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TITLE: Development of Live-Attenuated Old World Arenavirus Vaccines Based on Temperature-Sensitive Viruses

PRINCIPAL INVESTIGATOR: David Topham, PhD

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14. ABSTRACT In this application we will test the novel hypothesis that a temperature sensitive (ts)-based strategy can be used to develop safe, stable, immunogenic and protective live-attenuated vaccines (LAV) for the treatment of Old World Arenavirus (OWA) disease in humans. Although a few ts mutants have been previously used to generate attenuated viruses for their implementation as LAV (e.g. influenza), this will be the first demonstration that this ts-based approach could be used to develop LAV for the treatment of OWA. Importantly, our studies will also provide essential information on the biology of OWA and how mutations in their genome affect viral fitness at different temperatures. Moreover, results from this proposal will allow us to demonstrate that our ts-based approach also represents an excellent strategy to generate valid OWA surrogates that could be used safely in BSL2 containment to facilitate the study of these important human pathogens without the use of restrictive BSL4 laboratories. Because of the safety concerns and costs associated with hemorrhagic fever (HF)-causing OWA work under BSL4 facilities, we will use, as a proof of concept, the prototype OWA lymphocytic choriomeningitis virus (LCMV). To that end, we will combine the identification of mutations found in our ts r3LCMV individual clones with the power of reverse genetic approaches to generate unique rLCMV containing mutation(s) responsible of the ts phenotype (rLCMV/ts). The generated rLCMV/ts will be evaluated for their potential as safe, stable, immunogenic and effective LAV, using the extensively validated and well characterized animal model of LCMV infection and associated disease. Our long-term goal is to implement the same ts-based approach to develop LAV to combat disease caused by HF-causing OWA (e.g. LASV), currently outside the scope of this proof-of-concept exploratory proposal.

15. SUBJECT TERMS
Old World Arenavirus, biosafety level, hemorrhagic fever virus, live-attenuated vaccines, lymphocytic choriomeningitis virus, Lassa virus,reverse genetics, temperature sensitive mutants.

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1. INTRODUCTION

In a letter submitted in January 21, 2020, we indicated Ms. Lisa Sawyer our intention to leave University of Rochester and join Texas Biomedical effective February 2020. Our intention was to hope that University of Rochester can retain this award and established a subcontract agreement with Texas Biomed.

Our laboratory effectively relocated from University of Rochester to Texas Biomed in February 2020. We expended the two months before moving the laboratory (December 2019 and January 2020) finishing some research projects and packaging the lab.

In March 2020, just after arriving at Texas Biomed, and in response to the COVID-19 pandemic, San Antonio City and Bexar County officials implemented efforts to prevent the spread of the disease and maintain the health of our communities.

Texas Biomed's Leadership acted quickly to comply with efforts to ensure the safety and health of employees and their families. Operations were impacted and limited, prioritizing COVID-19 studies for the limited resources available during this time. These limited operations created a backlog of IACUC approvals, BSC approvals and laboratory operations. The confluence of these circumstances adversely impacted the establishment of my lab after relocation and progress on this project.

Because of these two reasons (relocation of the lab from University of Rochester to Texas Biomed and the COVID-19 pandemic), we have not been able to accomplish several of the goals in our initial proposal. With resources at Texas Biomed slowly increasing to reach closer to normal operations capacity recently, my lab is slowly establishing and gearing up to execute on contracts and grants. For this specific project, remaining tasks will execute as soon as possible and although the pandemic's impact and prevalence is unpredictable, Texas Biomed's leadership is committed to ensuring that I have resources available to successfully complete the goals of this research project.

Since the relocation of the lab and during the pandemic, we have been able to submit and receive Institutional Biosafety Committee (IBC) and Institutional animal care and use committee (IACUC) approval for the experiments in this project at the new institution, Texas Biomedical Research Institute. Moreover, we have been able to submit for ACURO approval (pending).

During the remaining funding period we will complete the proposed remaining studies that we have not been able to complete.

2. KEYWORDS

Biosafety level, hemorrhagic fever virus, lymphocytic choriomeningitis virus, Lassa virus, live-attenuated vaccine, reverse genetics, Old World arenavirus, temperature sensitive mutants.

3. ACCOMPLISHMENTS

Our progress on this project has been severely affected as result of several extenuating circumstances. I relocated to Texas Biomedical Research Institute in San Antonio, TX from University of Rochester, Rochester, New York, in February 2020. Shortly upon arrival, March 2020, a national emergency was declared as a result of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic and associated coronavirus disease 2019 (COVID-19). Since the national declaration, research at Texas Biomedical Research Institute has been focused on SARS-CoV-2 as mission critical, while at the same time limiting operations, capacity and research in other fields. Because of these two reasons (relocation of the lab from University of Rochester to Texas Biomed and the COVID-19 pandemic), we have not been able to accomplish several of the goals in our initial

proposal. With resources at Texas Biomed slowly increasing to reach closer to normal operations capacity recently, my lab is slowly establishing and gearing up to execute on contracts and grants. For this specific project, remaining tasks will execute as soon as possible and although the pandemic's impact and prevalence is unpredictable, Texas Biomed's leadership is committed to ensuring that I have resources available to successfully complete the goals of this research project. That being said, our goal is to continue working toward execution of the remaining studies during the duration of the project.

