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Chemical intervention of influenza virus RNA nuclear export

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
5R33AI119304-05	4R21AI119304-03	GARCIA-SASTRE, ADOLFO Other PIs	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

Description

Abstract Text

DESCRIPTION (provided by applicant): Influenza viruses cause approximately 36,000 deaths annually in the United States and ~500,000 deaths worldwide per year. Strains that are extremely pathogenic have been responsible for high numbers of deaths worldwide, such as the 1918 **pandemic** which led to ~30 million deaths around the world. Currently, there are only two approaches available for preventing or treating epidemic and **pandemic** influenza, vaccination and inhibitors of viral replication. Vaccination, although highly effective against homologous strains, looses efficacy in the elderly, and it is limited by the highly mutable nature of the viru, forcing the annual reformulation of the vaccine to match the antigenicity of the current influenza virus circulating strains. A number of drugs have been approved for the treatment of influenza. These drugs inhibit virus uncoating or virus spread but the use of these relatively small number of antiviral drugs is limited by the appearance of resistant virus strains. Thus, there is a clear need for additional therapeutic modalities for the treatment of influenza virus disease. In this application, we deal with the development of a new discovery platform for the identification of chemical compounds that inhibit influenza virus RNA nuclear export. Influenza virus RNAs are imported into the host cell nucleus for replication and are then exported from the nucleus as mRNAs or vRNAs to express viral proteins or generate new viral particles, respectively. Therefore, blockage of vRNAs or viral mRNAs in the nucleus results in inhibition of virus replication. We have evidence demonstrating that we can follow single viral vRNA and mRNA segments in intact infected cell and that this process can be regulated. We will use this assay to detect inhibition of viral RNA nuclear export using our ~200,000 compound library and our high throughput imaging platform. The screen is proposed for the R21 phase of the application. For the R33 phase, the selected hits will be subjected to structure activity relationship for improving potency, selectivity, stability and toxicity profile in cell based and animal based models with various strains of influenza virus. In sum, the identified compounds by this discovery platform will likely represent a new class of potential antivirals that could be useful for antagonizing influenza virus and possibly other viruses that use a similar nuclear export machinery.

Public Health Relevance Statement

PUBLIC HEALTH RELEVANCE: Influenza virus infection is a significant health and economic burden with limited therpeutic option. This application proposes to develop a new strategy for the identificationof a new class of antivirals.

NIH Spending Category

Biodefense Biotechnology Emerging Infectious Diseases Genetics Immunization Infectious Diseases Influenza Pneumonia & Influenza Prevention Vaccine Related

Project Terms

Animals Antiviral Agents Appearance Biological Assay Birds Cell Nucleus Cell physiology Cells Cessation of life Chemicals Chemistry Development Economic Burden Elderly Epidemic Epithelial Cells Growth Hour Human Image Analysis In Situ Hybridization In Vitro Infection Influenza Influenza A Virus, H1N1 Subtype Influenza A virus Influenza vaccination Intervention Libraries Luciferases Messenger RNA Modality Modeling Nature Nuclear Nuclear Export Nuclear RNA Pathogenicity Pharmaceutical Chemistry Pharmaceutical Preparations Phase RNA Resistance Specificity Structure-Activity Relationship Sum Testing Therapeutic Toxic effect United States

Read More

Details

Contact PI/ Project Leader

Name
GARCIA-SASTRE, ADOLFO

Title

Contact

Other PIs

Name
FONTOURA, BEATRIZ MA

Program Official

Name
KRAFFT, AMY

Contact
kraffta@niaid.nih.gov

Thank you for your feedback!

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City
NEW YORK

Country
UNITED STATES (US)

Organization Type
SCHOOLS OF MEDICINE

Congressional District
13

Other Information

FOA
RFA-AI-14-026

Study Section
ZAI1-LR-M(M2)

Fiscal Year
2019

Award Notice Date
06-June-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
078861598

CFDA Code
855

Project Start Date **01-July-2015**

Project End Date **30-June-2021**

Budget Start Date **01-July-2019**

Budget End Date **30-June-2021**

Project Funding Information for 2019

Total Funding
$500,998

Direct Costs
$361,998

Indirect Costs
$139,000

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$500,998

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$500,998	Biodefense; Biotechnology; Emerging Infectious Diseases; Genetics; Immunization; Infectious Diseases; Influenza; Pneumonia & Influenza; Prevention; Vaccine Related;

Sub Projects

No Sub Projects information available for 5R33AI119304-05

Publications

No Publications available for 5R33AI119304-05

Patents

No Patents information available for 5R33AI119304-05

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 5R33AI119304-05

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News and More

Related News Releases

No news release information available for 5R33AI119304-05

History

No Historical information available for 5R33AI119304-05

Similar Projects

No Similar Projects information available for 5R33AI119304-05