

AWARD NUMBER: W81XWH-15-2-0029

TITLE: Enhancing the Immunogenicity of a Tetravalent Dengue DNA Vaccine

PRINCIPAL INVESTIGATOR: Maya Williams

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REPORT DATE: August 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;Unlimited Distribution

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE AUGUST 2016		2. REPORT TYPE Annual		3. DATES COVERED 15JUL2015 - 14JUL2106	
4. TITLE AND SUBTITLE Enhancing the Immunogenicity of a Tetravalent Dengue DNA Vaccine				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-2-0029	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Maya Williams E-Mail: maya.williams1.mil@mail.mil				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Henry M. Jackson Foundation For the Advance of Military Medicine, Inc. Rockville, MD 20852				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Dengue fever ranks among the top infectious diseases that afflict US Military personnel deployed overseas. Developing a successful vaccine to prevent dengue fever in DoD personnel is priority research area for the US DoD. Phase 1 clinical trials demonstrated that the Naval Medical Research Center's DNA based dengue vaccine is safe and well tolerated, but does not elicit a sufficient immune response. The objectives of this project are to conduct studies in non-human primates to enhance the immunogenicity of the vaccine by (a) testing different modes of delivery of dengue DNA vaccine for optimal humoral and T cell responses, and (b) testing the optimal delivery method in conjunction with other vaccine platforms using a heterologous prime-boost regimen. All necessary contracts are in place, the vaccine product is ready and the first vaccinations to address objective (a) are scheduled for early October 2016.					
15. SUBJECT TERMS Nothing listed					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	5
5. Changes/Problems.....	6
6. Products.....	7
7. Participants & Other Collaborating Organizations.....	9
8. Special Reporting Requirements.....	10
9. Appendices.....	10

INTRODUCTION:

Dengue fever ranks among the top infectious diseases that afflict US Military personnel deployed overseas. Developing a successful vaccine to prevent dengue fever in DoD personnel is priority research area for the US DoD. Phase 1 clinical trials demonstrated that the Naval Medical Research Center's DNA based dengue vaccine is safe and well tolerated, but does not elicit a sufficient immune response. The objectives of this project are to conduct studies in non-human primates to enhance the immunogenicity of the vaccine by (a) testing different modes of delivery of dengue DNA vaccines for optimal humoral and T cell responses, and (b) testing the optimal delivery method in conjunction with other vaccine platforms using a heterologous prime-boost regimen.

1. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Dengue, DNA vaccine, immunogenicity, non-human primate, vaccine delivery method

2. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Select the vaccine delivery method which enhances the immunogenicity of the tetravalent dengue DNA vaccine. Vaccine delivery method plays an important role in the vaccine's performance. This is especially true for DNA based vaccines, where immunogenicity depends on the uptake of DNA by cells and de novo synthesis of antigens. The traditional method of delivery by intramuscular injection has proved sub-optimal for DNA vaccines, including TVDV. Technological development now makes it possible to consider delivery of DNA vaccines by needle-free devices intramuscularly or intradermally, and by electroporation. In this specific aim, we will evaluate the alternate methods of (a) intradermal electroporation, (b) intramuscular electroporation, and (c) intradermal liquid jet injection for enhancing TVDV in non-human primates.

Specific Aim 2: Develop an improved dengue vaccine using a heterologous prime boost approach. Heterologous prime-boost, in which two vaccines based on different platforms but using the same antigen has gained in popularity in recent years because of significantly enhanced immune responses. In this specific aim, we will evaluate this approach for enhancing TVDV. Specifically, we intend to test vaccine regimens that combine the following components: (1) TVDV administered using the vaccine delivery system selected from specific aim 1, (2) Live attenuated dengue virus vaccine (LAV), and (3) inactivated dengue virus vaccine.

What was accomplished under these goals?

Aim 1, Major task 1, Subtask 1: A contract with Ichor for use of their intramuscular and intradermal electroporation devices has been established.

Aim 1, Major task 1, Subtask 2: Due to the purchase of Bioject by another company, the Bioject devices were not available. In order to still meet aim 1, we identified and established a contract with another jet injection device company, PharmaJet.

Aim 1, Major Task 3, Subtask 1: Approval from the Wake Forest IACUC and USAMRMC has been received.

Aim 1, Major Task 3, Subtask 2: Non-human primates were screened for previous flavivirus exposure. Appropriate NHPs were identified, have been procured and are currently at Wake Forest. Vaccinations will proceed once the animals are released from quarantine.

