AWARD NUMBER: W81XWH-19-1-0019

TITLE: “DEVELOPMENT OF A MODIFIED MRNA-BASED VACCINE FOR LASSA VIRUS”

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14. ABSTRACT

Lassa virus (LASV) is a highly prevalent pathogen in West Africa, including Sierra Leone, Liberia, Guinea and Nigeria. The virus causes 100,000 to 300,000 infections per year, which lead to approximately 5,000 deaths annually. Lassa fever is currently on the WHO R&D Blueprint list of epidemic threats needing urgent R&D action, and therefore there is an unmet need for an effective LASV vaccine, especially one that prevents Service Members from becoming ill from epidemic disease exposure during operational deployments.

The innovative vaccine technology used in this funded project was developed based on mRNA modified by incorporation of pseudouridin, which dramatically minimizes the indiscriminate activation of innate immune sensing and increases translation by an order of magnitude. This revolutionary technology was used by Moderna Therapeutics, the partner in this project, for the development of highly effective vaccines against influenza virus, rabies, HIV, Zika virus and SARS-CoV-2; the influenza and SARS-CoV-2 vaccines have been tested recently in clinical trials. Dr. Bukreyev and Moderna have designed and tested two Ebola virus modified mRNA-based vaccines encapsulated in lipid nanoparticles (LNP), which induced neutralizing antibodies in immunized guinea pigs and completely prevented death and disease caused by Ebola virus challenge.

We used the LNP/modified mRNA vaccine platform to develop a vaccine against LASV. LASV single glycoprotein precursor GPC is the target of protective antibody response. GPC complex is a trimer of heterodimers, each containing the receptor-binding subunit GP1 and the class I transmembrane fusion-mediating subunit GP2. The protein exists in an unstable prefusion and a stable postfusion conformation and it is difficult to maintain GPC in its trimeric prefusion configuration when expressed recombinantly. Antibodies against the resulting separated subunits are not potently neutralizing. As a result, some of the prior vaccine approaches that included natural GPC failed to elicit an effective antibody response, leading vaccine developers to focus on the induction of cell-mediated immunity as the most likely mechanism of protection. The high-resolution three-dimensional structures of the LASV GPC in prefusion conformation in complex with neutralizing protective antibodies was determined in 2019 by the Saphire lab (Hastie KM *et al*., Cell 2019 Aug 8;178(4):1004-1015.e14. doi: 10.1016/j.cell.2019.07.020). The Saphire lab also found that the most protective antibodies are directed against quaternary epitopes on GPC formed by trimers of both GP1 and GP2 in *prefusion* conformation. Inclusion engineering and stabilization of GPCs in our approach may allow improvement of the type and quality of neutralizing antibodies elicited by our vaccine.

The **objective** of the proposed study is to develop a LNP-formulated, modified mRNA-based vaccine protective against all clades of LASV. The objective will be achieved by pursuing the following Specific Aims.

1. To generate LNP-formulated modified mRNA-based vaccine constructs expressing wild-type or stabilized prefusion clade IV LASV GPC proteins and compare their immunogenicity and protective efficacy in guinea pigs. This work has been completed, and we found that our construct provides uniform sterilizing immunity to lethal LASV challenge.
2. To generate LNP-formulated modified mRNA-based vaccine constructs expressing clades I, II, III LASV GPC proteins and test them for homologous protection in guinea pigs.
3. To test two different doses of the clade IV vaccine construct in NHPs for homologous protection.
4. To test immunogenicity and protective efficacy of the cocktail of clades I, II, III and IV vaccine constructs in guinea pigs and NHPs.

The vaccine under development has the following advantages: (A) Safety: as mRNA is non-infectious, non-integrating platform, there is no risk of infection or insertional mutagenesis. (B) Efficacy: the nucleoside modification make mRNA more translatable and more stable. (C) Possibility of repeated administration: as anti-vector immunity is avoided, mRNA vaccines can be administered repeatedly. This is particularly important for the areas endemic for multiple emerging pathogens. (D) Rapid manufacturing: Production of mRNA vaccines has the potential for rapid manufacturing by *in vitro* transcription and is therefore ideal for highly divergent emerging viruses such as LASV. (E) A possibility of room temperature formulations, which is highly advantageous for a vaccine against LASV, which is endemic for some remote parts of Africa.

