maritza (NIH/OD) [E] <carrascot@od.nih.gov>
Sent: Thursday, August 24, 2023 3:02 PM
To: Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>; OLAW Restricted Awards (NIH/OD) <olawra@od.nih.gov>
Cc: Carrasco, T. Maritza (NIH/OD) [E] <carrascot@od.nih.gov>
Subject: RE: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Dear Parvathy.

The awardee institution is a Domestic they have an assurance. Are you asking to restrict the whole grant or just for this specific site University of Western Australia (no assurance) ? I can restrict the grant, once I put the code 48 in the IMPAC system the restriction will be applied to the whole grant. Please let me know if you would like me to move forward. University of Western Australia don't have an assurance with OLAW.

University of Idaho don't have the IACUC approval - We can restrict the grant due to the IACUC approval
Since University of Western Australia don't have an assurance with OLAW, I can send you the language only.

Warmest Regards,

T. Maritza Carrasco
Lead Program Analyst, Division of Assurances
Office of Laboratory Animal Welfare, NIH
6700B Rockledge Drive, Suite 2500 - MSC 6910
Bethesda, Maryland 20892
Phone: (301) 402-5913
Email: carrascot@mail.nih.gov
Division of Assurances
E-Fax: (301) 451-5672
Email: olawdoa@mail.nih.gov

From: Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>
Sent: Thursday, August 17, 2023 8:31 AM
To: OLAW Restricted Awards (NIH/OD) <olawra@od.nih.gov>
Subject: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Good Morning,

The referenced award will need to be awarded with a restriction on Animal Subjects. The grantee organization will have a meeting next month and will provide an update on the foreign Assurance number.

Reason for restriction: IACUC Approval verification is needed and Animal Welfare Assurance is needed from the foreign site (Australia).
Award Number: 2R01GM122079-05A1
Project Title: A Mathematical Theory of Transmissible Vaccines
Principle Investigator: Dr. Scott Nuismer
Awardee Institution: University of Idaho
Performance sites: University of Idaho, University of Western Australia

Please let me know if you require any additional information.

Thank you,
Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

From:	Carrasco, T. Maritza (NIH/OD) [E]
To:	Panakal, Parvathy (NIH/NIGMS) [E]; OLAW Restricted Awards (NIH/OD)
Cc:	Carrasco, T. Maritza (NIH/OD) [E]
Subject:	Approved-#226-RA-No IACUC-2R01GM122079-05A1-#2-NIGMS
Date:	Thursday, August 24, 2023 8:13:34 PM
Attachments:	image001.png image002.png

Dear Parvathy.

You may issue a restricted award for the above-mentioned grant using circumstance #2 from the May 31, 2023 EOY memo. University Of Idaho

2. Assured Institutions lacking verification of IACUC approval

The following restriction is required on the Notice of Award when verification of IACUC approval is lacking:

Restriction: Funds included in this award for research involving live vertebrate animals are restricted and may not be used for any other purpose without [Insert IC abbreviation, e.g. NIAID] approval. Under governing PHS Policy no funds may be drawn down from the payment system and no obligations may be made against federal funds for research involving live vertebrate animals prior to submission of valid Institutional Animal Care and Use Committee (IACUC) approval in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals. The present award is made without currently valid verification of IACUC approval for this project. Only activities that do not involve live vertebrate animals may be conducted pending [Insert IC abbreviation, e.g., NIAID]'s acceptance of verification of IACUC approval. The verification of IACUC approval must be submitted to the Grants Management contact identified on the Notice of Award. Failure to submit the verification of IACUC approval or to otherwise comply with the above requirements can result in suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action.

ICs are responsible for ensuring that verification of IACUC approval is received and entered into IMPAC II. Upon notification by the IC, OLAW will change the code to 30, enter "R" (Resolved) in IMPAC II and notify the IC through e-mail that the restriction may be lifted.

Term to be used when removing a restriction applicable to a pending IACUC approval date:
This revised award reflects [IC abbreviation, e.g., NIAID]'s acceptance of the certification of Institutional Animal Care and Use Committee approval and removes the restrictive term on the Notice of Award issued on (date).

Warmest Regards,

T. Maritza Carrasco
Lead Program Analyst, Division of Assurances
Office of Laboratory Animal Welfare, NIH

6700B Rockledge Drive, Suite 2500 - MSC 6910
Bethesda, Maryland 20892
Phone: (301) 402-5913
Email: carrascot@mail.nih.gov
Division of Assurances
E-Fax: (301) 451-5672
Email: olawdoa@mail.nih.gov

From: Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>
Sent: Thursday, August 24, 2023 4:40 PM
To: Carrasco, T. Maritza (NIH/OD) [E] <carrascot@od.nih.gov>; OLAW Restricted Awards (NIH/OD) <olawra@od.nih.gov>
Subject: RE: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Good Afternoon,

I believe we will need to place a restriction on the whole grant since the animal work is only being done by the foreign collaborator. UWA is currently in the process of getting the IACUC approval based on their recent correspondence.

Thank you,
Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

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Sent: Thursday, August 24, 2023 3:02 PM
To: Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>; OLAW Restricted Awards (NIH/OD) <olawra@od.nih.gov>
Cc: Carrasco, T. Maritza (NIH/OD) [E] <carrascot@od.nih.gov>
Subject: RE: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Dear Parvathy.

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University of Idaho don't have the IACUC approval - We can restrict the grant due to the IACUC approval
Since University of Western Australia don't have an assurance with OLAW, I can send you the language only.

Warmest Regards,

T. Maritza Carrasco
Lead Program Analyst, Division of Assurances
Office of Laboratory Animal Welfare, NIH
6700B Rockledge Drive, Suite 2500 - MSC 6910
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Phone: (301) 402-5913
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To: OLAW Restricted Awards (NIH/OD) <olawra@od.nih.gov>
Subject: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Good Morning,

The referenced award will need to be awarded with a restriction on Animal Subjects. The grantee organization will have a meeting next month and will provide an update on the foreign Assurance number.

Reason for restriction: IACUC Approval verification is needed and Animal Welfare Assurance is needed from the foreign site (Australia).

Award Number: 2R01GM122079-05A1
Project Title: A Mathematical Theory of Transmissible Vaccines
Principle Investigator: Dr. Scott Nuismer
Awardee Institution: University of Idaho
Performance sites: University of Idaho, University of Western Australia

Please let me know if you require any additional information.

Thank you,
Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

From: OLAW Restricted Awards (NIH/OD)
To: Panakal, Parvathy (NIH/NIGMS) [E]
Cc: Carrasco, T. Maritza (NIH/OD) [E]
Subject: RE: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L
Date: Thursday, August 24, 2023 8:05:05 PM
Attachments: image001.png
image002.png
pol_eoy23_animal_grants.pdf

Dear Parvathy,

I will send you two different emails – 1 for UWA Assured Institutions lacking verification of IACUC approval and the other one for the foreign collaborator, Institutions lacking an Animal Welfare Assurance (they don't have an assurance, you will need to send a request to process the Foreign Assurance.)

Warmest Regards,

T. Maritza Carrasco
Lead Program Analyst, Division of Assurances
Office of Laboratory Animal Welfare, NIH
6700B Rockledge Drive, Suite 2500 - MSC 6910
Bethesda, Maryland 20892
Phone: (301) 402-5913
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Subject: RE: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Good Afternoon,

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Thank you,
Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

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Cc: Carrasco, T. Maritza (NIH/OD) [E] <carrascot@od.nih.gov>
Subject: RE: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

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University of Idaho don't have the IACUC approval - We can restrict the grant due to the IACUC approval
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Warmest Regards,

T. Maritza Carrasco
Lead Program Analyst, Division of Assurances
Office of Laboratory Animal Welfare, NIH
6700B Rockledge Drive, Suite 2500 - MSC 6910
Bethesda, Maryland 20892
Phone: (301) 402-5913
Email: carrascot@mail.nih.gov
Division of Assurances
E-Fax: (301) 451-5672
Email: olawdoa@mail.nih.gov

From: Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>
Sent: Thursday, August 17, 2023 8:31 AM
To: OLAW Restricted Awards (NIH/OD) <olawra@od.nih.gov>
Subject: Restricted Award: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Good Morning,

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Reason for restriction: IACUC Approval verification is needed and Animal Welfare Assurance is needed from the foreign site (Australia).
Award Number: 2R01GM122079-05A1
Project Title: A Mathematical Theory of Transmissible Vaccines
Principle Investigator: Dr. Scott Nuismer
Awardee Institution: University of Idaho
Performance sites: University of Idaho, University of Western Australia

Please let me know if you require any additional information.

Thank you,
Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

From: Everett, Eric (ericeverett@uidaho.edu)
To: Alec Redwood; Nuismer, Scott (snuismer@uidaho.edu); Panakal, Parvathy (NIH/NIGMS) [E]; Institutional Animal Care and Use Committee (iacuc@uidaho.edu); Remien, Christopher (cremien@uidaho.edu); Bull, James (jbull@uidaho.edu)
Cc: Baca Chan; AEC - PERKINS
Subject: [EXTERNAL] Re: Grant Number: 2R01GM122079 -05A1 PI Name: NUISMER, SCOTT L
Date: Wednesday, August 2, 2023 12:19:20 PM

Hello Parvathy,

I just wanted to update you that the University of Western Australia has set the date of review for their IACUC to be August 14. We will update you when they have approved and then when UI has approved as well.

Please let me know if you have any questions. Thank you.

ERIC EVERETT, '07
He/Him
PreAward Unit Lead
Sponsored Programs Administrator
Office of Sponsored Programs
ericeverett@uidaho.edu
1-208-885-2098 (please note this is a Microsoft Teams number and you must dial the country and area codes)
875 Perimeter Dr. MS 3020 | Moscow ID 83844-3020 | United States

Please note I am working remotely. You can reach me via email and phone from 8:30am to 5:00pm, Monday through Friday. Thank you for your patience.

From: Alec Redwood <alec.redwood@uwa.edu.au>
Sent: Tuesday, July 11, 2023 11:32 PM
To: Everett, Eric (ericeverett@uidaho.edu) <ericeverett@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>; Institutional Animal Care and Use Committee (iacuc@uidaho.edu) <iacuc@uidaho.edu>; Remien, Christopher (cremien@uidaho.edu) <cremien@uidaho.edu>
Cc: Baca Chan <baca.chan@uwa.edu.au>; AEC - PERKINS <aec@perkins.org.au>
Subject: Re: Grant Number: 2R01GM122079 -05A1 PI Name: NUISMER, SCOTT L

Thanks Everett, we will start the Ethics application process ASAP. As for OLAW it is our understanding that we cannot submit a request and that this is something that should be requested of us, and that this will not occur until the grant has been officially awarded.

" Institutions should not submit an Assurance unless requested to do so by OLAW. OLAW will not process unsolicited applications"

Regards Alec

From: Everett, Eric (ericeverett@uidaho.edu) <ericeverett@uidaho.edu>
Date: Wednesday, 12 July 2023 at 4:00 am

To: Alec Redwood <alec.redwood@uwa.edu.au>, Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>, Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>, Institutional Animal Care and Use Committee (iacuc@uidaho.edu) <iacuc@uidaho.edu>, Remien, Christopher (cremien@uidaho.edu) <cremien@uidaho.edu>
Cc: Baca Chan <baca.chan@uwa.edu.au>, AEC - PERKINS <aec@perkins.org.au>
Subject: Re: Grant Number: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Alec, Baca, and Cathy,

As a follow up, if this is awarded, UWA will need to apply for an OLAW Assurance Number. That process is described here: https://olaw.nih.gov/resources/documents/foreign.htm

ERIC EVERETT, '07
He/Him
PreAward Unit Lead
Sponsored Programs Administrator
Office of Sponsored Programs
ericeverett@uidaho.edu
1-208-885-2098 (please note this is a Microsoft Teams number and you must dial the country and area codes)
875 Perimeter Dr, MS 3020 | Moscow ID 83844-3020 | United States

Please note I am working remotely. You can reach me via email and phone from 8:30am to 5:00pm, Monday through Friday. Thank you for your patience.

From: Everett, Eric (ericeverett@uidaho.edu) <ericeverett@uidaho.edu>
Sent: Tuesday, July 11, 2023 12:12 PM
To: Alec Redwood <alec.redwood@uwa.edu.au>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>; Institutional Animal Care and Use Committee (iacuc@uidaho.edu) <iacuc@uidaho.edu>; Remien, Christopher (cremien@uidaho.edu) <cremien@uidaho.edu>
Cc: Baca Chan <baca.chan@uwa.edu.au>; AEC - PERKINS <aec@perkins.org.au>
Subject: Re: Grant Number: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

Thank you, Alec. Can you please start that process now?