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?

Ichor and PharmaJet will provide training on the use of their devices to personnel conducting the immunizations. Non-human primates will receive their first vaccinations in early October 2016 with subsequent vaccinations and blood draws for humoral and cellular immunogenicity measurements according to study protocols.

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

Due to the purchase of Bioject by another company, the Bioject devices were not available. In order to still meet aim 1, we identified and established a contract with another jet injection device company, PharmaJet.

PharmaJet offers equivalent intramuscular and intradermal devices with the exception of the maximum volume that can be delivered in one immunization with the intradermal device. We have increased the total number of injections such that the same dose of vaccine can be delivered.

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

See above.

Changes that had a significant impact on expenditures

Delays in establishing contracts and the required change from Bioject to PharmaJet delayed expenditures. All required contracts have now been established.

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

Significant changes in use or care of human subjects

N/A

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS:

- **Publications, conference papers, and presentations**
Report only the major publication(s) resulting from the work under this award.

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?

Name:	<u>LCDR Maya Williams</u>
Project Role:	PI
Nearest person month worked:	2
Contribution to Project:	Dr. Williams lead coordination/discussion with Wake Forest, PharmaJet and Ichor.
Funding Support:	Naval Medical Research Center
Name:	<u>Dr. Peifang Sun</u> - no change
Name:	<u>Dr. Kanakatte Raviprakash</u>
Project Role:	AI
Nearest person month worked:	2
Contribution to Project:	Dr. Raviprakash contributed to discussions with Wake Forest, Pharmajet and Ichor.
Funding Support:	Naval Medical Research Center
Name:	<u>Mr. Dan Ewing</u> - no change
Name:	<u>Ms. Nish Nagabhushana</u> - no change
Name:	<u>Ms. Shyuer-Min Wang</u>
Project Role:	Program manager
Nearest person month worked:	1
Contribution to Project:	Ms. Wang provided administrative support.

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

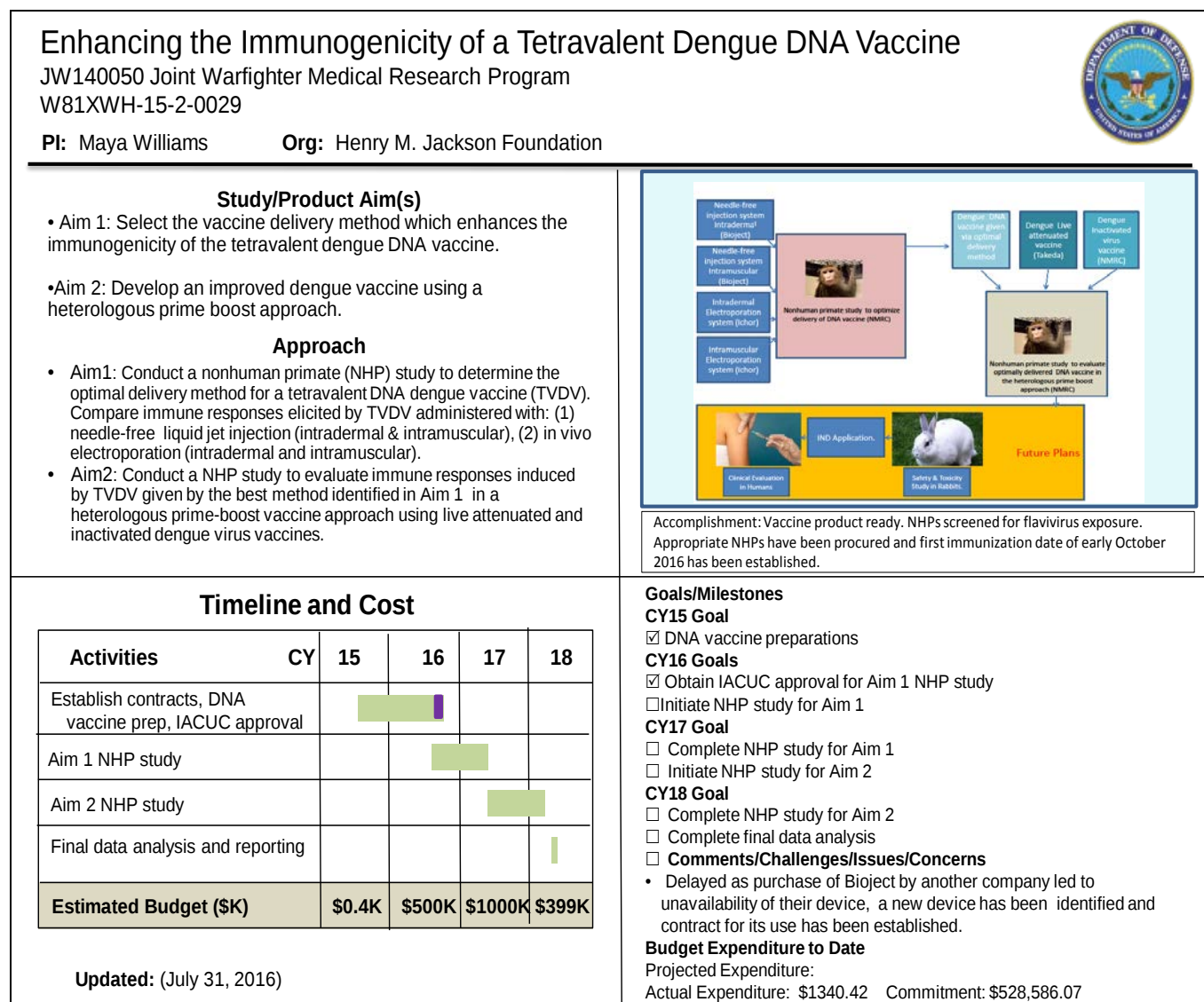
See appendix, updated information is in red.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS:



