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Remodeled glycoprotein for broad protection against ebolaviruses

Project Number
5R43AI136229-02

Contact PI/Project Leader
AMAN, M JAVAD

Awardee Organization
INTEGRATED BIOTHERAPEUTICS, INC.

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Description

Abstract Text

Project summary The 2014-2015 Ebola **virus** disease (EVD) outbreak in West Africa, caused by the Zaire Ebola **virus** (EBOV), resulted in over 28,000 cases and 11,000 deaths. This has been a sobering reminder of the growing threat of the filoviruses for global public health. Driven by the unprecedented dimension of this outbreak, most of the efforts to develop vaccines against the different species of ebolaviruses has been focused on EBOV. However, other ebolavirus species such as Sudan **virus** (SUDV) and Bundibugyo **virus** (BDBV) have also caused sizable outbreaks in the past 20 years and the species causing future EVD outbreaks cannot be predicted. The vaccines currently in development, including adenovirus-based vaccines and VSV-ZEBOV that was successfully tested in a Phase III clinical trial in Africa, are specific to EBOV and do not provide cross protection against SUDV or BDBV. A major obstacle for elicitation of broadly neutralizing responses is the fact that most conserved regions of the ebolavirus glycoprotein (GP), including the receptor binding site (RBS), are largely concealed on the viral surface. Using a special immunogen cocktail we have recently isolated several broadly neutralizing monoclonal antibodies (bNAbs), characterized their epitopes in collaboration with Integral Molecular, and for the first time, identified a cocktail of two antibodies that simultaneously protects against EBOV, SUDV, and BDBV. This body of knowledge can now be exploited to develop a single vaccine that protects against all ebolaviruses. Our proposal is based on two key and novel observations. i) We have identified several residues in the base of the EBOV GP trimer that, when mutated, increase the exposure of broadly neutralizing epitopes on the apical face of GP, including the RBS that is otherwise largely concealed. We have also demonstrated that immunization with such mutants broadens the antibody response towards SUDV and BDBV. ii) We have demonstrated that a proteolytically remodeled form of GP representing the post-entry form of GP in the host endosomes binds to the most potent bNAbs with very high affinity, suggesting that this “cleaved GP” (GPCL) can be a candidate pan- ebolavirus vaccine. Building upon these observations, this Phase I project is designed in three specific Aims. In Aim 1, using the information gained from our extensive alanine scanning mutagenesis studies, a variety of mutants will be generated on the backbone of VSV-EBOV GP pseudotype **virus**, and their ability to elicit broadly neutralizing responses will be evaluated. Aim 2 focuses on generation and functional testing of immunogens based on GPCL. Additional specific mutations identified in Aim 1 will be incorporated into GPCL immunogen and evaluated in immunogenicity studies. In Aim 3, the best candidates identified in Aims 1 and 2 will be tested in proof of concept efficacy studies in murine challenge models of EBOV and SUDV. Upon successful proof of concept, we anticipate a phase II to demonstrate efficacy of the vaccine against EBOV, SUDV, and BDBV in non-humane primate models of infection as well as initiation of IND enabling studies.

Public Health Relevance Statement

The 2014-2015 Ebola virus disease outbreak in West Africa, caused by the Zaire Ebola virus, resulted in over 28,000 cases and 11,000 deaths. While several vaccines have been tested against the Zaire strain of Ebola which caused the 2014-2015 outbreak, these vaccines do not protect against other ebolaviruses like Sudan and Bundibugyo viruses that also have cause deadly outbreaks. The goal of this proposal is to generate novel vaccine candidates that protect against all ebolaviruses.

NIH Spending Category

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

Project Terms

Accounting Adenoviruses Advanced Development Affinity Africa Agreement Alanine Amino Acid Substitution Animal Model Antibodies Antibody Response Antigens Apical Binding Binding Sites Biological Response Modifier Therapy Businesses Cavia Cessation of life Cleaved cell Clinical Trials Collaborations Communicable Diseases Data Democratic Republic of the Congo Development Dimensions Disease Outbreaks Ebola Hemorrhagic Fever Ebola Vaccines Ebola **virus** Endosomes Epitopes Excision Face Ferrets Filovirus Frequencies Funding Future Generations Glycoproteins Goals HIV Human Immunization Immunize Infection Influenza Intellectual Property

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INTEGRATED BIOTHERAPEUTICS, INC.

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City
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Country
UNITED STATES (US)

Department Type
Unavailable

Organization Type
Domestic For-Profits

State Code
MD

Congressional District
08

Other Information

FOA
PA-16-302

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

Fiscal Year
2019

Award Notice Date
26-December-2018

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
601000750

CFDA Code
855

Project Start Date
26-January-2018

Project End Date
31-December-2020

Budget Start Date
01-January-2019

Budget End Date
31-December-2020

Project Funding Information for 2019

Total Funding
$299,186

Direct Costs
$0

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$299,186

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$299,186	Biodefense; Biotechnology; Emerging Infectious Diseases; Immunization; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases; Vaccine Related;

Sub Projects

No Sub Projects information available for 5R43AI136229-02

Publications

No Publications available for 5R43AI136229-02

Patents

No Patents information available for 5R43AI136229-02

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No Outcomes available for 5R43AI136229-02

Clinical Studies

No Clinical Studies information available for 5R43AI136229-02

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No news release information available for 5R43AI136229-02

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No Historical information available for 5R43AI136229-02

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