Parvathy, I have attached the updated Other Support Forms. Is there a deadline to provide the IACUC information?

Thank you.

ERIC EVERETT, '07
He/Him
PreAward Unit Lead
Sponsored Programs Administrator
Office of Sponsored Programs
ericeverett@uidaho.edu
1-208-885-2098 (please note this is a Microsoft Teams number and you must dial the country and area codes)
875 Perimeter Dr, MS 3020 | Moscow ID 83844-3020 | United States

Please note I am working remotely. You can reach me via email and phone from 8:30am to 5:00pm, Monday through Friday. Thank you for your patience.

From: Alec Redwood <alec.redwood@uwa.edu.au>
Sent: Monday, July 10, 2023 6:19 PM
To: Everett, Eric (ericeverett@uidaho.edu) <ericeverett@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Panakal, Parvathy (NIH/NIGMS) [E] <parvathy.panakal@nih.gov>; Institutional Animal Care and Use Committee (iacuc@uidaho.edu) <iacuc@uidaho.edu>; Remien, Christopher (cremien@uidaho.edu) <cremien@uidaho.edu>
Cc: Baca Chan <baca.chan@uwa.edu.au>; AEC - PERKINS <aec@perkins.org.au>.
Subject: Re: Grant Number: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L

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I have our animal ethics contact, Cathy Pope, here.

Regards Alec

Dr Alec Redwood
Principal Research Fellow
National Centre for Asbestos Related Diseases
University of Western Australia
5th Floor, QQ Block, QEII 6 Verdun St Nedlands
6151 0895

Head, Vaccines and Viral Immunity Research Group
Institute for Respiratory Health
University of Western Australia
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Adjunct Associate Professor, University of Western Australia.
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Hi Parvathy,

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Cheers,

Scott

****
Scott Nuismer
Professor
Department of Biological Sciences and Mathematics
Program in Bioinformatics and Computational Biology
University of Idaho
Moscow, ID 83844
https://www.leeef.org/

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- IACUC Approval date.

Thank you!
Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED
PHS 398 OTHER SUPPORT

Name of Individual: Scott L. Nuismer
Commons ID: (b)(6)

This grant: (b)(6)
Other support: (b)(6)
Total LOE: (b)(6)

Other Support – Project/Proposal

(b)(4); (b)(6)

(b)(4); (b)(6)

Name of Individual: Scott L. Nuismer
Commons ID: (b)(6)

(b)(4); (b)(6)

Title: Role of Camels in Transmission of Brucella spp and Middle East Respiratory Syndrome Coronavirus to Humans in Marsabit and Kajiado Counties, Kenya

Major Goals: To develop mathematical models and statistical methods that allow the source of brucellosis spillover to be pinpointed and disrupted.

Status of Support: Current

Project Number: HDTRA12110041

Name of PD/PI: Eric Osoro (Washington St. University)

Source of Support: Defense Threat Reduction Agency

Primary Place of Performance: University of Idaho

Project/Proposal Start and End Date: 9/24/2021-9/26/2024

Total Award Amount: $250,000 subcontract to the University of Idaho

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2021	(b)(6)
2. 2022	
3. 2023	
4. 2024	

Title: Prediction of Spillover Potential and Interventional En Masse Animal Vaccination to Prevent Emerging Pathogen Threats in Current and Future Zones of US Military Operation.

Major Goals: To develop new computational approaches that allow the risk of pathogen spillover and emergence to be predicted. To develop a transmissible vaccine for Lassa virus that can be used to immunize the rodent reservoir and thus reduce the risk of spillover into the human population.

Status of Support: Current

Project Number: D18AC00028

Name of PD/PI: Brian Bird (UC Davis)

Source of Support: Defense Advanced Projects Research Agency

Primary Place of Performance: University of Idaho

Project/Proposal Start and End Date: 10/1/2018-9/30/2022

Name of Individual: Scott L. Nuismer
Commons ID: (b)(6)

Total Award Amount: $1,707,812 subcontract to the University of Idaho

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2018	(b)(6)
2. 2019	
3. 2020	
4. 2021	
5. 2022	

Title: Conference: Coordinating the development of self-disseminating vaccines for spillover prevention

Major Goals: The goal of this project is to organize and support a workshop that brings together Virologists, Immunologists, Ecologists, Evolutionary Biologists, and Sociologists to guide the future development of safe, effective, and societally acceptable self-disseminating vaccines.

Status of Support: Current

Project Number: DEB2216790

Name of PD/PI: Scott L. Nuismer

Source of Support: National Science Foundation

Primary Place of Performance: University of Idaho

Project/Proposal Start and End Date: 6/1/2022-5/31/2023

Total Award Amount: $71,669

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2022	(b)(6)
2. 2023	

IN-KIND

Nothing to report

Overlap: Work on this project is thematically aligned with work on the DARPA project that ends 9/30/2022, the NSF project organizing a workshop guiding the future development of self-disseminating vaccines, and (b)(4); (b)(6)

(b)(4); (b)(6)

Name of Individual: Scott L. Nuismer
Commons ID: (b)(6)

(b)(4); (b)(6)

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature: (b)(6)

Date: 9/28/2022

For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED
PHS 398 OTHER SUPPORT

Name of Individual: James J Bull
Commons ID: (b)(6)

This grant: (b)(6)
Other support: N/A
Total LOE: (b)(6)

Other Support – Project/Proposal

Nothing to report.

IN-KIND

Nothing to report

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Signature: (b)(6)

Date: 7/6/2023

For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED
PHS 398 OTHER SUPPORT

Name of Individual: Christopher H Remien
Commons ID: (b)(6)

This grant: (b)(6)
Other support: N/A
Total LOE: (b)(6)

Other Support – Project/Proposal

(b)(4); (b)(6)

(b)(4); (b)(6)

Name of Individual: Christopher H Remien
Commons ID: (b)(6)

(b)(4); (b)(6)

IN-KIND

Nothing to report

Overlap: Work on this project is thematically aligned with work on (b)(4); (b)(6)

(b)(4); (b)(6)

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Signature: (b)(6)

Date: 07/10/2023

For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED
PHS 398 OTHER SUPPORT

Name of Individual: Baca Chan
Commons ID: (b)(6)

This grant: (b)(6)
Other support: N/A
Total LOE: (b)(6)

Other Support – Project/Proposal

Nothing to report

IN-KIND

Nothing to report

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(b)(6)

Signature: _____

Date: 7/11/2023

For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED
PHS 398 OTHER SUPPORT

Name of Individual: Alec Redwood
Commons ID: (b)(6)

This grant: (b)(6)
Other support: N/A
Total LOE: (b)(6)

Title: Computational modelling to improving anti-cancer vaccine design.
Major Goals: Neoantigen vaccines, that target cancer specific mutations, are a new personalized approach to cancer immunotherapy. Although in early clinical trials they have demonstrated safety, convincing immune (T cell) responses and preliminary evidence of antitumor activity, the vast majority of predicted neoantigens are not recognized by patient T cells. The current neoantigen prediction and screening methodologies are, therefore, inadequate. To find additional neoantigens we propose to identify and target an entirely novel class of neoantigens that are derived from synonymous - silent, and seemingly silent - mutations. These mutations are currently ignored but make up approximately 33% of all single base pair mutations. They can affect splicing, the translation initiation site, or the co-translation folding process. This study has the following Aims;

1. Tailor and apply the gene expression models developed by the Tuller laboratory on whole genome sequence data from 30 patient with mesothelioma and predict novel neoantigens.
2. Determine the immunogenicity of up to 100 of these novel neoantigens and use these data to validate and improve neoantigen identification.
3. Adapt and use improved computational tools in a mouse model to identify and test potentially protective neoantigens in a cancer vaccine model.
Status of Support: Current, start pending signing of inter-institute agreements.

Project Number: (b)(4); (b)(6)

Name of PD/PI: Professor Bruce Robinson

Source of Support: (b)(4); (b)(6)

Primary Place of Performance: University of Western Australia

Project/Proposal Start and End Date: 1/7/2023 – 12/31/2025.

Total Award Amount: Requested 200, 000 USD

Title: An advanced digital monitoring and engagement platform for at-risk and confirmed COVID-19 individuals
Major Goals

1. To evaluate the efficacy, feasibility, adherence and patient satisfaction of EDICT digital remote monitoring systems in vulnerable patients with acute or chronic lung disease, early stage COVID-19 and self-isolating individuals. From this to understand the most important, and predictive, objective clinical features of infection or illness exacerbation of illness which is helpful in managing asymptomatic cases and which digital tools most reliably gather this information remotely

2. To evaluate the efficacy, feasibility, adherence and patient satisfaction of EDICT digital engagement system, including in aged and ethnic populations.

3. To evaluate the psychological effects of these approaches on isolated and quarantined patients and their families and optimise the mental health benefits of these approaches. This will include

Name of Individual: Alec Redwood
Commons ID: (b)(6)

building a systematic screening mental health tool for depression/anxiety/exacerbation of mental health issues in patients in COVID-19 isolation, a standardised, longitudinally repeated neuropsychological data base in all patients with COVID 19 (from diagnosis to recovery) in clinically and geographically inclusive populations and to identify effective short and long term interventional strategies to support and prevent psychiatric complications in patients with COVID-19 infection

4. To undertake pilot studies of the generation of a blood and viral sample biobank from Stage 1 CoVID-19 patients.

Status of Support: Current

Project Number: (b)(4); (b)(6)

Name of PD/PI: Prof. Bruce Robinson

Source of Support: (b)(4); (b)(6)

Primary Place of Performance: University of Western Australia

Project/Proposal Start and End Date: 02/04/21- 01/28/2024

Total Award Amount: 880, 000 AUD

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2021	(b)(6)
2. 2022	
3. 2023	
4. 2024	

Title: Improving mesothelioma therapy by boosting immune responses to mutations by vaccination and by immunogenic chemotherapy

Major Goals: Mesothelioma is an aggressive cancer that has proven to be quite resistant to the commonly used forms of cancer therapy. There is new evidence that immunotherapy might be a useful form of treatment for this cancer. This grant aims to develop new immunotherapies for mesothelioma. Specifically, this grant will study T-cell responses to neo-antigen, which are immune targets created by cancer specific mutation, with the goal of improving anti-mesothelioma immunotherapy and developing cancer specific vaccines.

Aim 1: Identify and measure patient T-cell responses to candidate mesothelioma neo-antigens.

Aim 2: Examine the effect of standard-of-care chemotherapy on patient neo-antigen specific T-cell responses.

Aim 3. Evaluate neo-antigen vaccines, chemotherapy and immunotherapy in pre-clinical models

Status of Support: Current, seeking a 1-year extension

Project Number: W81XWH-20-1-0537

Name of PD/PI: Professor Bruce Robinson

Name of Individual: Alec Redwood
Commons ID: (b)(6)

Source of Support: Dept of the Army - USAMRAA

Primary Place of Performance: University of Western Australia

Project/Proposal Start and End Date: 04/01/2020 – 04/01/2023

Total Award Amount: Requested 999,875 USD

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2020	(b)(6)
2. 2021	
3. 2022	
4. 2023	

IN-KIND

Title: Computational modelling to improving anti-cancer vaccine design. Project Number: (b)(4); (b)(6)

*Primary Place of Performance: University of Western Australia

Project/Proposal Start and End Date: 1/7/2023 – 12/31/2025.

*Person Months (Calendar/Academic/Summer) per budget period

Year	Person Months
3. 2022	(b)(6) (21, 960 AUD)
4. 2023	(43, 920 AUD)
5. 2024	(21, 960 AUD)

*Estimated Dollar Value of In-Kind Information: 87, 840 AUD

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Signature: (b)(6)

Date: 07/07/2023

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To: Alec Redwood; Nuismer, Scott (snuismer@uidaho.edu); Panakal, Parvathy (NIH/NIGMS) [E]; Institutional Animal Care and Use Committee (iacuc@uidaho.edu); Remien, Christopher (cremien@uidaho.edu)
Cc: Baca Chan; AEC - PERKINS
Subject: [EXTERNAL] Re: Grant Number: 2R01GM122079 - 05A1 PI Name: NUISMER, SCOTT L
Date: Tuesday, July 11, 2023 3:13:49 PM
Attachments: Chan_other_support_7_11_2023.docx
Redwood_other_support_07-07-23.docx
Nuismer_Other_Support_7_10_23.docx
Remien_other_support_07_10_23.docx
Bull_Other_Support_YI23.docx

Thank you, Alec. Can you please start that process now?

