AWARD NUMBER: W81XWH-19-1-0028

TITLE: “DEVELOPMENT OF A RECOMBINANT VSV-BASED VACCINE FOR NIPAH VIRUS”

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Nearly 20 years ago, Nipah virus (NiV) emerged and was shown to be a previously unknown paramyxovirus, now classified along with Hendra virus (HeV) and Cedar virus within the *Henipavirus* genus. NiV causes febrile encephalitis and severe respiratory disease in humans with a fatality rate as high as 100% in some outbreaks. Genetic analysis has identified at least two strains of NiV responsible for outbreaks in different geographical areas. The Malaysia strain (NiV_M) caused the initial outbreak of NiV from 1998-1999 in Malaysia and Singapore, in which over 270 people were infected with about 40% case fatality rate (CFR) with an additional 2014 outbreak in the Philippines with a CFR of approximately 52%. The Bangladesh strain (NiV_B) however has caused repeated outbreaks in Bangladesh and India between 2001 and 2018. The outbreaks of NiV_B have had higher CFRs averaging about 75% with human-to-human transmission also observed. The observations that these two strains reportedly display differences in CFRs and human-to-human transmission are interesting, as there is 91.8% nucleotide homology between the genomes. Importantly, we have developed nonhuman primate (NHP) models for both NiV_M and NiV_B, and recently shown that NiV_B is more pathogenic in African green monkeys (AGM) than NiV_M under identical experimental conditions.

Currently, there are no licensed vaccines for the prevention of NiV disease. Previously we developed single cycle recombinant vesicular stomatitis virus (rVSV) vaccine vectors expressing either the NiV F or NiV G proteins. These vaccines were evaluated 28 days after a single-dose vaccination in the NiV ferret model and were shown to completely protect ferrets from lethal challenge. An important consideration in regard to the pre-clinical animal studies conducted to date is that all of the studies assessed efficacy against the less pathogenic NiV_M strain and not the more pathogenic NiV_B strain. While the antigenicity of these vaccines should not be a concern considering that the HeV G protein can protect against NiV_M infection, there are new data on the NiV_B AGM model that are concerning. As noted above, NiV_B infection in AGMs is more pathogenic when compared to NiV_M infection. Importantly, this difference resulted in significantly reduced efficacy of antibody therapy. Specifically, the human monoclonal antibody m102.4, which had previously been shown to completely protect AGMs against lethal NiV_M disease when treatment was delayed until five days after virus exposure, failed to provide any protection when AGMs were challenged with NiV_B and treated beginning at day 5 after virus challenge. Considering this new data, the current vaccines against NiV_M need to be tested against the more pathogenic NiV_B infection. To address this concern, we recently evaluated our single-cycle, rVSV-based NiV_B vaccines in a uniformly lethal AGM model of NiV_B. Importantly, a single injection of the rVSV-based NiV_B vaccines provided complete protection to all AGMs when exposed to NiV_B 28 days after vaccination, with a rVSV-NiV_B vaccine expressing the NiV_B G inducing the most robust humoral responses.

The main objective of this proposal is to develop a rVSV-based vaccine against NiV that can provide both rapid protection and long term immunity against the most pathogenic Bangladesh strain of NiV. Data obtained from this work will be invaluable in moving this vaccine to advanced development. During the current reporting period we achieved a major success with the initial study to begin to define the minimum interval between vaccination and exposure to NiV_B required for protection. Importantly, we demonstrated that 6/6 AGMs immunized with a single injection of our rVSV-NiV_B vaccine 7 days before high dose exposure to NiV_B were completely protected from disease and death, while 3/3 control animals that received a nonspecific vaccine succumbed to NiV_B disease. This data shows that the rVSV-NiV_B vaccine can provide rapid protection against NiV_B. Further studies during the next reporting period will determine whether the interval required for protection can be reduced even further. These data have particular importance regarding impact on outbreak response and ring vaccination approaches.