3A. Major project goals

Specific Aims (SA):
SA 1. Identify the mutations responsible for the temperature sensitive phenotype of LCMV.
Timeline (Months): 1-6
Status: Complete

Major tasks:
Major Task 1. High-throughput next generation sequencing (NGS) to identify the mutations responsible for the ts phenotype of r3LCMV/ts individual clones.
Timeline (Months): 1-3
Status: Complete

Major Task 2. Generation and characterization of rLCMV/ts mutants
Timeline (Months): 4-6
Status: Complete

Milestone(s):
Milestone 1. Identification of the mutations responsible of the ts phenotype of r3LCMV/ts individual clones.
Status: Complete

Milestone 2. Generation of ts rLCMV/ts.
Status: Complete

Local IRB Approval: Submitted and approved at Texas Biomedical Research Institute.
Local IACUC Approval: Not applicable.

SA 2. Determine the genetic and phenotypic stability of rLCMV/ts
Timeline (Months): 7-12
Status: Ongoing

Major tasks:
Major Task 3. Assess the genetic and phenotypic stability or rLCMV/ts in cultured cells.
Timeline (Months): 7-9
Status: Ongoing

Major Task 4. Determine the genetic and phenotypic stability of rLCMV/ts in vivo.
Timeline (Months): 10-12
Status: Not yet initiated.

Milestone(s):
Milestone 1. Stability of rLCMV/ts in cultured cells.
Status: Ongoing

Milestone 2. Stability of rLCMV/ts in vivo.
Status: Not yet initiated.

Local IRB Approval: Submitted and approved at Texas Biomedical Research Institute.
Local IACUC Approval: Submitted and approved at Texas Biomedical Research Institute.
ACURO Approval: Submitted and pending.

SA 3. Characterize the safety, immunogenicity and protective efficacy of selected rLCMV/ts
Timeline (Months): 13-18
Status: Not yet initiated.

Major tasks:
Major Task 5. Characterize the ability of rLCMV/ts to induce fatal LCM.
Timeline (Months): 13-14
Status: Not yet initiated.

Major Task 6. Assess the immunogenicity of rLCMV/ts.
Timeline (Months): 15-16
Status: Not yet initiated.

Major Task 7. Evaluate the protection efficacy of rLCMV/ts against a lethal challenge with rLCMV/WT.
Timeline (Months): 17-18
Status: Not yet initiated.

Milestone(s):
Milestone 1. Safety of rLCMV/ts.
Status: Not yet initiated.

Milestone 2. Immunogenicity of rLCMV/ts.
Status: Not yet initiated.

Milestone 3. Protection efficacy of rLCMV/ts.
Status: Not yet initiated.
Local IRB Approval: Submitted and approved at Texas Biomedical Research Institute.
Local IACUC Approval: Submitted and approved at Texas Biomedical Research Institute.
ACURO Approval: Submitted and pending.

3A. What was accomplished under these goals?

As indicated above, the relocation of the lab from University of Rochester to Texas Biomed and the COVID-19 pandemic have severely impacted our progress and we have not been able to accomplish several of the goals in our initial proposal. Our laboratory effectively relocated from University of Rochester to Texas Biomed in February 2020. We expended the two months before moving the laboratory (December 2019 and January 2020) finishing some research projects and packaging the lab. In March 2020, just after arriving at Texas Biomed, and in response to the COVID-19 pandemic, San Antonio City and Bexar County officials implemented efforts to prevent the spread of the disease and maintain the health of our communities. With resources at Texas Biomed slowly increasing to reach closer to normal operations capacity recently, my lab is slowly establishing and gearing up to execute on contracts and grants. For this specific project, remaining tasks will execute as soon as possible and although the pandemic's impact and prevalence is unpredictable, Texas Biomed's leadership is committed to ensuring that I have resources available to successfully complete the goals of this research project. Since our last progress report in May 2020, we have not been able to conduct any research

related to this project because of the ongoing COVID-19 pandemic. During this time, we have been able to submit and receive Institutional Biosafety Committee (IBC) and Institutional animal care and use committee (IACUC) approval for the experiments in this project at the new institution, Texas Biomedical Research Institute. Moreover, we have been able to submit for ACURO approval (pending).

3B. What opportunities for training and professional development has the project provided?

Nothing to report.

3C. Dissemination of results to communities of interest.

Our results have not yet been presented in any scientific venues.

Since the last progress report in May 2020, and because of the restrictions at Texas Biomedical Research Institute to conduct research only associated with SARS-CoV-2/COVID-19, our work during the last year have focussed on bringing our expertise to combat the COVID-19 panedemic. Published or in pre-print studies we have conducted during the last year of fuding (May 2020-April 2021):

Varun Dwivedi, **JunGyu Park**, Stephen Grenon, Nicholas Medendorp Jr., Cory Hallam, Jordi B. Torrelles, **Luis Martinez-Sobrido**, Viraj Kulkarni. Rapid and Efficient Inactivation of SARS-CoV-2 from Surfaces using UVC Light Emitting Diode Device.
bioRxiv 2021.04.20.440654; doi: https://doi.org/10.1101/2021.04.20.440654. Accepted for publication.

