Project Details

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Description



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Transmissibility of avian influenza viruses in mammals

Project Number Former Number 4R01Al069274- 5R01Al069274- 09 09

Contact
PI/Project Leader
KAWAOKA,
YOSHIHIRO

Awardee
Organization
UNIVERSITY OF
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Description

Abstract Text

DESCRIPTION (provided by applicant): Since 1997, highly pathogenic avian influenza viruses of the H5N1 subtype have infected humans with high case fatality rates, although no sustained human-tohuman transmission has yet been reported. Currently, the molecular features and mechanisms that would result in human-to-human transmission of H5N1 viruses are not fully understood. Indeed, several attempts in the past to select transmissible H5 viruses (which typically do not transmit among mammals) were not successful, suggesting that influenza virus transmissibility is determined by several currently unknown factors. Recently, we screened H5 virus libraries possessing random mutations in the globular head region of the hemagglutinin (HA) protein and identified mutant H5 HAs that acquired the ability to bind to human-type receptors. These mutant H5 HAs did not support virus transmission among ferrets (an established influenza virus transmission model) via respiratory droplets, but acquired this ability after two passages of the virus in these animals, which resulted in the selection of additional mutations in HA. This marks the first conversion of an H5 virus that does not transmit among ferrets into one with efficient respiratory droplet transmission. Based on this finding, we propose to decipher the determinants of H5N1 virus transmission in mammals. In Aim 1, we plan "To Identify the Mechanisms That Control H5N1 Virus Transmissibility in Mammals". To gain a better understanding of the mutations in HA that result in transmissible viruses, we will select transmissible viruses based on H5 HA proteins derived from different subclades that have caused human infections. Our recent study suggested that HA stability may contribute to virus transmissibility. To test this concept, we also plan to identify mutations in HA that increase HA stability and then test these mutations for their significance in virus transmissibility. The HA proteins of all ferret-transmissible H5N1 viruses will then be characterized for their receptor-binding specificity, their structural consequences, their effects in other genetic backgrounds, and their pathogenicity in mice and ferrets. Mutations in HA that allow avian influenza viruses to bind to human-type receptors are most likely a prerequisite for transmission among mammals; however, findings by us and others indicate that human-type receptor binding is not sufficient for respiratory droplet transmission among ferrets, and that other viral genes also contribute to transmissibility. In Aim 2 ("To Characterize the Contribution of Viral Genes Other than HA to H5N1 Virus Transmissibility", we plan to passage non-transmissible viruses of different genetic backgrounds in ferrets to select transmissible mutants. Selected mutations will be characterized for their biological effects, using established assays for internalization, intracellular transport replication and transcription, assembly and budding, and interferon antagonism. Collectively, these studies are expected to generate critical information about the molecular determinants and mechanisms of H5N1 virus transmissibility in mammals.

Public Health Relevance Statement

PUBLIC HEALTH RELEVANCE: Our research seeks to understand the mechanisms that would allow highly pathogenic avian H5N1 influenza viruses to infect humans and transmit among them. This information is critical for basic research and the public health sector to monitor circulating and $n\epsilon$

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> emerging H5N1 strains for their pandemic potential and to develop countermeasures to such viruses.

NIH Spending Category

Biodefense **Emerging Infectious Diseases** Genetics **Infectious Diseases**

Influenza Pneumonia & Influenza

Project Terms

Affect Amino Acids Antibodies Address Animals Area **Avian Influenza A Virus Binding Basic Science** Biological **Biological Assay Birds Case Fatality Rates** Disease **Egypt Ferrets Foundations Funding** Genes Genetic **Genetic Transcription** H5 hemagglutinin Head Hemagglutinin Human Incidence Indonesia Infection Influenza A Virus, H1N1 Subtype Influenza A Virus, H5N1 Subtype **Interferons Intracellular Transport** Libraries Mammals Modeling Molecular **Monitor Pathogenicity** Mus Mutation **Other Genetics Population Property**

Details

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Read More

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MEDICINE

MADISON

Country

UNITED STATES (US)

Other Information

2016

2016

FOA Administering Institutes or **Project Start** 01-May-PA-11-260 Centers 2006 Date NATIONAL INSTITUTE OF Study Section

ALLERGY AND INFECTIOUS Project End 31-August-Virology - B Study Section[VIRB] **DISEASES** Date 2020

DUNS Number CFDA Code Award Notice Budget Start 01-161202122 855

Date September-Date Fiscal Year 09-August-2016

> **Budget End** 31-August-Date 2020

Thank you for your feedback!

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Project Funding Information for 2016

Total Funding Direct Costs Indirect Costs \$605,206 \$404,412 \$200,794

Year Funding IC

2016 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES \$605,206

NIH Categorical Spending <u>Click here for more information on NIH Categorical Spending</u>

Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	\$605,206	Biodefense; Emerging Infectious Diseases; Genetics; Infectious Diseases; Influenza; Pneumonia & Influenza;

品 Sub Projects

No Sub Projects information available for 4R01Al069274-09

Publications

No Publications available for 4R01AI069274-09

∀ Patents

No Patents information available for 4R01Al069274-09

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 4R01Al069274-09

Clinical Studies

No Clinical Studies information available for 4R01Al069274-09



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Related News Releases

No news release information available for 4R01AI069274-09



No Historical information available for 4R01AI069274-09

Similar Projects

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