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

Project Number
5R01AI141661-02

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 high-resolution 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 non-human 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 that cause a highly lethal disease in human, including marburgviruses Marburg and Ravn. This proposal is aimed at the development of a rationally designed structure-based next generation vaccine candidate 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.

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

Read More

Details

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Organization Type
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State Code
TX

Congressional District
14

Other Information

FOA
PA-18-484

Study Section
Special Emphasis Panel[ZRG1-IMM-C(02)]

Fiscal Year
2020

Award Notice Date
06-November-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
800771149

CFDA Code
855

Project Start Date
01-November-2018

Project End Date
31-October-2023

Budget Start Date
01-November-2019

Budget End Date
31-October-2020

Project Funding Information for 2020

Total Funding

Direct Costs

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NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
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 Related;

Sub Projects

No Sub Projects information available for 5R01AI141661-02

Publications

No Publications available for 5R01AI141661-02

Patents

No Patents information available for 5R01AI141661-02

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.

No Outcomes available for 5R01AI141661-02

Clinical Studies

No Clinical Studies information available for 5R01AI14

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UNIVERSITY OF TEXAS MED BR GALVESTON

No news release information available for 5R01AI141661-02

History

No Historical information available for 5R01AI141661-02

Similar Projects

No Similar Projects information available for 5R01AI141661-02

Thank you for your feedback!