Shattock: DNA Vaccination for HIV Immunogen Discovery

OVERVIEW

A globally effective HIV-1 vaccine will likely need to induce broadly neutralizing antibodies (bNAbs) against HIV-1. This proposal recognizes the strategic importance of performing iterative small human studies to accelerate HIV-1 immunogen discovery, where DNA vaccines offer the fastest and most cost effective approach for rapid screening of multiple immunogens. In contrast to previous approaches that aimed to only develop DNA immunization as a practical product development platform, this project aims to leverage DNA immunization as a platform to accelerate the discovery of HIV-1 immunogens capable of inducing bNAbs in humans. Additional benefit will be provided by the potential establishment of a platform for rapid generation of human monoclonal antibodies to antigens per se that could be used for passive immunization not only against HIV but also for other neglected diseases.

To meet this aim this project seeks to apply recent state of the art technological advances in DNA vaccination and immune monitoring, both at the single cell and molecular level, to enable detailed probing of developing vaccine induced antibody responses. In this respect it represents the first attempt in humans to use a DNA vaccine approach to investigate the development and focusing of B cell responses to vaccination. Should this approach be successful it will provide an important new strategy for rapidly conducting systematic clinical research studies in humans aimed at moving the HIV-1 vaccine field closer to achieving the key objective of identification of immunogens and vaccine strategies required for induction of bNAbs in humans.

Success of this project will be indicated on the basis of meeting the critical milestone: induction of sufficient B cell responses by DNA vaccination to facilitate antibody repertoire analysis. Successful achievement of the "go" criteria will trigger an expanded program of experimental iterative clinical DNA vaccine studies to identify and refine immunogens capable of driving B cells along rare but desirable maturation pathways towards the development of bNAbs. This would allow rapid up-selection of promising new approaches reducing the risk of failure in advanced clinical development.

Grant at a Glance

Principal Investigator
Robin Shattock, PhD

Grantee Institution
Imperial College, London, UK

Project Title
DNA Vaccination for HIV Immunogen Discovery

OPPID
1084580

Grant Award
Up to $1.8 Million, awarded November, 2013

Prof Shattock (PI) and Imperial College (IC) have considerable experience in running human vaccine studies and coordinating collaborative partnerships. Phase I clinical trials will be conducted at the IC and St Thomas' clinical research facilities under the joint direction of Profs Sheena McCormack, Julie Fox and Shattock. This project will engage all CAVD central services facilities including the CTVIMC to ensure full T cell evaluation, the CAVIMC to ensure comprehensive analysis of antibody function, the CVISC to ensure appropriate biostatistical analyses of clinical study data and IAVI's VxPDC for product development support. In addition this project will aim to work through the Foundation to engage ATRECA in parallel genomic and systems-level bioinformatics to capture a deeper genetic record of the evolving vaccine induced B cell responses to DNA vaccination.

Wayne Koff (IAVI), Barton Haynes (Duke CHAVI-ID), Dennis Burton (Scrips CHAVI-ID) and John Mascola (NIH VRC) will serve on the scientific advisory board of this project. If this project is successful in meeting its "go" criteria and were an expanded project funded, the members of the advisory board would become active partners in any expanded program. Engagement of this larger consortium will maximize the potential impact of a human DNA vaccine program focused on identification of immunogens and immunization strategies that aim to build a comprehensive roadmap to drive B cells along rare but desirable maturation pathways towards the development of bNAbs. This would provide an essential springboard to accelerate HIV vaccine research and development, a key strategic component of the Foundation's HIV/AIDS program.

RESEARCH OBJECTIVES

1.) Optimization of DNA vaccination to maximize B cell responses

2.) Characterization of evolving B cell repertoire in response to DNA vaccination

PROGRESS

All regulatory and ethical approvals are in place. All vaccinations and follow-up visits have been completed at the Trial Site. The Trial Site will be closed as soon as final monitoring has been performed. Research analysis has been completed and sent through to EMMES, who have drafted the CSR. This document will be finalized soon. Research analysis to be written up for publication and all trial documentation archived by Dec 18.