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3D. Plans for next reporting period.

As indicated above, our progress on this project has been severely delayed as result of two major extenuating circumstances. First, I relocated to Texas Biomedical Research Institute in San Antonio, TX from University of Rochester, Rochester, New York, in February 2020, around the time of my last annual report

of May 2020. Second, shortly upon arrival, March 2020, a national emergency was declared as a result of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic and associated coronavirus disease 2019 (COVID-19), also at approximately the time of my last annual report (May 2020). Since the national declaration, research activities at Texas Biomedical Research Institute has been focused on SARS-CoV-2 as mission critical, with very limited operations, capacity and research in other fields. Our goal is to continue working toward execution of the remaining studies during the duration of the project.

4. IMPACT

4A. What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report.

4B. What was the impact on other disciplines?
Nothing to Report.

4C. What was the impact on technology transfer?
Nothing to Report

4D. What was the impact on society beyond science and technology?
Nothing to Report.

5. CHALLENGES/PROBLEMS

5A. Changes in approach and reasons for change

Our laboratory relocated from University of Rochester to Texas Biomedical Research Institute in February 2020. Shortly after the relocation of our laboratory to Texas biomedical Research Institute in March 2020, the SARS-CoV-2 pandemic was declared a national threat that limited operations and research capacity at Texas Biomedical Research Institute, including research on this project.

Since the relocation of the lab and during the pandemic, we have been able to submit and receive Institutional Biosafety Committee (IBC) and Institutional animal care and use committee (IACUC) approval for the experiments in this project at the new institution, Texas Biomedical Research Institute. Moreover, we have been able to submit for ACURO approval (pending).

For this specific project, remaining tasks will execute as soon as possible and although the pandemic's impact and prevalence is unpredictable, Texas Biomed's leadership is committed to ensuring that I have resources available to successfully complete the goals of this research project.

5B. Actual or anticipated problems or delays and actions or plans to resolve them

Two of the major problems with this project during the last year has been: 1) the relocation or my laboratory from University of Rochester to Texas Biomedical Research Institute in San Antonio, Texas, in February 2020; and, 2) the SARS-CoV-2 pandemic that started early 2020. After joining Texas Biomedical Research Institute in February 2020, and because the SARS-CoV-2 pandemic, research at Texas Biomedical Research Institute, in response to the COVID-19 pandemic, were affected. San Antonio City and Bexar County officials implemented efforts to prevent the spread of the disease and maintain the health of our communities. Since March 2020, research at Texas Biomedical Research Institute has been focused on SARS-CoV-2 as mission critical, while at the same time limiting operations, capacity and research in other fields.

As indicated above, remaining tasks for this project will execute as soon as possible and although the pandemic's impact and prevalence is unpredictable, Texas Biomed's leadership is committed to ensuring that I have resources available to successfully complete the goals of this research project.

5C. Changes that had a significant impact on expenditures

As indicated elsewhere in this progress report, the relocation of my laboratory from University of Rochester to Texas Biomed in February 2020 and the restrictions beginning in March 2020 due to the SARS-CoV-2 pandemic has significantly affected the completion of the tasks outlined in the proposal. After joining Texas Biomedical Research Institute in February 2020, and because the SARSCoV- 2 pandemic response, research activities at Texas Biomedical Research Institute has been focused on SARS-CoV-2 as mission critical, with very limited operations, capacity and research in other fields. As indicated elsewhere in this project report, remaining tasks for this project will execute as soon as possible and although the pandemic's impact and prevalence is unpredictable, Texas Biomed's leadership is committed to ensuring that I have resources available to successfully complete the goals of this research project.

Since the relocation of the lab and during the pandemic, we have been able to submit and receive Institutional Biosafety Committee (IBC) and Institutional animal care and use committee (IACUC) approval for the experiments in this project at the new institution, Texas Biomedical Research Institute. Moreover, we have been able to submit for ACURO approval (pending). Funds have been utilized for personnel only; no supplies, reagents or animals have been purchased.

5D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
None.

5D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

IBC and IACUC documents have been submitted and approved at Texas Biomedical Research Institute for the completion of the proposed experiments.

ACURO approval has been submitted but still pending.

6. PRODUCTS

6A. Publications, conference papers, and presentations
No journal publications or books to date.

6B. Website(s) or other Internet site(s)
Nothing to report.

6C. Technologies or techniques
Nothing to report.

6D. Inventions, patent applications, and/or licenses
Nothing to report.

6E. Other Products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7A. What individuals have worked on the project?

