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Sofosbuvir Protection of the Fetal Brain from Zika Virus Infection in Pregnancy

Project Number	Contact PI/Project Leader	Awardee Organization
1R21AI144938-01	ADAMS WALDORF, KRISTINA M.	UNIVERSITY OF WASHINGTON

Description

Abstract Text

PROJECT SUMMARY Zika **virus** (ZIKV) is a flavivirus, primarily transmitted to humans by the bite of infected mosquitoes and can infect a variety of cells in the placenta and fetal brain. An unexpected surge in congenital microcephaly cases in Brazil suggested that the **virus** was teratogenic in pregnancy, which we and others confirmed in nonhuman primate models. Although the initial epidemic was geographically limited, outbreaks will recur, and the US remains at risk for a ZIKV epidemic. Thus, there is an urgent and enduring need to investigate therapeutics and vaccines to prevent pregnancy infections that can permanently injure the fetus. We have developed a highly relevant nonhuman primate (NHP, Macaca nemestrina, pigtail macaque) model of the congenital ZIKV syndrome in which we have identified a consistent injury pattern to the fetal brain. We can now leverage this model to enable investigation of novel therapeutics for protection of the fetal brain from ZIKV infection during pregnancy. Our central hypothesis is that prophylactic Sofosbuvir will prevent maternal-fetal transmission of ZIKV in a pregnant nonhuman primate model. Sofosbuvir (Sovaldi®, Gilead Sciences, Inc.) is an antiviral therapeutic licensed for treatment of chronic Hepatitis C infection, which targets ZIKV NS5, a non-structural protein important for replication of the viral genome. We have chosen to test Sofosbuvir due to evidence for: 1) inhibition of ZIKV infection in a cell lines and pregnant mice, 2) a solid safety profile with no known risks in human pregnancy, 3) a tiered pricing structure for low- and middle-income countries, and 4) possible cross-viral protection due to homologies in viral NS5 proteins. In one Aim, we will determine the ability of prophylactic Sofosbuvir to prevent maternal ZIKV viremia and congenital infection in a pregnant NHP model. We will administer oral Sofosbuvir daily for 3 days prior to and 7 days after ZIKV challenge at ~100 days gestation (second trimester) and perform Cesarean section 7 days after inoculation, followed by necropsy of the dam and fetus. The primary study outcome is detection of ZIKV RNA in the dam sera on Days 2-3 post-inoculation, which is a high-risk state for maternal-fetal transmission. Secondary outcomes include: 1) detection of replicating **virus** or viral nucleic acids in maternal, placental or fetal tissues or fluids (amniotic fluid, cord blood) and 2) fetal neuropathology focused on identification of periventricular injury. If successful, prophylactic Sofosbuvir could represent the first therapeutic option to protect pregnancies from ZIKV infection for women living in areas with local mosquito-borne transmission or for pregnant women (or their sexual partners) traveling to these areas. Further, a strategy to prevent ZIKV viremia in the adult mother could be translated to other vulnerable adult populations (e.g. elderly, immunocompromised adults) with increased susceptibility to neurologic complications associated with ZIKV infection. These studies will allow us to obtain pilot data in preparation for an R01 proposal to determine the efficacy, pharmacokinetics (in pregnancy) and fetal safety of using Sofosbuvir to prevent congenital ZIKV infections.

Public Health Relevance Statement

PROJECT NARRATIVE The goal of our proposal is to study the ability of Sofosbuvir to prevent maternal-fetal transmission of Zika virus during pregnancy in a highly relevant nonhuman primate model of congenital Zika virus infection. Completion of this work will provide novel information on how prophylactic use of Sofosbuvir may prevent maternal-fetal transmission of Zika virus.

NIH Spending Category

Biodefense Emerging Infectious Diseases Infectious Diseases Maternal Health Neurosciences Orphan Drug Pediatric Perinatal Period - Conditions Originating in Perinatal Period Pregnancy Prevention Rare Diseases Vector-Borne Diseases Women's Health

Project Terms

Adult Americas Amniotic Fluid Anatomy Animal Model Antiviral Agents Ants Area Astrocytes Autopsy Basic Science Blood Brain Brazil Cell Line Cells Cesarean section Chronic Hepatitis C Clinical Clinical Sciences Culicidae Dangerousness Data Detection Development Disease Outbreaks Drug Kinetics Elderly Epidemic Eye Injuries Fetal Development Fetal Tissues Fetal safety Fetus Flavivirus Foundations Geography Goals Host Defense Human Human Bites Immune Immunocompromised Host Immunofluorescence Immunologic Infection Infectious Pregnancy Complications Injury Interferons Investigation Liquid substance Macaca nemestrina Magnetic Resonance Imaging

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Contact PI/Project Leader
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Congressional District
07

Country
UNITED STATES (US)

Other Information

FOA
PA-18-048

Study Section
Special Emphasis Panel[ZRG1 IDM-Y (82)]

Fiscal Year
2019

Award Notice Date
22-February-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
605799469

CFDA Code
855

Project Start Date
01-March-2019

Project End Date
28-February-2021

Budget Start Date
01-March-2019

Budget End Date
29-February-2020

Project Funding Information for 2019

Total Funding
$264,500

Direct Costs
$150,000

Indirect Costs
$114,500

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$264,500

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$264,500	Biodefense; Emerging Infectious Diseases; Infectious Diseases; Maternal Health; Neurosciences; Orphan Drug; Pediatric; Perinatal Period - Conditions Originating in Perinatal Period; Pregnancy; Prevention; Rare Diseases; Vector-Borne Diseases; Women's Health;

Sub Projects

No Sub Projects information available for 1R21AI144938-01

Publications

No Publications available for 1R21AI144938-01

Patents

No Patents information available for 1R21AI144938-01

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No Outcomes available for 1R21AI144938-01

Clinical Studies

No Clinical Studies information available for 1R21AI144938-01

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Related News Releases

No news release information available for 1R21AI144938-01

History

No Historical information available for 1R21AI144938-01

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