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Viral Hemorrhagic Fevers: Disease Modeling and Transmission

Project Number
1ZIAAI001089-12

Contact PI/Project Leader
FELDMANN, HEINRICH

Awardee Organization
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Description

Abstract Text

(A) Study pathogenesis and pathophysiology of high biocontainment viral pathogens utilizing molecular technologies including reverse genetics systems: We continue to optimize mouse models for Crimean-Congo hemorrhagic fever virus (CCHFV) to study pathogenesis, immune responses and develop countermeasures. We defined favipiravir as a potent antiviral against CCHFV infection. Recently, we have established a mouse adapted CCHFV that leads to severe infection in wildtype mice. This will be an extremely valuable tool for future countermeasure development. (Hawman et al.) Using the Collaborative Cross (CC) mouse model of differential Ebola virus disease severity, we identified clinical, virologic, and transcriptomic features distinguishing outcomes. Tolerance is associated with rapid regulated induction of immune responses, including altered quantities of specialized effector cells. Lethal disease results from suppressed early gene expression, followed by uncontrolled inflammatory signaling. Gene expression signatures developed in mice predicted outcome in a cohort of West African Ebola patients demonstrating the potential for developing clinical prognostic tools in mice. (collaboration with A. Rasmussen & I. Lipkin, Columbia University) We have continued to establish a disease model for Reston ebolavirus (RESTV) in a commercial pig breed. Young pigs, ranging in age from 3 7 months, were highly susceptible to oral-nasal inoculation of RESTV. The animals developed acute severe respiratory distress with high but not uniform lethality. Most pigs succumb within a week of infection; some animals recover from severe disease. RESTV replicates mainly in respiratory tissues and virus is shed through mucosal membranes of the oronasal tract. The model will be instrumental for countermeasure development against a potential transboundary pathogen. (Haddock et al. & collaboration with J. Richt, Kansas State University) (B) Study immune responses to infection and vaccination of high containment viral pathogens and develop new vaccine candidates: We have continued to better define the use of VSV -based vaccine vectors against filoviruses. We could show that a single low-dose vaccination with VSV-EBOV protected cynomolgus macaques from lethal Ebola challenge. This work has implications for vaccine production, availability and use during public health response activities. (Marzi et al.) We could show that prior vaccination with VSV-EBOV did not interfere with post exposure antibody treatment, an important clinical aspect in the field for the treatment of recently VSV-EBOV vaccinated individuals. (collaboration with T. Geisbert, UTMB Galveston) Furthermore, we could demonstrate the usefulness of a quadrivalent VSV-based vaccine approach against several filoviruses. (collaboration with T. Geisbert, UTMB Galveston) We report the development and assessment of a DNA-based vaccine for CCHFV in the cynomolgus macaque model. Macaques were vaccinated with a DNA-based vaccine using in vivo electroporation-assisted delivery. The vaccine contained two plasmids encoding the glycoprotein precursor (GPC) and the nucleoprotein (NP) of CCHFV. This is the first evidence of a vaccine that can protect against CCHFV-induced disease in a nonhuman primate model. Clinical development of the vaccine is in progress. (Hawman et al & collaboration with CCHFVaccine Consortium) (C) Study vector/reservoir transmission of high containment viral pathogens using appropriate animal models: We continued to study infection kinetics of Lassa virus in the Mastomys reservoir utilizing a unique colony established here at RML. The animals support virus replication and shedding for several weeks before Lassa virus gets cleared. The model will allow for important transmission studies. (Rosenke et al.). We also developed immunological tools to study host responses in Mastomys. (Tang et al.) A wildlife vaccine project we have isolated and characterized Mastomys-specific cytomegaloviruses. Viral vectors are currently being designed. (Rosenke et al. & collaboration with M. Jarvis, Plymouth University, DARPA PREEMPT project) We also have studied host competency of Mastomys for the African relapsing fever spirochete Borrelia crocidurae. (Rosenke et al.) (D) Utilize in vitro and in vivo systems to study the interactions between viral pathogen or viral components and host cells and develop new antiviral strategies: We utilized the CCHFV Cynomolgus macaque disease model to test for antiviral efficacy of favipiravir. In this model, favipiravir was only of limited benefit compared to the mouse model. Nevertheless, given the bad performance of ribavirin in animal models, we propose to start human trials with favipiravir as the drug seems more potent against CCHFV. (Hawman et al.) We have demonstrated efficacy of monoclonal antibodies against Andes virus (hantavirus) in the Syrian hamster disease model. Neutralizing antibodies against the glycoproteins protected against lethal challenge. This approach can now be considered for clinical trials as there is no other animal model for this hantavirus. (Feldmann et al. & collaboration with F. Krammer, Mount Sinai) We studied the role of supportive care on Ebola virus infection in the lethal cynomolgus macaque model. We found that the animals developed progressive severe organ dysfunction and profound shock preceding death. While the overall impact of supportive care on the observed pathophysiology was limited, we did observe some time-dependent positive responses. (collaboration with J. Strong, Public Health Agency of Canada) (E) Study the epidemiology and ecology of high biocontainment pathogens utilizing newly developed rapid, sensitive and specific diagnostic test systems including those that can be applied under field conditions: Field studies for rodent-borne viruses have been started in the Bitterroot Valley. The initial phase of this project focused on Sin nombre hantavirus in deer mice. We found up to 20% of deer mice positive for SNV RNA in the lungs. We were unable to obtain a SNV isolate from the lungs but could passage SNV from lung tissue into nave deer mice. This is important for local public health as there is potential for human SNV infection. (Williamson et al.) For overseas filed studies, please see Annual Report on Mali ICER and Uganda ICER project.

Public Health Relevance Statement

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Infectious Diseases Lung Prevention Rare Diseases Vaccine Related Vector-Borne Diseases

Project Terms

Acute African Age Andes Virus Animal Model Animals Annual Reports Antibody Therapy Antiviral Agents Arenavirus Biology Borrelia Bunyaviridae Canada Cells Cessation of life Clinical Clinical Trials Clinical Virology Collaborations Competence Containment Crimean-Congo Hemorrhagic Fever Virus Cytomegalovirus DNA Deer Mouse Development Diagnostic Diagnostic tests Disease Disease model Dose Ebola Ebola Hemorrhagic Fever Ebola virus Ecology Effector Cell Electroporation Emerging Communicable Diseases Epidemiology Family suidae Filovirus Fostering Functional disorder Future Gene Expression Gene Expression Profile Glycoproteins Goals

Read More

Details

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

City

Country

Department Type
Unavailable

Organization Type
Unavailable

State Code

Congressional District

Other Information

FOA

Study Section

Fiscal Year
2020

Award Notice Date

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number

CFDA Code

Project Start Date

Project End Date

Budget Start Date

Budget End Date

Project Funding Information for 2020

Total Funding
$1,998,462

Direct Costs
$0

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,998,462

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Sub Projects

No Sub Projects information available for 1ZIAAI001089-12

Publications

No Publications available for 1ZIAAI001089-12

Patents

No Patents information available for 1ZIAAI001089-12

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 1ZIAAI001089-12

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