Name: David J. Topham
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000000294358673
Nearest person month worked: 0 months
Contribution to Project: Dr. David Topham recently took over as contact PI at the University of Rochester upon Dr. Luis Martinez-Sobrido leaving the University of Rochester. Dr. Topham provides contract award administrative oversight. All work is being performed at Texas Biomedical Research Institute, under the direction of Dr. Martinez-Sobrido.
Funding Support: This award

Name: Luis Martinez-Sobrido
Project Role: Subaward PI
Researcher Identifier (e.g. ORCID ID): 0000-0001-7084-0804
Nearest person month worked: 0.96 months
Contribution to Project: Dr. Martinez-Sobrido directly oversaw or supervised all project studies. Dr. Martinez-Sobrido is well experienced in the molecular biology and virological aspects of arenavirus. He has worked on arenavirus for more than 10 years and is expert in the use of plasmid-based reverse genetics techniques to rescue recombinant arenavirus, the identification and characterization of arenavirus interferon antagonist proteins, the development of trisegmented and single-cycle infectious arenavirus, and in the implementation of the codon optimization approach for the generation of safe vaccines
for the treatment of arenavirus infections.
Funding Support: This award

Name: Chengjin Ye
Project Role: Post-doctoral fellow
Researcher Identifier (e.g. ORCID ID): Not available
Nearest person month worked: 7 months
Contribution to Project: Dr. Ye has been responsible of conducting the experiment described in this proposal. Dr. Ye has more than 5 years of experience working with negative- and positive-stranded RNA viruses, last of them in Dr. Martinez-Sobrido's laboratory. Dr. Ye is an expert in reverse genetic techniques to generate recombinant wild-type and mutated negative- and positive-stranded RNA viruses, and work with animal model of virus infection.
Funding Support: This award

7B. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes.

7C. What other organizations were involved as partners?

None.

8. SPECIAL REPORTING REQUIREMENTS

None.

9. APPENDICES

OTHER SUPPORT

TOPHAM, D.J.

ACTIVE

HHSN272201400005C (Topham) 04/01/21-03/31/22 .6 Calendar
NIH/NIAID $200,000 TPC
"NIAID Centers of Excellence in Influenza Research and Surveillance - Administrative support for the following non-severable options:

- Nayak Option 16D/16D EA - Effect of frequency and type of influenza vaccination on the development of the anti-influenza CD4 T cell and B cell response
- Topham Option 16J - Increasing the vaccine cross-protection against IAVs by improving the NA antigen response
- Sant Option 16I - Unique features of CD4 T cell epitope distribution, localization and effector functions elicited by intranasal administration of HA-ferritin vaccines
- Sant Option 17A EA - Potentiating broadly protective local immunity to influenza virus through a novel vaccine platform
- Subbararo Option 12B/12B EA – The effect of prior natural infection or vaccination ('imprinting') on subsequent response to influenza vaccine in children

Role: PD/PI

HHSN272201400005C (Topham) 08/30/18-03/31/22 0 Calendar
NIH/NIAID $200,000 TPC
"NIAID Centers of Excellence in Influenza Research and Surveillance - 16J - Increasing the vaccine cross-protection against IAVs by improving the NA antigen response"
The deliverables of this study are (1) Development of CVVs that encode for currently recommended NA antigens with variations in stability AND (2) Evaluations of different strategies to extrinsically stabilize NA during the CVV isolation process and to increase NA yields from CVVs
Role: Project PI

HHSN272201400005C (Topham) 08/30/18-09/30/21 0 Calendar
NIH/NIAID $457,362 TPC
"NIAID Centers of Excellence in Influenza Research and Surveillance – 16GEA - Memory B cell and serum antibody responses compared in healthy adults receiving licensed seasonal influenza vaccines…"
This project addresses whether adaptations in the influenza hemagglutinin during culture in eggs affects the antigenicity of the vaccine, diminishing induction of protective immunity. Further, it addresses the goals of understanding vaccine failures, which is the major overall theme of the NYICE and CEIRS
Role: Project PI

HHSN272201400005C (Topham) 04/08/20-05/20/22 .6 Calendar
NIH/NIAID $1,140,049 TPC
"NIAID Centers of Excellence in Influenza Research and Surveillance – 12CEA - Natural history of SARS-CoV-2 in comparison to influenza A virus: a multi-site study focused in the Southern Hemisphere and equatorial regions"
The COVID-19 pandemic demands a strong and sustained research response aimed at informing policy decisions and the design of effective countermeasures. To help meet this challenge, the CEIRS Network proposes a unified human surveillance effort designed to gather critical information on the spectrum of disease, risk factors, duration of viral shedding, viral genomics, viral dynamics within and between populations an

innate and memory immune responses to infection.
Role: Project PI

5 P01 AI102851-07 (Fowell) 9/1/19-8/31/24 2.4 Calendar
NIH/NIAID $12,111,690 TPC
"Tissue Regulation of T Cell Function: Project 3 - Formation, Positioning, Motility, and Function of Tissue Resident Memory CD8+ T cells After Influenza Infection" ($2,039,980 TPC - Topham, Project 3)
To determine the mechanisms that determine differentiation, establishment, and maintenance of TRM subsets after influenza infection; Investigate mechanisms of T cell-epithelial cell-matrix interactions required for motility and positioning in the airways; and determine the functions of CD49a and CD103 in optimizing immune protection.
Role: Project 3 PI

5 R01 AI129988-04 (Takimoto) 09/25/17-08/31/22 1.2 Calendar
NIH/NIAID $1,925,000 TPC
"Influenza virus host shutoff mechanism"
The proposed research will characterize the novel influenza virus protein PA-X for its activity to shutoff host gene expression.
Role: Co-Inv

