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Coronavirus antiviral nucleoside analogs: inhibition and reduced susceptibility

Project Number	Contact PI/Project Leader	Awardee Organization
5F31AI133952-03	AGOSTINI, MARIA	VANDERBILT UNIVERSITY

Description

Abstract Text

PROJECT SUMMARY Coronaviruses (CoVs) are a family of positive-sense RNA viruses that cause respiratory illnesses in humans ranging from the common cold to severe and lethal disease. The emergence of SARS-coronavirus (CoV) in 2002 and the continued circulation of MERS-CoV emphasize the capacity of CoVs to cause new zoonotic infections with **pandemic** potential. Despite the high mortality rates of these infections, no therapeutics or vaccines against any CoVs are currently available. Broadly active antiviral nucleoside analogs such as Ribavirin (RBV) are ineffective against CoVs. This limitation is attributed to a unique proofreading exoribonuclease (ExoN) in nonstructural protein 14 (nsp14-ExoN) that aids the RNA-dependent RNA polymerase (RdRp) encoded in nonstructural protein 12 (nsp12-RdRp) in high fidelity replication of these large positive-strand RNA viruses. We have identified two antiviral nucleoside analogs, GS-5734 and EIDD-1931, in collaboration with Gilead Sciences and the Emory Institute for Drug Development, respectively, which are broadly active against multiple CoVs with minimal cytotoxicity. In addition, we have identified two mutations within the predicted fingers domain of the nsp12-RdRp that reduce susceptibility to GS-5734, a C-adenosine nucleoside analog. The goals of this proposal are to define mechanisms through which these antiviral compounds inhibit CoV replication and determine the impact of resistance mutations on viral fitness, replication fidelity, and nucleotide selectivity. In Specific Aim 1, the basis of GS-5734 and EIDD-1931-mediated inhibition of CoV replication will be defined using deep sequencing, RT-qPCR, and Northern blot analysis to distinguish between the two most common mechanisms of antiviral action displayed by nucleoside analogs: chain termination and lethal mutagenesis. Experiments proposed in Specific Aim 2 will determine the impact of mutations that reduce susceptibility to GS-5734 and EIDD-1931 on coronavirus replication fidelity, viral fitness, and susceptibility to other nucleoside analogs. Together, these studies will probe mechanisms of GS-5734 and EIDD-1931 inhibition of CoV replication and explore the potential for these antiviral nucleoside analogs to individually and cooperatively serve as potent therapies against existing and emerging CoVs. This research also will inform the development of broadly active and complementary antiviral approaches to combat CoV infections. Finally, these studies will utilize GS-5734 and EIDD-1931 as tools to better understand mechanisms and viral mediators of CoV replication efficiency and fidelity.

Public Health Relevance Statement

PROJECT NARRATIVE Coronaviruses are a family of positive-sense RNA viruses that cause human illnesses ranging from the common cold to severe and lethal respiratory diseases, including as severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS). The continued emergence of zoonotic coronaviruses into human populations represents a significant threat to global human health, and vaccines and antivirals for coronaviruses have, thus far, remained elusive. The proposed research will investigate newly identified antiviral nucleoside analogs that are active against coronaviruses to better understand their mechanisms of action and impact of reduced viral susceptibility, information that will aid in the clinical development of these compounds for treatment of coronavirus infections, inform understandings of high-fidelity coronavirus replication and illuminate viral targets for future drug discovery.

NIH Spending Category

Biodefense Emerging Infectious Diseases Infectious Diseases Lung

Project Terms

5'-exoribonuclease Adenosine Affect Antiviral Agents Antiviral Therapy Blood Circulation Collaborations Common Cold Complex Coronavirus Coronavirus Infections Defective Viruses Development Disease Excision Exons Exoribonucleases Family Fingers Future Genome Goals HIV Health Hepatitis B Virus Hepatitis C virus Herpesviridae Human Individual Infection Institutes Interruption Life Cycle Stages Lung diseases Mediating Mediator of activation protein Middle East Respiratory Syndrome Coronavirus Modeling Murine hepatitis virus

Read More

Details

Contact PI/ Project Leader

Name
AGOSTINI, MARIA

Title

Contact

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Other PIs

Not Applicable

Program Official

Name
STEMMY, ERIK J

Contact

View Email

Organization

Name
VANDERBILT UNIVERSITY

City
Nashville

Country
UNITED STATES (US)

Department Type
PATHOLOGY

Organization Type
SCHOOLS OF MEDICINE

State Code
TN

Congressional District
05

Other Information

FOA
PA-16-309

Study Section
Special Emphasis Panel[ZRG1-F13-C(20)L]

Fiscal Year
2019

Award Notice Date
05-August-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
965717143

CFDA Code
855

Project Start Date
30-September-2017

Project End Date
31-October-2019

Budget Start Date
30-September-2019

Budget End Date
31-October-2019

Project Funding Information for 2019

Total Funding
$4,919

Direct Costs
$4,919

Indirect Costs

Thank you for your feedback!

