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Structural studies of virulence activation in Francisella tularensis

Project Number	Contact PI/Project Leader	Awardee Organization
1F31AI150138-01A1	TRAVIS, BRADY A	DUKE UNIVERSITY

Description

Abstract Text

PROJECT SUMMARY/ABSTRACT The etiological agent of **tularemia**, Francisella tularensis, is one of the most infectious pathogens known and a potential bioweapon. Francisella virulence stems from a gene cluster known as the Francisella pathogenicity island (FPI) whose expression is under the control of a unique set of transcriptional regulators. MglA, SspA, and PigR collaborate with the stress signal, guanosine tetraphosphate, or ppGpp, to activate transcription at the FPI. However, the molecular mechanisms these factors use to drive virulence activation is unclear. In recent studies, we have shown that MglA and SspA may be an integral subunit of Francisella RNA polymerase (RNAP), MglA and SspA form a heterodimeric complex with an open cavity that binds ppGpp, and PigR, which has a predicted winged helix-turn-helix motif and unstructured N- and C-termini, interacts with MglA-SspA in a ppGpp-dependent manner. Based on this data, our central hypothesis is that virulence activation at the FPI occurs by a novel mechanism where MglA-SspA is a subunit of RNAP and PigR bridges from (MglA-SspA)-ppGpp to DNA to enhance transcription. The goal of this proposal is to uncover the mechanisms MglA-SspA uses to interact with RNAP and PigR uses to bind DNA and (MglA-SspA)-ppGpp. This work will be accomplished through the completion of two specific aims. First, I will solve a high-resolution (MglA-SspA)-PigR structure to aide in structure-based drug design. In the second part of this aim, I will screen a small library of inhibitors identified via in silico screening by Atomwise, Inc. For my second aim, I propose to utilize single-particle cryo-EM to solve structures of multiple Francisella RNAP complexes. I will follow up on these structural studies with functional assays to test our structure-based hypotheses. We expect that this work will lead to an understanding of the mechanisms underlying virulence activation in this highly infectious pathogen and, importantly, our structures will provide novel targets unique to Francisella to be used for rational drug design. A significant part of my training plan is to gain expertise in X-ray crystallography and single-particle cryo-EM. I propose to do this through coursework, training from my sponsor, Dr. Schumacher, and collaborator, Dr. Bartesaghi, who are experts in these fields. I also explain how I will strengthen my background in microbiology, learn to lead a research project, become an excellent mentor and collaborator, and improve upon my scientific communication skills. The training plan will equip me with the knowledge and skills needed to complete the proposed research and achieve my long-term goal of becoming an independent researcher in the field of structural biology. This research will be conducted in the Schumacher laboratory as part of the Department of Biochemistry at Duke University, which has a rich history of training remarkable investigators and will provide an outstanding environment and resources that will allow me to accomplish my goals.

Public Health Relevance Statement

NARRATIVE Virulence activation in Francisella tularensis, a category A bioweapon, is regulated by a novel circuity involving RNA polymerase, transcription factors unique to Francisella, and a small molecule “alarmone,” ppGpp. Elucidating the molecular mechanisms controlling transcription activation at virulence promoters would provide a framework for the design of novel therapeutics. Importantly, this would give us an alternative approach to combat multidrug-resistant, weaponized strains of F. tularensis.

NIH Spending Category

Biodefense **Emerging Infectious Diseases** **Genetics** **Infectious Diseases**

Rare Diseases **Vector-Borne Diseases**

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DNA-Binding Proteins DNA-Directed DNA Polymerase DNA-Directed RNA Polymerase Data Development Disease Drug Design Environment Etiology Fluorescence Polarization Francisella Francisella tularensis Gene Cluster Gene Expression Genes Genetic Transcription Goals Growth Guanine Guanosine Tetraphosphate

Read More

Details

Contact PI/ Project Leader

Name
TRAVIS, BRADY A

Title
F31 FELLOWSHIP RECIPIENT

Contact
brady.travis@duke.edu

Other PIs

Not Applicable

Program Official

Name
MUKHOPADHYAY, SUMAN

Contact
mukhopadhyays@mail.nih.gov

Organization

Name
DUKE UNIVERSITY

City
DURHAM

Country
UNITED STATES (US)

Department Type
BIOCHEMISTRY

Organization Type
SCHOOLS OF MEDICINE

State Code
NC

Congressional District
04

Other Information

FOA
PA-19-195

Study Section
Special Emphasis Panel[ZRG1 F04B-T (20)]

Fiscal Year
2020

Award Notice Date
27-May-2020

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
044387793

CFDA Code
855

Project Start Date
01-July-2020

Project End Date
31-January-2023

Budget Start Date
01-July-2020

Budget End Date
30-June-2021

Project Funding Information for 2020

Total Funding	Direct Costs	Indirect Costs
$39,302	$39,302	$0

Year	Funding IC	
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$39,302

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Infectious Diseases; Rare Diseases; Vector-Borne Diseases;

Sub Projects

No Sub Projects information available for 1F31AI150138-01A1

Publications

No Publications available for 1F31AI150138-01A1

Patents

No Patents information available for 1F31AI150138-01A1

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 1F31AI150138-01A1

Clinical Studies

No Clinical Studies information available for 1F31AI150138-01A1

News and More

Related News Releases

No news release information available for 1F31AI150138-01A1

History

No Historical information available for 1F31AI150138-

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