000792 - UNIV/Cornell Subaward (Topham) 08/08/17-07/31/22 .24 Calendar
NIH/NIAID - Prime 5 U01 AI131348-04 (Rudd) 216,319 TPC (Rochester Subaward)
"Roles for Developmentally Regulated microRNAs in Neonatal Immunity"
The major goal of this grant is to identify the key gene regulatory networks that underlie cell-intrinsic differences between neonatal and adult CD8+ T cells.
Role: Subaward PI

5 UM1 AI148450-02 (Falsey, Branche) 12/11/19-11/30/26 1.2 Calendar
NIH/NIAID $4,309,471 TPC
"University of Rochester Vaccine and Treatment Evaluation Unit (VTEU)"
The University of Rochester VTEU site can offer the necessary scientific, clinical, administrative, and organizational structure to support these endeavors: evaluation of vaccines, preventive biologics, therapeutics, diagnostics, predictive markers and devices for the treatment and prevention of infectious diseases.
Role: Co-Investigator

W81XWH1810071 (Topham) 05/01/18-10/31/21 0 Calendar
DOD/ARMY $193,990 TPC
"Development of Live-Attenuated Old World Arenavirus Vaccines Based on Temperature-Sensitive Viruses"
The major goals of this project are to characterize the safety, immunogenicity and protective efficacy of selected rLCMV/ts in mice.
Role: PI

PENDING

R21 (Dumont) 09/01/21-08/31/23 .36 Calendar
NIH $423,500 TPC
"Development of the S2 subunit of the SARS-CoV-2 Spike as an Immunogen"
The overall goal of this project is to develop new classes of immunogens that can elicit immune responses directed at the spike S2 subunit as a step towards development of escape-resistant pancoronavirus vaccines.
Role: Co-Investigator

R21 AI159415 Resubmission (Thakar) 09/01/21-08/31/23 .6 Calendar
NIH $423,500 TPC
"Mechanistic modeling to discover control in unterferon and cytokine/chemokine signaling in influenza virus and coronavirus infections"
We propose to re-use valuable open- access data collected by BRCs to address the significant research gap in understanding the balance of early innate anti-viral response to influenza and SARS-CoV2 across viral strains and cell-types.
Role: Co-Investigator

U01 AI165330 (Topham, Evans, Falsey) 01/01/22-12/31/23 1.2 Calendar
NIH/NIAID $1,951,163 TPC
"A Phase 1, Open-Label Study to Evaluate the Effect of Varied Boosting Regimens on the Immune Response to ChAdOx1-MERS"
We intend to conduct a large, first-of-its-kind 10-arm study to examine the relation between pre-immune responses and post-boost measurements, and to begin to build models that may be used by other investigators to further this area of investigation.
Role: MPI

DP2 (Anderson) 07/01/21-06/30/26 .24 Calendar
NIH $2,310,000 TPC
"The airway microbiota as a driver of clinical severity following influenza infection"
The goal of this proposal is to test how host responses to influenza virus infection are modulated by the airway microbiota
Role: Co-Investigator

R21 (McGrath) 07/01/21-06/30/23 .24 Calendar
NIH $423,500 TPC
"Small extracellular vesicle-based detection of anti-viral B cell subsets"
We propose to develop a novel method to detect these antigen specific B cell subtypes, including those resident in lymphoid organs and peripheral tissues. If successful, this could be adapted into a high throughput method for rapid screening of populations to assess their B cell subset responses to specific antigens.
Role: Co-Investigator

OVERLAP
There is no scientific overlap in the above applications.

MARTINEZ-SOBRIDO, LUIS

ACTIVE

W81XWH1810071 (Topham) 2/1/2020 – 10/31/2021 1.20 calendar
Department of Defense $117,201
Development of Live-Attenuated Old World Arenavirus Vaccines Based on Temperature-Sensitive Viruses
The major goals of this project are to characterize the safety, immunogenicity and protective efficacy of selected rLCMV/ts in mice.

R21AI135284 (Martinez-Sobrido) 2/1/2020 – 12/31/2021 0.60 calendar
National Institutes of Health $73,178
Attenuation of Lassa virus via codon deoptimization
The major goals of this project are to generate a recombinant LASV containing a codon deoptimized (CD) glycoprotein (GP) as a novel approach for the development of a LASV live--attenuated vaccine (LAV). Moreover, rLASV/GPCD will provide us with a valid LASV surrogate that could be safely used in BSL2 facilities to facilitate the investigation of LASV by removing the obstacles posed by the requirement of BSL4 containment to work with live forms of LASV.

R01AI141607 (de Figueiredo) 2/1/2020 – 5/31/2024 0.60 calendar
NIH/NHLBI $51,521
Development of a High-Throughput Microfluidics-Enabled Functional Assay for Rapidly Identifying Neutralizing Antibodies
The major goal of this project is to test the working hypothesis that PRESCIENT can identify in a mixed population of individual human hybridoma cells neutralizing antibodies against pH1N1 virus.