The *short-term impact* of the proposed study will be the initial development of LASV vaccine, which will require some additional testing in NHPs, such as dose optimization and testing of the duration of vaccine-induced protection. The *long-term impact* will be protection of our deployed service members and general population in West Africa against LASV infections.

15. SUBJECT TERMS					
Lassa virus, Lassa fever, vaccine, emerging viruses, tropical disease, virology, vaccinology, mRNA, mRNA vaccine, hemorrhagic fever, biodefense					
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2020 ANNUAL REPORT for W81XWH1910019: "Development of a Modified mRNA-Based Vaccine for Lassa Virus"

1. INTRODUCTION:

The objective of this project is to develop a potent vaccine against all four clades of Lassa virus (LASV) using a modified mRNA-based vaccine platform and an approach facilitated by recent discoveries in the field of LASV structural biology. Previously, most LASV vaccines have been vector-based, and aside from those that provide strong cell-mediated immunity, none has provided uniform protection against disease or sterilizing immunity. This is because the form of the LASV glycoprotein (GP) that presents the most effectively targeted epitopes is highly unstable and is not readily expressed in vectored vaccine systems. Our approach avoids these pitfalls by expressing a stabilized form of this protein conformation using a modified mRNA construct.

2. KEYWORDS:

KEYWORDS: Lassa virus, vaccine, emerging viruses, tropical disease, virology, vaccinology, mRNA, mRNA vaccine, hemorrhagic fever, biodefense.

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

The Aims and progress for this reporting period are as follows:

Specific Aim 1. To generate lipid nanoparticle (LNP)-formulated modified mRNA-based vaccine constructs expressing wild- type (wt) or stabilized prefusion clade IV LASV glycoprotein precursor (GPC) proteins and compare their immunogenicity and protective efficacy in guinea pigs.

- Major Task 1. To generate LNP-formulated modified mRNA vaccines based on wt and prefusion-stabilized clade IV LASV GPC for immunization of guinea pigs. *Original target date: Months 1-4.* **Completed in January 2020.**

- Major Task 2. To test LNP-formulated modified mRNA vaccines based on wt and prefusion-stabilized clade IV LASV GPC in guinea pigs. *Original target date: Months 1-11.* **Majority of work was completed May 2020. The final analysis is ongoing.**

Specific Aim 2. To generate LNP-formulated modified mRNA-based vaccine constructs expressing clades I, II, III LASV GPC proteins and test them for homologous protection in guinea pigs.

- Major Task 3. To generate LNP-formulated modified mRNA-based vaccine constructs expressing clades I, II, III LASV GPC proteins. *Original target date: Months 1-11.* **In progress.**

- Major Task 4. To test LNP-formulated modified mRNA-based vaccine constructs expressing clades I, II, III, IV LASV GPC proteins for homologous protection in guinea pigs. *Original target date: Months 1-17.* **In progress.**

Please note that the following Aims and Tasks are beyond the scope for this reporting period.

Specific Aim 3. To test two different doses of the clade IV vaccine construct in nonhuman primates (NHPs) for homologous protection.

- Major Task 5. To generate LNP-formulated modified mRNA-based vaccine constructs expressing clades I, II, III LASV GPC proteins at the scale sufficient for immunization of NHPs. *Original target date: Months 18-19.*
- Major Task 6. To test two different doses of the clade IV vaccine construct in NHPs for homologous protection. *Original target date: Months 17-24.*

Specific Aim 4. To test immunogenicity and protective efficacy of the cocktail of clades I, II, III and IV vaccine constructs in guinea pigs and NHPs.

- Major Task 7. To test the immunogenicity and protective efficacy of the cocktail of clades I, II, III and IV vaccine constructs in guinea pigs. *Original target date: Months 17-24.*
- Major Task 8. To generate the cocktail of clades I, II, III and IV vaccine constructs at a scale sufficient for immunization of NHPs. *Original target date: Months 25-26.*

- Major Task 9. To test immunogenicity and protective efficacy of the cocktail of clades I, II, III and IV vaccine constructs in NHPs. *Original target date: Months 26-36.*

o **What was accomplished under these goals?**

In this reporting period, we have completed nearly all major tasks for **Specific Aim 1**.

