Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

IDENTIFICATION AND CHARACTERIZATION OF RNA STRUCTURES IN THE GENOME OF INFLUENZA VIRUS

Project Number
5R01AI139251-02

Contact PI/Project Leader
BOON, ADRIANUS CM

Awardee Organization
WASHINGTON UNIVERSITY

Description

Abstract Text

PROJECT SUMMARY Influenza poses a significant health risk worldwide. It is estimated that between 250,000 and 500,000 people die each year from the virus. This number can increase dramatically during an influenza **pandemic**, such as the 1918 Spanish influenza **pandemic**, when more than 25 million people died. The genome of influenza A virus consists of eight segments of single-stranded, negative-sense RNA that are encapsidated as individual ribonucleoprotein complexes (RNPs). Each RNP contains one strand of RNA, a viral polymerase complex and multiple copies of the viral nucleoprotein (NP). The segmented nature of influenza virus allows for reassortment or mixing of gene-segment and this is a major contributor to the emergence of **pandemic** influenza viruses. Image analysis of individual RNP complexes show a double-helical conformation of two strands of NP connected by a small loop and the polymerase proteins at the termini of the complex. The organization of the viral RNA in this structure is not known, which limits our ability to understand and to target RNA dependent processes that contribute to the generation of **pandemic** influenza viruses. To address this gap, we applied a new technology, cross-linking and immunoprecipitation coupled with next-generation sequencing (CLIP-seq), to discern the organization of the RNA in native RNP complexes of IAV. Analysis of the immunoprecipitated viral RNA revealed non-uniform binding of the NP to the genome. Specifically, we identified 34 regions that range in size between 14-85 nucleotides that are significantly underrepresented in the NP-bound RNA fraction. Nearly 50% of the low-NP binding regions are predicted to form stable secondary structures, including RNA hairpins and RNA pseudoknot structures. This led us to hypothesize that the RNA structural features, that are poorly bound by NP, are pivotal for gene-segment interactions and are the primary features controlling IAV segment packaging at the molecular level. In support of this hypothesis we found that the introduction of synonymous structural mutations that disrupt the predicted RNA structures attenuated the resulting viruses without exception. In contrast, synonymous mutations that did not alter the predicted RNA structure, or mutations in control regions had no impact on the growth of the virus. The attenuation in low-NP binding mutant viruses was due to a defect in genome packaging. The goal of this application is to determine the mechanism by which low-NP binding regions affect IAV replication, genome packaging, and virus reassortment.

Public Health Relevance Statement

Narrative Influenza viruses will continue to reassort and generate novel pandemic influenza viruses. This project will identify the organization and folding of the viral RNA in the genome of IAV and discern how structural features of the RNA impact virus replication, genome packaging and reassortment. These novel insights may yield safer vaccines and uncover new treatment options for this deadly disease.

NIH Spending Category

Biodefense Emerging Infectious Diseases Genetics Infectious Diseases Influenza Pneumonia & Influenza

Project Terms

Address Affect Attenuated Avian Influenza A Virus Binding Biochemical Birds Cells Complex Coupled Defect Disease

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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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Read More

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Name
WASHINGTON UNIVERSITY

City
SAINT LOUIS

Country
UNITED STATES (US)

Department Type
INTERNAL MEDICINE/MEDICINE

Organization Type
SCHOOLS OF MEDICINE

State Code
MO

Congressional District
01

Other Information

FOA
PA-16-160

Study Section
Virology - A Study Section[VIRA]

Fiscal Year	Award Notice Date
2019	21-June-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
068552207

CFDA Code
855

Project Start Date	13-July-2018
Project End Date	30-June-2022
Budget Start Date	01-July-2019
Budget End Date	30-June-2020

Project Funding Information for 2019

Total Funding
$504,545

Direct Costs
$321,366

Indirect Costs
$183,179

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$504,545

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category

Thank you for your feedback!

Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

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Diseases;
Influenza;
Pneumonia &
Influenza;

Sub Projects

No Sub Projects information available for 5R01AI139251-02

Publications

No Publications available for 5R01AI139251-02

Patents

No Patents information available for 5R01AI139251-02

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 5R01AI139251-02

Clinical Studies

No Clinical Studies information available for 5R01AI139251-02

News and More

Related News Releases

No news release information available for 5R01AI139251-02

History

No Historical information available for 5R01AI139251-

Thank you for your feedback!

Back to Search Results

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Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

Project Number
5R01AI139251-02

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