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Epitope-Based Design and Modified RNA Platform for Bivalent Marburgvirus Vaccine

Project Number 5R01Al141661-02 **Contact PI/Project Leader BUKREYEV, ALEXANDER** Other PIs

Awardee Organization **UNIVERSITY OF TEXAS MED BR GALVESTON**



Description

Abstract Text

PROJECT SUMMARY/ABSTRACT The Marburg virus (MARV) and Ravn virus (RAVV), which both belong to the genus Marburgvirus of the family Filoviridae, cause the severe disease in humans, with case fatality rates up to 90%. There are no licensed vaccines against marburgviruses. Clinical trials of vaccine candidates against Ebola virus (EBOV), which belongs to the genus Ebolavirus of the family Filoviridae, demonstrated that the high vaccine doses that are required to induce an immune response at the protective level result in toxic effects associated with their principal component EBOV glycoprotein (GP). We and others have recently isolated and characterized human monoclonal antibodies (mAbs) to MARV and EBOV and defined the principal antigenic determinants for neutralization and protection on filovirus GP. We have demonstrated the successful protection of non-human primates against MARV by passively transferred mAbs. The central hypothesis of this study is that the epitopes of naturally-occurring human protective antibodies from survivors of a MARV infection can be used as templates for optimal rationally-designed structure-based vaccines. This hypothesis is supported by our recent extensive progress in the isolation of protective mAbs from survivors in conjunction with the recent advances in computational immunology techniques. We propose the rational design of structure-based vaccine MARV candidates that present the immunogenic determinants on GP. As in the wild-type (wt) GP, antigenic elements on the protein are obscured by glycosylation, the glycan cap and the mucin-like domain. The designed antigens are expected to better present protective determinants than the wt GP. We also propose that a vaccine based on conserved GP epitopes will be protective against both MARV and RAVV. The vaccine will use a highly innovative vaccine delivery platform based on pseudouridin-modified RNA delivered in a lipid nanoparticle formulation. The proposal is based on an interdisciplinary approach with a diverse team of experts in computational modeling, antibody and antigen discovery, filovirus virology, immunology and vaccinology. The Meiler computational group will use the ROSETTA software platform techniques to design novel structure- based vaccine candidate antigens, using highresolution structures of antigen-antibody complexes in the GP receptor-binding domain. The Crowe laboratory will generate recombinant antigens and antibodies, validate proper structure and function of the constructs, and determine the fine details of their biomolecular interaction. Moderna Therapeutics will provide the innovative **mRNA vaccine** platform. The Bukreyev and Geisbert laboratories will test the vaccine constructs expressing the designed antigens in rodent and nonhuman primate models of marburgviruses, and the Bukreyev laboratory will perform in-depth characterization of the immune response. The completion of this proposal will result in the development of a universal and safe next-generation vaccine, which will be protective against both MARV and RAVV. The generated antigen will be compatible with any existing advanced vaccine platform currently in clinical trials.

Public Health Relevance Statement

PROJECT NARRATIVE The unprecedented epidemic of filovirus Ebola in Western Africa in 2013-2016 demonstrated the urgent need in the development of vaccines against this and other filoviruses the cause a highly lethal disease in human, including marburgviruses Marburg and Ravn. This propos aimed at the development of a rationally designed structure-t

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that presents the highly conserved immunogenic determinants of marburgvirus GP and will be based on an innovative modified RNA-based platform. This proposal is relevant to the NIH mission because it will result in the development of a vaccine that will be protective against both Marburg and Ravn viruses and will be safer than vaccines based on the authentic marburgvirus GP.

NIH Spending Category

Biodefense Bioengineering Biotechnology Emerging Infectious Diseases

Genetics Immunization Infectious Diseases Orphan Drug Prevention

Rare Diseases Vaccine Related

Project Terms

Adverse effects Algorithm Design Animal Model Antibodies Antibody Repertoire Antigen-Antibody Complex Antigens Binding Central Africa Clinical Trials Bundibugyo virus Case Fatality Rates Cells **Complex Computational Biology Computer software Computer Models** Crystallization **Data Dermal Dermatitis Development** Disease **Disease Outbreaks Ebola Ebola Vaccines** Ebola virus **Elements** Dose **Epidemic Epitopes Family Formulation Epitope Mapping Filovirus** Geography Frankfurt-Marburg Syndrome Virus **Future Generations Read More**

Details

Contact PI/ Project Other PIs Program Official

Leader Name Name

Name

CROWE, JAMES E

DUPUY, LESLEY CONRAD

MEILER, JENS

Contact

BUKREYEV, ALEXANDER Contact

Title <u>lesley.dupuy@nih.gov</u>
PROFESSOR

Organization

abukreye@utmb.edu

Contact

Name Department Type State Code
UNIVERSITY OF TEXAS MED PATHOLOGY TX

BR GALVESTON
Organization Type
Congressional District

City SCHOOLS OF MEDICINE 14
GALVESTON

Country

Other Information

UNITED STATES (US)

FOA Administering Institutes or Project Start 01Centers Pate Novem

Study Section NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS

Date November2018

Special Emphasis
Panel ZRG1-IMM-C(02)

DUNS Number CFDA Code

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Project End

31-October
2023

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Budget Start

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Year

Award Notice

Date

31-October-**Budget End** Fiscal Year 06-November-2020 2019 Date 2020

2019

Project Funding Information for 2020

Total Funding Indirect Costs Direct Costs \$769,175 \$689,873 \$79,302

Funding IC

2020 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES \$769,175

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES \$769,175 Biodefense; Bioengineering Biotechnology, Emerging Infectious Diseases; Genetics; Immunization; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases; Vaccine	NIH Categorical Spending	Click here for more information on NIH Categorical Spending		
Bioengineering Biotechnology Emerging Infectious Diseases; Genetics; Immunization; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases; Vaccine	Funding IC		FY Total Cost by IC	NIH Spending Category
Related,	NATIONAL INSTITUTE OF ALLERGY AND	INFECTIOUS DISEASES	\$769,175	Bioengineering; Biotechnology; Emerging Infectious Diseases; Genetics; Immunization; Infectious Diseases; Orphan Drug; Prevention; Rare Diseases;

品 Sub Projects

No Sub Projects information available for 5R01Al141661-02

Publications

No Publications available for 5R01Al141661-02

Patents

No Patents information available for 5R01Al141661-02

Outcomes

The Project Outcomes shown here are displayed verbatim as submitted by the Principal Investigator (PI) for this award. Any opinions, findings, and conclusions or recommendations expressed are those of the PI and do not necessarily reflect the views of the National Institutes of Health. NIH has not endorsed the content below.

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No Clinical Studies information available for 5R01Al141661-02



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Related News Releases

No news release information available for 5R01Al141661-02

History

No Historical information available for 5R01Al141661-02

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