Parvathy, I have attached the updated Other Support Forms. Is there a deadline to provide the IACUC information?

Thank you.

ERIC EVERETT, '07
He/Him
PreAward Unit Lead
Sponsored Programs Administrator
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ericeverett@uidaho.edu
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Scott

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Scott Nuismer
Professor
Department of Biological Sciences and Mathematics
Program in Bioinformatics and Computational Biology
University of Idaho
Moscow, ID 83844
https://www.leeef.org/

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Parvathy

Parvathy Panakal
Grants Management Specialist
DHHS/NIH/NIGMS/BBCB
45 Center Drive, Room 2AN44
Bethesda, MD 20814
panakalpr@nih.gov

NIGMS Pilot Payment Authorization

In accordance with NIH Grants Administration Manual 4204-204C, Notification of Funding, costs provided in the grant application, as described here, can vary from those awarded based on the outcome of negotiations of the final budget with the applicant institution. The official documentation of funding is the Notice of Award.

Authorization Date: 03/17/2023

Grant Number: 2R01GM122079-05A1 **Pay Plan Name:** BBCB-23-028 R01 T2 Oct

Project Title: A Mathematical Theory of Transmissible Vaccines

Institution: UNIVERSITY OF IDAHO

PI: NUISMER, SCOTT L

FOA: PA20-185 **PCC:** B120YJ **Council Date:** 202210 **FY:** 2023

Project Period: 08/01/2016-09/30/2026 **Budget Period:** 10/01/2022-09/30/2023

Percentile: (b)(6) **Priority Score:** (b)(6) **Requested Years:** 4 **Authorized Years:** 4

Budget Authorization Information:

Year	FY	CAN	Task	Requested Direct Cost	Program Recommended Direct Cost	IC Admin Cut %	Authorized Direct Cost	Authorized F&A Cost	Authorized Total Cost
5	2023	8472185	2023.100	$365,404	$291,000	0.0	$291,000	$92,394	$383,394
6	2024	8472185		$422,354	$281,000	0.0	$281,000	$79,894	$360,894
7	2025	8472185		$296,216	$281,000	0.0	$281,000	$81,394	$362,394

Year	FY	CAN	Task	Requested Direct Cost	Program Recommended Direct Cost	IC Admin Cut %	Authorized Direct Cost	Authorized F&A Cost	Authorized Total Cost
8	2026	8472185		$167,788	$167,788	0.0	$167,788	$83,894	$251,682

Review and Approval Information:

Approval	Approved By	Date	Comments
Division Director	Beckett, DOROTHY	Mar 8, 2023	Pay Plan has been reviewed and is approved.
BO	Powell, Paula	Mar 8, 2023	
Deputy Director	ZUK, DORIT	Mar 9, 2023	Titles OK
DEA Director	Brown, Erica L.	Mar 10, 2023	
GMO	Olascoaga, Grace	Mar 17, 2023	

Additional Comments:

Direct Costs include consortium total costs. Year 1 EQ $10,000. Foreign involvement needs state department clearance. Raise to pay justification: PI proposes to combine mathematical modeling and experimentations to develop a framework for self-transmissible vaccines used in controlling and preventing the spread of zoonotic pathogens. (b)(4); (b)(6)

(b)(4); (b)(6)

Progress Report

WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1. Develop a mathematical framework predicting the extent of protection provided by a transmissible vaccine. For a transmissible vaccine to be useful, it must be able to invade the target population and immunize a larger number of individuals than could be achieved using a traditional vaccine. We will develop mathematical models, novel approximations, and individual-based simulations that allow us to predict the fate of a transmissible vaccine.

Aim 2. Develop a mathematical framework predicting the evolution of a transmissible vaccine. Developing a transmissible vaccine requires that an infectious agent be manipulated, either by adding genes that confer immunity or by eliminating or altering genes that cause virulence. We will develop mathematical models, novel approximations, and individual-based simulations to determine when these genetic modifications are evolutionarily robust and to study the epidemiological consequences when they are not.

Aim 3. Test model predictions using an experimental viral model. A recombinant vector vaccine is a type of engineered vaccine that is being tested in many contexts — against Ebola, HIV, and in wild-life. We will test whether a recombinant Murine cytomegalovirus will evolve within the host to lose expression of its antigenic insert.

WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

Aim 1. Work on the first specific aim is complete. During the past reporting period, we summarized and synthesized the implications of work on this aim for preventing pathogen spillover and emergence (Nuismer and Bull, 2020).

Aim 2. Our previous work on this aim established that vaccine reversion within attenuated transmissible vaccines posed little problem for their efficacy at the population level unless rates of reversion are extremely high (Nuismer et al. 2016). In contrast, subsequent work focused on recombinant vector transmissible vaccines demonstrated that vaccine reversion can result in failure even if rates of reversion are tiny (Basinski et al. 2017). The basis of this difficulty with recombinant vectored vaccines is that when a recombinant vector vaccine reverts, the result is a free vector (now lacking the antigenic insert) that may have a competitive advantage due to its reduced immune profile and reduced costs of expressing the antigenic insert. Our model results indicated that the fate of a recombinant vector vaccine may rest on two key parameters: 1) the rate the antigenic insert is deleted, or its expression suppressed, and 2) the consequences of deletion or reduced expression for competition with intact vaccine. Work during this reporting period finalized and published results from a more integrative modeling approach that quantified the evolutionary robustness of transmissible vaccines (Layman et al 2021). This new modeling framework allowed us to identify critical rates of antigenic deletion or downregulation above which a recombinant vector vaccine will perform no better than a conventional vaccine. We also addressed the more general problem of antigenic loss for a live recombinant vector vaccine within single hosts (Bull et al. 2019). In addition, (b)(4); (b)(6)

(b)(4); (b)(6)

(b)(4); (b)(6)

Aim 3. A leading vector candidate for use in recombinant vector transmissible vaccines (and indeed, for any recombinant vector vaccine) is cytomegalovirus (CMV). CMV is a promising vector candidate because of its high species specificity, its large genome size and stability, and its apparent ability to reinfect hosts that already carry CMV. Because our mathematical models demonstrate that the success of a recombinant vector vaccine depends on the rate at which it ejects or downregulates its antigenic insert, we constructed a model vaccine: murine CMV engineered to express ovalbumin as a model antigen. The goal was to test stability of the virus in mice, but as animal work was not requested in the RPPR Page 3 B.2 (Accomplishments Text March 2019.pdf) original application, we had to await NIH permission and IACUC approvals at the University of Texas before for implementing the mouse studies. Our initial question is the simple but important one of whether the insert is evolutionarily stable, or instead, whether the replicating virus will evolve within the host to lose or downregulate the ovalbumin gene. Stability of antigen expression is obviously required for vaccine success. The design introduced the engineered CMV into mice; tissues were sampled over time; viral titers from those tissues were obtained; PCR analysis of CMV from those tissues has been conducted to determine relative amounts of virus with and without ovalbumin insert. The PCR products from late in the infection often did not obey expected sizes, and indeed, sometimes exhibited multiple bands, making interpretation challenging. Fortunately, through a collaboration with Dr. Alec J. Redwood, we have gained access to in vitro experiments studying transgene loss in recombinant CMV vaccines. We have applied our maximum likelihood method for estimating mutation and selection to these in vitro data, where it has begun to yield insights into how evolution acts on immunogenic transgenes. We are currently waiting for the results of in vivo studies from Dr. Redwood (Redwood's work is funded by another mechanism). Data from these experiments will allow us to develop a more complete understanding of how recombinant vector transmissible vaccines evolve in vivo and further parameterize our population level models (Aim 2). *Covid-19 resulted in unanticipated delays in this experiment as our collaborator's lab was temporarily shut down, but the work is now nearly complete.*

WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Aim 1. The first specific aim is complete.

Aim 2. Work is now almost entirely complete, (b)(4); (b)(6)

(b)(4); (b)(6)

Aim 3. Work during the extension will continue to analyze the Redwood in vitro data on antigenic stability. Our analyses will be used to parameterize the population level models of transmissible vaccines developed in Aim 2. We anticipate the in vivo studies will be completed soon, allowing us to apply the maximum likelihood methods developed in Aim 2 to estimate the rate at which mutation creates antigen free mutants and the strength of within host selection favoring the spread of these antigen free mutants. (We already know that this evolution depends on details of the viral engineering.)

This analysis will allow us to parameterize the population level models developed in Aim 2 with the most relevant data on recombinant vector vaccine evolution.

The preceding paragraphs describe our work that is most directly tied to the Aims. We also researched broad aspects of vaccine design and delivery that is more peripheral but still relevant to transmissible vaccines. The list of references includes the full suite of publications that the grant has been used to fund.

JUSTIFICATION FOR EXTENSION

Covid-19 resulted in unanticipated delays in key experiments being performed by our collaborator, Dr. Alec J. Redwood. Data from these experiments are crucial for completion of our third specific aim. An additional one-year extension will allow us to complete this specific aim. We have corresponded with our program director, Dr. Veerasamy Ravichandran about this extension and this correspondence is appended at the end of this document.

REFERENCES

1. Basinski, A.J. T.J. Varrelman, M.W. Smithson, R.H. May, C.H. Remien, and S.L. Nuismer. 2017. Evaluating the promise of recombinant transmissible vaccines. ***Vaccine***. 36:675-682.
2. Basinski, A.J., SL Nuismer, CH Remien. 2019. A little goes a long way: Weak vaccine transmission facilitates oral vaccination campaigns against zoonotic pathogens. ***PLoS neglected tropical diseases*** 13 (3), e0007251
3. Bull, J.J., S.L. Nuismer, R. Antia. 2019. Recombinant vector vaccine evolution. ***PLoS computational biology*** 15 (7), e1006857
4. Bull, J.J., M.W. Smithson, and S.L. Nuismer. 2017. Transmissible viral vaccines. ***Trends in Microbiology***. 26:6-15.
5. Nuismer S.L. 2016. Eradicating infectious disease using weakly transmissible vaccines. ***Proceedings of the Royal Society of London Series B-Biological Sciences.*** 283:20161903.
6. Nuismer, S.L., May R, Basinski A, Remien C.H. 2018. Controlling epidemics with transmissible vaccines. ***PLoS ONE*** 13(5): e0196978.
7. Nuismer, S.L., A.J. Basinski, J.J. Bull. 2019. Evolution and containment of transmissible recombinant vector vaccines. ***Evolutionary Applications*** 12 (8), 1595-1609
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9. Nuismer S.L., J.J. Bull. 2020. Self-disseminating vaccines to suppress zoonoses. ***Nature Ecology and Evolution***. 4 (9), 1168-1173.
10. Layman, N.C., B.M. Tuschhoff, A.J. Basinski, C.H. Remien, J.J. Bull, S.L. Nuismer 2020. Suppressing evolution in genetically engineered systems through repeated supplementation. ***Evolutionary Applications***. 00:1–12.
11. Layman, N.C., B.M. Tuschhoff, A.J. Basinski, C.H. Remien, J.J. Bull, S.L. Nuismer 2020. Suppressing evolution in genetically engineered systems through repeated supplementation. ***Evolutionary Applications***. 00:1–12.
12. Layman, N., B.M. Tuschhoff, S.L. Nuismer. 2021. Designing transmissible viral vaccines for evolutionary robustness and maximum efficiency. **Virus Evolution**. doi.org/10.1093/ve/veab002.
13. Schreiner, C., S.L. Nuismer, A.J. Basinski. 2020. When to vaccinate a fluctuating wildlife population: is timing everything? ***Journal of Applied Ecology***. 57 (2), 307-319.

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15. Varrelman, T.J., A.J. Basinski, C.H. Remien, S.L. Nuismer. 2019. Transmissible vaccines in heterogeneous populations: Implications for vaccine design. ***One Health*** 7, 100084

SUPPORTING CORRESPONDENCE

From: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Sent: Tuesday, December 15, 2020 9:51 AM
To: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>
Subject: RE: Additional extension for R01 GM122079-04

Hi Scott,

Yes, please include this on to your NCE request and send it to me through your authorized administrative official. And, for the renewal, if you are not eligible to come for MIRA (R35), you could use parent R01 FOA. I have some breathing time next week, may be around Wednesday, if you want to have a chat.

