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Infection Site Targeted Antitoxin Antibody (ISTAb) against Bacillus anthracis

Project Number
2R42AI122666-03

Contact PI/Project Leader
ADHIKARI, RAJAN P Other PIs

Awardee Organization
INTEGRATED BIOTHERAPEUTICS, INC.

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Description

Abstract Text

Project Summary Bacillus anthracis (Ba) is a Gram-positive spore forming bacterium that is listed as an agent of highest concern (Category A) by NIAID and CDC. Ba is easy to grow, and its spores can be formulated into highly stable powder form and disseminated as aerosol or used to contaminate food or water. In 2001, letters laced with powdered anthrax spores were mailed to several US politicians. Twenty-two people, including 12 mail handlers, were infected, and five of them died. B. anthracis virulence largely depends on two key toxins generated by combination of the protective antigen (PA) associated with either lethal factor (LF) or edema factor (EF). Although some oral antibiotics and a vaccine are available for use, in practice these treatments cannot adequately address the adverse effects of bacterial toxins released post exposure. In our recently completed R41 project, we developed and tested a novel approach to target neutralizing anti-PA antibodies specifically to the site of infection in vitro and in vivo. The approach exploits the cell wall targeting domains (CWT) of well characterized phage endolysins (PlyG, PlyL and PlyB) that bind with species-specificity and high affinity to cell wall components of Ba. These CWTs are fused to specific antitoxin neutralizing monoclonal antibodies (mAbs) to generate Infection Site Targeted Antitoxin antibodies (ISTAbs). ISTAb technology provides two therapeutic advantages: immediate toxin neutralization at the site of infection preventing toxemia, and opsonophagocytic killing by phagocytes to simultaneously clear both bacteria and toxin. We compared nine ISTAb candidates (three CWTs and three mAbs) based on in vitro assays (cell binding and toxin neutralization) and selected one ISTAb (AVP-21D9-PlyG) for pre- and post-challenge in vivo studies in mice. This ISTAb exhibited significantly higher level of protection than the parental IgG. This R42 is aimed to take this lead ISTAb molecule into the next level in therapeutic pipeline. In this proposal, we will produce and extensively characterize next-generation AVP-21D9-PlyG ISTAbs, including stability and in vivo efficacy studies in mice and nonhuman primates (NHP), and develop a stable formulation. In Aim 1, we will use computer-aided optimizations to generate 3-5 ISTAb variants to remove potential liabilities that may complicate downstream development. In Aim 2, two lead candidates will be tested in mouse models. One lead molecule will be tested in an NHP model for PK and post-challenge efficacy. In Aim 3: The final ISTAb will be subjected to accelerated stability and PK studies, formulation, and generation of stable cell lines in CHO-S cells. The combination of immediate toxin clearance, phagocytic killing, and concurrent use of antibiotics, is expected to create synergy and yield a treatment that is far superior to the current standard of care. Furthermore, this technology can be applied to a variety of other bacterial pathogens where toxins play a key role in pathogenesis. Overall, this approach has board application as a platform technology across multiple pathogens.

Public Health Relevance Statement

Bacillus anthracis (Ba), a spore-forming bacterium is listed as a select agent by CDC. It can cause disease in animals and humans by three routes of infection: inhalational, gastrointestinal, and skin. Ba is a Tier 1 agent that poses the greatest risk of misuse, with significant potential for mass casualties. For instance, in 2001, powdered anthrax spores containing letter were deliberately mailed to two U.S. Senators and several news media offices. Twenty-two people contracted anthrax and five died as a result (http://www.cdc.gov/anthrax/bioterrorism/threat.html). Protective antigen (PA), a binding protein is a crucial component of anthrax toxin. It can form a toxic pair when combine either with: lethal factor (LF) or edema factor (EF). In this proposal, we seek to use a novel technology called Infection site targeted antitoxin antibodies (ISTAbs), a fusion protein fused with Ba bacteriophage CWT with anti-PA monoclonal antibody to target antitoxins exactly to the site of infection. This technology can provide a novel approach for treatment of Bacillus anthracis infections.

NIH Spending Category

Anthrax Biodefense Bioengineering Biotechnology Emerging Infectious Diseases Immunization Infectious Diseases Orphan Drug Prevention Rare Diseases Vaccine Related

Project Terms

Address Adverse effects Aerosols Affect Affinity African Animals Anthrax Vaccines Anthrax disease Antibiotic Therapy Antibiotics Antibodies Antigens Antitoxins Asians Bacillus anthracis Bacillus anthracis spore Bacteria Bacterial Toxins Bacteriophages Binding Binding Proteins Biological Assay Bioterrorism C-terminal Cartoons Catalytic Domain Categories Cell Line Cell Wall Cells Centers for Disease Control and Prevention (U.S.) Characteristics Chimeric Proteins Chinese Hamster Ovary Cell Comparative Study Complex Computer Assisted Contracts Country Developed Countries Developing Countries Developmen

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Contact PI/ Project Leader

Name
ADHIKARI, RAJAN P

Title

Contact
rajan@integratedbiotherapeutics.com

Other PIs

Name
HAKAMI, RAMIN M.
NELSON, DANIEL C.

Program Official

Name
LIU, BAOYING

Contact
baoying.liu@nih.gov

Organization

Name
INTEGRATED BIOTHERAPEUTICS, INC.

City
ROCKVILLE

Country
UNITED STATES (US)

Department Type
Unavailable

Organization Type
Domestic For-Profits

State Code
MD

Congressional District
08

Other Information

FOA
PA-18-575

Study Section
Special Emphasis Panel[ZRG1 IMM-R (12)]

Fiscal Year
2019

Award Notice Date
05-July-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
601000750

CFDA Code
855

Project Start Date **15-February-2017**

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

Budget Start Date **05-July-2019**

Budget End Date **30-June-2020**

Project Funding Information for 2019

Total Funding
$999,997

Direct Costs
$0

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$999,997

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$999,997	Anthrax; Biodefense; Bioengineering; Biotechnology; Emerging Infectious Diseases; Immunization; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases; Vaccine Related;

Sub Projects

No Sub Projects information available for 2R42AI122666-03

Publications

No Publications available for 2R42AI122666-03

Patents

No Patents information available for 2R42AI122666-03

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No Outcomes available for 2R42AI122666-03

Clinical Studies

No Clinical Studies information available for 2R42AI122666-03

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Related News Releases

No news release information available for 2R42AI122666-03

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