R01 AI142985 (de la Torre) 2/1/2020 – 3/31/2023 1.20 calendar
National Institutes of Health $125,000
Roles of the Nucleoprotein 3'-5' Exonuclease Domain in Arenavirus Biology
The major goals of this project are to provide a better understanding of arenavirus-host innate defense interactions, which can facilitate the development of novel strategies to combat human pathogenic mammarenaviruses.

R01 AI145332 (Kobie) 2/1/2020 – 8/31/2023 0.96 calendar
National Institutes of Health $150,000
Dynamics of the protective vaccine-induced human influenza neuraminidase B cell response
The major goals of this project are to define how various influenza vaccine types impact the characteristics of neuraminidase specific antibodies in humans and what properties of neuraminidase specific antibodies are most effective at preventing influenza infection against diverse strains.

W81XWH1710168 (Dewhurst) 2/1/2020 – 8/31/2021 0.6 calendar
Department of Defense $75,160
Development of a new, more effective live-attenuated influenza vaccine: an essential platform for future pandemic protection
The major goals of this project are to develop a new, more effective live-attenuated influenza vaccine (LAIV) capable of eliciting broadly cross-protective immune responses to conserved internal viral proteins - thereby providing the basis for a universal influenza vaccine.

R01 HL091968 (O'Reilly) 2/1/2020 – 8/31/2022 0.42 calendar
National Institutes of Health $12,627
Effects of Neonatal Hyperoxia on Alveolar Development and Infection
The major goal of this project is to test the hypothesis that neonatal hyperoxia enhances sensitivity to IAV infection by inducing epigenetic changes in proliferating AEC2s that are maintained even when they become AEC1s and these changes are mediated by the persistent expression of Ki67.

PO 7450001209283 (Gupta) 7/8/2020 – 6/30/2021 0.12 calendar
Univ of Texas, Health Sci Center at San Antonio $10,000
Probing the Binding Interfaces of RNA Synthesis and Processing Complex of SARS-Co-V-2
The major goal of this project is to investigate SARS-CoV-2 and identify key molecular interfaces in RSP complex for their immunogenic disruption. Additionally, we will conduct in vitro and in vivo testing of peptides for immunogenic molecular disruption.

N/A (Gupta) 7/1/2020 – 6/30/2021 0.60 calendar
San Antonio Partnership for Precision Therapeutics $50,000
Mechanism-based Targeting of an RNA Processing Pathway of SARS-CoV-2
The major goal of this project is to determine the structural basis of RNA processing in host immune and inflammatory response critical for viral survival and growth and will conduct HTS screening, medicinal chemistry, and in vitro and in vivo studies towards rapid clinical translation.

N/A (Ivanov) 7/1/2020 – 6/30/2021 0.24 calendar
San Antonio Partnership for Precision Therapeutics $80,000
Blocking SARS-CoV-2 evasion from innate antiviral defenses
The major goal of this project is to determine the effectivity of AT-100 post-infection in blocking SARS-CoV-2 infectivity.

W81XWH1910496 (Martinez-Sobrido) 8/1/2020 – 6/30/2021 1.80 calendar
Department of Defense $207,344
Development of Live-Attenuated Vaccine Platform Against Hemorrhagic fever causing Arenaviruses
The major goal of this project is to demonstrate that recombinant forms of the prototypic mammarenavirus lymphocytic choriomeningitis virus (LCMV) containing a codon deoptimized (CD) nucleoprotein (NP) expressing glycoproteins (GP) of HF-causing LASV and JUNV (rLCMV/NPCD/GPHF) can be used for the development of a safe and protective individual or blended live-attenuated vaccine (LAV) to combat HF disease caused by LASV and JUNV infections.

Proposal 20-243 (Torrelles) 9/1/2020 – 7/31/2021 0.20 calendar
Heat Biologics Inc. $75,293
Test gp96-based SARS-CoV-2 vaccine in hACE2 Tg mice – COVID-19 Efficacy Challenge Study
The major goal of this project is to understand if our proprietary product (N. Oleander) is effective as a prophylactic and/or for treatment and follow-up therapy for COVID-19 infected animals.

INV-019155 (Torrelles) 9/16/2020 – 9/30/2021 0.02 calendar
Bill & Melinda Gates Foundation $75,293
COVID-19 CTA: Preclinical models for SARS-CoV-2 infection
The major goal of this project is to determine if human monoclonal antibodies (hmAbs) shown in vitro to block SARS-CoV-2 infection are also effective, alone or in combination, in vivo using two rodent animal models of SARS-CoV-2 infection and associated COVID-19 disease.

Proposal 20-295 (Kulkarni) 11/1/2020 – 9/23/2021 0.10 calendar
Particle, Inc. $75,293
Particle COVID-19 Efficacy Study
The major goal of this project is to perform in vitro testing and evaluation of viral replication on the first screening of ASO #11-30.

MSA 5/24/2017; SOW (Torrelles) 11/1/2020 – 7/31/2021 0.14 calendar
Inovio Pharmaceuticals $43,890
SARS-CoV-2 live virus challenge of K18 hACE2-transgenic mice immunized with SARS-CoV-2 vaccines
The major goal of this project is to measure the protection against viral disease at peripheral and mucosal surfaces afforded by in vivo-produced, neutralizing DNA-encoding monoclonal antibodies (DMAbs).