Thanks,

Best Regards,

Ravi

Veerasamy "Ravi" Ravichandran, Ph.D.
Program Director
Biomedical Technology, Bioinformatics and Computational Biology Division
National Institute of General Medical Sciences
National Institutes of Health, Bld 45, Room 2AN12M
45 Center Drive, MSC 6200
Bethesda, Maryland 20892-6200
301-451-9822 (phone)
301-480-0884 (fax)
Veerasamy.Ravichandra@nih.gov

From: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>
Sent: Tuesday, December 15, 2020 12:45 PM
To: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Subject: Additional extension for R01 GM122079-04

Dear Ravi,

Due to complications with COVID-19 shutting down the lab of a collaborator, we have been unable to complete work on our third specific aim parameterizing our models in the CMV system. Our existing NCE will expire this April. Would it be possible to get another 1 year extension for this award?

Also, I would very much like to continue work on this project and was wondering if you would have time to discuss with me how best to seek a renewal? I am relatively new to the NIH system and any advice would be appreciated.

Cheers,

Scott

****

Scott Nuismer
Professor
Department of Biological Sciences and Mathematics
Program in Bioinformatics and Computational Biology
University of Idaho
Moscow, ID 83844
https://www.leeef.org/

University of Idaho

Office of Research
and Economic Development

Office of Sponsored Programs

875 Perimeter Drive MS 3020
Moscow, ID 83844–3020
Phone: 208-885-6651
Fax: 208-885-4990
osp@uidaho.edu
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December 15, 2020

Dr. Ravichandran Veerasamy
National Institutes of Health
45 Center Drive MSC 6200
Bethesda, MD 20892-6200

Dear Dr. Veerasamy:

The Regents of the University of Idaho is requesting a no cost time extension for the project entitled "*A mathematical theory of transmissible vaccines*" funded under (R01 GM122079-01). We are requesting this extension for the following reason(s):

Due to complications with COVID-19 shutting down the lab of a collaborator, we have been unable to complete work on our third specific aim parameterizing our models in the CMV system. Extending our project for an additional year (4/30/2022) will allow us to complete this final specific aim.

We are therefore respectfully requesting the term of this project be extended by one year through 4/30/2022.

If you have any questions, please contact the Post Award Contract Administrators, at postaward@uidaho.edu.

Sincerely,

(b)(6)

Scott L. Nuismer
Principal Investigator

Estimated Unobligated Balance:

Personnel	$2,864
Equipment	$0
Travel	$2,967
Other Direct Costs	$78,638
Indirect Costs	$38,521
Total Direct and Indirect Costs	$122,989

From: Singletary, Annette (NIH/NIGMS) [E]
To: Singletary, Annette (NIH/NIGMS) [E]
Subject: FW: no cost time extension for grant 1R01GM122079-04
Date: Wednesday, March 3, 2021 4:37:49 PM
Attachments: Budget Document.pdf
NCTE.pdf
Progress Report.pdf

Annette Singletary, M.Ed
Grants Management Specialist GAB/BBCB
National Institutes of Health
National Institute of General Medical Sciences
Bldg. 45
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Direct phone: 301-827-1707
Annette.Singletary@nih.gov

From: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Sent: Wednesday, March 3, 2021 10:04 AM
To: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Subject: RE: no cost time extension for grant 1R01GM122079-04

Hi Annette,

Given the reason they provide due to COVID-19, it's reasonable to approve the PI's second NCE; hence, I approve the request. I don't see any other program concern or issue.

Thanks,

Ravi

From: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Sent: Tuesday, March 02, 2021 9:47 PM
To: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Cc: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Subject: FW: no cost time extension for grant 1R01GM122079-04

Hi Ravi,

Attached and below for your review, is a 2nd NCE request for the above referenced grant.

At your earliest opportunity, please review and provide your feedback.

Thank you.

Annette Singletary, M.Ed
Grants Management Specialist GAB/BBCB
National Institutes of Health
National Institute of General Medical Sciences
Bldg. 45
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Direct phone: 301-827-1707
Annette.Singletary@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Sent: Tuesday, March 2, 2021 5:07 PM
To: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Cc: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>
Subject: RE: no cost time extension for grant 1R01GM122079-04

Annette,

Thank you so much for getting back to me. The IACUC approval has expired.

Please see our attached request and let me know if you need anything further.

Application Information

PD/PI User ID (b)(6)	**Name of PD/PI** NUISMER, SCOTT L	**Grants Management Specialist** Trujillo, Maricela maricela.trujillo@nih.gov 301-594-3927	**Program Official** Ravichandran, Veerasamy veerasamy.ravichandra@nih.gov
Grant # Type Act IC Serial# Year Suffix 5R01GM122079-04		**Application Title** COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES	
Institution UNIVERSITY OF IDAHO		**Budget Period** 05/01/2019 - 04/30/2021	**Project Period** 08/01/2016 - 04/30/2021

Cheers,

Kendra Christensen

Assistant Sponsored Programs Administrator
Office of Sponsored Programs
Office: Morrill Hall 209
postaward@uidaho.edu
208-885-6270
875 Perimeter Drive MS 3020 | Moscow ID 84843 | United States

University of Idaho

From: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Sent: Tuesday, March 2, 2021 1:44 PM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Cc: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Subject: FW: no cost time extension for grant 1R01GM122079-04

Hi Kendra,

Thanks for your outreach. Please use the IACUC approval date associated with this grant if it is still current. If the approval has expired, you may at your earliest opportunity forward to my attention the prior approval request for a second no cost extension.

Do not hesitate to contact me at your earliest opportunity should you have additional questions and/or concerns.

Thank you!

Annette Singletary, M.Ed
Grants Management Specialist GAB/BBCB
National Institutes of Health
National Institute of General Medical Sciences
Bldg. 45
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Direct phone: 301-827-1707
Annette.Singletary@nih.gov

Official correspondence must be submitted by an Authorized Business Official in the Office of Sponsored Programs. (AOR/BO/SO MUST have SO Role in eRA Commons).

From: Walker, Tiffany (NIH/NIGMS) [E] <walkerti@mail.nih.gov>
Sent: Monday, March 1, 2021 9:20 AM
To: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Cc: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Subject: RE: no cost time extension for grant 1R01GM122079-04

Hi Ravi,

The current assigned specialist is Annette Singletary, so I have cc'd Annette on this email.

Regards,

Tiffany

From: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Sent: Friday, February 26, 2021 4:41 PM
To: Walker, Tiffany (NIH/NIGMS) [E] <walkerti@mail.nih.gov>
Subject: FW: no cost time extension for grant 1R01GM122079-04

Hi Tiffany,

Do you know who has inherited this R01GM122079 From Maricela?

Thanks,

Ravi

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Sent: Friday, February 26, 2021 4:28 PM
To: maricela.trujillo@nih.gov; Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Cc: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Bull, James (jbull@uidaho.edu) <jbull@uidaho.edu>
Subject: FW: no cost time extension for grant 1R01GM122079-04

Good afternoon,

Is it possible to get a response to our no cost time extension question below? The end date is 4/29/2021.

Can you please confirm receipt of this email? Any help would be greatly appreciated.

Thank you,

Kendra Christensen

Assistant Sponsored Programs Administrator
Office of Sponsored Programs
Office: Morrill Hall 209
postaward@uidaho.edu
208-885-6270
875 Perimeter Drive MS 3020 | Moscow ID 84843 | United States

University of Idaho

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>.
Sent: Monday, February 22, 2021 4:53 PM
To: maricela.trujillo@nih.gov; veerasamy.ravichandra@nih.gov
Cc: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Bull, James (jbull@uidaho.edu) <jbull@uidaho.edu>
Subject: no cost time extension for grant 1R01GM122079-04

Good afternoon,

We are trying to submit our second no cost time extension for grant 1R01GM122079-04 in ERA Commons. The request is asking for an IACUC approval date. The IACUC protocol is closed and has been for over a year. Can you please advise us on how to move forward with this request? It won't let me submit the request unless there is a date there.

Any help would be greatly appreciated. Thank you in advance.

Cheers,

Kendra Christensen

Assistant Sponsored Programs Administrator
Office of Sponsored Programs
Office: Morrill Hall 209
postaward@uidaho.edu
208-885-6270
875 Perimeter Drive MS 3020 | Moscow ID 84843 | United States

University of Idaho

From: Singletary, Annette (NIH/NIGMS) [E]
To: postaward@uidaho.edu
Cc: Singletary, Annette (NIH/NIGMS) [E]
Subject: FW: no cost time extension for grant 1R01GM122079-04
Date: Tuesday, March 2, 2021 4:44:13 PM

Hi Kendra,

Thanks for your outreach. Please use the IACUC approval date associated with this grant if it is still current. If the approval has expired, you may at your earliest opportunity forward to my attention the prior approval request for a second no cost extension.

Do not hesitate to contact me at your earliest opportunity should you have additional questions and/or concerns.

Thank you!

Annette Singletary, M.Ed
Grants Management Specialist GAB/BBCB
National Institutes of Health
National Institute of General Medical Sciences
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45 Center Drive, MSC 6200
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Annette.Singletary@nih.gov

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From: Walker, Tiffany (NIH/NIGMS) [E] <walkerti@mail.nih.gov>
Sent: Monday, March 1, 2021 9:20 AM
To: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Cc: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Subject: RE: no cost time extension for grant 1R01GM122079-04

Hi Ravi,

The current assigned specialist is Annette Singletary, so I have cc'd Annette on this email.

Regards,

Tiffany

From: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Sent: Friday, February 26, 2021 4:41 PM

To: Walker, Tiffany (NIH/NIGMS) [E] <walkerti@mail.nih.gov>
Subject: FW: no cost time extension for grant 1R01GM122079-04

Hi Tiffany,

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Thanks,

Ravi

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Sent: Friday, February 26, 2021 4:28 PM
To: maricela.trujillo@nih.gov; Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Cc: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Bull, James (jbull@uidaho.edu) <jbull@uidaho.edu>
Subject: FW: no cost time extension for grant 1R01GM122079-04

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Can you please confirm receipt of this email? Any help would be greatly appreciated.

Thank you,

Kendra Christensen

Assistant Sponsored Programs Administrator
Office of Sponsored Programs
Office: Morrill Hall 209
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University of Idaho

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Sent: Monday, February 22, 2021 4:53 PM

To: maricela.trujillo@nih.gov; veerasamy.ravichandra@nih.gov
Cc: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Bull, James (jbull@uidaho.edu) <jbull@uidaho.edu>
Subject: no cost time extension for grant 1R01GM122079-04

Good afternoon,

We are trying to submit our second no cost time extension for grant 1R01GM122079-04 in ERA Commons. The request is asking for an IACUC approval date. The IACUC protocol is closed and has been for over a year. Can you please advise us on how to move forward with this request? It won't let me submit the request unless there is a date there.

Any help would be greatly appreciated. Thank you in advance.

Cheers,

Kendra Christensen

Assistant Sponsored Programs Administrator
Office of Sponsored Programs
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208-885-6270
875 Perimeter Drive MS 3020 | Moscow ID 84843 | United States

University of Idaho

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
To: Singletary, Annette (NIH/NIGMS) [E]
Cc: Nuismer, Scott (snuismer@uidaho.edu); Mattoon, Michele (mmattoon@uidaho.edu)
Subject: RE: Grant Number: 5R01GM122079 - 04 PI Name: NUISMER, SCOTT L
Date: Monday, March 8, 2021 11:34:15 AM

Good morning Annette,

Thank you for the email. Both the PI and key personnel will maintain measurable effort.

Let me know if you have any further questions.

Thank you,

Kendra Christensen

Assistant Sponsored Programs Administrator
Office of Sponsored Programs
Office: Morrill Hall 209
postaward@uidaho.edu
208-885-6270
875 Perimeter Drive MS 3020 | Moscow ID 84843 | United States

From: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Sent: Monday, March 8, 2021 7:56 AM
To: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Office of Sponsored Programs (osp@uidaho.edu) <osp@uidaho.edu>
Cc: Singletary, Annette (NIH/NIGMS) [E] <annette.singletary@nih.gov>
Subject: Grant Number: 5R01GM122079 - 04 PI Name: NUISMER, SCOTT L

Dear Business Official,

The above referenced grant is currently under review for 2nd no cost extension. At your earliest opportunity, please confirm whether the PI and key personnel will maintain measurable effort during the 2nd NCE.

Thank you in advance to your attention to this request.

