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Project 1 - Coronavirus

Parent Project Number	Sub-Project ID	Contact PI/Project Leader	Awardee Organization
1U19AI142759-01	7962	DENISON, MARK R.	UNIVERSITY OF ALABAMA AT BIRMINGHAM

Description

Abstract Text

PROJECT SUMMARY Zoonotic coronaviruses (CoVs) such as SARS-CoV and MERS-CoV are **pandemic** threats. MERS-CoV continues to cause new zoonotic and human transmission and illness with ~35% mortality. Currently, there are no FDA-approved therapies to treat any CoV. New zoonotic CoVs likely will emerge from heterogeneous virus pools in animal reservoirs, thus requiring antiviral strategies aimed at completely conserved and vulnerable targets. CoVs rapidly select for resistance to multiple classes of inhibitors, demonstrating the need for approaches to prevent resistance emergence. Both SARS and MERS infections manifest as severe immunopathologic damage, potentially limiting the therapeutic window for direct-acting antivirals (DAAs). Immunomodulation in the absence of antivirals has been shown to not be beneficial and to even exacerbate SARS and MERS disease. Thus, combinations of DAAs and targeted immunomodulators may be necessary for effective treatment of established infection. The overall goal of our program is to develop CoV antiviral strategies that broadly inhibit known and future potential **pandemic** zoonotic CoVs, prevent emergence of resistance, and extend the therapeutic window by targeting host immunopathologic responses. The proposed research will advance preclinical development of the CoV-inhibitory nucleoside analogue EIDD- 1931/2801 and other nucleoside analogues in the pipeline and test two small-molecule hits identified as highly active against SARS-CoV for treatment and prevention of epidemic and pre-emergent CoVs. In Specific Aim 1, the spectrum of antiviral activity and therapeutic efficacy of compounds will be defined. The antiviral efficacy, metabolism, and cytotoxicity of each compound will be determined in cultures of primary human lung cells targeted by SARS- and MERS-CoV. The prophylactic and therapeutic efficacy of lead compounds will be evaluated in young, aged, and immunosuppressed murine models of SARS and MERS pathogenesis. In Specific Aim 2, the mechanism of action of lead compounds and kinetics of drug resistance will be determined. The antiviral effect of compounds on virus replication, fidelity, and induction of innate immunity will be assessed. Resistance mutations in genomes of MERS- and SARS-CoV passaged in the presence of increasing concentrations of drug will be determined by deep sequencing. The impact of resistance on SARS- and MERS- CoV virulence, sensitivity to other drugs, and therapeutic efficacy of lead compounds will be determined. Specific Aim 3 will focus on the development of combination regimens for the treatment of emerging CoVs. The combined therapeutic efficacy of DAAs against infections with both wild-type and drug-resistant SARS- and MERS-CoV will be defined using cultured cells and mice. The therapeutic effect of treatment combining a DAA with an immunomodulator will be assessed in mouse models of SARS and MERS. These studies will generate mechanistic and efficacy data necessary for IND filing and origination of human clinical trials.

Public Health Relevance Statement

Data not available.

NIH Spending Category

Antimicrobial Resistance Biodefense Emerging Infectious Diseases Infectious Diseases Lung Orphan Drug Prevention Rare Diseases

Project Terms

Acute Address Adult Respiratory Distress Syndrome Animals Antiviral Agents Antiviral resistance Cell Culture Techniques Cells Clinical Trials Combined Modality Therapy Coronavirus Cultured Cells Data Development Disease Drug Kinetics Drug resistance Epidemic Epithelial Cells Evaluation Exons Exoribonucleases FDA approved Future Genome Goals Human Immunomodulators In Vitro Infection Innate Immune Response Institutes Lead Lung Lung diseases Medical Metabolism Middle East Respiratory Syndrome Coronavirus Mus Mutagens Natural Immunity Pathogenesis Pathogenicity Pathology Pharmaceutical Preparations Prevention RNA RNA Viruses

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mark.denison@vanderbilt.edu

Organization

Name
UNIVERSITY OF ALABAMA AT BIRMINGHAM

City
BIRMINGHAM

Country
UNITED STATES (US)

Department Type
Unavailable

Organization Type
Domestic Higher Education

State Code
AL

Congressional District
07

Other Information

FOA
RFA-AI-17-042

Study Section
Special Emphasis Panel[ZAI1 LG-M (J2)]

Fiscal Year
2019

Award Notice Date
06-March-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
063690705

CFDA Code

Project Start Date

Project End Date

Budget Start Date
01-March-2019

Budget End Date
29-February-2020

Project Funding Information for 2019

Total Funding
$1,047,304

Direct Costs
$1,023,054

Indirect Costs
$24,250

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,047,304

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	$1,047,304	Antimicrobial Resistance; Biodefense; Emerging Infectious Diseases; Infectious Diseases; Lung; Orphan Drug; Prevention; Rare Diseases;

Sub Projects

No Sub Projects information available for 1U19AI142759-01 7962

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iCite
A trans-complementation system for SARS-CoV-2 recapitulates authentic viral replication without virulence.					
Cell 2021 04 15; 184 (8) 2229-2238.e13	Zhang, Xianwen; Liu, Yang; Liu, Jianying; Bailey, Adam L;	2021			
View All					
Antibody potency, effector function, and combinations in protection and therapy for SARS-CoV-2 infection in vivo.					
The Journal of experimental medicine 2021 03 01; 218 (3)	Schäfer, Alexandra; Muecksch, Frauke; Lorenzi, Julio C C;	2021			50.40
View All					
Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies.					

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Zika virus oncolytic activity requires CD8+ T cells and is boosted by immune checkpoint blockade.

JCI insight 2021 01 11; 6 (1) — Nair, Sharmila; Mazzoccoli, Luciano: Jash. Ariiita: Govero. — 2021 — iCite 2.48

View All

Coronavirus-Specific Antibody Cross Reactivity in Rhesus Macaques Following SARS-CoV-2 Vaccination and Infection.

Journal of virology 2021 Mar 10; — Jacob-Dolan, Catherine; Feldman, Jared; McMahan. — 2021

View All

Engineering SARS-CoV-2 using a reverse genetic system.

Nature protocols 2021 03; 16 (3) 1761-1784 — Xie, Xuping; Lokugamage, Kumari G; Zhang, Xianwen; Vu, Michelle N; Muruato, Antonio E; Menachery, Vineet D; Shi, Pei-Yong — 2021 — iCite 11.45

Patents

No Patents information available for 1U19AI142759-01 7962

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 1U19AI142759-01 7962

Clinical Studies

No Clinical Studies information available for 1U19AI142759-01 7962

News and More

Related News Releases

No news release information available for 1U19AI142759-01 7962

History

No Historical information available for 1U19AI142759-01 7962

Similar Projects

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