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Small Molecule Inhibitors of Ebola Virus Polymerase Function

Project Number
5R01AI125453-03

Contact PI/Project Leader
BASLER, CHRISTOPHER F

Awardee Organization
GEORGIA STATE UNIVERSITY

Description

Abstract Text

Project Summary Filoviruses, which include the ebolaviruses and marburgviruses, are non-segmented, negative-sense RNA viruses (NNSVs) that cause severe human **disease**. These viruses are of concern as **emerging** pathogens and as potential bioterrorism threats. Their importance and public health impact are reinforced by the West Africa epidemic that began in winter of 2014 and has resulted in more than 11,000 deaths and the export of Ebola virus **disease** to the U.S., the U.K. and Europe. Although the past year has seen progress toward development of effective vaccines and treatments, current prophylactic and treatment options remain limited. Particularly lacking are effective small molecule inhibitors. Complicating development of anti-filovirus drugs is the biosafety level 4 (BSL4) containment needed to work with live filoviruses, which is only available at a few locations worldwide. With substantial restrictions on the number of investigators who have access to such facilities, antiviral testing against **infectious** virus in a high throughput setting is problematic. An alternate approach is to develop assays of specific viral functions that can be assessed without generation of **infectious** materials. The viral RNA-dependent RNA polymerase (RDRP) complex is a particularly promising candidate. The complex consists of the viral nucleoprotein (NP), viral protein of 35KDa (VP35), VP30 and the large protein (L) which is the enzymatic component of the complex and the only enzyme encoded by the virus. The RDRP complex is required for viral mRNA expression and viral genome replication and is therefore essential for virus growth. Inhibition of the RDRP complex would arrest virus replication. The Basler and Shaw laboratories collaborated to optimize for 384-well high throughput screening a minigenome assay in which a functional EBOV RDRP complex is reconstituted by transfection of plasmids that express its four components into mammalian cells. RDRP activity is measured through the co-expression of a model viral RNA (minigenome RNA) that encodes a reporter gene flanked by the appropriate virus-derived cis-acting regulatory sequences. This system has been successfully transferred to collaborator Sumit Chanda at Sanford Burnham Prebys Medical Discovery Institute where a 6,400 compound pilot screen was performed. This screen yielded hits which were carried through to BSL4 testing by Robert Davey at Texas Biomedical Research Institute and demonstrated to inhibit Ebola virus replication. We propose to exploit this assay and this drug discovery pipeline to identify novel small molecule inhibitors of the Ebola virus polymerase. We will also develop additional HTS-compatible minigenome assays based on other filoviruses associated with deadly human **disease**, including Bundibugyo ebolavirus and Marburg virus, to identify and prioritize hits with pan-filovirus activity. A combination of minigenome assay and filovirus BSL4 experiments will define mechanisms of action, and together with initial SAR studies will prioritize hits for future development. The completion of these studies will significantly expand the number of potential therapeutic small molecules and provide significant insight into inhibition of the filovirus RDRP complex.

Public Health Relevance Statement

Project Narrative Ebola virus and other filoviruses are serious threats to human health, but effective treatments are lacking. The work described here will develop new candidate drugs that target the machinery needed for filovirus growth. !

NIH Spending Category

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

Project Terms

Africa Antiviral Agents Biological Assay Biology Biomedical Research Bioterrorism Cell physiology Cessation of life Clinical Collaborations Collection Complex Containment DNA-Directed RNA Polymerase Development **Disease** Outbreaks Dose Drug Targeting Ebola Hemorrhagic Fever Ebola virus Encapsulated Enzymes Epidemic Europe Filovirus Frankfurt-Marburg Syndrome Virus Future Generations Growth Health Human Impairment Infection Institutes Integration Host Factors Laboratories Libraries Lipids Location Mammalian Cell Measures Medical Modeling Molecular Bank Nucleoproteins Pharmaceutical Chemistry Pharmaceutical Preparations Plasmids Polymerase

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Contact PI/Project Leader
BASLER, CHRISTOPHER F

Awardee Organization
GEORGIA STATE UNIVERSITY

Contact
CHRIS.BASLER@MSSM.EDU

Organization

Name
GEORGIA STATE UNIVERSITY

Department Type
MISCELLANEOUS

State Code
GA

City
ATLANTA

Organization Type
ORGANIZED RESEARCH UNITS

Congressional District
05

Country
UNITED STATES (US)

Other Information

FOA
PA-16-160

Study Section
Special Emphasis Panel[ZRG1-IDM-S(02)M]

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
837322494

CFDA Code
855

Project Start Date
15-February-2017

Project End Date
31-January-2022

Fiscal Year
2019

Award Notice Date
04-February-2019

Budget Start Date
05-February-2019

Budget End Date
31-January-2020

Project Funding Information for 2019

Total Funding
$779,570

Direct Costs
$717,547

Indirect Costs
$62,023

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$779,570

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	$779,570	Biodefense; Biotechnology; Emerging Infectious Diseases; Genetics; Infectious Diseases; Orphan Drug; Rare Diseases;

Sub Projects

No Sub Projects information available for 5R01AI125453-03

Publications

No Publications available for 5R01AI125453-03

Patents

No Patents information available for 5R01AI125453-03

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

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Clinical Studies

No Clinical Studies information available for 5R01AI125453-03

News and More

Related News Releases

No news release information available for 5R01AI125453-03

History

No Historical information available for 5R01AI125453-03

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