Best,

Annette Singletary, M.Ed
Grants Management Specialist GAB/BBCB
National Institutes of Health
National Institute of General Medical Sciences
Bldg. 45
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Direct phone: 301-827-1707
Annette.Singletary@nih.gov

Official correspondence must be submitted by an Authorized Business Official in the Office of Sponsored Programs. (AOR/BO/SO MUST have SO Role in eRA Commons).

From:	Martonick, Sarah (smartonick@uidaho.edu)
To:	Soremekun, Oladunni (NIH/NIGMS) [C]
Cc:	Nuismer, Scott (snuismer@uidaho.edu); Ravichandran, Veerasamy (NIH/NIGMS) [E]; Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Subject:	RE: Grant Number: 5R01GM122079 - 03 PI Name: NUISMER, SCOTT L
Date:	Friday, March 16, 2018 11:26:54 AM

Good morning Ms. Soremekun,

The University of Texas, Austin, is still an active performance site. That was an input error on our part. Are we able to revise the submitted report to correct that omission?

Thank you,
Sarah

Sarah Martonick
Post Award Manager
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow ID 83844-3020
208-885-2145
postaward@uidaho.edu

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser:
https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

Fall/Winter 2017 Schedule: I am in the office 7:00 am – 3:00 pm.

Advance notice:

From: Soremekun, Oladunni (NIH/NIGMS) [C] [mailto:oladunni.soremekun@nih.gov]
Sent: Friday, March 16, 2018 4:56 AM
To: Martonick, Sarah (smartonick@uidaho.edu) <smartonick@uidaho.edu>
Cc: Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>
Subject: Grant Number: 5R01GM122079 - 03 PI Name: NUISMER, SCOTT L
Importance: High

Dear Ms. Martonick,

The University of Texas, Austin was not listed in section G.8 as a performance site. Please confirm if the consortium is still active.

Thanks,

Ms. Oladunni Soremekun
Grants Management Specialist (C)
NIH/National Institute of General Medical Sciences (NIGMS)
45 Center Drive
Bethesda, MD 20892
Email: oladunni.soremekun@nih.gov

From:	Ravichandran, Veerasamy (NIH/NIGMS) [E]
To:	Rosenzweig, Justin (NIH/NIGMS) [E]
Subject:	FW: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Date:	Thursday, July 27, 2017 9:12:58 AM
Attachments:	University of Texas IMK050-SB-001 Change in SOW & Vertebrate Animal Section (IMK050).pdf Request for Subawardee Change In Scope of Work For Award 1R01GM122079-01 (IMK050) S.pdf
Importance:	High

Good Morning Justin,

I have been in close touch with the PIs on this request. The change of scope is for the University of Texas, but the PI's main proposal remains unchanged. This requested change of scope is reasonable and I approve the request. Please let me know if you need any additional details from myside.

Thanks,

Ravi

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Wednesday, July 26, 2017 7:24 PM
To: rozenzwj@mail.nih.gov
Cc: Ravichandran, Veerasamy (NIH/NIGMS) [E] <veerasamy.ravichandra@nih.gov>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; bull@austin.utexas.edu; osp@austin.utexas.edu
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Mr. Rosenzweig,

Attached find the Regents of the University of Idaho's request for a change in scope of work for subawardee University of Texas for award R01GM122079 (IMK050). Please reply with a decision or an amendment via email to postaward@uidaho.edu.

Feel free to call or email me if you have any questions.

Thank you,

Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020

Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser:
https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

From:	Rosenzweig, Justin (NIH/NIGMS) [E]
To:	OLAW Division of Assurances (NIH/OD)
Subject:	Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)
Date:	Friday, September 22, 2017 2:49:00 PM
Attachments:	University of Texas IMK050-SB-001 Change in SOW & Vertebrate Animal Section (IMK050).pdf Request for Subawardee Change In Scope of Work For Award 1R01GM122079-01 (IMK050) S.PDF ApprovalLetter_IACUC (2).pdf PO Approval.pdf

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Re: 5 R01 GM122079-02
PI: NUISMER, SCOTT L
Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES
Institution: UNIVERSITY OF IDAHO
Code Requested: 30
Current Code: 10
Performance Site: UNIVERSITY OF TEXAS AT AUSTIN

Hello OLAW,

The above referenced grantee is requesting permission to add VAS work using the University of Texas at Austin as the performance site. The current VAS code is 10 so we're requesting a code change to 30. Attached is the relevant information, including the VAS, IACUC approval letter and Program Officer approval. The grantee's AWA is A3852-01. Please let me know if the provided information is sufficient or if additional details are required.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
National Institute of General Medical Sciences, NIH/DHHS
45 Center Drive, Room 2AN.50C
Bethesda, MD 20892
Phone: (301) 594-0158
Fax: (301) 480-2554
Email: Justin.Rosenzweig@nih.gov

From:	OLAW Division of Assurances (NIH/OD)
To:	Rosenzweig, Justin (NIH/NIGMS) [E]; OLAW Division of Assurances (NIH/OD)
Subject:	PI" Response: Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)
Date:	Wednesday, September 27, 2017 10:39:03 AM

Good Morning Mr. Rosenzweig,

I have reviewed the VAS but ***cannot*** approve as submitted. The following needs to be addressed before receiving approval:

1. **Description of Procedures**
   1) Please provide the age of the mice to be used on the proposed studies.
   2) Please provide the volume of CMV that will be injected IV in mice.
   3) Please provide a concise description of the procedures involved in the sampling for urine, saliva and blood in mice. Also, please provide a description of the procedures involved in the possible routes of inoculation i.e. IP, footpad and subcutaneous, proposed in mice for the preliminary work. The description must include sufficient detail to allow evaluation of the procedures and should include handling; restraint; frequency, anatomical site, frequency and volume of blood collection; any additional biological fluid collection (e.g. urine, saliva).

3. **Minimization of Pain and Distress**
   1) Will there be any proposed pharmaceutical interventions e.g. **anesthesia**, **analgesia** to alleviate discomfort, distress or pain? If no, please justify why pain or distress cannot be alleviated using pharmaceutical agents. If yes, please state the name or class of the proposed pharmaceutical agent(s) which will be used and the frequency and route(s) of administration?
   2) Will there be any non-pharmaceutical measures to avoid discomfort, distress, pain or injury, such as palliative or supportive care?
   3) Are there indicators for veterinary intervention to alleviate discomfort, distress, or pain (e.g., body scoring, weighing)?
   4) Please provide specific indicators for humane experimental endpoints and euthanasia?

4. **Euthanasia**
   1) Please state all proposed methods of euthanasia and indicate if the method(s) of euthanasia is/are consistent with AVMA guidelines. If consistent, no further information is needed. If it isn't consistent, please describe the method of euthanasia and provide scientific justification.

Very Respectfully,

Tiffani T. Soto
Program Assistant
Office of Laboratory Animal Welfare, NIH
Phone: (301) 451-4211
Email: tiffani.soto@nih.gov

Division of Assurances
E-Fax (301) 451-5672
Email: OLAWdoa@mail.nih.gov

individuals. If you have received this message in error, please contact the sender.

Quote:
Tell me and I forget, Teach me and I remember, Involve me and I learn.
Benjamin Franklin

From: Rosenzweig, Justin (NIH/NIGMS) [E]
Sent: Friday, September 22, 2017 2:50 PM
To: OLAW Division of Assurances (NIH/OD) <assurances.olaw@od.nih.gov>
Subject: FW to Dr. Gopee for Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)

Re: 5 R01 GM122079-02
PI: NUISMER, SCOTT L
Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES
Institution: UNIVERSITY OF IDAHO
Code Requested: 30
Current Code: 10
Performance Site: UNIVERSITY OF TEXAS AT AUSTIN

Hello OLAW,

The above referenced grantee is requesting permission to add VAS work using the University of Texas at Austin as the performance site. The current VAS code is 10 so we're requesting a code change to 30. Attached is the relevant information, including the VAS, IACUC approval letter and Program Officer approval. The grantee's AWA is A3852-01. Please let me know if the provided information is sufficient or if additional details are required.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
National Institute of General Medical Sciences, NIH/DHHS
45 Center Drive, Room 2AN.50C
Bethesda, MD 20892
Phone: (301) 594-0158
Fax: (301) 480-2554
Email: Justin.Rosenzweig@nih.gov

From: OLAW Division of Assurances (NIH/OD)
To: Rosenzweig, Justin (NIH/NIGMS) [E]; OLAW Division of Assurances (NIH/OD)
Subject: RE: PI" Response: Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)
Date: Monday, November 06, 2017 12:05:26 PM

Good Afternoon Mr. Rosenzweig,

OLAW has reviewed and approved the VAS.

Very Respectfully,

Tiffani T. Soto
Program Assistant
Office of Laboratory Animal Welfare, NIH
Phone: (301) 451-4211
Email: tiffani.soto@nih.gov

Division of Assurances
E-Fax (301) 451-5672
Email: OLAWdoa@mail.nih.gov

Quote:
Tell me and I forget, Teach me and I remember, Involve me and I learn.
Benjamin Franklin

From: Rosenzweig, Justin (NIH/NIGMS) [E]
Sent: Monday, November 06, 2017 11:28 AM
To: OLAW Division of Assurances (NIH/OD) <assurances.olaw@od.nih.gov>
Subject: FW: PI' Response: Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)
Importance: High

Hi Tiffani,

I'm following up on the email below, can you let me know if the attached document addresses the questions from your original email? Please let know when you can, the grantee is getting anxious. Please let me know if you need any additional information, many thanks!

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Rosenzweig, Justin (NIH/NIGMS) [E]
Sent: Friday, October 13, 2017 2:43 PM
To: OLAW Division of Assurances (NIH/OD) <assurances.olaw@od.nih.gov>
Subject: RE: PI' Response: Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)

Hi Tiffani,

The grantee provided the attached document to address the questions below, starting on page 6 (I think the euthanasia portion starts on page 16). Please let me know if the attachment is sufficient or if you need additional information.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: OLAW Division of Assurances (NIH/OD)
Sent: Wednesday, September 27, 2017 10:39 AM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>; OLAW Division of Assurances (NIH/OD) <assurances.olaw@od.nih.gov>
Subject: PI' Response: Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)

Good Morning Mr. Rosenzweig,

I have reviewed the VAS but ***cannot*** approve as submitted. The following needs to be addressed before receiving approval:

1. **Description of Procedures**

   1) Please provide the age of the mice to be used on the proposed studies.

   2) Please provide the volume of CMV that will be injected IV in mice.

   3) Please provide a concise description of the procedures involved in the sampling for urine, saliva and blood in mice. Also, please provide a description of the procedures involved in the possible routes of inoculation i.e. IP, footpad and subcutaneous, proposed in mice for the preliminary work. The description must include sufficient detail to allow evaluation of the procedures and should include handling; restraint; frequency, anatomical site, frequency and volume of blood collection; any additional biological fluid collection (e.g. urine, saliva).

3. **Minimization of Pain and Distress**

1) Will there be any proposed pharmaceutical interventions e.g. **anesthesia**, **analgesia** to alleviate discomfort, distress or pain? If no, please justify why pain or distress cannot be alleviated using pharmaceutical agents. If yes, please state the name or class of the proposed pharmaceutical agent(s) which will be used and the frequency and route(s) of administration?

2) Will there be any non-pharmaceutical measures to avoid discomfort, distress, pain or injury, such as palliative or supportive care?

3) Are there indicators for veterinary intervention to alleviate discomfort, distress, or pain (e.g., body scoring, weighing)?

4) Please provide specific indicators for humane experimental endpoints and euthanasia?

4. **Euthanasia**

1) Please state all proposed methods of euthanasia and indicate if the method(s) of euthanasia is/are consistent with AVMA guidelines. If consistent, no further information is needed. If it isn't consistent, please describe the method of euthanasia and provide scientific justification.