15. SUBJECT TERMS
Nipah virus, vaccine, virology

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1. **INTRODUCTION:**
The goal of the study is advance the development of a recombinant vesicular stomatitis virus (rVSV)-based vaccine that expresses the glycoprotein (G) of the Bangladesh strain of Nipah virus (NiV_B). This will be accomplished by determining the ability of the rVSV-NiV_BG vaccine to serve as a rapid acting vaccine in nonhuman primates (NHPs), determining the durability of the rVSV-NiV_BG vaccine in NHPs, and determining the correlates of protection of the rVSV-based rVSV-NiV_BG vaccine in NHPs.

2. **KEYWORDS:**
Nipah virus, vaccine, virology

3. **ACCOMPLISHMENTS:**
   - **What were the major goals of the project?**

Note that the original Aim 1, to determine the neurovirulence of the rVSV- NiV_BG vaccine in mice, was not funded by the Sponsor. The other Aims and progress for this reporting period are as follows:

1. **Specific Aim 2: Determine the ability of the rVSV-NiV_BG vaccine to serve as a rapid acting vaccine in African green monkeys (AGMs).** *Original target date: Months 8 to 20.*
   a. Major Task 2: Determine the ability of the rVSV- NiV_BG vaccine to serve as a rapid acting vaccine in nonhuman primates (NHPs) with a 7-day interval between vaccination and virus challenge.
      i. Subtask 1. In-life portion of Aim 2-1. [6 AGMs + 3 AGM controls = 9 AGMs total]; **completed on 11 August 2020.**
      ii. Subtask 2: Assess humoral and cellular immune responses, clinical pathology assays, viremia by PCR and plaque assay; perform necropsies on AGMs from Subtask 1 [Cell line: Vero E6 to assess viral load by plaque assay]; **25% complete; clinical pathology assays completed by 11 August 2020; necropsies completed by 11 August 2020**.
   b. Major Task 3: Determine the ability of the rVSV- NiV_BG vaccine to serve as a rapid acting vaccine in NHPs at with a 3 or 14 day interval between vaccination and virus challenge
      i. Subtask 1. In-life portion of Aim 2-2 [6 AGMs + 3 AGM controls = 9 AGMs total]; animals purchased; **0% complete. Space reserved and study scheduled to start on 16 October 2020.**
      ii. Subtask 2: Assess humoral and cellular immune responses, clinical pathology assays, viremia by PCR and plaque assay; perform necropsies on NHPs from Subtask 1 [Cell line: Vero E6 to assess viral load by plaque assay]. **0% complete (see above).**

2. **Specific Aim 3: Determine the durability of the rVSV-NiV_BG vaccine in AGMs.** *Original target date: Months 14 to 20.*
   a. Major Task 4: Determine protection using prime only or prime-boost regimens
      i. Subtask 1. In-life portion of Aim 3. [9 vaccinated AGMs + 9 unvaccinated controls = 18 AGMs total]. No work scheduled for the current reporting period. **Animals purchased and delivery scheduled for 6 October 2020.**
      ii. Subtask 2: Assess humoral and cellular immune responses, clinical pathology assays, viremia by PCR and plaque assay; perform necropsies on AGMs from Subtask 1. [Cell line: Vero E6 to assess viral load by plaque assay]. **No work scheduled for the current reporting period.**

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

Major Task 2: Subtask 1. The in-life portion of Aim 2.1. [6 AGMs + 3 AGM controls = 9 AGMs total] was completed on 11 August 2020. Importantly, all 6 AGMs that received the specific rVSV-NiV_BG showed no evidence of clinical disease and survived to the study

endpoint (day 35), while the three control animals that received an irrelevant vaccine (rVSV-EBOV 76) succumbed to NiVB disease on postexposure days 7, 8, and 9, respectively (**Figure 1**).

