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Messenger RNA immunogens for initiation of HIV V3-glycan neutralizing B cell lineages

Project Number
5U19AI135902-03

Contact PI/Project Leader
HAYNES, BARTON F.

Awardee Organization
DUKE UNIVERSITY

Description

Abstract Text

A key goal of HIV-1 **vaccine** development is to induce long-lasting broadly neutralizing antibodies (bnAbs) that can inhibit HIV-1 infection. Messenger (m) RNA has emerged as a promising new **vaccine** modality that can elicit potent immune responses, while avoiding the safety risks and anti-vector immunity associated with some live virus vaccines. Important targets for bnAb induction are N301, N332 glycans at the base of the gp120 V3 loop. Our overall goals in this grant are 1) To design an **mRNA** that encodes a V3-glycan mimetope that, when expressed, will bind a V3 glycan UCA; 2) To select and produce **mRNA** formulations non-GMP that encode HIV-1 Envs for immunization in humanized mice and RMs; and 3) To produce the sequential V3-glycan **mRNA vaccine** under CGMP conditions, perform toxicity studies, and prepare an IND for testing in a Phase I trial in man. Overall Specific Aim 1. Develop **mRNA** delivery constructs for sequential Env trimers for V3-glycan bnAb B cell lineage vaccinations. Hypotheses: Messenger RNA vaccination of humanized mice, Rhesus macaques and humans will induce long-lasting anti-V3 glycan bnAb epitope antibodies, and **mRNA** vaccination will promote sequential somatic hypermutations and affinity maturation in V3-glycan targeted B cell lineages. Overall Specific Aim 2. Produce CGMP **mRNA** immunogens. Hypotheses: Messenger RNAs can be produced and encapsulated in potent nanoparticle formulations under CGMP for use in human Phase I trials, and will be safe and immunogenic. Moreover, the **mRNA** immunogens selected for CGMP production will produce stable Env trimers upon transfection of cell lines in vitro and after immunization in vivo in humanized mice. Expectations and Impact on the Field. Messenger RNAs are the current most promising **vaccine** strategy for inducing high-titered and long-lasting antibody responses. A successful first in man Phase I clinical trial with clinical trials materials produced in this IPCAVD will change the field by showing the plausibility of initiation of V3-glycan bnAb B cell lineages.

Public Health Relevance Statement

Nucleoside-modified messenger (m) RNAs are the current most promising vaccine strategy for inducing high- titered and long-lasting antibody responses. This IPCAVD Program has the potential to change the field with a successful first in man Phase I clinical trial by showing the plausibility of initiation of V3-glycan bnAb B cell lineages with Man9-V3 glycopeptide primes and sequential nucleoside-modified mRNA boosts.

Project Terms

Affinity Antibodies Antibody Response Antigens B-Lymphocytes Binding Cell Line Cell Lineage Clinical Trials Contracts Doctor of Philosophy Encapsulated Epitopes Formulation Glycopeptides Goals Grant HIV HIV Envelope Protein gp120 HIV-1 HIV-1 **vaccine** Human Immune response Immunity Immunization Immunoglobulin Somatic Hypermutation In Vitro Infection Investigational New Drug Application Lead Letters Macaca mulatta Messenger RNA Modality Mus NIH **Vaccine** Research Center Nucleosides

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Department Type
INTERNAL MEDICINE/MEDICINE

Organization Type
SCHOOLS OF MEDICINE

State Code
NC

Congressional District
04

Other Information

FOA
PAR-15-330

Study Section
ZAI1-JRR-A(S1)

Fiscal Year
2020

Award Notice Date
04-February-2020

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
044387793

CFDA Code
855

Project Start Date
08-February-2018

Project End Date
31-January-2023

Budget Start Date
01-February-2020

Budget End Date
31-January-2021

Project Funding Information for 2020

Total Funding
$4,527,376

Direct Costs
$2,934,035

Indirect Costs
$1,593,341

Year	Funding IC	
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$4,527,376

Sub Projects

No Sub Projects information available for 5U19AI135902-03

Publications

No Publications available for 5U19AI135902-03

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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 5U19AI135902-03

Clinical Studies

No Clinical Studies information available for 5U19AI135902-03

News and More

Related News Releases

No news release information available for 5U19AI135902-03

History

No Historical information available for 5U19AI135902-03

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