Very Respectfully,

Tiffani T. Soto
Program Assistant
Office of Laboratory Animal Welfare, NIH
Phone: (301) 451-4211
Email: tiffani.soto@nih.gov

Division of Assurances
E-Fax (301) 451-5672
Email: OLAWdoa@mail.nih.gov

Quote:
Tell me and I forget, Teach me and I remember, Involve me and I learn.
Benjamin Franklin

From: Rosenzweig, Justin (NIH/NIGMS) [E]
Sent: Friday, September 22, 2017 2:50 PM
To: OLAW Division of Assurances (NIH/OD) <assurances.olaw@od.nih.gov>

Subject: FW to Dr. Gopee for Request for Code Change re: 5 R01 GM122079-02 (PI: NUISMER, SCOTT L)

Re: 5 R01 GM122079-02
PI: NUISMER, SCOTT L
Project Title: COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES
Institution: UNIVERSITY OF IDAHO
Code Requested: 30
Current Code: 10
Performance Site: UNIVERSITY OF TEXAS AT AUSTIN

Hello OLAW,

The above referenced grantee is requesting permission to add VAS work using the University of Texas at Austin as the performance site. The current VAS code is 10 so we're requesting a code change to 30. Attached is the relevant information, including the VAS, IACUC approval letter and Program Officer approval. The grantee's AWA is A3852-01. Please let me know if the provided information is sufficient or if additional details are required.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
National Institute of General Medical Sciences, NIH/DHHS
45 Center Drive, Room 2AN.50C
Bethesda, MD 20892
Phone: (301) 594-0158
Fax: (301) 480-2554
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
To: Rosenzweig, Justin (NIH/NIGMS) [E]
Cc: Mattoon, Michele (mmattoon@uidaho.edu); Nuismer, Scott (snuismer@uidaho.edu)
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Date: Wednesday, August 9, 2017 11:47:12 AM
Attachments: ApprovalLetter_IACUC (2).pdf

Hello Justin,

Please find attached the IACUC approval number from University of Texas at Austin for the above referenced project. Their Animal Welfare Assurance # is A4107-01 and the UI assurance # is below.

If any other information is needed, please let me know. I am assisting with this one, as Vicki is on annual leave this week!

Thank you,
Sarah

Sarah Martonick
Post Award Manager
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow ID 83844-3020
208-885-2145
postaward@uidaho.edu

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser:
https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

Summer 2017 Schedule: June 4 – August 11 I am in the office 7:00 am – 3:00 pm.

Advance Notice: I am out of the office (and not returning email) August 14-22.

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Sent: Friday, July 28, 2017 1:33 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

UI's DHHS Animal Assurance number is A3852-01.

Thanks,

Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser:
https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

From: Rosenzweig, Justin (NIH/NIGMS) [E] [mailto:rosenzwj@nigms.nih.gov]
Sent: Friday, July 28, 2017 11:50 AM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hi Vicki,

Just to be clear, it has to be Idaho's AWA number. The IACUC approval can come from Texas, but the AWA has to be the assurance number that your institution (Idaho) has on file with OLAW.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Friday, July 28, 2017 2:46 PM

To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello Mr. Rosenzweig,

As soon as University of Texas (subawardee) provided the requested information then I will email to you.

Thank you,

Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

From: Rosenzweig, Justin (NIH/NIGMS) [E] [mailto:rosenzwj@nigms.nih.gov]
Sent: Thursday, July 27, 2017 6:01 AM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello,

Could you please provide Idaho's animal welfare assurance number and a copy of the IACUC approval letter?

Sincerely,

Justin Rosenzweig
Grants Management Specialist

Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Wednesday, July 26, 2017 7:27 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Mr. Rosenzweig,

Attached find the Regents of the University of Idaho's request for a change in scope of work for subawardee University of Texas for award R01GM122079 (IMK050). Please reply with a decision or an amendment via email to postaward@uidaho.edu.

Feel free to call or email me if you have any questions.

Thank you,

Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser:
https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

From:	Rosenzweig, Justin (NIH/NIGMS) [E]
To:	"Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)"
Cc:	"Mattoon, Michele (mmattoon@uidaho.edu)"; "Nuismer, Scott (snuismer@uidaho.edu)"; "Bull, James J"
Subject:	RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Date:	Thursday, September 28, 2017 10:46:00 AM

Hi Vicki,

Regarding the request to add VAS research to the above referenced project, the Office of Laboratory Animal Welfare has asked that you address the following:

1. **Description of Procedures**
    1. Please provide the age of the mice to be used on the proposed studies.
    2. Please provide the volume of CMV that will be injected IV in mice.
    3. Please provide a concise description of the procedures involved in the sampling for urine, saliva and blood in mice. Also, please provide a description of the procedures involved in the possible routes of inoculation i.e. IP, footpad and subcutaneous, proposed in mice for the preliminary work. The description must include sufficient detail to allow evaluation of the procedures and should include handling; restraint; frequency, anatomical site, frequency and volume of blood collection; any additional biological fluid collection (e.g. urine, saliva).

3. **Minimization of Pain and Distress**
    1. Will there be any proposed pharmaceutical interventions e.g. **anesthesia**, **analgesia** to alleviate discomfort, distress or pain? If no, please justify why pain or distress cannot be alleviated using pharmaceutical agents. If yes, please state the name or class of the proposed pharmaceutical agent(s) which will be used and the frequency and route(s) of administration?
    2. Will there be any non-pharmaceutical measures to avoid discomfort, distress, pain or injury, such as palliative or supportive care?
    3. Are there indicators for veterinary intervention to alleviate discomfort, distress, or pain (e.g., body scoring, weighing)?
    4. Please provide specific indicators for humane experimental endpoints and euthanasia?

4. **Euthanasia**
    1. Please state all proposed methods of euthanasia and indicate if the method(s) of euthanasia is/are consistent with AVMA guidelines. If consistent, no further information is needed. If it isn't consistent, please describe the method of euthanasia and provide scientific justification.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Rosenzweig, Justin (NIH/NIGMS) [E]
Sent: Friday, September 8, 2017 4:31 PM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)

<postaward@uidaho.edu>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Bull, James J <bull@austin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

The Request is with NIH OEP and they should have a response back by October, unless they require additional information.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Friday, September 08, 2017 4:24 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Bull, James J <bull@austin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Mr. Rosenzweig,

I'm following up in the Regents of the University of Idaho's request for a change in scope of work for subawardee University of Texas for award R01GM122079 (IMK050) emailed to you on 07/26/17 and the phone message I left you. As of today we have not received a reply. Please update me as to where the request is in the process.

Thank you,
Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Sent: Monday, August 21, 2017 10:43 AM
To: 'Rosenzweig, Justin (NIH/NIGMS) [E]' <rosenzwj@nigms.nih.gov>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; 'bull@asutin.utexas.edu' <bull@asutin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Mr. Rosenzweig,

I'm following up with this email to the phone message I left you today. Please update me as to where the Regents of the University of Idaho' request for a change scope is for the University of Texas, UI award R01GM122079 (IMK050).

Thank you,

Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Sent: Wednesday, August 09, 2017 8:45 AM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079

(IMK050)

Hello Justin,

Please find attached the IACUC approval number from University of Texas at Austin for the above referenced project. Their Animal Welfare Assurance # is A4107-01 and the UI assurance # is below.

If any other information is needed, please let me know. I am assisting with this one, as Vicki is on annual leave this week!

Thank you,
Sarah

Sarah Martonick
Post Award Manager
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow ID 83844-3020
208-885-2145
postaward@uidaho.edu

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser:
https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

Summer 2017 Schedule: June 4 – August 11 I am in the office 7:00 am – 3:00 pm.

Advance Notice: I am out of the office (and not returning email) August 14-22.

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Sent: Friday, July 28, 2017 1:33 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

UI's DHHS Animal Assurance number is A3852-01.

Thanks,

Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser:
https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

From: Rosenzweig, Justin (NIH/NIGMS) [E] [mailto:rosenzwj@nigms.nih.gov]
Sent: Friday, July 28, 2017 11:50 AM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hi Vicki,

Just to be clear, it has to be Idaho's AWA number. The IACUC approval can come from Texas, but the AWA has to be the assurance number that your institution (Idaho) has on file with OLAW.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Friday, July 28, 2017 2:46 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello Mr. Rosenzweig,

As soon as University of Texas (subawardee) provided the requested information then I will email to you.

Thank you,

Vicki

Vicki Russell
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---

From: Rosenzweig, Justin (NIH/NIGMS) [E] [mailto:rosenzwj@nigms.nih.gov]
Sent: Thursday, July 27, 2017 6:01 AM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello,

Could you please provide Idaho's animal welfare assurance number and a copy of the IACUC approval letter?

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)

[mailto:postaward@uidaho.edu]
Sent: Wednesday, July 26, 2017 7:27 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Mr. Rosenzweig,

Attached find the Regents of the University of Idaho's request for a change in scope of work for subawardee University of Texas for award R01GM122079 (IMK050). Please reply with a decision or an amendment via email to postaward@uidaho.edu.

Feel free to call or email me if you have any questions.

Thank you,
Vicki

Vicki Russell
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Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

From:	Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
To:	Rosenzweig, Justin (NIH/NIGMS) [E]
Cc:	Mattoon, Michele (mmattoon@uidaho.edu); Nuismer, Scott (snuismer@uidaho.edu); Bull, James J
Subject:	RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Date:	Friday, October 06, 2017 2:15:16 PM
Attachments:	Bull_IACUC.PDF
Importance:	High

Hello Justin,

Attached is the IACUC form from University of Texas Austin which addresses all the points below. Dr. Bull is the second PI on the protocol and Jason Upton is the CMV guy at University of Texas Austin.

Feel free to call or email me if you have any questions.

Thank you,

Vicki

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Sent: Thursday, September 28, 2017 7:46 AM
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Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Bull, James J <bull@austin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hi Vicki,

Regarding the request to add VAS research to the above referenced project, the Office of Laboratory Animal Welfare has asked that you address the following:

1. **Description of Procedures**

1) Please provide the age of the mice to be used on the proposed studies.

2) Please provide the volume of CMV that will be injected IV in mice.

3) Please provide a concise description of the procedures involved in the sampling for urine, saliva and blood in mice. Also, please provide a description of the procedures involved in the possible routes of inoculation i.e. IP, footpad and subcutaneous, proposed in mice for the preliminary work. The description must include sufficient detail to allow evaluation of the procedures and should include handling; restraint; frequency, anatomical site, frequency and volume of blood collection; any additional biological fluid collection (e.g. urine, saliva).

3. Minimization of Pain and Distress

1) Will there be any proposed pharmaceutical interventions e.g. **anesthesia**, **analgesia** to alleviate discomfort, distress or pain? If no, please justify why pain or distress cannot be alleviated using pharmaceutical agents. If yes, please state the name or class of the proposed pharmaceutical agent(s) which will be used and the frequency and route(s) of administration?

2) Will there be any non-pharmaceutical measures to avoid discomfort, distress, pain or injury, such as palliative or supportive care?

3) Are there indicators for veterinary intervention to alleviate discomfort, distress, or pain (e.g., body scoring, weighing)?

4) Please provide specific indicators for humane experimental endpoints and euthanasia?

4. Euthanasia

1) Please state all proposed methods of euthanasia and indicate if the method(s) of euthanasia is/are consistent with AVMA guidelines. If consistent, no further information is needed. If it isn't consistent, please describe the method of euthanasia and provide scientific justification.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Rosenzweig, Justin (NIH/NIGMS) [E]
Sent: Friday, September 8, 2017 4:31 PM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Bull, James J <bull@austin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

The Request is with NIH OEP and they should have a response back by October, unless they require additional information.

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Sent: Friday, September 08, 2017 4:24 PM
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Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Bull, James J <bull@austin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Mr. Rosenzweig,

I'm following up in the Regents of the University of Idaho's request for a change in scope of work for subawardee University of Texas for award R01GM122079 (IMK050) emailed to you on 07/26/17 and the phone message I left you. As of today we have not received a reply. Please update me as to where the request is in the process.

Thank you,

Vicki

Vicki Russell
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208) 885-4984

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Sent: Monday, August 21, 2017 10:43 AM
To: 'Rosenzweig, Justin (NIH/NIGMS) [E]' <rosenzwj@nigms.nih.gov>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; 'bull@asutin.utexas.edu' <bull@asutin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079

(IMK050)
Importance: High

Hello Mr. Rosenzweig,

I'm following up with this email to the phone message I left you today. Please update me as to where the Regents of the University of Idaho' request for a change scope is for the University of Texas, UI award R01GM122079 (IMK050).

Thank you,
Vicki

Vicki Russell
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University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Sent: Wednesday, August 09, 2017 8:45 AM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello Justin,

Please find attached the IACUC approval number from University of Texas at Austin for the above referenced project. Their Animal Welfare Assurance # is A4107-01 and the UI assurance # is below.

If any other information is needed, please let me know. I am assisting with this one, as Vicki is on annual leave this week!

Thank you,
Sarah

Sarah Martonick
Post Award Manager
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow ID 83844-3020
208-885-2145
postaward@uidaho.edu

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Sent: Friday, July 28, 2017 1:33 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

UI's DHHS Animal Assurance number is A3852-01.