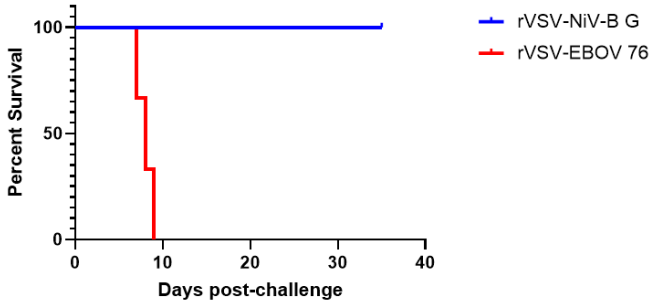

Figure 1. Survival outcome of AGMs specifically vaccinated with rVSV-NiV$_B$G (n = 6) or a nonspecific rVSV-EBOV 76 vaccine and challenged 7 days later with NiVB.

Major Task 2: Subtask 2: Clinical pathology assays, necropsies, and gross pathology analysis were performed, and formalin-fixed tissues were embedded in paraffin.

- **What opportunities for training and professional development has the project provided?**
  Nothing to report.

- **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?**
  Major Task 2: Subtask 2: In the next reporting period the remaining work from the 7-day interval NHP study will be performed and data analyzed. Specifically, this will include performing the PCR and plaque assays, humoral and cellular assays, and histopathology as well as all of the data.

  Major Task 3 Subtask 1 and 2: Based on the success of the 7-day interval vaccine study, a 3 day interval vaccine study will be performed with the vaccination scheduled for 16 October 2020 and NiVB challenge scheduled for 19 October 2020. It is anticipated that Subtask 3.1 will be completed during the next study period and that most (>75%) of Subtask 3.2 will be completed during the next reporting period.

  Major Task 4: Subtask 1. We have purchased the 18 AGMs for this durability study and they are scheduled to arrive on 6 October 2020. The vaccination portion of this study will begin in mid-to-late October of 2020 with monthly sample collection occurring throughout the next reporting period as originally scheduled.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**
  Nothing to report.

- **What was the impact on other disciplines?**
  Nothing to report.

- **What was the impact on technology transfer?**
  Nothing to report.

- **What was the impact on society beyond science and technology?**
  Nothing to report.

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**
  Nothing to report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  All non-COVID-19 research at UTMB was suspended from 24 March 2020 until 18 May 2020 due to the COVID-19 pandemic. This mandated shut down has resulted in a substantial backlog in BSL-4 activities, as many studies had to be delayed and rescheduled. Our main focus for this project during this reporting period, and as a result of the SARS-CoV-2 pandemic, has been to stay on schedule with the in-life portion of the originally proposed NHP work. We have stayed on track so far with the in the in-life portion of the project and should stay on track with the in-life portion of the NHPs for this reporting period. Fortunately, decisions regarding work during the current reporting period and the next reporting period are determined by survival rather than by analysis of the host response. Likewise, the durability study has not yet been impacted because the first 12 months of that task is the vaccination phase. The main work impacted by the pandemic has been the performance of assays and analysis of data collected (e.g., PCR assays, host response assays, pathology). It is possible that small delays in the performance of assays and analysis of data may occur during the next reporting period as a result of the delays caused by the pandemic. In the event that some assays or data analysis initially planned for the next reporting period are delayed, we will conduct any such efforts during the Year 3 reporting period.

- **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**
  Nothing to report.

- **Significant changes in use or care of human subjects.**
  Nothing to report.

- **Significant changes in use or care of vertebrate animals.**
  Nothing to report.

- **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**
    Nothing to report.
  - **Inventions, patent applications, and/or licenses**
    Nothing to report.