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$4,919

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	$29,698	Biodefense; Emerging Infectious Diseases; Infectious Diseases; Lung;

Sub Projects

No Sub Projects information available for 5F31AI133952-03

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iCite RCR
The coronavirus proofreading exoribonuclease mediates extensive viral recombination.					
PLoS pathogens 2021 01; 17 (1) e1009226	Gribble, Jennifer;	2021			18.03

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publicatic
An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice.			
Science translational medicine 2020 04 29; 12 (541)	Sheahan, Timothy P;	2020	88.86

View All

Fitness Barriers Limit Reversion of a Proofreading-Deficient Coronavirus.			
Journal of virology 2019 10 15; 93 (20)	Graepel, Kevin W; Agostini, Maria L; Lu, Xiaotao; Sexton, Nicole R; Denison, Mark R	2019	0.60
Small-Molecule Antiviral β-d-N 4-Hydroxycytidine Inhibits a Proofreading-Intact Coronavirus with a High Genetic Barrier to Resistance.			
Journal of virology 2019 12 15; 93 (24)	Agostini, Maria L; Pruijssers,	2019	8.79

View All

Patents

No Patents information available for 5F31AI133952-03

Outcomes

Thank you for your feedback!

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 5F31AI133952-03

Clinical Studies

No Clinical Studies information available for 5F31AI133952-03

News and More

Related News Releases

News	Journal Article	PubMed Abstract
Findings may help close door on COVID-19		January 2021

History

Total project funding amount for 3 projects is $62,851*

** Only NIH, CDC and FDA funding data*

Export

Project Number	Sub	Principal Investigator(s)/ Project Leader(s)	Organization	Fiscal Year	Admin IC	
		Project Leader(s)				Cost by IC
Coronavirus antiviral nucleoside analogs: inhibition and reduced susceptibility						
5F31AI133952-03		AGOSTINI, MARIA	VANDERBILT UNIVERSITY	2019	NIAID	NIAID $4,919
Coronavirus antiviral nucleoside analogs: inhibition and reduced susceptibility						
5F31AI133952-02		AGOSTINI, MARIA	VANDERBILT UNIVERSITY	2018	NIAID	NIAID $29,206
Coronavirus antiviral nucleoside analogs: inhibition and reduced susceptibility						
1F31AI133952-01		AGOSTINI, MARIA	VANDERBILT UNIVERSITY	2017	NIAID	NIAID $28,726

Similar Projects

		STEVEN GARY	KENTUCKY			
SARS-CoV-2 and Autophagy						
342	1R21AI158134-01	JACKSON, WILLIAM T	UNIVERSITY OF MARYLAND BALTIMORE	2020	NIAID	NIAID
Develop Potent Methyltransferase Inhibitors to Target Severe Acute Respiratory Syndrome (SARS-CoV-2)						
407	1R21AI158176-01	ZHENG, Y. GEORGE	UNIVERSITY OF GEORGIA	2021	NIAID	NIAID
Development of Broad-Spectrum Antiviral Therapeutics by Destabilizing the Main Protease Coronaviruses						
391	1R21AI158210-01	TANG, WEIPING	UNIVERSITY OF WISCONSIN-MADISON	2020	NIAID	NIAID
Identifying Genetic Regulators and New Models of Wild						

Thank you for your feedback!

Match Score	Project Number	Sub	Principal Investigator(s)/ Project Leader(s)	Organization	Fiscal Year	Admin IC	Funding IC
508	5R21AI145372-02		GRALINSKI, LISA	UNIV OF NORTH CAROLINA CHAPEL HILL	2021	NIAID	NIAID
Immunomodulatory effects of coronavirus membrane proteins E, M, and S.							
336	1R21AI158229-01		STEPHENS, EDWARD BRICE KALAMVOKI, MARIA	UNIVERSITY OF KANSAS MEDICAL CENTER	2020	NIAID	NIAID
Mechanisms and functional implications of SARS-CoV-2 mRNA capping and modification.							
358	1R21AI158335-01		WILUSZ, JEFFREY GEISS, BRIAN	COLORADO STATE UNIVERSITY	2020	NIAID	NIAID
Advancing the development of a novel class of small molecules for treating pan-coronaviru							
456	1R01AI158569-01		EINAV, SHIRIT	STANFORD UNIVERSITY	2021	NIAID	NIAID
Identifying host and viral correlates for coronavirus pathogenesis							
450	5R01AI153602-02		MENACHERY, VINEET D	UNIVERSITY OF TEXAS MED BR GALVESTON	2021	NIAID	NIAID

Thank you for your feedback!