Thanks,
Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
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875 Perimeter Drive MS 3020
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Sent: Friday, July 28, 2017 11:50 AM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

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Sincerely,

Justin Rosenzweig
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Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Friday, July 28, 2017 2:46 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello Mr. Rosenzweig,

As soon as University of Texas (subawardee) provided the requested information then I will email to you.

Thank you,
Vicki

Vicki Russell

Contract Administrator
Office of Sponsored Programs
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From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Wednesday, July 26, 2017 7:27 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

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subawardee University of Texas for award R01GM122079 (IMK050). Please reply with a decision or an amendment via email to postaward@uidaho.edu.

Feel free to call or email me if you have any questions.

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Vicki

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From:	Rosenzweig, Justin (NIH/NIGMS) [E]
To:	"Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)"
Cc:	Mattoon, Michele (mmattoon@uidaho.edu); Nuismer, Scott (snuismer@uidaho.edu); Bull, James J
Subject:	RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Date:	Monday, November 06, 2017 3:06:00 PM

Hi Vicki,

The request to add vertebrate animal research as described in the submitted attachments has been approved by the Office of Laboratory Animal Welfare. A revised year 2 Notice of Award will be issued within the next two weeks. Please let me know if you have any other questions or concerns.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Friday, November 03, 2017 1:34 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Bull, James J <bull@austin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Justin,

I'm following up in the Regents of the University of Idaho's request for a change in scope of work for subawardee University of Texas for award R01GM122079 (IMK050) emailed to you on 07/26/17 with a follow up email to some questions you had on 10/06/17. As of today we have not received a reply. Please update me as to where the request is in the process.

Thank you,
Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu

208) 885-4984

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu)
Sent: Friday, October 06, 2017 11:14 AM
To: 'Rosenzweig, Justin (NIH/NIGMS) [E]' <rosenzwj@nigms.nih.gov>
Cc: Mattoon, Michele (mmattoon@uidaho.edu) <mmattoon@uidaho.edu>; Nuismer, Scott (snuismer@uidaho.edu) <snuismer@uidaho.edu>; Bull, James J <bull@austin.utexas.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Justin,

Attached is the IACUC form from University of Texas Austin which addresses all the points below. Dr. Bull is the second PI on the protocol and Jason Upton is the CMV guy at University of Texas Austin.

Feel free to call or email me if you have any questions.

Thank you,
Vicki

Vicki Russell
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Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hi Vicki,

Regarding the request to add VAS research to the above referenced project, the Office of Laboratory Animal Welfare has asked that you address the following:

1. **Description of Procedures**
    1. Please provide the age of the mice to be used on the proposed studies.
    2. Please provide the volume of CMV that will be injected IV in mice.
    3. Please provide a concise description of the procedures involved in the sampling for urine, saliva and blood in mice. Also, please provide a description of the procedures involved in the possible routes of inoculation i.e. IP, footpad and subcutaneous, proposed in mice for the preliminary work. The description must include sufficient detail to allow evaluation of the procedures and should include handling; restraint; frequency, anatomical site, frequency and volume of blood collection; any additional biological fluid collection (e.g. urine, saliva).

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    1. Will there be any proposed pharmaceutical interventions e.g. **anesthesia**, **analgesia** to alleviate discomfort, distress or pain? If no, please justify why pain or distress cannot be alleviated using pharmaceutical agents. If yes, please state the name or class of the proposed pharmaceutical agent(s) which will be used and the frequency and route(s) of administration?
    2. Will there be any non-pharmaceutical measures to avoid discomfort, distress, pain or injury, such as palliative or supportive care?
    3. Are there indicators for veterinary intervention to alleviate discomfort, distress, or pain (e.g., body scoring, weighing)?
    4. Please provide specific indicators for humane experimental endpoints and euthanasia?

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    1. Please state all proposed methods of euthanasia and indicate if the method(s) of euthanasia is/are consistent with AVMA guidelines. If consistent, no further information is needed. If it isn't consistent, please describe the method of euthanasia and provide scientific justification.

Sincerely,

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Phone: (301) 594-0158
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Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079

(IMK050)
Importance: High

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Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

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Sent: Friday, July 28, 2017 1:33 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

UI's DHHS Animal Assurance number is A3852-01.

Thanks,
Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu

208) 885-4984

University of Idaho faculty and staff: Please let us know if we are serving your needs. Click here to take a three question survey to help us improve our services. If the hyperlink does not work, you can copy and paste this link directly to your browser: https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

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From: Rosenzweig, Justin (NIH/NIGMS) [E] [mailto:rosenzwj@nigms.nih.gov]
Sent: Friday, July 28, 2017 11:50 AM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hi Vicki,

Just to be clear, it has to be Idaho's AWA number. The IACUC approval can come from Texas, but the AWA has to be the assurance number that your institution (Idaho) has on file with OLAW.

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Friday, July 28, 2017 2:46 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello Mr. Rosenzweig,

As soon as University of Texas (subawardee) provided the requested information then I will email to you.

Thank you,
Vicki

Vicki Russell

Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

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https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

From: Rosenzweig, Justin (NIH/NIGMS) [E] [mailto:rosenzwj@nigms.nih.gov]
Sent: Thursday, July 27, 2017 6:01 AM
To: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) <postaward@uidaho.edu>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)

Hello,

Could you please provide Idaho's animal welfare assurance number and a copy of the IACUC approval letter?

Sincerely,

Justin Rosenzweig
Grants Management Specialist
Phone: (301) 594-0158
Email: Justin.Rosenzweig@nih.gov

From: Office of Sponsored Programs Univ of Idaho - Post Award (postaward@uidaho.edu) [mailto:postaward@uidaho.edu]
Sent: Wednesday, July 26, 2017 7:27 PM
To: Rosenzweig, Justin (NIH/NIGMS) [E] <rosenzwj@nigms.nih.gov>
Subject: RE: Request for a Subawardee Change In Scope of Work For Award R01GM122079 (IMK050)
Importance: High

Hello Mr. Rosenzweig,

Attached find the Regents of the University of Idaho's request for a change in scope of work for

subawardee University of Texas for award R01GM122079 (IMK050). Please reply with a decision or an amendment via email to postaward@uidaho.edu.

Feel free to call or email me if you have any questions.

Thank you,

Vicki

Vicki Russell
Contract Administrator
Office of Sponsored Programs
University of Idaho
875 Perimeter Drive MS 3020
Moscow, ID 83844-3020
postaward@uidaho.edu
208) 885-4984

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https://uidaho.co1.qualtrics.com/jfe/form/SV_e3Wd1L5Wt1mhNEp

Grant Number	1R01GM122079-01	**Priority**	(b)(6)	**Budget Start**	08/01/16
Grantee Organization	UNIVERSITY OF IDAHO	**Percentile**		**Budget End**	04/30/17
Principal Investigator	SCOTT NUISMER	**PCC**	B120VR	**Project Start**	08/01/16
Program Official	Veerasamy Ravichandran	**Council**	201605	**Project End**	04/30/20
Grants Management Specialist	Justin Rosenzweig	**FY**	2016	**EIN**	
Years Requested	4	**Years Recommended**	4	**Years Authorized**	4

Item/Category	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04		Grand Total
Salary & Wages	72,069	86,419	86,419	86,419		331,326
Fringe Benefits	26,725	26,725	26,725	26,725		106,900
Total Salary, Wages, & Fringe Benefits	98,794	113,144	113,144	113,144		438,226
Consultant Services						
Equipment	12,000					12,000
Materials and Supplies	2,500	1,500	1,500	1,500		7,000
Travel	3,150	3,150	3,150	3,150		12,600
Patient Care						
Alterations and Renovations						
Other	2,000	4,500	4,500	4,500		15,500
Subaward/Consortium/Contractual Costs	72,484	72,561	72,561	72,561		290,167
Publication Costs						
ADP/Computer Services						
Equipment or Facility Rental/User Fees						
SBIR/STTR Technical						
Tuition Remission						
Participant Subsistence						
Participant Stipend						
Participant Travel						
Participant Tuition/Fee/Health Insurance						
Participant Other						
Total Direct Costs by Budget Period	190,928	194,855	194,855	194,855		775,493
Include for Consortia F&A Rollup	Yes	Yes	Yes	Yes	Yes	
Rate 1	46.00%	46.00%	47.50%	47.50%		
Base 1	131,444	20,382	122,294	122,294		
Subtotal Indirect (F&A)	60,464	9,376	58,090	58,090		186,020
Include for Consortia F&A Rollup	Yes	Yes	Yes	Yes	Yes	
Rate 2		47.50%				
Base 2		101,912				
Subtotal Indirect (F&A)		48,408				48,408
Total Indirect (F&A) by Budget Period	60,464	57,784	58,090	58,090		234,428
Total Direct & Indirect (F&A) by Budget Period	251,392	252,639	252,945	252,945		1,009,921
Fee by Budget Period						
Total DC, F&A, & Fee by Budget Period	251,392	252,639	252,945	252,945		1,009,921
Offset (Unobligated Balance) Authorized						
Total DC, F&A, & Fee by Budget Period	251,392	252,639	252,945	252,945		1,009,921

Grant Number	1R01GM122079-01	Priority	(b)(6)	Budget Start	08/01/16		
Grantee Organization	UNIVERSITY OF IDAHO	Percentile		Project Start	08/01/16		
Principal Investigator	SCOTT NUISMER	PCC	B120VR	Budget End	04/30/17		
Program Official	Veerasamy Ravichandran	Council	201605	Project End	04/30/20	Number of Sub Awards	
Grants Management Specialist	Justin Rosenzweig	FY	2016	EIN	1826000945A1		
Yrs Requested	4	Yrs Recommend	4	Yrs Authorized	4		
Component Organization	UNIVERSITY OF IDAHO	Component Name	Project-001	Component type (Project, Sub Award, Consortia Project)		Project	

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
Requested (424) Personnel																									
Name/Project Role	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**
Nuismer		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121					
Remien			9,339	2,951	12,290			9339	2951	12,290			9339	2951	12,290			9339	2951	12,290					
Postdoc Assoc			52,000	20,383	72,383			52,000	20,383	72,383			52,000	20,383	72,383			52,000	20,383	72,383					
Graduate Students																									
Undergrad Students							12	14,350		14,350		12	14,350		14,350		12	14,350		14,350					
Secretarial/Clerical																									
Additional / Combined Personnel																									
Total Requested Personnel			**72,069**	**26,725**	**98,794**			**86,419**	**26,725**	**113,144**			**86,419**	**26,725**	**113,144**			**86,419**	**26,725**	**113,144**					
Remien	31.60%																								

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
Allowable & IRG Recommended Personnel																									
Reduction Amount																									
Reduction Percentage																									
Name/Project Role	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**
Nuismer		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121					
Remien			9,339	2,951	12,290			9,339	2,951	12,290			9,339	2,951	12,290			9,339	2,951	12,290					
Postdoc Assoc			52,000	20,383	72,383			52,000	20,383	72,383			52,000	20,383	72,383			52,000	20,383	72,383					
Graduate Students																									
Undergrad Students							12	14,350		14,350		12	14,350		14,350		12	14,350		14,350		12			
Secretarial/Clerical																									
Additional / Combined Personnel																									
Total Allowable & IRG Recommended Personnel			**72,069**	**26,725**	**98,794**			**86,419**	**26,725**	**113,144**			**86,419**	**26,725**	**113,144**			**86,419**	**26,725**	**113,144**					

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
IC Funding/Awarded Personnel																									
Reduction Amount																									
Reduction Percentage																									
Reduction Post T2 Target																									
Name/Project Role	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**	**#**	**mos**	**salary**	**fringe**	**total**
Nuismer		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121		(b)(6)	10,730	3,391	14,121					
Remien			9,339	2,951	12,290			9,339	2,951	12,290			9,339	2,951	12,290			9,339	2,951	12,290					
Postdoc Assoc			52,000	20,383	72,383			52,000	20,383	72,383			52,000	20,383	72,383			52,000	20,383	72,383					
Graduate Students																									
Undergrad Students							12	14,350		14,350		12	14,350		14,350		12	14,350		14,350		12			
Secretarial/Clerical																									
Additional / Combined Personnel																									
Total IC Funding/Awarded Personnel			**72,069**	**26,725**	**98,794**			**86,419**	**26,725**	**113,144**			**86,419**	**26,725**	**113,144**			**86,419**	**26,725**	**113,144**					

