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Development of a Broad-Spectrum Inhibitor against Seasonal and Highly-Pathogenic Influenza Viruses

Project Number
1R01AI141222-01

Contact PI/Project Leader
PLEMPER, RICHARD K.

Awardee Organization
GEORGIA STATE UNIVERSITY

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Description

Abstract Text

Summary Influenza viruses are the leading cause of human disease due to respiratory viral infection worldwide. It is the overarching objective of this partnership to advance a novel pyrimidine analog anti-influenza virus class towards an investigational new drug-enabling package. The design of this program is driven by our underlying hypothesis that effective next-generation therapeutics for the treatment of influenza must be orally available, display a broad indication spectrum against influenza virus isolates of human, avian, and swine lineages, and covers both influenza A (IAV) and B (IBV) viruses. These product profile demands are derived from the clinical burden imposed by the diverse spectrum of seasonal influenza viruses, the **pandemic** potential arising from spillover of zoonotic viruses into the human population, and current FDA recommendations that recognize non- hospitalized adults suffering from seasonal influenza as the primary patient population for initial clinical testing. These developmental objectives are best met with direct acting therapeutics, since host-targeted antiviral therapies, although often tantalizingly broad in indication range, are prone to unacceptable side effects that are incompatible with the primary patient group pursued. Under the umbrella of a long-term academia/industry antiviral partnership, we have established a dual- pathogen drug screening protocol that allows the simultaneous automated identification of target virus-specific and broad-spectrum candidates. Implementation of this assay in a large-scale drug screening campaign has yielded a cytidine analog with sub-micromolar antiviral potency. In pilot studies underpinning this preclinical program, we have demonstrated that potent inhibitory activity extends to IAV and IBV isolates, covers viruses representing human and zoonotic lineages, and includes highly pathogenic avian H5N1 and H7N9 viruses of major **pandemic** threat. The lead compound is orally bioavailable, efficiently converted to the active triphosphate in vivo, and showed sustained micromolar lung tissue concentrations. We have demonstrated oral efficacy in mice against seasonal and highly pathogenic avian influenza viruses with **pandemic** potential and observed substantial suppression of viral spread in the guinea pig IAV transmission model. In preparation of clinical testing, this lead class will be subjected to mechanistic characterization and resistance profiling (aim 1). In parallel, phospholipid prodrug formulations will be explored to boost drug tissue concentrations for severe disease indications and a structurally independent alternative identified in our screen will be advanced through chemical lead development for back-up to alleviate the potential risk of developmental failure (aim 2). Pharmacokinetic and pharmacodynamic profiles of emerging phospholipid prodrug and back-up leads will be generated and in vivo tolerability determined (aim 3). Efficacy of clinical candidates against seasonal and highly-pathogenic viruses will be tested in mice and ferrets, the effect of prior drug exposure on pathogenesis examined, and the impact on viral spreads assessed in guinea pigs (aim 4).

Public Health Relevance Statement

Narrative Influenza viruses are the leading cause of respiratory disease due to viral infection worldwide and responsible for over 40,000 case fatalities annually in the United States in non-pandemic years. Efficacy of the existing seasonal vaccine is moderate especially in older adults, who are disproportionally at risk of severe disease, and licensed antivirals are increasingly compromised by pre-existing viral resistance in circulating strains. Building on a successful long-term antiviral partnership, this project will advance a novel class of orally efficacious ribonucleoside analogs towards an investigational new drug study package.

NIH Spending Category

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

Project Terms

Academia | Address | Adult | Anabolism | Animal Model | Animals | Antiviral Agents | Antiviral Therapy | Avian Influenza A Virus | Back | Bioavailable | Biological Assay | Biological Availability | Birds | Canis familiaris | Cavia | Cells | Cessation of life | Chemicals | Clinic | Clinical | Complex | Cytidine | Development | Disease | Disease Management | Drug Exposure | Drug Kinetics | Drug Screening | Elderly | Eligibility Determination | Esters | Failure | Family suidae | Ferrets | Formulation | Frequencies | Generations | Human | Industry | Infection | Influenza | Influenza A Virus, H5N1 Subtype | Influenza A Virus, H7N9 Subtype | Influenza A virus | Influenza B Virus | Investigational Drugs | Joints | Lead | Lung diseases

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1R01AI141222-01

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City
ATLANTA
Country
UNITED STATES (US)

Department Type
MISCELLANEOUS
Organization Type
ORGANIZED RESEARCH UNITS

State Code
GA
Congressional District
05

Other Information

FOA
RFA-AI-17-026
Study Section
Special Emphasis Panel[ZAI1 AZ-M (S1)]
Fiscal Year
2019
Award Notice Date
08-January-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DUNS Number
837322494
CFDA Code
855

Project Start Date
08-January-2019
Project End Date
31-December-2023
Budget Start Date
08-January-2019
Budget End Date
31-December-2019

Project Funding Information for 2019

Total Funding
$1,103,435
Direct Costs
$927,934
Indirect Costs
$175,501

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,103,435

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	$1,103,435	Antimicrobial Resistance; Biodefense; Biotechnology; Emerging Infectious Diseases; Infectious Diseases; Influenza; Lung; Pneumonia & Influenza;

Sub Projects

No Sub Projects information available for 1R01AI141222-01

Publications

No Publications available for 1R01AI141222-01

Patents

No Patents information available for 1R01AI141222-01

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No Outcomes available for 1R01AI141222-01

Clinical Studies

No Clinical Studies information available for 1R01AI141222-01

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Related News Releases

No news release information available for 1R01AI141222-01

History

No Historical information available for 1R01AI141222-01

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