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Dengue virus mRNA lipid nanoparticle vaccine

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
1R01AI150672-01A1	1R01AI150672-01	RICHNER, JUSTIN	UNIVERSITY OF ILLINOIS AT CHICAGO

Description

Abstract Text

Nearly 400 million people are infected with dengue virus (DENV) each year through the bite of infected mosquitos concentrated in the tropical and subtropical regions of the world. Symptoms can range from febrile illness to severe dengue that manifests as plasma leakage, sudden loss of blood pressure, organ failure, and shock that can ultimately lead to death. Severe dengue complications are often associated with a secondary heterotypic infection of one of the four circulating serotypes. In this scenario, humoral immune responses targeting cross- reactive, poorly-neutralizing epitopes lead to increased infectivity of susceptible cells via antibody-dependent enhancement (ADE). Additionally, DENV immunity has been implicated in increased susceptibility to Zika virus through ADE. Currently there are no available therapeutics to combat DENV disease. Dengvaxia, the only licensed DENV **vaccine**, was found to increase hospitalization rates in naïve populations, and thus is not recommended for a large portion of at-risk individuals. There is an urgent need for a safe and efficacious **vaccine** that elicits a robust, balanced, neutralizing response to all four DENV serotypes. We propose to develop a novel DENV **vaccine** utilizing an emergent platform: **mRNA** encoding for viral proteins encapsidated in a lipid nanoparticle (LNP). **mRNA**-LNP vaccines elicit robust humoral and cell-mediated immune responses in a safe, non-infectious platform. Additionally, we can direct the host immune response towards neutralizing epitopes by mutating the **mRNA** encoding for the viral protein. We hypothesize that a sequence-engineered tetravalent **mRNA**-LNP **vaccine** will induce a balanced, protective immune response against all four serotypes of dengue without the potential of causing immune enhancement and ADE. In Aim 1 of this study we will generate and optimize **mRNA** constructs encoding for the pre-membrane and envelope viral glycoproteins for all four serotypes of DENV. We will mutate the poorly-neutralizing, cross-reactive epitopes that drive ADE. In Aim 2 we will characterize the immune response to the vaccines in a mouse model. In addition to quantifying humoral and cellular immune responses, we will also measure the immune enhancement capacity of all vaccines. In Aim 3, we will evaluate **vaccine** efficacy and safety in susceptible mouse models, by challenging vaccinated mice with different DENV serotypes to monitor protection and ADE. We will also determine mechanism of protection via adoptive transfer experiments. Through this study, we will identify DENV vaccines that demonstrate broad protection and lack of immune enhancement for further evaluation as candidate human vaccines.

Public Health Relevance Statement

Dengue virus has a profound impact on human health with 390 million infections and 25,000 deaths annually worldwide. In this study, we will develop and characterize a vaccine against dengue virus utilizing the mRNA platform. With this approach, mRNA encoding for viral proteins is encapsidated in a lipid nanoparticle which will allow us to rapidly generate and screen for vaccines which are efficacious and safe that will be further evaluated as candidate human vaccines.

Project Terms

Adoptive Transfer | Animal Model | Animals | Antibodies | Antibody Repertoire | Antibody-Dependent Enhancement | Antigens | Antiviral Agents | B-Lymphocytes | Bite | Blood Pressure | Cells | Cessation of life | Clinical | Clinical Trials | Contracts | Culicidae | Data | Dengue | Dengue **Vaccine** | Dengue Virus | Dengvaxia | Disease | Engineering | Epitopes | Evaluation | Extravasation | Fever | Flavivirus | Future | Glycoproteins | Health | Hemorrhage | Human

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Former Number
1R01AI150672-01

Contact PI/Project Leader
RICHNER, JUSTIN

Awardee Organization
UNIVERSITY OF ILLINOIS AT CHICAGO

Contact PI/ Project Leader

Name
RICHNER, JUSTIN

Title
ASSISTANT PROFESSOR

Contact
jrichner@iitri.org

Other PIs

Not Applicable

Program Official

Name
MORABITO, KAITLYN MELISSA

Contact
dambachkm@mail.nih.gov

Organization

Name
UNIVERSITY OF ILLINOIS AT CHICAGO

City
Chicago

Country
UNITED STATES (US)

Department Type
MICROBIOLOGY/IMMUN/VIROL(

Organization Type
SCHOOLS OF MEDICINE

State Code
IL

Congressional District
07

Other Information

FOA
PA-20-185

Study Section
Vaccines Against Microbial Diseases Study Section[VMD]

Fiscal Year
2021

Award Notice Date
12-August-2021

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
098987217

CFDA Code
855

Project Start Date
12-August-2021

Project End Date
31-July-2025

Budget Start Date
12-August-2021

Budget End Date
31-July-2022

Project Funding Information for 2021

Total Funding
$454,113

Direct Costs
$317,088

Indirect Costs
$137,025

Year	Funding IC	
2021	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$454,113

Sub Projects

No Sub Projects information available for 1R01AI150672-01A1

Publications

No Publications available for 1R01AI150672-01A1

Thank you for your feedback!

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The Project Outcomes shown here are displayed verbatim as submitted by the Principal Investigator (PI) for this award. Any opinions, findings, and conclusions or recommendations expressed are those of the PI and do not necessarily reflect the views of the National Institutes of Health. NIH has not endorsed the content below.

No Outcomes available for 1R01AI150672-01A1

Clinical Studies

No Clinical Studies information available for 1R01AI150672-01A1

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Related News Releases

No news release information available for 1R01AI150672-01A1

History

No Historical information available for 1R01AI150672-01A1

Similar Projects

No Similar Projects information available for 1R01AI150672-01A1

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