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Molecular mechanisms and novel biological-based therapies for anthrax lethal toxin-induced mortality

Project Number
1R56AI148134-01A1

Contact PI/Project Leader
LIU, SHIHUI

Awardee Organization
UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Description

Abstract Text

Abstract Bacillus anthracis, the causative agent of **anthrax** disease, has remained as a top bioterrorism concern since the 2001 **anthrax** attack. B. anthracis causes **anthrax** through a combination of bacterial infection and toxemia. As a major virulence factor, the **anthrax** lethal toxin (LT) plays an essential role during multiple steps of the disease. Due to the rapid course of **anthrax** disease, in particular, the non-specific, flu-like symptoms of inhalational **anthrax**, patients usually seek medical assistance when the disease is already in the middle/late stages, making the clinical management of **anthrax** patients an extremely challenging task. Current treatments include antibiotics and anti-toxin antibodies that respectively eliminate the pathogen and neutralize the toxin. However, there is no therapy available to deal with the cellular/tissue damage caused by LT already having reached its molecular targets inside cells. Mortality usually follows when the host fails to repair this damage, the so called “point-of-no- return” for current therapy. Thus, even with intensive medical care, the mortality rate of systemic **anthrax** is high, reaching > 50%. Therefore, there is an urgent unmet clinical need to develop better targeted therapies to avert **anthrax** -induced mortality. Our goal in this application is to discover the molecular mechanisms underlying LT- induced lethality and to develop potential targeted therapeutics to treat patients beyond the “point-of-no-return”. Here, we set out to determine the specific roles of disrupting each of the ERK, p38, and JNK pathways in **anthrax**-induced lethality, discover the underlying molecular mechanisms, and develop the concept of reactivation /mobilization of these pathways as a targeted therapy for **anthrax**-induced mortality. In Aim 1, we will determine the role of specifically disrupting the ERK pathway in **anthrax**-induced lethality and explore ERK pathway reactivation as a targeted therapy. Among the three core MAPK pathways targeted by LT, the ERK pathway is fundamental to many biological processes, including cell proliferation and survival. Thus, we hypothesize that disrupting the ERK pathway is the major cause of **anthrax**-induced lethality. We will generate and use novel mouse models containing MEK1 and MEK2 alleles that are resistant to LT-cleavage to understand the precise role of ERK pathway inactivation in **anthrax** pathogenesis. We will further test this hypothesis and explore ERK pathway reactivation as a targeted therapy for **anthrax**-induced tissue damage. Importantly, our preliminary data demonstrate that the LT-disrupted ERK pathway can be reactivated by the addition of potent mitogens, such as epidermal growth factor. In Aim 2, we will further determine the roles of disrupting the p38 and JNK pathways in **anthrax** pathogenesis and explore the feasibility of mobilizing these pathways in **anthrax**-targeted therapy. Upon completion of these studies, it is our expectation that we will provide significant conceptual advances in our understanding of the underlying molecular mechanisms of **anthrax** LT and offer an evidence-based framework for developing **anthrax**-targeted therapies, which will complement the current therapies with antibiotics and anti-toxin antibodies, to prevent **anthrax** mortality, even at advanced stages of **anthrax** infection.

Public Health Relevance Statement

Narrative Anthrax is an acute infectious disease that affects both animals and humans with a high mortality rate. The proposed research is highly relevant to public health because the discovery of the molecular mechanisms of anthrax lethal toxin, the major virulence factor in anthrax infection, is critically important in order to develop potential therapeutics that could prevent anthrax-induced mortality. This application will develop the new concept of the reactivation/mobilization of toxin-disrupted pathways as a mechanistic-based targeted therapy.

NIH Spending Category

Anthrax Biodefense Emerging Infectious Diseases Infectious Diseases Rare Diseases

Project Terms

Acute Affect Alleles Animals **Anthrax** Attack **Anthrax** disease Antibiotics Antibodies Bacillus anthracis Bacterial Infections Bioenergetics Biological Biological Process Bioterrorism Cardiac Myocytes Caring Cell Proliferation Cell Survival Cells Cessation of life Clinical Clinical Management Communicable Diseases Complement Data Defense Mechanisms Disease Epidermal Growth Factor Goals Human Impairment Infection Inhalation MAP Kinase Gene MAP2K1 gene MAPK8 gene MEKs Medical Medical Assistance Metabolism Metalloproteases Mitogens Molecular Molecular Target Organ Pathogenesis Pathway interactions Patients Play Public Health Research Resistance Role

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Department Type
INTERNAL MEDICINE/MEDICINE

Organization Type
SCHOOLS OF MEDICINE

State Code
PA

Congressional District
18

Other Information

FOA
PA-19-056

Study Section
Host Interactions with Bacterial Pathogens Study Section[HIBP]

Fiscal Year
2020

Award Notice Date
08-September-2020

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
004514360

CFDA Code
855

Project Start Date
15-September-2020

Project End Date
31-August-2021

Budget Start Date
15-September-2020

Budget End Date
31-August-2021

Project Funding Information for 2020

Total Funding
$517,522

Direct Costs
$330,685

Indirect Costs
$186,837

Year	Funding IC	FY Total Cost by IC
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$517,522

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$517,522	Anthrax; Biodefense; Emerging Infectious Diseases; Infectious Diseases; Rare Diseases;

Sub Projects

No Sub Projects information available for 1R56AI148134-01A1

Publications

No Publications available for 1R56AI148134-01A1

Patents

No Patents information available for 1R56AI148134-01A1

Outcomes

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Clinical Studies

No Clinical Studies information available for 1R56AI148134-01A1

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No news release information available for 1R56AI148134-01A1

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No Historical information available for 1R56AI148134-01A1

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