9. APPENDICES

Appendix: Updated Support

APPENDIX

UPDATED KEY PERSONNEL CURRENT AND PENDING SUPPORT

LCDR MAYA WILLIAMS RESEARCH SUPPORT

CURRENT

Title: NMRC/WRAIR Global sequence analysis and antigenic characterization of currently circulating influenza strains using antigenic cartography

Time Commitments: 5% 0.6 calendar months

Supporting Agency: GEIS

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/1/15-09/30/16

Funding: \$109,000

Goals and Specific Aims: Support GEIS partners by using sequence and phenotypic data in order to provide a comprehensive genetic and antigenic characterization of influenza viruses circulating around the globe. This information can be used to identify new and emerging strains of influenza as well as inform decision makers in the process to select the next season's influenza vaccine.

There is no overlap with the proposed project.

Title: Serological survey for Zika virus and other vector-borne pathogen exposures among DoD personnel deployed to Liberia for Operation United Assistance (OUA)

Time Commitments: 5% 0.6 calendar months

Supporting Agency: GEIS

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/1/15-09/30/16

Funding: \$105,100

Goals and Specific Aims: This study will provide a more accurate picture of the efficacy of force health protection measures in place during OUA and will inform force health protection measures during future deployments to the region. Aim1: Determine the seroprevalence and seroincidence of antibodies against a range of vector-borne, zoonotic, and other pathogens among DoD personnel deployed to Liberia for Operation United Assistance (OUA) and stationed in other locations with potentially high burden for vector-borne diseases. Aim 2: Determine the pathogens associated with overt febrile illness.

There is no overlap with the proposed project.

Title: Investigation of the role of dengue non-structural proteins NS3 and NS5 in immune protection in a mouse model

Time Commitments: 5% 0.6 calendar months

Supporting Agency: Military Infectious Disease Research Program

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/01/15-09/30/16

Funding: \$203,000

Goals and Specific Aims: This proposal will investigate the contribution of NS5 in addition to NS3 for enhancing neutralizing antibody titers and T-cell responses when co-immunized with a PIV vaccine that lacks these components. This proposal will also evaluate the

contribution of NS3 and NS5 alone to protect mice against DENV infection, and its underlying mechanism.

There is no overlap with the proposed project.

Title: The Role of Antibody-dependent Cell Cytotoxicity (ADCC) and Antibody-Dependent Cell-mediated Viral Inhibition (ADCVI) in Host Defense against Dengue Infection

Time Commitments: 5% 0.6 calendar months

Supporting Agency: Military Infectious Disease Research Program

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/01/15-09/30/16

Funding: \$259,000

Goals and Specific Aims: The goal of this research is to investigate ADCC and ADCVI in natural dengue virus infections and vaccine trials. ADCC and ADCVI are areas which have been relatively under-looked compared to antibody neutralization and antibody-dependent enhancement; therefore this work will open a new window for seeking potential surrogate markers of immune protection to aid dengue vaccine development.

There is no overlap with the proposed project.

