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Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Project Number
5R01AI132178-03

Contact PI/Project Leader
BARIC, RALPH SOther PIs

Awardee Organization
UNIV OF NORTH CAROLINA CHAPEL HILL

Description

Abstract Text

Project Summary Zoonotic viruses, like filoviruses and coronaviruses (CoV), represent a continuous and growing threat to global public health because they unpredictably emerge causing devastating outbreaks of **pandemic** disease. In the 21st century, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) emerged from zoonotic pools of viruses, causing severe disease in humans. MERS-CoV is endemic in camels in the Middle East with continuous new infections in humans. Although SARS-CoV is not currently a threat, several "prepandemic" SARS-like CoVs have been isolated from bats that replicate efficiently in human cells and are resistant to existing therapies. With the unpredictable overlap of human and wild animal ecologies, the potential for novel CoV emergence into humans is highly probable. Currently, there are no approved antiviral therapies for any human CoV infection. Broad-spectrum CoV therapies that control known human and zoonotic CoV infections would address an immediate unmet medical need and could counter future **pandemic** episodes. In partnership with Gilead Sciences, we have demonstrated that the nucleoside prodrug, GS-5734, is highly efficacious in inhibiting multiple human and zoonotic CoV in vitro and SARS-CoV in vivo. The primary goal of our program is to accelerate the preclinical development of GS-5734 and promote IND licensure for the MERS-CoV indication. To thoroughly evaluate the breadth of antiviral activity and predict efficacy against future emerging CoV, we will also assess efficacy against a panel of CoV representative of family-wide genetic diversity, including prepandemic zoonotic strains poised for emergence. Focusing on the highly pathogenic MERS-CoV, our unique partnership integrates: i) metagenomics and recombinant virus synthetic genome recovery, ii) primary human lung cell models, iii) cutting edge virology and biochemistry, iv) robust murine and primate models of human disease and v) state of the art metabolic and pharmacokinetic analysis. In Aim 1, we refine the pharmacokinetics, pharmacodynamics and breadth of GS-5734 through efficacy and metabolism studies in various primary human cells with a diverse array of human and zoonotic CoV and through the evaluation of in vivo efficacy in murine and non-human primate models of MERS- and SARS-CoV. In Aim 2, we select for resistance against SARS-CoV and MERS- CoV, and determine the effect of resistance on virus replication, fitness and susceptibility to treatment. In Aim 3, we determine if the mechanism of action of GS-5734 is a result of direct effects on viral RNA replication and/or alteration of antiviral immunity via deep sequencing and single molecule RNA fluorescence in situ hybridization of vehicle or drug treated infected cells and mice. We articulate a development strategy for broad-spectrum therapeutics that could be extended to a multitude of emerging viral pathogens threatening global public health.

Public Health Relevance Statement

Project Narrative In partnership with Gilead Sciences, we aim to accelerate the preclinical development of GS-5734 and promote IND licensure. We define the pharmacokinetics, pharmacodynamics, resistance profile, efficacy breadth and mechanism of action of GS-5734 against MERS-CoV and related emerging CoV.

NIH Spending Category

Biodefense Biotechnology Emerging Infectious Diseases Genetics Infectious Diseases Lung Orphan Drug Rare Diseases

Project Terms

Address Animal Model Animals Antiviral Agents Antiviral Therapy Attenuated Biochemistry Birds Camels Cell Culture Techniques Cell model Cells Chiroptera Clinical Trials Coronavirus Coronavirus Infections Data Development Disease Disease Outbreaks Drug Kinetics Endothelium Engineering Epithelial Cells Exons Family Filovirus Fluorescent in Situ Hybridization Fostering Future Generations Genetic Genetic Variation Genome Goals Hepatitis Human Immune In Vitro Infection Innate Immune Response Licensure Lung Mammals Measurement Mediating Medical Metabolic Metabolism Metagenomics Middle East Middle East Respiratory Syndrome Coronavirus

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Awardee Organization
UNIV OF NORTH CAROLINA CHAPEL HILL

RBARIC@EMAIL.UNC.EDU

Organization

Name
UNIV OF NORTH CAROLINA CHAPEL HILL

City
CHAPEL HILL

Country
UNITED STATES (US)

Department Type
PUBLIC HEALTH & PREV MEDICINE

Organization Type
SCHOOLS OF PUBLIC HEALTH

State Code
NC

Congressional District
04

Other Information

FOA
RFA-AI-16-034

Study Section
ZAI1-LR-M(M2)

Fiscal Year
2019

Award Notice Date
15-July-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
608195277

CFDA Code
855

Project Start Date **09-August-2017**

Project End Date **31-July-2022**

Budget Start Date **01-August-2019**

Budget End Date **31-July-2020**

Project Funding Information for 2019

Total Funding
$1,166,670

Direct Costs
$919,427

Indirect Costs
$247,243

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,166,670

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	$1,166,670	Biodefense; Biotechnology; Emerging Infectious Diseases; Genetics; Infectious Diseases; Lung; Orphan Drug; Rare Diseases;

Sub Projects

No Sub Projects information available for 5R01AI132178-03

Publications

No Publications available for 5R01AI132178-03

Patents

No Patents information available for 5R01AI132178-03

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.

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No Clinical Studies information available for 5R01AI132178-03

News and More

Related News Releases

No news release information available for 5R01AI132178-03

History

No Historical information available for 5R01AI132178-03

Similar Projects

No Similar Projects information available for 5R01AI132178-03

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