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Discovery of broad-spectrum influenza antivirals with a high genetic barrier to drug resistance by targeting the viral polymerase

Project Number
1R21AI144887-01

Contact PI/Project Leader
WANG, JUN

Awardee Organization
UNIVERSITY OF ARIZONA

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Description

Abstract Text

Project Summary Despite the existence of vaccines and antiviral drugs, global annual death tolls attributed to influenza virus infection are ~500,000. Currently there is only one orally bioavailable drug, oseltamivir, that is still in use to treat influenza infection. The alarming fact is that oseltamivir-resistant influenza strains have already been isolated from human patients, and several of them appear to have adapted the fitness of transmission. Thus there is a pressing need to develop novel antivirals to combat these drug-resistant influenza viruses. They can be used either alone to inhibit oseltamivir-resistant strains or in combination with oseltamivir to decrease the pace of drug resistance evolution. Moreover, as the influenza viruses circulating among humans consist of at least two influenza A strains (H1N1 and H3N2) and two B strains (Yamagata and Victoria), it is also desirable to have one antiviral drug with broad-spectrum antiviral activity against all four strains. In response to the need for a next generation of antiviral drugs with broad-spectrum antiviral activity, especially against multidrug-resistant influenza viruses, we performed an in silico screening of an in-house library of small molecules predominantly prepared by one-pot multicomponent reaction (MCR) methodologies against the virus polymerase PA subunit and have identified several promising hits. One compound, UAWJ85, inhibits several multidrug-resistant influenza A and B viruses with EC50 values range from single to sub-micromolar. This compound also displays a high in vitro genetic barrier to drug resistance, as no resistant viruses were selected after 10 passages with increasing concentrations of the compound. Mechanistic studies confirmed the inhibition of polymerase PA-PB1 subunit interactions by UAWJ85. The broad-spectrum antiviral activity and high in vitro genetic barrier to drug resistance of UAWJ85, coupled with the expeditious structure–activity relationship studies using the one-pot Ugi- Azide 4CR methodology, have led us to further optimize the antiviral potency, selectivity index, in vitro and in vivo PK properties of lead compounds and test their in vivo antiviral efficacy in mice. In Aim 1, we will optimize the in vitro antiviral and pharmacokinetic properties of UAWJ85. A list of criteria was imposed for compound progression. The goal is to prioritize lead compounds for in vivo mice studies. In Aim 2, we will will test the in vivo PK and antiviral activity of UAWJ85 or its analogs using the influenza virus infected mice model. In summary, the advantage of exploring MCR products for broad-spectrum anti-influenza drugs has been clearly demonstrated by the preliminary results. This proposal, if successfully implemented, will lead to the urgently needed antivirals to combat both seasonal outbreaks and the next influenza **pandemic**.

Public Health Relevance Statement

PROJECT NARRATIVE The limited efficacy of currently approved antiviral drugs in combating emerging drug-resistant influenza viruses highlights the immediate need for novel anti-influenza drugs. This application undertakes an innovative approach by exploring expeditious multicomponent reaction products for broad-spectrum anti-influenza drugs. We have identified several promising drug candidates that are active against multiple human clinical isolates of influenza A and B viruses, including strains that are resistant to oseltamivir. This project, if successfully implemented, is likely to yield the first-in-class “Virological Penicillin.”

NIH Spending Category

Antimicrobial Resistance | Biodefense | Emerging Infectious Diseases | Infectious Diseases | Influenza | Pneumonia & Influenza

Project Terms

A549 | Amantadine resistance | Antiviral Agents | Azides | Binding | Bioavailable | Biological Assay | Biological Availability | Body Weight | California | Cell Line | Cell Membrane Permeability | Cessation of life | Clinical | Coca | Complex | Computer Simulation | Coupled | Development | Disease Outbreaks | Dose | Drug Kinetics | Drug resistance | Ensure | Enzyme-Linked Immunosorbent Assay | Evolution | Exhibits | Genetic | Goals | Human | In Vitro | Inbred BALB C Mice | Infection | Influenza | Influenza A Virus, H1N1 Subtype | Influenza A virus | Influenza B Virus | Lead | Maximum Tolerated Dose | Methodology | Methods | Monitor | Multi-Drug Resistance | Mus | Mutation | North America | Oral | Oseltamivir | Outcome

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Project Number
1R21AI144887-01

Contact PI/Project Leader
WANG, JUN

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Awardee Organization
UNIVERSITY OF ARIZONA

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Name
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City
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Country
UNITED STATES (US)

Department Type
PHARMACOLOGY

Organization Type
SCHOOLS OF PHARMACY

State Code
AZ

Congressional District
03

Other Information

FOA
PA-18-489

Study Section
Special Emphasis Panel[ZRG1 IDM-Y (82)]

Fiscal Year
2019

Award Notice Date
27-February-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
806345617

CFDA Code
855

Project Start Date
01-March-2019

Project End Date
28-February-2021

Budget Start Date
01-March-2019

Budget End Date
29-February-2020

Project Funding Information for 2019

Total Funding
$220,848

Direct Costs
$150,000

Indirect Costs
$70,848

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$220,848

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	$220,848	Antimicrobial Resistance; Biodefense; Emerging Infectious Diseases; Infectious Diseases; Influenza; Pneumonia & Influenza;

Sub Projects

No Sub Projects information available for 1R21AI144887-01

Publications

No Publications available for 1R21AI144887-01

Patents

No Patents information available for 1R21AI144887-01

Outcomes

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Clinical Studies

No Clinical Studies information available for 1R21AI144887-01

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No news release information available for 1R21AI144887-01

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No Historical information available for 1R21AI144887-01

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