Ho: Engineered Bispecific bNAbs for Prevention

OVERVIEW

The overall aim of this grant is to accelerate the development of a broadly neutralizing antibody (bNAb) product for passive immunization against HIV. Passive administration of an HIV-neutralizing monoclonal antibody on an infrequent basis has the potential, like long-acting anti-retrovirals (ARVs), to fill a critical gap between now and the launch of an effective, active vaccine against HIV.

The key obstacle for development of bNAbs for HIV prevention has been the discovery of an antibody that possesses suitable breadth, potency, and pharmacokinetics (PK). Next generation antibody-like molecules that could achieve greater potency and breadth would provide a more practical, low cost product generally more feasible for most of the countries hit hardest by HIV/AIDS.

This grant to Dr. Ho seeks to capture promising new results based on bispecific antibodies. Bispecific antibodies targeting both an epitope on HIV and the host cell receptor on HIV's target cells can have a greater than 100-fold increase in potency and increased breadth of coverage, over either antibody alone or the combination, in laboratory studies. If fully developed, such next generation engineered bNAbs would meet the requirements for the low cost products for populations in developing countries.

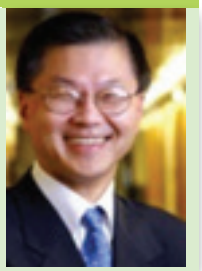
RESEARCH OBJECTIVES

1.) Develop a lead bispecific antibody-like molecule with much enhanced anti-HIV breadth and potency that could be administered on a bimonthly basis

2.) Assess the "developability" of the best candidate bispecific antibodies and advance one lead molecule into clinical development

3.) Express a bispecific antibody in vivo by gene transfer using mini-circle DNA delivered into muscle via electroporation

Grant at a Glance



Principal Investigator
David Ho, MD

Grantee Institution
Aaron Diamond AIDS Research Center, New York, USA

Project Title
Ibalizumab-based Bispecific Antibodies for HIV Prevention

OPPID
1040731

Grant Award
Up to $12.1 Million, awarded April, 2012

Collaborating Institutions
- Tulane National Primate Research Center
- WuXi Biologics

PROGRESS

The Ho research consortium has generated a panel of over 200 antibody-like molecules, most of which are bispecific with one arm directed to one of the viral receptors and one arm directed to an element on the viral envelope glycoprotein. In collaboration with Dr. Michael Seaman at the Beth Israel Deaconess Medical Center, part of the Montefiore Antibody Vaccine Immune Monitoring Consortium (Ab VIMC), a select pool of these antibodies were identified to be extremely potent and broad at neutralizing a large panel of HIV isolates. While the Ho consortium continues to expand this antibody library in order to identify additional potent and broad antibody-like molecules, a largely empirical process, they in parallel are advancing the top antibody candidates already identified through preclinical development activities. The Ho consortium has characterized the developability, manufacturability, and in vivo properties of the top antibody candidates identified and selected a lead candidate, 10E8.4/iMab, for further clinical development as passive immunization for HIV prevention. In addition, the Ho consortium is developing an antibody gene-transfer method to deliver DNA encoding for potent bispecific antibodies by electroporation. This technology has the potential to express physiologically relevant levels of a bispecific antibody for an extended period after administration while circumventing many of the cost and production barriers that may limit traditional monoclonal antibody therapeutic approaches. The ultimate goal of the consortium is to create a novel bispecific antibody that has dramatically improved anti-HIV breadth and potency as well as a pharmacokinetic profile suitable for bimonthly administration to humans.