- **Major Task 1:** Development and production of LNP-formulated modified mRNA vaccines for LASV Josiah by Moderna was completed. This includes quality control testing of the resulting constructs and formulations, and antigen expression testing. Flow cytometry was used to determine that the antigen is successfully expressed on the surface of 293T cells.

- **Major Task 2:** Testing of the LASV Josiah vaccine constructs in Hartley guinea pigs with a guinea pig adapted LASV Josiah challenge was completed.

  Prior to the start of work, regulatory permissions and local authorization were sought and acquired, including IACUC protocols for animal work.

  Performing challenge experiments in the guinea pig model using adapted virus required local testing and validation of the guinea pig-adapted virus, which was performed over the course of two experiments. The first experiment was intended to produce a sufficient stock of virus for future experiments and establish procedures and historical control data for future experiments. This effort was successful and permitted us to generate a large quantity of adapted virus for use in future experiments. Experiment Two was intended to validate the lethality of the guinea pig adapted virus stock generated in Experiment One, and further develop procedures and acquire historical control data. Satisfactory lethality was confirmed, and protocols and procedures for future challenge studies were finalized. This included developing multiple assays and standard operating procedures, such as reliable plaque assays, necropsy procedures, and sedation procedures for guinea pigs that minimize the incidence of anesthetic-related death of experimental subjects. Optimal sampling times and intervals and correlates of disease severity were established.

  Guinea pigs were vaccinated with either of the two clade IV Josiah constructs at one of two doses (10 µg and 50 µg). Blood was collected for serology before each vaccination, and before challenge. Animals were challenged with guinea pig-adapted LASV. Sterilizing immunity was achieved with both constructs in the 10 µg groups. No significant weight loss occurred in these animals (**Figure 1B**), and no viremia was detected at any point (**Figure 1D**). Animals in the 50 µg groups showed some signs of disease, including weight loss. One animal in the wt GPC group became transiently viremic, and a single animal in the prefusion stabilized construct group was viremic and succumbed to disease (**Figure 1A**). However, the presentation of disease in this animal was atypical, with relatively mild histopathology compared to control animals. All control animals succumbed to disease, and all animals in the wt 10 ug, wt 50 ug, and prefusion stabilized 10 ug groups survived (**Figure 1A**; bar for 100% survivors shows the wt 10 ug group as the

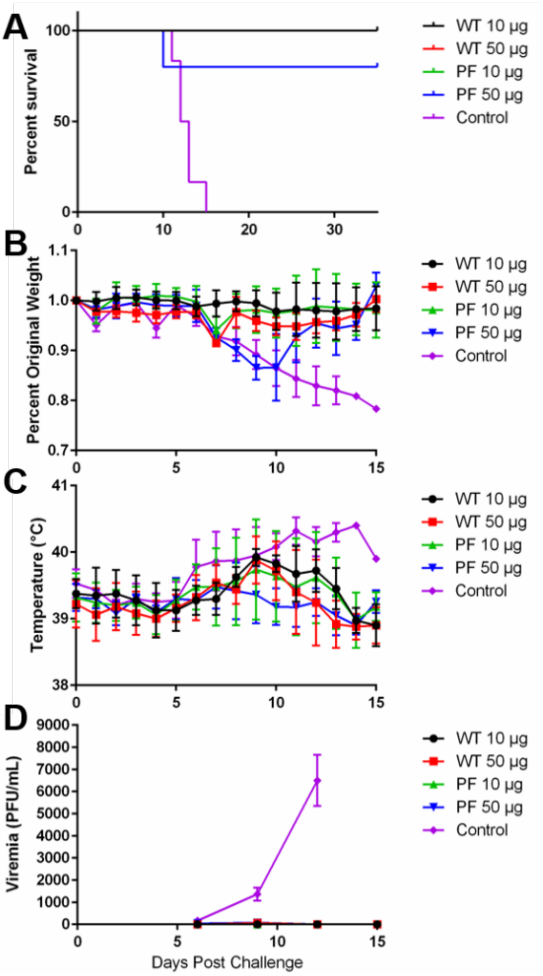

Fig. 1: Challenge data. (A) Survival by group. **(B)** Body weight by group. **(C)** Temperature by group. **(D)** Viremia by group. WT=wild-type construct; PF=prefusion stabilized construct.

black line, but also includes wt 50 ug [red line] and PF 10 ug [green line]). We therefore chose to proceed only with the 10 µg dose. Given that no differences were observed between the two constructs at this stage, it was decided that the results of the serology assays would be used to determine which construct should be developed further.

