Mechanisms of Marburg virus gene expression

Project Number
5R01AI133486-02

Contact PI/Project Leader
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Awardee Organization
BOSTON UNIVERSITY MEDICAL CAMPUS

Description

Abstract Text

Marburg virus (MARV) belongs to the filovirus family and is highly pathogenic in humans. Despite being classified as Category A Priority Pathogen by NIAID, and its potential to cause large-scale outbreaks, similar to the recent Ebola virus outbreak, research on MARV lags significantly behind that on other non-segmented negative sense (NNS) RNA viruses. Here, we propose to perform in-depth analyses of MARV transcription and gene expression. Dissecting the mechanisms of MARV gene expression will not only be instrumental for the targeted development of antiviral drugs, it will also reveal unifying paradigms and distinctions between the NNS RNA viruses. The filovirus genome is transcribed by a virally encoded RNA-dependent RNA polymerase complex, which is capable of generating capped and polyadenylated mRNAs. This process occurs in the cell cytoplasm, close to ribosomes and cellular RNA binding proteins. This project will examine three different stages of MARV gene expression. In Aim 1, we will elucidate the mechanism of transcription initiation at the MARV promoter and investigate the role of structural features of the polymerase in this process. Notably, the MARV promoter sequence has some unusual features, and we intend to explore the functional relevance of these characteristics. In Aim 2, we will determine the function of conserved hairpin loops that are formed at the 5´ end of each MARV mRNA. We will explore the effect of these structures on transcription, RNA stability, trafficking and translation. In Aim 3, we will focus on mRNA polyadenylation and release. The mechanism of mRNA release is not well understood for any NNS RNA virus, and the results obtained in this aim will help to broaden our understanding of NNS RNA virus transcription strategies. This proposal brings together expertise in studying NNS RNA polymerases, MARV molecular biology, and mRNA-protein interactions. Together, the research team has established a unique tool set to achieve the goals of this proposal, including a MARV in vitro polymerase assay, various MARV reverse genetics systems, and highly innovative single molecule mRNA-protein binding assays. These studies will shine new light on a crucial aspect of MARV infection and enhance our understanding of NNS RNA virus biology.

Public Health Relevance Statement

Marburg virus is a highly pathogenic virus, closely related to Ebola virus, that has the potential to cause an outbreak of similar scale and destruction. The goal of this project is to elucidate the processes by which Marburg virus genes are expressed as messenger RNAs and proteins, and to identify in what ways these processes are similar or different from those of other viruses. This work will help identify what aspects of Marburg virus gene expression could potentially be targeted with antiviral drugs.

NIH Spending Category

Biodefense Biotechnology Emerging Infectious Diseases Genetics Infectious Diseases Rare Diseases

Project Terms

Affect Africa Antiviral Agents Attention Binding Proteins Biological Assay Biology Category A pathogen Cells Characteristics Chiroptera Complex Computer Analysis Cytoplasm Cytoplasmic Inclusion DNA-Directed RNA Polymerase Data Development Disease Outbreaks ENG gene Ebola virus Elements Ensure Environment Family Family member Filovirus Frankfurt-Marburg Syndrome Virus Future Gene Expression Gene Expression Regulation Genes Genetic Transcription Genome Goals Heart Human Image In Vitro Length Light Maps Messenger RNA Metabolism Microscopy Molecular Biology National Institute of Allergy and Infectious Disease Pathogenicity Play

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Details

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Country
UNITED STATES (US)

Department Type
MICROBIOLOGY/IMMUN/VIROLOGY

Organization Type
SCHOOLS OF MEDICINE

State Code
MA

Congressional District
07

Other Information

FOA
PA-16-160

Study Section
Virology - A Study Section[VIRA]

Fiscal Year
2019

Award Notice Date
28-April-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
604483045

CFDA Code
855

Project Start Date
08-May-2018

Project End Date
30-April-2023

Budget Start Date
01-May-2019

Budget End Date
30-April-2020

Project Funding Information for 2019

Total Funding
$529,282

Direct Costs
$360,365

Indirect Costs
$168,917

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$529,282

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	$529,282	Biodefense; Biotechnology; Emerging Infectious Diseases; Genetics; Infectious Diseases; Rare Diseases;

Sub Projects

No Sub Projects information available for 5R01AI133486-02

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iCit
CD209L/L-SIGN and CD209/DC-SIGN Act as Receptors for SARS-CoV-2.					
ACS central science 2021 Jul 28; 7 (7) 1156-1165	Amraei, Razie; Yin, Wenqing; Napoleon, Marc A; Suder, Ellen	2021		iCite 3.97	
View All					
CD209L/L-SIGN and CD209/DC-SIGN act as receptors for SARS-CoV-2.					
bioRxiv : the preprint server for biology 2021 Jun 14;	Amraei, Razie; Yin, Wenqing; Napoleon, Marc A; Suder, Ellen	2021		iCite 24.49	
View All					
RSV M2-1 Protein in Complex with RNA: Old Questions Are Answered and a New One Emerges.					

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Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iCite RCR
Structure (London, England : 1993) 2020 09 01; 28 (9) 977-978	Kleiner, Victoria Anne; Fearns, Rachel	2020			0.87
Actionable Cytopathogenic Host Responses of Human Alveolar Type 2 Cells to SARS-CoV-2.					
Molecular cell 2020 12 17; 80 (6) 1104-1122.e9	Hekman, Ryan M; Hume, Adam J; Goel, Raghuveera	2020			3.32
View All					
Recent advances in marburgvirus research.					
F1000Research 2019; 8	Olejnik, Judith; Mühlberger, Elke; Hume, Adam J	2019			0.09
The Respiratory Syncytial Virus Polymerase: A Multitasking Machine.					
Trends in microbiology 2019 12; 27 (12) 969-971	Fearns, Rachel	2019			0.23
Distinct Genome Replication and Transcription Strategies within the Growing Filovirus Family.					
Journal of molecular biology 2019 10 04; 431 (21) 4290-4320	Hume, Adam J; Mühlberger, Elke	2019			0.89
Ebolavirus polymerase uses an unconventional genome replication mechanism.					
Proceedings of the National Academy of Sciences of the United States of America 2019 04 23; 116 (17) 8535-8543	Deflubé, Laure R; Cressey, Tessa N; Hume, Adam J;	2019			1.08

Patents

No Patents information available for 5R01AI133486-02

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 5R01AI133486-02

Clinical Studies

No Clinical Studies information available for 5R01AI133486-02

News and More

Related News Releases

No news release information available for 5R01AI133486-02

History

No Historical information available for 5R01AI133486-02

Similar Projects

No Similar Projects information available for 5R01AI133486-02

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