Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

Mimicking evolution to define mechanisms of airborne transmission of H7N9 viruses

Project Number
1R21AI144135-01

Contact PI/Project Leader
SUTTON, TROY CLAVELL

Awardee Organization
PENNSYLVANIA STATE UNIVERSITY-UNIV PARK

Description

Abstract Text

The Asian lineage H7N9 avian influenza viruses (AIV) have caused >1500 human zoonotic infections with 615 deaths. These viruses have not spread in humans; however, there is a high potential for these viruses to evolve to transmit via the airborne route and cause a pandemic. Using ferrets, we previously evaluated the ability of the prototypic Asian lineage virus, A/Anhui/1/2013 (H7N9), to undergo two continuous rounds of airborne transmission. In these studies, we found that the virus was able to transmit to 50-66% of respiratory contact ferrets during both rounds of transmission. In a subsequent deep sequence analysis, we identified 2-5 mutations in 90-99% of all variant viruses that transmitted. These mutations were in the hemagglutinin (HA), neuraminidase (NA), and viral polymerase genes. As airborne transmission is associated with enhanced binding and replication in cells of the upper airways, we hypothesize that the identified mutations will alter the molecular properties of the virus to enhance replication in primary human nasal and tracheal epithelial cells. Our aims are: Aim 1. Determine the role of previously identified HA and NA mutations in an H7N9 virus with the A/PR/8 vaccine backbone. Viruses carrying the H7N9 HA and NA on the A/PR8 vaccine backbone will generated. Mutations will be introduced into the HA and NA gene segments and several properties including receptor-binding preference, pH of fusion, thermostability, NA activity, and changes in antibody recognition via immune serum will be evaluated. Aim 2. Evaluate the role of previously identified mutations on the viral polymerase. To assess the impact of mutations in the viral polymerase, in vitro polymerase reconstitution assays will be performed. Specifically, the activity of the wild-type H7N9 polymerase with and without the identified mutations will be assessed. Aim 3. Determine if the introduction of previously identified mutations alters viral replication in primary human airway epithelial cells. To determine if the identified mutations impact viral replication, we will evaluate the replication kinetics of recombinant H7N9-A/PR8 viruses for their growth in primary human airway epithelial cells. Primary human cells will include nasal, tracheal, bronchial, and small airway epithelial cells. Collectively, these studies will determine the effect of the identified mutations on different molecular properties of the virus, while also determining if the mutations alter the viral tropism in human cells. Our findings will generate new insight on how AIV evolve to transmit via the airborne route and will yield critical knowledge required to interpret the evolution and assess the pandemic potential of H7N9 viruses.

Public Health Relevance Statement

The Asian lineage H7N9 avian influenza viruses pose a significant pandemic threat. To initiate a pandemic these viruses must evolve to transmit via the airborne route; however, the changes that would result in airborne transmission are currently unknown. This proposal will yield insight into the effect of previously identified mutations that were associated with airborne transmission of an H7N9 virus on the molecular properties of the virus. As several of the identified mutations have been identified in viruses circulating in nature or have arisen through passage in the laboratory, understanding the impact of these mutations on viral replication or transmission will yield new knowledge that can facilitate the risk assessment of emerging influenza viruses.

Project Terms

Antibodies Asians Avian Influenza A Virus Binding Biological Assay Cells Cessation of life Epithelial Cells Evolution Ferrets Genes Growth Hemagglutinin Human Immune Sera In Vitro Influenza A Virus, H1N1 Subtype Influenza A Virus, H7N9 Subtype Kinetics

Back to Search Results

Description

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

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UNITED STATES (US)

Department Type
VETERINARY SCIENCES

Organization Type
EARTH SCIENCES/RESOURCES

State Code
PA

Congressional District
12

Other Information

FOA
PA-18-489

Study Section
Virology - B Study Section[VIRB]

Fiscal Year
2021

Award Notice Date
02-September-2021

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
003403953

CFDA Code
855

Project Start Date
02-September-2021

Project End Date
31-August-2023

Budget Start Date
02-September-2021

Budget End Date
31-August-2022

Project Funding Information for 2021

Total Funding
$226,169

Direct Costs
$150,000

Indirect Costs
$76,169

Year	Funding IC	
2021	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$226,169

Sub Projects

No Sub Projects information available for 1R21AI144135-01

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Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

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Patents

No Patents information available for 1R21AI144135-01

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 1R21AI144135-01

Clinical Studies

No Clinical Studies information available for 1R21AI144135-01

News and More

Related News Releases

No news release information available for 1R21AI144135-01

History

No Historical information available for 1R21AI144135-01

Similar Projects

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