Following this result, we elected to use the terminal sera collected from the 10 µg vaccine group animals to conduct a passive transfer study. Sera from all animals in either the wt or prefusion stabilized construct group were pooled and 5 mL of serum was administered via intraperitoneal (IP) injection to three 400 g female Hartley guinea pigs. Three additional animals received naïve sera as a control. Twenty-four hours later, animals were challenged with LASV Josiah. At day five post-challenge, 3 mL of the appropriate 1:20 diluted sera was administered to each group, again via IP injection. One animal in each treatment group succumbed, with two survivors per treatment group. Two of three animals that received naïve sera succumbed. We interpreted this to mean that the sera were at least partially protective.

- An IgG ELISA was developed to detect guinea pig anti-LASV antibodies in sera from vaccinated animals. In parallel, a virus neutralization assay was developed to ascertain neutralizing antibody titers. However, despite providing sterilizing immunity, neither the wt or prefusion construct elicited meaningful neutralizing antibody titers, and, in fact, using a conventional ELISA, no binding antibodies were detected at all above the limit of detection (1:80) (**Figure 2A, B**). By contrast, an ELISA using a prefusion stabilized version of LASV GPC found substantial binding (**Figure 2C, D**). There was only a minimal difference in binding between the two constructs. This would seem to indicate that our vaccine design was successful in eliciting a targeted antibody response. The lack of strong neutralization is curious and would appear to suggest that protection was the result of a combination of Fc-mediated effects and cell-mediated immunity.

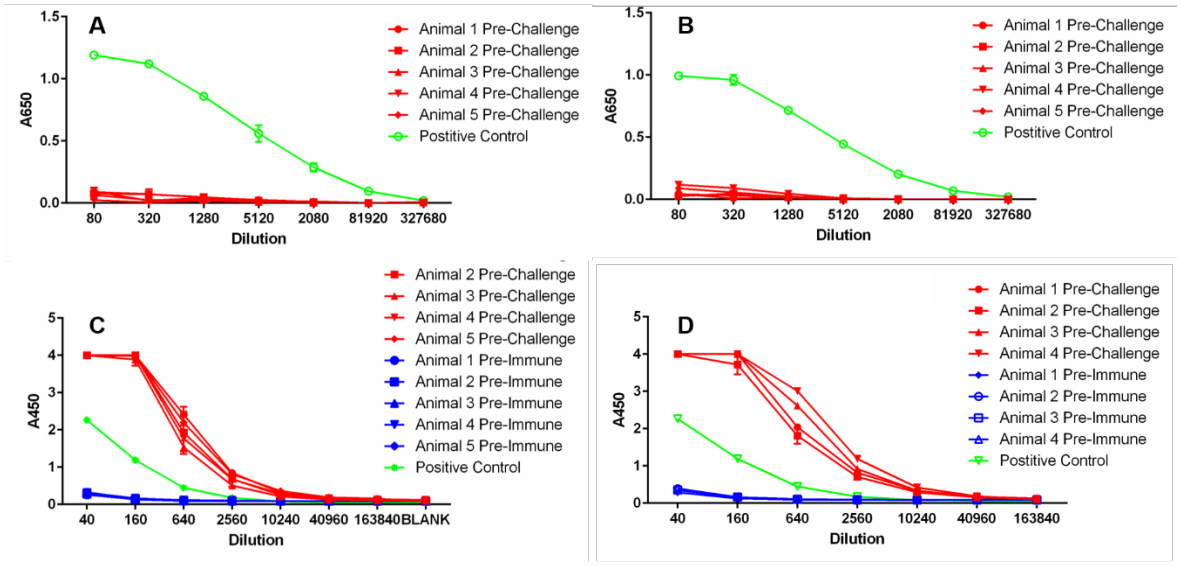

Fig. 2: Antibody binding data. (A) Postfusion antigen ELISA with sera from 10ug wild-type GPC group animals. **(B)** Postfusion antigen ELISA with sera from 10ug wild-type prefusion group animals. **(C)** Prefusion antigen ELISA with sera from 10ug wild-type GPC group animals. **(D)** Prefusion antigen ELISA with sera from 10ug prefusion GPC group animals.

