Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

Mechanisms of viral proteases in coronavirus replication and pathogenesis

Project Number
5R01AI085089-10

Contact PI/Project Leader
BAKER, SUSAN C.Other PIs

Awardee Organization
LOYOLA UNIVERSITY CHICAGO

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Description

Abstract Text

DESCRIPTION (provided by applicant): The goal of our research is to determine how viral proteases function in the replication and pathogenesis of coronaviruses (CoVs). CoVs are a family of positive strand RNA viruses and include Severe Acute Respiratory Syndrome (SARS) CoV and Middle East Respiratory Syndrome (MERS) CoV which are significant human pathogens with **pandemic** potential. Previously, we dissected the multifunctional nature of CoV papain-like proteases (PLPs) and found that CoV PLPs cleave the viral replicase polyprotein, act as deubiquitinases (DUBs) and deISGylases (deISGs) by removing ubiquitin (Ub) or ISG15 conjugated to lysine residues on proteins, and that PLPs can antagonize the innate immune response, likely by deubiquitylating signaling molecules. Using detailed biochemical and PLP-Ub co-crystal structural analysis, we identified residues within CoV PLPs that differentially affec enzymatic activity in vitro and in cell-based assays. Our initial studies were performed using SARS-CoV PLpro. Here we provide preliminary in vitro and structural data demonstrating that these results can be extended to the BSL-2 model coronavirus mouse hepatitis virus (MHV-A59) papain-like protease. We hypothesize that multifunctional PLP/DUB activity contributes to viral pathogenesis and that selectively disrupting DUB activity will allow activation of innate immunity and reduced viral pathogenesis. To test this hypothesis, we will determine if a modified PLP/DUB enzymatic activity alters viral replication, innate immune response or pathogenesis. We will use reverse genetics to generate murine CoVs encoding PLPs with distinct enzymatic profiles such as DUB deficient, deISGylation deficient, or hyperactive protease. These novel viruses will be evaluated in cell culture and in mice for kinetics of viral RNA synthesis, production of infectious virus, and kinetics of activation of innate immune responses. To extend these studies to other CoVs, we will determine the enzymatic profile (EP) and enzymatic fingerprint (EF) of alpha- and beta-CoV papain-like proteases including bat CoV PLPs. We will express the PLP domain from 10 different CoV species and determine the peptide cleavage activity, deubiquitinating activity, deISGylating activity, and lysine-linkage preferences for each enzyme. With this profile in hand, we will use existing and new X-ray structures combined to guide mutagenesis experiments to differentially disrupt DUB activity and identify the fingerprint associated with reduced DUB activity. We will also determine the role of differential activity in regulating the innate immune response in bat cells. Also, we identified an interaction of the CoV ADP-ribose-1"-phosphatase (ADRP) domain with PLP and we will determine the effect of modifying this interaction on enzymatic activity, viral replication and pathogenesis. These studies will reveal new information on viral protease/DUB activity that will be useful for designing antiviral therapies and vaccines for coronaviruses and other protease/DUB-encoding viruses.

Public Health Relevance Statement

PUBLIC HEALTH RELEVANCE: Coronaviruses can emerge from animal reservoirs and infect humans resulting in outbreaks of pneumonia, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). We want to identify how coronaviruses evade the early warning system of the immune response. These studies will teach us how coronaviruses, and potentially other viruses, slip under the radar of our immune defenses and cause disease.

NIH Spending Category

Biodefense Emerging Infectious Diseases Infectious Diseases Rare Diseases

Project Terms

Adenosine Diphosphate Ribose Affect Amino Acid Sequence Animals Antiviral Agents Antiviral Therapy Attenuated Biochemical Biological Assay Body Weight decreased C57BL/6 Mouse Cell Culture Techniques Cells Chiroptera Cleaved cell Coronavirus Crystallization Data Disease Disease Outbreaks Enzymes FDA approved Family Fingerprint Funding Goals Hand Health Human Hyperactive behavior ISG15 gene Immune Immune response Immune system In Vitro Innate Immune Response Intervention Kinetics Liver Lysine Middle East Respiratory Syndrome Coronavirus Modeling Monitor Murine hepatitis virus Mus Mutagenesis Mutate Mutation Natural Immunity Nature

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Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

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Contact PI/Project Leader
BAKER, SUSAN C.Other PIs

Awardee Organization
LOYOLA UNIVERSITY CHICAGO

sbaker1@luc.edu

Organization

Name
LOYOLA UNIVERSITY CHICAGO

City
MAYWOOD

Country
UNITED STATES (US)

Department Type
MICROBIOLOGY/IMMUN/VIROLOGY

Organization Type
SCHOOLS OF MEDICINE

State Code
IL

Congressional District
07

Other Information

FOA
PA-13-302

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

Fiscal Year
2019

Award Notice Date
19-June-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
791277940

CFDA Code
855

Project Start Date **01-July-2010**

Project End Date **30-June-2022**

Budget Start Date **01-July-2019**

Budget End Date **30-June-2022**

Project Funding Information for 2019

Total Funding
$705,182

Direct Costs
$562,754

Indirect Costs
$142,428

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$705,182

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$705,182	Biodefense; Emerging Infectious Diseases; Infectious Diseases; Rare Diseases;

Sub Projects

No Sub Projects information available for 5R01AI085089-10

Publications

No Publications available for 5R01AI085089-10

Patents

No Patents information available for 5R01AI085089-10

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.

Back to Search Results

Description
Details
Sub-Projects
Publications
Patents
Outcomes
Clinical Studies
News and More
History
Similar Projects

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Project Number	Contact PI/Project Leader	Awardee Organization
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No Clinical Studies information available for 5R01AI085089-10

News and More

Related News Releases

No news release information available for 5R01AI085089-10

History

No Historical information available for 5R01AI085089-10

Similar Projects

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