OVERVIEW

Development of an HIV vaccine that can elicit long-lived protective immunity against new HIV infections offers the best promise to end the AIDS epidemic. The low-level (31%) efficacy observed in the RV144 Thai trial suggests that a preventive HIV vaccine may be possible and that anti-Env antibodies, including those lacking classical neutralizing activities, may play some role in human protection. To advance the field and improve efficacy, new HIV vaccine designs are needed, and particularly those that retain native trimer structures; express conserved, cross-reactive epitopes; and that induce potent, durable anti-viral effector antibodies that can access and bind these epitopes.

This grant will employ experimental phase 1 human studies led by Julie McElrath (Fred Hutchinson Cancer Research Center [FHCRC]) with in-depth immunologic analyses in blood and draining lymph nodes to determine if the novel HIV-1 Env native trimer BG505 SOSIP.664 glycoprotein with adjuvant formulations can induce greater antibody potency and durability than seen with alum-formulated envelope proteins more commonly used in clinical studies. The overall experimental design will determine if one or more Env/adjuvant formulation(s) can induce anti-Env antibodies capable of autologous and/or broadly reactive tier 2 neutralizing antibodies, and can heighten the peak and extend the duration of antibody (Ab) responses at year one and thereafter. The planned adjuvants are 3M-052+Alum, GLA-LSQ, CpG 1018+Alum, and Alum, based upon their ability to trigger diverse innate pathways, the feasibility of obtaining and formulating stable, clinical grade material in a timely way, and the agreement among adjuvant developers to provide and compare products in head-to-head studies.

This grant is a collaborative effort led by M. Juliana McElrath, MD, PhD (FHCRC), John Moore, PhD (Cornell Weill Medical College), Darrick Carter, PhD and Chris Fox, PhD (Infectious Disease Research Institute), Michael Pensiero, PhD (NIH NIAID, DAIDS), and Mingchao Shen, PhD (FHCRC). It includes collaborative interactions with Andrew Ward, PhD (The Scripps Research Institute), Robert Coffman, PhD (Dynavax), and Mark Tomai, PhD (3M). It will also leverage CAVD Central Services Facilities, including Vaccine Product Development Center led by Tom Hassell, PhD (IAVI), and Comprehensive Antibody and Cellular Vaccine Immune Monitoring Cores. The award was received in November, 2014 with an initial agreement length of 5 years.

RESEARCH OBJECTIVES

Assess the immunogenicity of an HIV-1 subunit vaccine when formulated with several novel adjuvants, with alum as an adjuvant comparator. Initial target responses include:

1.) 5-10 fold greater peak binding Ab titers to the homologous Env antigen and significantly greater peak response rates after 3 doses.

2.) 5-10 fold greater binding Ab titers to the homologous Env antigen and significantly greater response rates one year after the last immunization.

3.) Neutralization of autologous and a panel of Tier 2 virus strains.

4.) 2-fold greater frequency of circulating Env-specific CD4+ T cells with significantly greater polyfunctionality at the peak response.

5.) Significantly improved qualitative Ab responses, such as avidity, anti-viral effector function, and/or somatic hypermutation/affinity maturation.

6.) Distinct innate immune profiles for each adjuvant.

PROGRESS

We have conducted formulation compatibility studies and evaluated the effects of adjuvants on BG505 SOSIP.664 trimer structures by electron microscopy, BLI, ELISA, and other assays. The native trimer structures were retained in most cases, but were affected by some adjuvants in dose dependent and time dependent manners.

We are conducting a guinea pig study to assess the immunogenicity of BG505 SOSIP.664 with various adjuvants. Autologous tier 2 neutralizing antibodies were induced in most of the study groups. We will measure the durability of neutralizing and binding antibody responses. We are also conducting a rabbit study to assess the immunogenicity of BG505 SOSIP.664 with various adjuvants.

We conducted a pilot rat study of BG505 SOSIP.664 with adjuvants and showed that the vaccines are immunogenic in rats. We have started a GLP toxicity study in rats to demonstrate the safety and tolerability of BG505 SOSIP.664 with these adjuvants. Upon completion of the toxicity study, we will prepare to start a clinical trial in collaboration with HVTN.

Grant at a Glance

Principal Investigator
M. Juliana McElrath, PhD

Grantee Institution
Fred Hutchinson Cancer Research Center, Seattle, USA

Project Title
Durability of HIV-specific protective Ab responses in human immunology-based experimental medicine trials

OPPID
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Grant Award
Up to $4.7 million, awarded in November, 2014

Collaborating Institutions
- Infectious Disease Research Institute, USA
- The Scripps Research Institute, USA
- Weill Cornell Medical College, USA
- International AIDS Vaccine Initiative, USA
- National Institute of Allergy and Infectious Diseases, NIH, USA
- Dynavax Technologies, USA
- 3M, USA