In this reporting period, work was begun on some components of **Specific Aim 2**.

- **Major Task 3:** Generation of LNP-formulated modified mRNA-based vaccine constructs expressing clades I, II, III LASV GPC proteins is being done by Moderna. They produced a LNP-formulated modified mRNA vaccine for LASV-Josiah (clade IV). However, this Task has been delayed due to Moderna's efforts on vaccine development in response to the coronavirus pandemic, combined with results from Dr. Bukreyev's group at the University of Texas Medical Branch (UTMB) showing that the prefusion GPC elicits a better antibody response than the postfusion GPC. Therefore, the challenge viruses for clades I, II, and III are being resequenced to

make the vaccines exactly match the virus. Following resequencing, Moderna will fabricate the clade I, II, and III constructs.

- **Major Task 4:** A colony of Strain 13 guinea pigs has been established at UTMB, and sufficient numbers of animals for experiments will soon be available. Viruses for challenge have been acquired and propagated.

  Regulatory and local IACUC permissions were sought and received to establish a local colony of Strain 13 guinea pigs. Six animals were imported from NIH's Bethesda campus in two groups. The breeding program was designed in consultation with UTMB's Animal Resource Center veterinary staff. As of this writing, the colony has expanded to more than 20 individuals after three rounds of breeding. We are currently averaging 2.5 live pups per litter.

  Based upon published data with another clade III strain that indicated that this strain is uniformly lethal in Hartley guinea pigs, we tested the lethality of the clade III LASVs we have in hand (Ojoko) in guinea pigs. Unfortunately, this virus was not lethal.

  We are currently working on the generation of Hartley guinea pig adapted strains of clade I, II, and III LASVs in the event that we are unable to breed sufficient numbers of Strain 13 guinea pigs in time to meet the goals of the project.

  We acquired wt clade I, II, III, and IV LASVs and have propagated these to produce stocks for animal challenge studies and other experiments.

- **What opportunities for training and professional development has the project provided?**

  This project supports a postdoctoral fellow, who has primary responsibility for the execution of the UTMB portion of project, and who is also mentoring a graduate student.

- **How were the results disseminated to communities of interest?**

  Nothing to report.

- **What do you plan to do during the next reporting period to accomplish the goals?**

  Having completed major work for Specific Aim 1, we plan to begin production of vaccine constructs for clades I, II, and III. This will require continued expansion of our existing colony of Strain 13 guinea pigs, which is ongoing.

  We are currently designing experiments to evaluate cell-mediated immunity in greater detail than previously planned, given that protection provided by our constructs appears to have a strong cell-mediated component.

  We are currently profiling both the epitopes targeted by the antibodies elicited by our constructs and the FC-mediated effects they facilitate.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**

  We have demonstrated the utility of the Moderna mRNA-based vaccine platform in the context of LASV. Two doses of a modified mRNA-based vaccine construct elicited antibodies against the prefusion form of LASV GPC almost exclusively and provided uniform sterilizing immunity and protection against lethal LASV challenge. Immunity was conferred in the absence of significant quantities of neutralizing anti-LASV antibodies.

  Previously, most LASV vaccines have been vector-based. This poses problems and limits the deployability of these vaccines, as they frequently require cryopreservation and/or other specialized supply chain management. An mRNA-based vaccine formulated into lipid nanoparticles has the potential for significantly enhanced shelf stability, including room temperature storage. This has the

potential to dramatically increase the availability of such a vaccine in high-need areas and could facilitate long-term stockpiling for readiness purposes.

- **What was the impact on other disciplines?**

  Nothing to report.

