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Development of a Replicon RNA-based Universal Vaccine against Dengue and Zika

Project Number
1R56AI148635-01

Contact PI/Project Leader
SHRESTA, SUJAN

Awardee Organization
LA JOLLA INSTITUTE FOR IMMUNOLOGY

Description

Abstract Text

ABSTRACT The long-term goal of this project is to develop a **mRNA** replicon-based **vaccine** that provides long-lived protection against the four serotypes of dengue (DENV1-4) and Zika (ZIKV) viruses. To date, flavivirus **vaccine** development has focused almost exclusively on the induction of neutralizing antibodies (nAbs), as they have been assumed to be the key mechanism for protection against natural infection. However, DENV and perhaps ZIKV are unusual in that weak Ab responses to vaccination or prior infection can induce antibody-dependent enhancement (ADE) of infection and pathogenesis during subsequent reinfections. In fact, ADE with severe sequalae has been documented in children given the only currently licensed DENV **vaccine**. Thus, the primary objective of this application is to develop an effective **vaccine** against DENV and ZIKV that cannot mediate ADE. We hypothesize that this **vaccine** will need to elicit both strong nAb responses and strong T cell effector responses that will counterbalance the presence of any ADE-mediating Abs, based on our work investigating the interplay between Ab and T cell responses to DENV and ZIKV. In particular, we have shown that CD8 T cells mediate cross-protection against heterotypic DENV and ZIKV infections, and that DENV **vaccine**-elicited CD8 T cells can prevent ADE. In addition, our preliminary data show that a **mRNA** replicon-based **vaccine** expressing ZIKV nonstructural protein 3 elicits only T cell but not Ab responses and confers protection against ZIKV challenge in mice. Thus, we hypothesize that our pan-flavivirus **mRNA** replicon-based **vaccine** expressing both Ab- and T cell-targeting proteins of DENV1-4 and ZIKV will produce humoral and cellular immune responses that provide robust, long-term protection against all five viruses. We will test this hypothesis by achieving the following Specific Aims: 1: To evaluate immunogenicity and protective efficacy of a pan-flavivirus **vaccine** against DENV1-4 and ZIKV designed to elicit CD8 T cell and Ab responses in wild-type mice. 2: To assess durability and immune mechanisms underlying the pan-flavivirus **vaccine**-induced protective immunity and ADE in mice. 3: To assess the immune response and protection induced by the pan-flavivirus **vaccine** in nonhuman primates.

Public Health Relevance Statement

NARRATIVE DENV and ZIKV are significant causes of morbidity and mortality worldwide, as half of the world's population is at risk of DENV and ZIKV infection in tropical and subtropical regions. DENV and ZIKV vaccines are a global public health priority. To avoid the risk of immune-mediated enhancement of disease, DENV and ZIKV vaccines should ideally induce long-lasting, protective immunity to all four DENV serotypes and ZIKV. This project evaluates a novel pan-flavivirus vaccine designed to induce both nAb responses and T cell responses and to provide long-lived protection against infection with DENV1- 4 and ZIKV.

NIH Spending Category

Biodefense Biotechnology Emerging Infectious Diseases Genetics Immunization Infectious Diseases Orphan Drug Prevention Rare Diseases Vaccine Related Vector-Borne Diseases

Project Terms

Alphavirus Animal Model Antibody Formation Antibody Response Antibody-Dependent Enhancement C57BL/6 Mouse CD4 Positive T Lymphocytes

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Read More

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City
LA JOLLA

Country
UNITED STATES (US)

Department Type
Unavailable

Organization Type
Research Institutes

State Code
CA

Congressional District
52

Other Information

FOA
PA-19-056

Study Section
Vaccines Against Microbial Diseases Study Section[VMD]

Fiscal Year
2020

Award Notice Date
14-September-2020

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
603880287

CFDA Code
855

Project Start Date
14-September-2020

Project End Date
31-May-2021

Budget Start Date
14-September-2020

Budget End Date
31-May-2021

Project Funding Information for 2020

Total Funding
$761,992

Direct Costs
$428,068

Indirect Costs
$333,924

Year	Funding IC	
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$761,992

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category

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Immunization; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases; Vaccine Related; Vector-Borne Diseases;

Sub Projects

No Sub Projects information available for 1R56AI148635-01

Publications

No Publications available for 1R56AI148635-01

Patents

No Patents information available for 1R56AI148635-01

Outcomes

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 1R56AI148635-01

Clinical Studies

No Clinical Studies information available for 1R56AI148635-01

News and More

Related News Releases

No news release information available for 1R56AI148635-01

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