Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

JAK-STAT Control of Zika Virus-Induced Fetal Injury

Project Number
1R01AI143265-01A1

Contact PI/Project Leader
ADAMS WALDORF, KRISTINA M.Other PIs

Awardee Organization
UNIVERSITY OF WASHINGTON

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Description

Abstract Text

PROJECT SUMMARY/ABSTRACT The recent epidemic of Zika virus (ZIKV) in the Americas was deemed a global public health emergency after an unexpected surge in congenital microcephaly cases suggested that the virus was teratogenic in pregnancy. ZIKV is a flavivirus, primarily transmitted to humans by the bite of infected mosquitoes. ZIKV can infect a variety of placental cells and is also highly neurotropic to target neural progenitor cells, astrocytes and neurons in all stages of development. The congenital ZIKV syndrome describes a severe pattern of placental and fetal brain injury associated with pregnancy infection including microcephaly, ventriculomegaly, and ocular injury. Although the epidemic is now in decline, outbreaks will recur and the US remains at risk for an epidemic. Thus, an enduring need remains to define the viral-host interactions that support ZIKV infection, replication, and maternal-fetal transmission, and to develop a clinically relevant animal model for studies of pathogenesis. Relevant animal models are essential to define the outcome of viral-host interaction within the progression of ZIKV infection and to evaluate the efficacy of vaccines and therapeutics to control ZIKV infection and emergence. We have developed a highly relevant nonhuman primate model of the congenital ZIKV syndrome (Macaca nemestrina, pigtail macaque) in addition to clinically relevant in vitro and ex vivo models of placental and neural stem cell infection. We have shown that ZIKV (1) mediates a broad blockade to the JAK-STAT pathway in infected cells to abrogate cytokine signaling mediated by STATs 1-6, to suppress interferon antiviral defenses; (2) infects trophoblast, myeloid, epithelial, and neural progenitor cells to impose a JAK-STAT blockade through the actions of viral nonstructural protein(s); (3) infects a variety of maternal and fetal tissues in our nonhuman primate model including the neural progenitor cells in the developing fetal brain, and (4) infection reprograms the STAT-dependent fetal brain transcriptome in vivo to alter developmental gene networks. In this resubmission, we present new preliminary data to reveal that ZIKV NS5 binding to HSP90 disrupts the essential interaction of Jak and Tyk2 kinases with HSP90 that otherwise promotes kinase folding and function. The ZIKV NS5-HSP90 interaction suppresses JAK-STAT signaling to abrogate interferon antiviral defenses, which also presents a blockade to cytokine-directed cell-fate decisions signaled via the JAK-STAT pathway that, in part, underlie ZIKV disease. Our central hypothesis is that acute ZIKV infection induces a broad blockade of JAK-STAT signaling involving multiple STATs to suppress antiviral defenses, which enhances vertical transmission and alters fetal brain development. In Aim 1, we will determine how ZIKV mediates a broad JAK-STAT signaling suppression (STAT 1-6) in vitro and ex vivo to control innate immune defenses, viral trafficking and injury. A new feature of Aim 1 is that we will define the outcome of ZIKV NS5 binding to host cell HSP90, which we hypothesize will disrupt client Jak and Tyk2 kinase actions. In Aim 2, we will determine how viral control of JAK-STAT impacts vertical transmission and pathogenesis of fetal brain injury in vivo in a nonhuman primate model of the congenital ZIKV syndrome.

Public Health Relevance Statement

PROJECT NARRATIVE The goal of our proposal is to investigate ZIKV blockade of JAK-STAT signaling as a mechanism for enhancing viral pathogenesis, vertical transmission and altering fetal neurodevelopment. These experiments are fundamental for understanding the pathogenesis of maternal-fetal transmission and fetal brain injury induced by ZIKV and will provide the necessary foundation for testing novel therapeutics and vaccines for fetal protection.

NIH Spending Category

Biodefense Clinical Research Conditions Affecting the Embryonic and Fetal Periods Emerging Infectious Diseases Health Disparities Human Fetal Tissue Infectious Diseases Injury (total) Accidents/Adverse Effects Injury - Childhood Injuries Minority Health Neurosciences Pediatric Perinatal Period - Conditions Originating in Perinatal Period Pregnancy Rare Diseases Stem Cell Research Stem Cell Research - Nonembryonic - Human Vector-Borne Diseases Women's Health

Project Terms

Acute Americas Anatomy Animal Model Animals Antiviral Agents Applications Grants Area Astrocytes Binding Brain Cell Nucleus Cell physiology Cells Client Complex Culicidae Cytokine Signaling Data Data Set Development Developmental Gene Disease Disease Outbreaks Epidemic Epithelial Eye Injuries Fetal Development Fetal Tissues Flavivirus Foundations Gene Expression Profile Goals Heat-Shock Proteins 90

Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

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Department Type
OBSTETRICS & GYNECOLOGY
Organization Type
SCHOOLS OF MEDICINE

State Code
WA
Congressional District
07

Other Information

FOA
PA-18-484
Study Section
Special Emphasis Panel[ZRG1 IDM-X (02)]
Fiscal Year
2019
Award Notice Date
21-June-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DUNS Number
605799469
CFDA Code
855

Project Start Date
01-July-2019
Project End Date
30-June-2024
Budget Start Date
01-July-2019
Budget End Date
30-June-2020

Project Funding Information for 2019

Total Funding
$919,950
Direct Costs
$609,116
Indirect Costs
$310,834

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$919,950

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$441,576	Health Disparities; Minority Health;
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$919,950	Biodefense; Clinical Research; Conditions Affecting the Embryonic and Fetal Periods; Emerging Infectious Diseases; Human Fetal Tissue; Infectious Diseases; Injury (total) Accidents/Adverse Effects; Injury - Childhood Injuries; Neurosciences; Pediatric; Perinatal Period - Conditions Originating in Perinatal Period; Pregnancy; Rare Diseases; Stem Cell Research; Stem Cell Research - Nonembryonic - Human; Vector-Borne Diseases; Women's Health;

Sub Projects

No Sub Projects information available for 1R01AI143265-01A1

Publications

Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

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No Patents information available for 1R01AI143265-01A1

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 1R01AI143265-01A1

Clinical Studies

No Clinical Studies information available for 1R01AI143265-01A1

News and More

Related News Releases

No news release information available for 1R01AI143265-01A1

History

No Historical information available for 1R01AI143265-01A1

Similar Projects

No Similar Projects information available for 1R01AI143265-01A1