Title: A humanized mouse model for studying human immunology and pathogenesis of dengue virus infection

Time Commitments: 5% 0.6 calendar months

Supporting Agency: Military Infectious Disease Research Program

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/01/15-09/30/16

Funding: \$151,000

Goals and Specific Aims: This proposal received funding to support preliminary experiments to explore if the DRAG-A mouse model is susceptible to infection by dengue virus. The current proposal is an extension of this work and would support a full characterization, validation and refinement of the model including additional metrics of the immune response.

There is no overlap with the proposed project.

Title: Anti-dengue human polyclonal antibodies from transchromosomal cattle as therapeutic and/or prophylactic agents against dengue virus infection

Time Commitments: 5% 0.6 calendar months

Supporting Agency: Military Infectious Disease Research Program

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/01/15-09/30/16

Funding: \$185,000

Goals and Specific Aims: The hypothesis to be tested in this proposal is that fully human anti-dengue polyclonal antibodies produced in transchromosomal bovines are able to protect mice and non-human primates from dengue virus challenge.

There is no overlap with the proposed project.

Title: Use of the Dual Platform Immunization (DuPI) Approach to Develop a Tetravalent Dengue Vaccine **Time Commitments:** 8% 0.96 calendar months

Supporting Agency: DoD Peer Reviewed Medical Research Program, USAMRAA

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/1/14-09/30/16

Funding: \$811,398/2years

Goals and Specific Aims: The goal of this project is to evaluate an immunization strategy that uses two different types of dengue vaccines administered simultaneously.

There is no overlap with the proposed project.

PENDING

Title: Development and Validation of the DRAG Humanized Mouse Model for Dengue Virus Infection and Vaccine Evaluation (JW160011)

Time Commitments: 15% 1.8 calendar months

Supporting Agency: the Congressionally Directed Medical Research Programs (CDMRP)

HJF Contact: Lisa Straker, 240-694-4016

Performance Period Proposed: 10/1/16-09/30/19

Funding: \$2,666,773

Goals and Specific Aims: (#1) Determine if in vivo infection with a variety of serotypes and strains of DENV in humanized DRAGA mice results in infection associated with viremia, manifestations of disease, and the generation of a humanized immune response, and perform a comparative analyses of performance with a live dengue virus human challenge study. (#2) Characterize the immune response following in vivo vaccination of DRAGA mice with several dengue candidate vaccine formulations, determine efficacy by challenge with each dengue virus serotype, and compare the results with the live virus human challenge model.

DR. KANAKATTE RAVIPRAKASH RESEARCH SUPPORT

CURRENT

Title: Sustainment of Core Capability within DoD for Influenza serology and diagnostics to enable and support sero-epidemiological, vaccine efficacy, and related studies by GEIS partners

Time Commitments: 10% 1.2 calendar months

Supporting Agency: GEIS

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/01/15-09/30/16

Funding: \$205K

Goals and Specific Aims: Goal of this project is to maintain NMRC as a DoD reference laboratory for influenza serology by developing assays and standard reagents for partnering DoD/other laboratories.

Title: Immune responses to sequential annual influenza vaccination in US Military personnel

Time Commitments: 10% 1.2 calendar months

Supporting Agency: GEIS

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/01/15-09/30/16

Funding: \$223K

Goals and Specific Aims: Goal of this project is to determine if repeated annual vaccination against influenza results in stunted immune responses to vaccination. Study will provide data that could help in developing future vaccination recommendations.

Title: Anti-dengue Tc-bovine antibody

Time Commitments: 10% 1.2 calendar months

Supporting Agency: Military Infectious Disease Research Program

NMRC Contact: Cheryl Carr, 301-319-7334

Performance Period: 10/01/15-09/30/16

Funding: \$259,039

Goals and Specific Aims: Goal of this project is to demonstrate efficacy of Tc-bovine derived anti-dengue human IgG in a non-human primate model.

Title: Convalescent plasma therapy to treat patients with severe influenza.

Time Commitments: 5% 0.6 calendar months

Supporting Agency: IDCRP (DoD Infectious Diseases Clinical Research Program)

IDCRP Contact: Samuel Davis, 301-816-8415

Performance Period: 08/01/16-04/30/17

Funding: \$176K

Goals and Specific Aims: Goal of this project is to screen serum/plasma samples from human donors for anti-influenza antibody. The screen will help select plasma units for use in the clinical trial. Selected plasma units are also used in the preparation of IVIG to be used in the clinical trial.

PENDING

None