3V FFS (Proposal 20-375) (Dwivedi) 11/17/2020 – 5/31/2021 0.14 calendar
3V Medical Research Group, Inc. $79,203
To determine the anti-SARS-CoV-2 effect of 3VM-1000 suspension in K18 hACE-2 mice
The major goal of this project is to assess the effect of 3VM1000 Suspension solution API on SARS-CoV-2 infectivity of host cells in a transgenic mouse model.

Proposal 20-372 (Kulkarni) 11/20/2020 – 11/20/2021 0.03 calendar
MedMira Inc. $31,075
Performance Evaluation of a Working Prototype, VYRA, for Simultaneous Detection of SARS-CoV-2 and **Influenza A/B in the Human Saliva or Oropharyngeal Specimens**
The major goal of this project is to evaluate the VYRA prototype for Simultaneous Detection of SARS-CoV-2 and Influenza A/B in the Human Saliva or Oropharyngeal Specimens.

3V FFS (Proposal 20-389) (Martinez-Sobrido) 12/4/2020 – 5/31/2021 0.23 calendar
3V Medical Research Group, Inc. $43,354
Single-cycle infections SARS-CoV-2
The major goal of this project is to assess the effect of 3VM1000 Suspension solution API on SARS-CoV-2 infectivity of host cells in a transgenic mouse model.

Proposal 20-336 (Martinez-Sobrido) 1/1/2021 – 12/31/2021 0.01 calendar
Texas Biomedical Forum $60,000
Single-cycle infectious SARS-CoV-2
The major goal of this project is to test the hypothesis that S- or E-deficient sciSARS-CoV-2 can be used for the development of a safe, immunogenic and protective LAV to combat COVID-19 disease caused by SARS-CoV-2 infection.

W81XWH2110095 (Shetty) 2/1/2021 – 1/31/2023 0.6 calendar
Department of Defense $33,037
Development of a Novel Drug Candidate, CSP7, for the Treatment of COVID-19
Our laboratory will be responsible for the experiments involving infection with SARS-CoV-2 USA-WA1/2020 strain for the development of a novel drug candidate, CSP7, for the treatment of COVID-19.

Proposal 20-376 (Turner) 1/4/2021 – 7/31/2021 0.09 calendar
Southwest Research Institute $166,691
Study 1: Pilot Efficacy of Compounds in ACE2 mice against SARS-CoV-2
The major goal of this project is to identify and develop compounds as a treatment against SARS-CoV-2.

Proposal 20-377 (Turner) 1/4/2021 – 7/31/2021 0.09 calendar
Southwest Research Institute $166,691

Study 2: Pilot Efficacy of Compounds in ACE2 mice against SARS-CoV-2
The major goal of this project is to identify and develop compounds as a treatment against SARS-CoV-2.

UT Austin FFS (Kulkarni) 2/01/2021 – 5/31/2021 0.01 calendar
The University of Texas at Austin $15,063
Evaluate the antiviral activity of CUSTOMER COMPOUNDS against SARS-CoV-2
The major goal of this project is to evaluate the antiviral activity of certain compounds against COVID-19.

Fidia FFS (Martinez-Sobrido) 3/02/2021 – 12/31/2021 0.23 calendar
Fidia Farmaceutici $65,814
In-vivo antiviral activity against SARS-CoV-2 of 2 compounds from Fidia farmaceutici S.p.A.
The purpose of this study is to assess the effect of 3VM1000 Suspension solution API on SARS-CoV-2 infectivity of host cells in a transgenic mouse model.

W81XWH2110103 (Pertsemlidis) 2/01/2021 – 1/31/2022 0.60 calendar
Department of Defense $27,123
SARS-CoV-2 Viral RNAs as Unique Biomarkers and Therapeutic Targets
The purpose of this study is to identify and characterize novel small RNAs produced by SARS-CoV-2 and exploit them as biomarkers and therapeutic targets. We propose a combination of computational biology, synthetic biology, genome editing, and chemistry approaches. The successful delivery of a v-miRNA inhibitor in cell culture will establish a foundation for preclinical and clinical characterization.

Proposal 20-127 (O'Connor) 6/1/2020-5/31/2021 0.36 calendar
University of Texas Health Science Center at San Antonio $15,000
Therapeutic application of antidepressants in COVID-19: mitigating the cytokine storm
Determine whether AD's exert their anti-inflammatory effect via direct action on immune cells and identify most effective anti-inflammatory AD using in vitro human whole blood immunoassay. Characterize the anti-inflammatory efficacy of ADs in vivo using non-pathogenic COVID-19 mouse model. Evaluate the ability to ADs to mitigate SARS-CoV-2 pathogenesis in hACE2 mouse model.