- **What was the impact on technology transfer?**

  Results have been shared with partners at Moderna Therapeutics and potential collaborators.

- **What was the impact on society beyond science and technology?**

  We have demonstrated that an mRNA-based vaccine construct with the potential for development into a shelf-stable, rapidly produced vaccine provides uniform, sterilizing immunity against lethal LASV challenge in a guinea pig model. LASV is a major public health challenge in West Africa, and a readily available and effective vaccine would have an enormous impact on the health and economic stability of the region.

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

  - To preempt potential difficulties in producing sufficient Strain 13 guinea pigs from our colony, adaptation of clade I, II, and III LASVs to Hartley guinea pigs has begun.

  - Given that the results of our first vaccine experiment indicate that protection may have a significant cell-mediated component, we are developing a detailed experimental plan to characterize the cell-mediated immunity afforded by our construct. This will include development of a correlate of protection.

  - As our construct appears to have failed to elicit strong neutralizing antibody production, but did stimulate strong binding to the prefusion form of LASV GPC, we are working to analyze the role of Fc-mediated effects in protection.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  The ongoing SARS-CoV-2/COVID-19 pandemic has caused significant delays in all components of work, and is continuing to do so. Dr. Bukreyev was unable to perform any non-SARS-CoV-2 related work for a prolonged period per institutional policy (at UTMB). This caused significant delays in analyzing data from the first vaccine challenge experiment. Breeding of Strain 13 guinea pigs has been slower than initially anticipated. Dr. Bukreyev's breeding program has been accelerated by acquiring an additional group of animals. His laboratory is also actively working on adaptation of clade I, II, and III LASVs to replace or reduce the use of Strain 13 guinea pigs in the event that their breeding colony is unable to provide sufficient numbers of animals in time to meet the goals of this project. The lethality of a clade III LASV in Hartley guinea pigs based upon published data was also assessed, but this attempt to reduce the requirement for Strain 13 guinea pigs was unsuccessful.

  The COVID-19 pandemic has affected the timeline for producing the mRNAs for different clades of LASV by Moderna, since their efforts in the beginning of 2020 have been focused on advancing their mRNA-1273 vaccine against SARS-CoV-2. Moderna did produce mRNA-based vaccine constructs expressing clade IV LASV glycoprotein protein precursor protein. Comparative serology results (discussed above) have shown that prefusion variants are more effective than postfusion variants at binding antibody. Therefore, prefusion variants for clades I, II, and III will be fabricated shortly, and Task 4 should be back on track for completion.

- **Changes that had a significant impact on expenditures**

  Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  - Four additional guinea pig protocols added. These are previously described in this report.
  - Dates of approval:
    - Verification of lethality of adapted virus: 31 July 2019
    - Adaptation of clade I, II, and III viruses: 12 February 2020
    - Test of lethality of a clade III virus in Hartley guinea pigs: 13 February 2020
    - Passive transfer of immune sera from initial vaccine experiment: 22 May 2020

- **Significant changes in use or care of human subjects**

  Not applicable.

- **Significant changes in use of biohazards and/or select agents**

  Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  - **Journal publications.**

    Nothing to report.

  - **Books or other non-periodical, one-time publications.**

    Nothing to report.

  - **Other publications, conference papers, and presentations.**

    Nothing to report.

- **Website(s) or other Internet site(s)**

  Nothing to report.

- **Technologies or techniques**

  - A guinea pig-specific, low-cost IgG ELISA.
  - A reliable protocol for lethal challenge of guinea pigs older than 8 weeks with guinea pig-adapted LASV.
  - All technologies and techniques will be published with final data from these experiments and are available to qualified individuals upon request.

- **Inventions, patent applications, and/or licenses**

  Nothing to report.

