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Molecular and Immunologic Analysis of the Pathobiology of Human Anthrax

Project Number
3U19AI062629-17S2

Contact PI/Project Leader
COGGESHALL, KENNETH MARK

Awardee Organization
OKLAHOMA MEDICAL RESEARCH FOUNDATION

Description

Abstract Text

The present application is a competing renewal of a CCHI grant on the human immune response to Bacillus anthracis and the vaccine that protects the military, and that was first awarded in 2004. The goals of the original application were threefold: (a) To study the human immune response to a flawed vaccine, (b) To understand the mechanism for the high lethality of the inhalation form of the disease, (c) To understand the cellular basis of the host response to the pathogen. We have learned much about the human vaccine with our collection of nearly 3,000 samples, including samples of individuals who have naturally been infected with B. anthracis. Especially notable is our finding that fully 50% of vaccinees are unprotected. This is so, despite more than 6 vaccinations immunized against the pathogen's toxins in an onerous vaccine schedule. We have evidence, in contrast to prevailing views, that the high rate of mortality is due to bacterial sepsis and not the **anthrax** toxins. We made the seminal discovery that immune complexes of peptidoglycan and pre-existing serum opsonins present in all humans may be the source of the massive inflammation and coagulopathy accompanying infection by B. anthracis. We have new evidence that the infection is accompanied by release of proinflammatory and procoagulant nucleosome material (DAMPs) and that the **anthrax** toxins can modulate the clearance of this material. In this renewal application, we will follow up on these exciting discoveries to determine: (a) In the early- and mid-stage of disease, how are DAMPS released by the host, how they are cleared by the host innate immune system and how does toxin affect these processes. (b) In the late stage of the disease, how does opsonized peptidoglycan influence the outcome of the disease. (c) Why the vaccine is imperfect in stimulating the maturation of germinal center B cells in adults. These studies are supported by 2 scientific cores: An animal core that applies a non-human primate model we established in previous funding cycles and a flow cytometry core with state-of-the-art sorting and analyzing capacity. We also have a Technology Development Project that seeks to develop a generalized model by which pathogens, including **anthrax** spores but also other bacterial and viral pathogens, move across epithelial and endothelial barriers to infect tissue. The studies in this renewal application are focused and thematically organized around the key roles of peptidoglycan and the **anthrax** toxins in the human innate and adaptive immune responses. They have great potential to identify novel means of interrupting the pathology caused by this model Gram-positive pathogen.

Public Health Relevance Statement

The present application is a competing renewal of a CCHI grant on the human immune response to Bacillus anthracis. In this renewal application, we will study (a) In the early- and mid-stage of disease, how are DAMPS in the form of proinflammatory and procoagulant nucleosomes are released by the host, how they are cleared by the host innate immune system and how does toxin affect these processes, (b) In the late stage of the disease, how does opsonized peptidoglycan influence the outcome of the disease; (c) Why the vaccine is imperfect in stimulating the maturation of germinal center B cells in adults. The results will greatly inform the field of bacterial sepsis, particularly that of Gram-positive pathogens, and in issues surrounding adult vaccinations.

NIH Spending Category

Anthrax Biotechnology Clinical Research Coronaviruses Emerging Infectious Diseases Hematology Immunization Infectious Diseases Orphan Drug Prevention Rare Diseases Sepsis Vaccine Related

Project Terms

Adult Affect Affinity Agonist Animal Model Animals **Anthrax** Vaccine Absorbed **Anthrax** Vaccines **Anthrax** disease Antibodies Antigen-Antibody Complex Antigens Apoptotic B-Lymphocytes Bacillus anthracis Bacillus anthracis spore Bacteria Biological Blood Coagulation Disorders Blood coagulation Cause of Death Cells Cessation of life Collection Complement Complement Activation Dendritic cell activation Disease Disease Outcome Endothelium Epithelial Epithelium Exposure to Fc Receptor First Independent Research Support and Transition Awards Flow Cytometry Funding Goals Grant Human IgG4 Immune Immune response Immunize Immunologics Immunosuppression

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Contact PI/Project Leader
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OKLAHOMA MEDICAL RESEARCH FOUNDATION

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Department Type
Unavailable

Organization Type
Research Institutes

State Code
OK

Congressional District
05

Other Information

FOA
PA-18-591

Study Section
ZAI1-PA-I(J1)

Fiscal Year
2020

Award Notice Date
16-September-2020

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
077333797

CFDA Code
855

Project Start Date
08-June-2020

Project End Date
31-August-2022

Budget Start Date
01-September-2020

Budget End Date
31-August-2022

Project Funding Information for 2020

Total Funding
$916,783

Direct Costs
$540,230

Indirect Costs
$376,553

Year	Funding IC	FY Total Cost by IC
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$916,783

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 ALLERGY AND INFECTIOUS DISEASES	$916,783	Anthrax; Biotechnology; Clinical Research; Coronaviruses; Emerging Infectious Diseases; Hematology; Immunization; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases; Sepsis; Vaccine Related;

Sub Projects

No Sub Projects information available for 3U19AI062629-17S2

Publications

No Publications available for 3U19AI062629-17S2

Patents

No Patents information available for 3U19AI062629-17S2

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Clinical Studies

No Clinical Studies information available for 3U19AI062629-17S2

News and More

Related News Releases

No news release information available for 3U19AI062629-17S2

History

No Historical information available for 3U19AI062629-17S2

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