<u>PENDING</u>

Proposal 20-162 (Mallory) 4/01/2021 – 9/30/2022 0.9 calendar
Department of Defense $189,394
Viral and Microbial Decontamination Strategies for Medical Treatment Facilities, Close Quarters, and Austere Settings
The major goals of this project are to test the hypothesis that surfaces treated with zeolite will become inhospitable to bacterial and destroy the virulence of viruses coming in contact with treated surfaces for extended periods of time without reapplications. In addition, it is hypothesized that transition metal-zeolites, in combination with atmospheric hydrogen peroxide (<0.05ppm) will have a greater impact on pathogen destruction.

Proposal 20-329 (Forsthuber) 7/01/2021 – 6/30/2023 0.6 calendar
National Institutes of Health $12,776
Restraining organ pathology in a mouse model of SARS-CoV-2 infection with combinatorial MIF inhibition and glucocorticoid treatment
The major goal of this project is to evaluate the treatment of SARS-CoV-2 infection with combinatorial MIF inhibition and a glucocorticoid.

Proposal 20-306 (Kulkarni) 7/01/2021 – 6/30/2023 0.36 calendar
National Institutes of Health $178,766
CRISPR-based antivirals against SARS-CoV-2
Using established safe and effective gene delivery tools, like adeno-associated virus vectors and nanoparticle encapsulated RNA, we propose to test the efficacy of our approach in SARS-CoV-2 susceptible transgenic mice model. The knowledge from the proposed study will advance the field of CRISPR as an alternate countermeasure for SARS-CoV-2 and pave the path forward to clinical trials.

R21 Proposal 20-391 (Martinez-Sobrido) 7/01/2021 – 6/30/2023 0.6 calendar
National Institutes of Health $208,125
Codon deoptimization for the development of a SARS-CoV-2 live-attenuated vaccine
The major goal of this project is to generate, using our recently developed state-of-the-art reverse genetics approaches, a recombinant (r)SARS-CoV-2 containing a codon deoptimized (CD) Spike (S) glycoprotein (rSARS-CoV-2/CD) as a novel approach for the development of a safe, stable, immunogenic, and protective live-attenuated vaccine (LAV) to combat COVID-19 disease caused by SARS-SoV-2 infection.

POP Biotech SBIR Subaward(Huang) 7/1/2021 – 6/30/2022 0.6 calendar
National Institutes of Health $50,000
Developing a thermostable SARS-CoV-2 RBD-particle vaccine
The major goal of this project is to conduct the experiments related to the in vivo studies with SARS-CoV-2 in K18 hACE2-expressing transgenic mice in order to develop a thermostable vaccine for SARS-CoV-2.

Scripps R21 Subaward (De la Torre) 7/01/2021 – 6/30/2023 0.6 calendar
National Institutes of Health $75,000
Generation and Use of a Single-Cycle Infectious SARS-CoV-2
The major goal of this project is to generate and characterize S and E stably expressing Vero E6 cell lines that will be used to generate and characterize the sciSARS-CoV2ΔS and sciSARS-CoV2ΔE.

R01 Subaward-Proposal 21-021 (Sahay) 9/01/2021 – 8/31/2026 1.2 calendar
National Institutes of Health $249,999
Inhalable mRNA therapeutics for the treatment of SARS-CoV-2
The major goal of this project is to determine whether shACE2-based vaccine candidates protect mice and hamsters from a challenge with SARS-CoV-2.

R01 Subaward-Proposal 21-033 (Gupta) 9/01/2021 – 8/31/2026 0.6 calendar
National Institutes of Health $70,000
Mechanism-based Targeting of the RNA Processing Machinery of SARS-CoV-2
The major goal of this project is to determine the prophylactic and therapeutic activities of the identified compounds in vitro in cultured cells and in vivo in K18 human angiotensin converting enzyme 2 (hACE2) transgenic (wild-type SARS-CoV-2) or wild-type (mouse adapted SARS-CoV-2) mice and/or golden Syrian hamsters to determine their antiviral activity against SARS-CoV-2.

R21 Subaward-Proposal 21-035 (Kurdowska) 9/01/2021 – 8/31/2023 0.3 calendar
National Institutes of Health $55,000
Development of targeted therapies for severe lung inflammation triggered by SARS-CoV-2 virus
The major goal of this project is use to generate acute lung injury in mice by utilizing novel coronavirus SARS-CoV-2 in order to develop targeted therapies.

BioOasis STTR Subaward (Adhikari) 12/31/2021 – 12/31/2023 0.18 calendar
National Institutes of Health $50,000
ACE2-CoVbiotics, Lactobacillus based novel anti-SARS-COV2 probiotic: production, characterization and efficacy studies
The major goal of this project is to conduct the experiments related to the in vivo studies with SARS-CoV-2 in K18 hACE2-expressing transgenic mice in order to develop a vaccine for SARS-CoV-2.

UAB R01 Subaward-Proposal 21-063 (Kobie) 9/01/2021 – 8/31/2024 1.2 calendar
National Institutes of Health $207,907
The origin and future protective activity of SARS-CoV-2 RBD specific neutralizing antibodies
The major goal of this project is to perform the experiments related to the use of SARS-CoV-2 in vitro and in vivo on the mouse model.

OVERLAP
NONE

*Note: If any of the pending grants are funded, effort on existing projects will be re-located and accommodated as necessary to eliminate potential over-commitment.