- **Other Products**

  - Extensive histopathology slide sets from Lassa virus-infected guinea pigs
  - Gross pathology imagery from Lassa virus-infected guinea pigs

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Project Role:	Researcher Identifier (ORCID ID):	Nearest person month worked:	Contribution to Project:	Funding Support:
Alexander Bukreyev	Principal Investigator	0000-0002-0342-4824	2	Provided general oversight, directing research, participating in guinea pig experiments	NA (all personnel were supported by this award for the effort shown)
Thomas Geisbert	Co-Investigator	0000-0003-0858-1877	1	Provided advice regarding constructs and animal experiments	
Thomas Ksiazek	Co-Investigator	0000-0003-4160-8218	4	Provided wt viruses and participated in design of experiments and interpretation of experimental data	
Andrea Carfi	Co-Investigator	0000-0001-5508-3809	1	Lead efforts on generation of the LASV vaccine batches.	
Kimberly Schuenke	Program Administra-tor	NA	1	Assisted with establishment of grant and prepared reports	
Palaniappan Ramanathan	Research Scientist	0000-0001-8121-7647	8	Responsible for analysis of antibody and cell-mediated responses to the vaccines	
Adam Ronk	Postdoc	0000-0001-8202-9154	12	Responsible for preparation of virus batches and assisting with analysis of antibody and cell-mediated immune responses	
Delphine Malherbe	Research Scientist	0000-0001-6416-6227	3	Responsible for analysis of cytokine and chemokine responses in guinea pigs after challenge with LASV and analysis of antibody and cell-mediated responses after vaccinations	

- **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. Michael Watson (co-Investigator) left Moderna Therapeutics, and his role on the project was assumed by Andrea Carfi. Dr. Carfi is the Head of Research, Infectious Disease at Moderna. He is a discovery leader with 15 years' experience managing global teams and projects in pharmaceutical R&D organizations. Dr. Carfi has a strong background in vaccine development, drug discovery, infectious disease, protein biochemistry, and structural biology. Over the years he has provided critical contributions to the discovery, design and advancement of novel vaccine candidates and small molecule drugs, as well as validation of targets for therapeutic intervention. Results of his research have led to 100 publications in peer-reviewed journals and several patent applications.

- **What other organizations were involved as partners?**

    - **Organization Name:** Moderna, Inc.

    - **Location of Organization:** Cambridge, MA, USA

    - **Partner's contribution to the projec**t

        - **Facilities.** Dr. Carfi will use the Moderna facilities to fabricate the mRNAs that will be used for this research, and has already made LNP-formulated modified mRNA vaccines for LASV (strain Josiah, clade IV).

        - **Collaboration.** Dr. Carfi consults with Dr. Bukreyev regarding the design and development of the mRNAs.

        - **Other.** Moderna has a subaward with UTMB for their portion of the project to provide preclinical grade mRNAs for different clades of LASV that will be characterized *in vitro*, as well as for use in *in vivo* guinea pig and NHP models by collaborators at UTMB.

8. SPECIAL REPORTING REQUIREMENTS

- **AWARD CHART**

  See next page for updated Award Chart.

9. APPENDICES:

Not applicable.

Award #W81XWH1910019: "Development of a Modified mRNA-Based Vaccine for Lassa Virus"

PI: Alexander Bukreyev, University of Texas Medical Branch at Galveston, Texas

Budget: $3,033,132.00

Topic Area: Vaccine Development for Infectious Disease

Mechanism: Peer Reviewed Medical Research Program (PRMRP) Technology/ Therapeutic Development Research Award

Research Area(s): 0500 – Immunology; 0501 – Molecular Immunology; 0503 – Regulation of the Immune Response

Award Status: Funded 01SEP2019 to 31AUG2022

Study Goals:

The goal of the study is to develop a modified mRNA-based vaccine for Lassa virus (LASV).

Specific Aims:

1. To generate lipid nanoparticle (LNP)-formulated, modified mRNA-based vaccine constructs expressing wild type or stabilized prefusion clade IV LASV GPC proteins and compare their immunogenicity and protective efficacy in guinea pigs.
2. To generate LNP-formulated, modified mRNA-based vaccine constructs expressing clades I, II, III LASV GPC proteins and test them for homologous protection in guinea pigs.
3. To test two different doses of the clade IV vaccine construct in NHPs for homologous protection.
4. To test immunogenicity and protective efficacy of the cocktail of clades I, II, III and IV vaccine constructs in guinea pigs and NHPs.

Key Accomplishments and Outcomes:

Publications: none to date
Patents: none to date
Funding Obtained: none to date