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Monoclonal antibodies targeting novel sites of vulnerability in marburg virus glycoprotein

Project Number
1R41AI147929-01

Contact PI/Project Leader
AMAN, M JAVADOther PIs

Awardee Organization
INTEGRATED BIOTHERAPEUTICS, INC.

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Description

Abstract Text

Filoviruses, consisting of two major **virus** families including the ebolaviruses and marburgviruses (MARV and RAVV), cause periodic outbreaks of severe viral hemorrhagic fever with mortality rates as high as 90%. Since it is difficult to predict the species that would dominate future outbreaks, development of broadly protective therapeutics to prevent and manage future filovirus outbreaks is of high priority. In sharp contrast to the recent major breakthrough reported by us and others on isolation and development of a number of effective and broadly neutralizing mAbs (bNAbs) for ebolaviruses, only a single class of mAbs against marburgvirus GP has been described that target the same epitope within the receptor binding site (RBS) of MARV and RAVV GP. MR191 is the only MARV/RAVV GP RBS-specific monoclonal antibody (mAb) that has been shown to protect against MARV infection in nonhuman primates (NHPs) however at very high doses (2 doses of 50 mg/kg each). Thus, it is important to identify novel sites of vulnerability in MARV/RAVV GP and develop more potent immunotherapeutics against these deadly viruses. Having a variety of bNAbs will allow the design of therapeutic cocktails containing multiple mAbs targeting distinct epitopes, a strategy that has been shown tobe extremely effective against ebolaviruses to combat possible **virus** escape variants. There has been a long-standing and productive collaboration between Integrated BioTherapeutics (IBT) and University of Maryland (UMD) that has recently resulted in highly potent ebolavirus bNAbs with remarkable efficacy in animal models including nonhuman primate (NHP) and ferret models of EBOV, SUDV, and BDBV infection (Zhao et al., Cell 169, 891-904 e815 (2017)). Lately, using a prime/boost immunization strategy in NHPs combined with a novel memory B cell counter-screening with engineered GP mutants, we were able to isolate, for the first time, a group of highly potent MARV/RAVV bNAbs that target a new class of epitopes distinct from the RBS-binding MR series. In this STTR application, we aim to address the major challenge of MARV immunotherapy by developing top lead candidate marburgvirus therapeutic antibodies derived from these novel MARV/RAVV bNAbs. We will i) select 3-4 lead therapeutic mAbs among the current bNAb candidates; ii) optimize the lead mAbs and select for the final humanized/optimized candidate by state-of-the-art computer-aided optimization and efficacy study in a stringent guinea pig model of MARV infection; and iii) identify the final lead mAb (or cocktail) by testing the efficacy of candidates in NHP model of MARV infection. Upon completion of the proposed Phase I project we envision a Phase II project with the following objectives: i) expand the efficacy studies to RAVV and dose optimization in NHPs; ii) develop manufacturing cell lines in CHO cells, iii) develop bioanalytical methods for product release and PK, and iv) conduct safety and tissue cross reactivity studies using the GLP-grade clinical candidate. If successful, we anticipate further development of the product under DoD or BARDA funding and approval under FDA Animal Rule.

Public Health Relevance Statement

Filoviruses are among the deadliest pathogens known to humans. The Ebola virus disease outbreak in West Africa (2014-2016), caused by the Zaire Ebola virus, resulted in over 28,000 cases and 11,000 deaths. In addition to Ebola virus, a related filovirus called Marburg has caused five outbreaks in the past 10 years with high fatality rates. This proposal is aimed at developing effective immunotherapeutics against Marburg virus. We have generated several antibody drug candidates that protect against Marburg infection. Under this proposal we will further characterize these drug candidates and test their efficacy in mice and nonhuman primates. This study, if successful, will set the stage for clinical development of an effective therapeutic for human use.

NIH Spending Category

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

Project Terms

Address Affinity Africa Animal Model Antibodies Back Binding Sites Biochemical Biological Response Modifier Therapy Cavia Cell Line Cells Cessation of life Chinese Hamster Ovary Cell Collaborations Computer Assisted Contracts Democratic Republic of the Congo Development Disease Outbreaks Dose Drug Kinetics Ebola Hemorrhagic Fever Ebola **virus** Engineering Epitopes Family Fatality rate Ferrets Filovirus Frankfurt-Marburg Syndrome **Virus** Funding Future Glycoproteins Gold Government Human Immunization Immunotherapeutic agent Immunotherapy Infection Intellectual Property Knock-in Mouse Lead Legal patent Macaca mulatta Maryland

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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
12-July-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
601000750

CFDA Code
855

Project Start Date	12-July-2019
Project End Date	30-June-2021
Budget Start Date	12-July-2019
Budget End Date	30-June-2020

Project Funding Information for 2019

Total Funding
$300,000

Direct Costs
$0

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$300,000

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$300,000	Biodefense; Biotechnology; Emerging Infectious Diseases; Immunization; Immunotherapy; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases; Vaccine Related;

Sub Projects

No Sub Projects information available for 1R41AI147929-01

Publications

No Publications available for 1R41AI147929-01

Patents

No Patents information available for 1R41AI147929-01

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No Outcomes available for 1R41AI147929-01

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No Clinical Studies information available for 1R41AI147929-01

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No news release information available for 1R41AI147929-01

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