Requested (424) Other Costs	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04
Salaries	72,069	86,419	86,419	86,419
Fringe	26,725	26,725	26,725	26,725
Total Personnel	98,794	113,144	113,144	113,144
Equipment	12,000			
Travel	3,150	3,150	3,150	3,150
Participant Tuition & Fees				
Participant Stipend				
Participant Travel				
Participant Subsistence				
Participant Other				
Participant Number of Participants				

Materials & Supplies	2,500	1,500	1,500	1,500	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual					
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1	2,000	4,500	4,500	4,500	
Other 2					
Other 3					
Total Requested (424) Other Costs	**19,650**	**9,150**	**9,150**	**9,150**	
Total Requested (424) Costs	**118,444**	**122,294**	**122,294**	**122,294**	
Allowable & IRG Recommended Other Costs	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Reduction Amount					
Reduction Percentage					
Salaries	72,069	86,419	86,419	86,419	
Fringe	26,725	26,725	26,725	26,725	
Total Personnel	98,794	113,144	113,144	113,144	
Equipment	12,000				
Travel	3,150	3,150	3,150	3,150	
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					
Materials & Supplies	2,500	1,500	1,500	1,500	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual	72,484	72,561	72,561	72,561	
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1 - please select Other type	2,000	4,500	4,500	4,500	
Other 2 - please select Other type					
Other 3 - please select Other type					
Total Allowable and IRG Recommended Other Costs	**92,134**	**81,711**	**81,711**	**81,711**	
Total Allowable and IRG Recommended Costs	**190,928**	**194,855**	**194,855**	**194,855**	
IC Funding/Awarded Other Costs	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Reduction Amount					
Reduction Percentage					
Reduction post T2 Target					
Salaries	72,069	86,419	86,419	86,419	
Fringe	26,725	26,725	26,725	26,725	
Total Personnel	98,794	113,144	113,144	113,144	
Equipment	12,000				
Travel	3,150	3,150	3,150	3,150	
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					
Materials & Supplies	2,500	1,500	1,500	1,500	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual	72,484	72,561	72,561	72,561	
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1 - please select Other type	2,000	4,500	4,500	4,500	
Other 2 - please select Other type					
Other 3 - please select Other type					
Total IC Funding/Awarded Other Costs	**92,134**	**81,711**	**81,711**	**81,711**	
Total IC Funding/Awarded Costs	**190,928**	**194,855**	**194,855**	**194,855**	
Indirect (F&A) Costs Exclusions	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Equipment	12,000				
Subaward/Consortium/Contractual	47,484	72,561	72,561	72,561	

Patient Care					
Alterations/Renovations					
Tuition					
Other Exclusions					
Other Exclusions Less Staff Adjustment					
Total Exclusions	59,484	72,561	72,561	72,561	
Total Base	131,444	122,294	122,294	122,294	
Indirect (F&A) Costs Base Type	MTDC				
Indirect (F&A) Costs Breakdown	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Requested Base 1	106,444	122,294	122,294	122,294	
Requested Rate 1	46.00%	46.00%	46.00%	46.00%	
Requested Subtotal Indirect (F&A) 1	48,964	56,255	56,255	56,255	
Rate(s) 1 at Time of Award	46.00%	46.00%	47.50%	47.50%	
Months	12	2	12	12	
Base 1 Less IRG/IC Reductions	131,444	20,382	122,294	122,294	
Rate(s) 1b at Time of Award	46.00%	47.50%			
Months (Split Rate 1)		10			
Base 1b Less IRG/IC Reductions		101,912			
Subtotal Indirect (F&A) 1 Authorized	60,464	57,784	58,090	58,090	
Total Indirect (F&A) Costs Authorized	60,464	57,784	58,090	58,090	
PROJECT SUMMARY	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Total Direct Costs Authorized	190,928	194,855	194,855	194,855	
Total Indirect (F&A) Costs Authorized	60,464	57,784	58,090	58,090	
Total Direct & Indirect (F&A) Costs Authorized	251,392	252,639	252,945	252,945	
Fee Authorized					
Total Direct, Indirect (F&A) Costs, & Fee Authorized	251,392	252,639	252,945	252,945	
Subaward / Consortia Project Allowable in Base	25,000				
Comments	No changes from requested level.				

Grant Number	1R01GM122079-01	Priority	(b)(6)	Budget Start	08/01/16
Grantee Organization	UNIVERSITY OF IDAHO	Percentile		Project Start	08/01/16
Principal Investigator	SCOTT NUISMER	PCC	B120VR	Budget End	04/30/17
Program Official	Veerasamy Ravichandran	Council	201605	Project End	04/30/20
Grants Management Specialist	Justin Rosenzweig	FY	2016	EIN	1826000945A1
Yrs Requested	4	Yrs Recommend	4	Yrs Authorized	4
Component Organization	*University of Texas at Austin*	Component Name	Project001Sub001	Component type (Project, Sub Award, Consortia Project)	Sub Award

Number of Sub Awards

Requested (424) Personnel

Name/Project Role	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total
Bull		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360					
Tech			20,004	6,001	26,005			20004	6001	26,005			20004	6001	26,005			20004	6001	26,005					
Postdoc Assoc																									
Graduate Students																									
Undergrad Students																									
Secretarial/Clerical																									
Additional / Combined Personnel																									
Total Requested Personnel			27,204	8,161	35,365			27,204	8,161	35,365			27,204	8,161	35,365			27,204	8,161	35,365					
Tech	30.00%																								

Allowable & IRG Recommended Personnel

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
Reduction Amount																									
Reduction Percentage																									
Name/Project Role	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total
Bull		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360					
Tech			20,004	6,001	26,005			20,004	6,001	26,005			20,004	6,001	26,005			20,004	6,001	26,005					
Postdoc Assoc																									
Graduate Students																									
Undergrad Students																									
Secretarial/Clerical																									
Additional / Combined Personnel																									
Total Allowable & IRG Recommended Personnel			27,204	8,161	35,365			27,204	8,161	35,365			27,204	8,161	35,365			27,204	8,161	35,365					

IC Funding/Awarded Personnel

	Bud Period 1 / Yr. 01					Bud Period 2 / Yr. 02					Bud Period 3 / Yr. 03					Bud Period 4 / Yr. 04									
Reduction Amount																									
Reduction Percentage																									
Reduction Post T2 Target																									
Name/Project Role	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total	#	mos	salary	fringe	total
Bull		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360		(b)(6)	7,200	2,160	9,360					
Tech			20,004	6,001	26,005			20,004	6,001	26,005			20,004	6,001	26,005			20,004	6,001	26,005					
Postdoc Assoc																									
Graduate Students																									
Undergrad Students																									
Secretarial/Clerical																									
Additional / Combined Personnel																									
Total IC Funding/Awarded Personnel			27,204	8,161	35,365			27,204	8,161	35,365			27,204	8,161	35,365			27,204	8,161	35,365					

Requested (424) Other Costs

	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Salaries	27,204	27,204	27,204	27,204	
Fringe	8,161	8,161	8,161	8,161	
Total Personnel	35,365	35,365	35,365	35,365	
Equipment					
Travel	1,000	1,000	1,000	1,000	
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					

Materials & Supplies	10,000	10,000	10,000	10,000	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual					
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1					
Other 2					
Other 3					
Total Requested (424) Other Costs	**11,000**	**11,000**	**11,000**	**11,000**	
Total Requested (424) Costs	**46,365**	**46,365**	**46,365**	**46,365**	
Allowable & IRG Recommended Other Costs	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Reduction Amount					
Reduction Percentage					
Salaries	27,204	27,204	27,204	27,204	
Fringe	8,161	8,161	8,161	8,161	
Total Personnel	35,365	35,365	35,365	35,365	
Equipment					
Travel	1,000	1,000	1,000	1,000	
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					
Materials & Supplies	10,000	10,000	10,000	10,000	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual					
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1 - please select Other type					
Other 2 - please select Other type					
Other 3 - please select Other type					
Total Allowable and IRG Recommended Other Costs	**11,000**	**11,000**	**11,000**	**11,000**	
Total Allowable and IRG Recommended Costs	**46,365**	**46,365**	**46,365**	**46,365**	
IC Funding/Awarded Other Costs	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Reduction Amount					
Reduction Percentage					
Reduction post T2 Target					
Salaries	27,204	27,204	27,204	27,204	
Fringe	8,161	8,161	8,161	8,161	
Total Personnel	35,365	35,365	35,365	35,365	
Equipment					
Travel	1,000	1,000	1,000	1,000	
Participant Tuition & Fees					
Participant Stipend					
Participant Travel					
Participant Subsistence					
Participant Other					
Participant Number of Participants					
Materials & Supplies	10,000	10,000	10,000	10,000	
Publication Costs					
Consultant Costs					
ADP/Computer Services					
Subaward/Consortium/Contractual					
Equipment or Facility Rental/User Fees					
Alterations/Renovations					
Other 1 - please select Other type					
Other 2 - please select Other type					
Other 3 - please select Other type					
Total IC Funding/Awarded Other Costs	**11,000**	**11,000**	**11,000**	**11,000**	
Total IC Funding/Awarded Costs	**46,365**	**46,365**	**46,365**	**46,365**	
Indirect (F&A) Costs Exclusions	**Bud Period 1 / Yr. 01**	**Bud Period 2 / Yr. 02**	**Bud Period 3 / Yr. 03**	**Bud Period 4 / Yr. 04**	
Equipment					
Subaward/Consortium/Contractual					

Patient Care					
Alterations/Renovations					
Tuition					
Other Exclusions					
Other Exclusions Less Staff Adjustment					
Total Exclusions					
Total Base	46,365	46,365	46,365	46,365	
Indirect (F&A) Costs Base Type	MTDC				
Indirect (F&A) Costs Breakdown	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Requested Base 1	46,365	46,365	46,365	46,365	
Requested Rate 1	55.00%	55.00%	55.00%	55.00%	
Requested Subtotal Indirect (F&A) 1		25,501	25,501	25,501	
Rate(s) 1 at Time of Award	55.00%	56.50%	56.50%	56.50%	
Months	1	12	12	12	
Base 1 Less IRG/IC Reductions	5,152	46,365	46,365	46,365	
Rate(s) 1b at Time of Award	56.50%				
Months (Split Rate 1)	8				
Base 1b Less IRG/IC Reductions	41,213				
Subtotal Indirect (F&A) 1 Authorized	26,119	26,196	26,196	26,196	
Total Indirect (F&A) Costs Authorized	26,119	26,196	26,196	26,196	
PROJECT SUMMARY	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Total Direct Costs Authorized	46,365	46,365	46,365	46,365	
Total Indirect (F&A) Costs Authorized	26,119	26,196	26,196	26,196	
Total Direct & Indirect (F&A) Costs Authorized	72,484	72,561	72,561	72,561	
Fee Authorized					
Total Direct, Indirect (F&A) Costs, & Fee Authorized	72,484	72,561	72,561	72,561	
Subaward / Consortia Project Allowable in Base	25,000				
Subaward F&A Inclusion/Exclusion	Bud Period 1 / Yr. 01	Bud Period 2 / Yr. 02	Bud Period 3 / Yr. 03	Bud Period 4 / Yr. 04	
Subaward Inclusion	25,000				
Subaward Exclusion	47,484	72,561	72,561	72,561	
Comments					

Joint DMS/NIGMS Initiative to Support
Research at the Interface of the
Biological and Mathematical Sciences (DMS/NIGMS)

RPG, 201605 Council
BBCB

PL# 16-240

CAN 8472185

#	Score	Council	Budget Start	Type	Actv	IC	Serial Num	Yr	Sfx	PI Name (Contact)	Title	Institution	PCC	Program Rec DC	TC	Notes	GS (Grant Specialist)	Abs	Img
1	(b)(6)	201605	2016/08/01	1	R01	GM	122079	1		NUISMER, SCOTT L	COLLABORATIVE RESEARCH: A MATHEMATICAL THEORY OF TRANSMISSIBLE VACCINES	UNIVERSITY OF IDADO	B120VR	$190,310	$249,854	5 years	ROSENZWEIG, JUSTIN	Abs	Img

Grace Y. Olascoaga -S

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Date: 2016.06.15 16:54:16 -04'00'

Ann A. Hagan -S

Digitally signed by Ann A. Hagan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, cn=Ann A. Hagan -S, 0.9.2342.19200300.100.1.1=0010146544
Date: 2016.06.16 11:19:36 -04'00'