- **Other Products**
  Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

o

Name:	Project Role:	Researcher Identifier (ORCID ID):	Nearest person month worked:	Contribution to Project:	Funding Support:
Thomas W. Geisbert	Principal Investigator	0000-0003-0858-1877	1	Provided general oversight, directing research, participating in AGM experiments.	NA (all personnel were supported by this award for the effort shown)
Krystle W. Agans	BSL-4 Research Technician	0000-0002-7319-6935	1	Performing various procedures with AGM clinical samples including hematology, clinical chemistry, virology, immunology, and RT-PCR assays.	
Viktoriya Borisevich	BSL-4 Research Technician	none	1	Performing various procedures with AGM clinical samples including hematology, clinical chemistry, virology, immunology, and RT-PCR assays.	
Robert Cross	BSL-4 Research Scientist	0000-0001-7718-1522	1	Assisting Dr. Geisbert with hands-on procedures with the AGMs, including phlebotomy, clinical observations, euthanasia, and necropsy. Also performing virology and immunology assays on clinical samples.	
Daniel Deer	BSL-4 Research Technician	none	1	Hands-on procedures with the AGMs, including phlebotomy, clinical observations, euthanasia, and necropsy.	
Natalie Dobias	BSL-4 Research Technician	none	2	Assisting Dr. Fenton with AGM necropsies, preparing tissues for histology.	
Karla Fenton	BSL-4 Veterinary Pathologist	0000-0002-5530-6969	1	Hands-on procedures with the AGMs, including, clinical observations, euthanasia, and necropsy, and histology.	
Brittany Franshaw	BSL-4 Research Technician	none	2	Hands-on procedures with the AGMs, including phlebotomy, clinical observations, euthanasia, and necropsy. Also performing clinical pathology and virology assays on clinical samples.	

Name:	Project Role:	Researcher Identifier (ORCID ID):	Nearest person month worked:	Contribution to Project:	Funding Support:
Brittany Franshaw	BSL-4 Research Technician	none	2	Hands-on procedures with the AGMs, including phlebotomy, clinical observations, euthanasia, and necropsy. Also performing clinical pathology and virology assays on clinical samples.	NA (all personnel were supported by this award for the effort shown)
Joan Geisbert	BSL-4 Technical Director	none	1	Laboratory set-up, supervision of the BSL-4 research associates and postdoctoral fellows, and hands-on participation in these experiments including challenge and phlebotomy of the AGMs.	
Liana Medina	BSL-4 Postdoctoral Fellow	none	1	Performing virology, immunology, and clinical pathology assays on clinical samples.	
Kevin Melody	BSL-4 Postdoctoral Fellow	0000-0003-2713-5338	2	Hands-on procedures with the AGMs, including phlebotomy, clinical observations, euthanasia, and necropsy. Also performing clinical pathology, immunology, and virology assays on clinical samples.	
Kimberly Schuenke	Program Administrator	0000-0002-6661-7631	1	Assisted with establishment of grant and prepared reports.	
Courtney Williams	BSL-4 Postdoctoral Fellow	0000-0003-3389-0137	1	Performing various procedures with AGM clinical samples including hematology, clinical chemistry, virology plaque, and immunology assays.	
Kira Zapalac	BSL-4 Research Technician	none	1	Assists senior research techs with AGM clinical sample assays.	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  Nothing to report.
- **What other organizations were involved as partners?**
  Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**
  Not applicable.
- **AWARD CHART:**
  See next page for updated Award Chart.

9. APPENDICES:

Not applicable.

Award #W81XWH1910028: "Development of a Recombinant VSV-Based Vaccine for Nipah Virus"

PI: Thomas W. Geisbert, PhD, University of Texas Medical Branch at Galveston, Texas

Budget: $1,864,897.00

Topic Area: Vaccine Development for Infectious Diseases

Mechanism: Peer Reviewed Medical Research Program (PRMRP) Investigator-Initiated Research Award

Research Area(s): 0608 - Biological Prevention / Prophylactic Vaccines; 0499 – Pathobiology, Not Otherwise Specified

Award Status: 01SEP2019 to 31AUG2022

Study Goals:

The goal of the study is advance the development of a recombinant vesicular stomatitis virus (rVSV)-based vaccine that expresses the glycoprotein (G) of the Bangladesh strain of Nipah virus (NiV_B).

Specific Aims:

1. To determine the ability of the rVSV-NiV_BG vaccine to serve as a rapid acting vaccine in nonhuman primates (NHPs).
2. To determine the durability of the rVSV-NiV_BG vaccine in NHPs.
3. To determine correlates of protection of the rVSV-based rVSV-NiV_BG vaccine in NHPs.

Note that the original Aim 1 (to determine the neurovirulence of the rVSV-NiV_BG vaccine in mice) was deleted at the request of DoD.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date