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Structural Studies of Coronavirus Fusion Proteins

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
3R01GM120553-04S1	5R01GM120553-03	VEESLER, DAVID	UNIVERSITY OF WASHINGTON

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Description

Abstract Text

Enveloped viruses use specialized proteins present at the virus surface to translocate their genetic material across the host cell membrane during infection. For coronaviruses, homotrimers of the spike glycoprotein promote host cell attachment and fusion of the viral and host membranes. Although coronaviruses have a significant **pandemic** potential, the lack of high-resolution data for any coronavirus spike trimer limits our mechanistic understanding of infection by this family of viruses. The objective of the proposed work is to obtain high-resolution snapshots corresponding to the various stages of the fusion reaction mediated by coronavirus spikes and to study the structural determinants associated with antibody inhibition of viral infection. In Aim I, we propose to elucidate the architecture of the Mouse Hepatitis Virus (MHV) pre-fusion spike using cryoEM. Aim II will be dedicated to studying the conformational changes associated with the fusion reaction with an emphasis on the first intermediate (extended intermediate) and the post-fusion spike. In Aim III, we will characterize the 3D organization of human coronavirus spikes to understand how these viruses overcome the species barrier and to identify structurally conserved regions that could be potential targets for therapeutic initiatives. The final aim will rely on structure-guided protein design to engineer antibodies targeting human coronavirus spikes with the goal of identifying immunogens for raising broadly-neutralizing antibodies.

Public Health Relevance Statement

Project Narrative The tremendous pandemic potential of coronaviruses has already been demonstrated twice in the last decade as two global outbreaks of deadly pneumonia. Coronavirus spike glycoproteins are responsible for virus entry into host cells, by promoting fusion of the viral and host membranes, and represent important therapeutic targets. We are exploiting MHV as a model system to grasp the structural and thermodynamic parameters of the membrane fusion process. This work is extended to the spikes of human pathogenic coronaviruses to identify structurally conserved regions that could be potential targets for vaccinology initiatives.

NIH Spending Category

Emerging Infectious Diseases Immunization Infectious Diseases Vaccine Related

Project Terms

3-Dimensional Address Antibodies Antigens Architecture Attention Binding Biological Assay Biological Models Cell fusion Cell membrane Cell-Matrix Junction Cells Chimeric Proteins Complement Complex Coronavirus Coronavirus Infections Coronavirus spike protein Cryoelectron Microscopy Data Data Analyses Disease Outbreaks Family Fostering Future Genetic Materials Genome Glycoproteins Goals Health Human Immunization Immunoglobulin Fragments Infection Kinetics Lead Mediating Membrane Membrane Fusion Middle East Respiratory Syndrome Coronavirus Modeling Molecular Molecular Conformation Murine hepatitis virus Mus Mutagenesis N-terminal Negative Staining

Read More

Details

Contact PI/ Project Leader

Name
VEESLER, DAVID
Title
Contact
dveesler@uw.edu

Other PIs

Not Applicable

Program Official

Name
FLICKER, PAULA F
Contact
flickerp@nigms.nih.gov

Organization

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Other Information

FOA
PA-18-591

Study Section
Macromolecular Structure and Function C Study Section[MSFC]

Fiscal Year
2019

Award Notice Date
23-August-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

DUNS Number
605799469

CFDA Code
859

Project Start Date	01-August-2016
Project End Date	31-July-2021
Budget Start Date	01-August-2019
Budget End Date	31-July-2020

Project Funding Information for 2019

Total Funding
$89,600

Direct Costs
$89,600

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES	$89,600

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 GENERAL MEDICAL SCIENCES	$89,600	Emerging Infectious Diseases; Immunization; Infectious Diseases; Vaccine Related;

Sub Projects

No Sub Projects information available for 3R01GM120553-04S1

Publications

No Publications available for 3R01GM120553-04S1

Patents

No Patents information available for 3R01GM120553-04S1

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 3R01GM120553-04S1

Clinical Studies

No Clinical Studies information available for 3R01GM120553-04S1

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History

No Historical information available for 3R01GM120553-04S1

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