OVERVIEW

Despite significant efforts over the last 30 years, and exceptional recent scientific advances, it seems highly unlikely that we will be able to develop an effective active anti-HIV vaccine in the near future. In the interim, there is a need for HIV prophylaxis methods that are effective in controlling new infections, deliverable in areas most in need (such as sub-Saharan Africa), and economically feasible in these regions. Passive immunization with broadly neutralizing monoclonal antibodies (bNAbs) is being considered in this context. Passive bNAb immunization has been shown to prevent SHIV infection in rhesus macaque models, can be delivered subcutaneously (enabling self-administration in some settings), and the antibodies have a long half-life. This is particularly true of antibodies such as the two that will be investigated in this grant, 3BNC117-LS and 10-1074-LS, which have been specifically modified to have increased half-lives in vivo. This grant will be used to evaluate the safety, tolerability, pharmacokinetic profile, and antiretroviral effects of two human anti-HIV neutralizing antibodies given in combination in humans, with the long-term goal of achieving high levels of efficacy in preventing HIV acquisition.

3BNC117-LS and 10-1074-LS are broad and potent anti-HIV neutralizing antibodies recognizing the HIV-1 envelope CD4 binding site and the V3 loop of the HIV-1 envelope, respectively. Two amino acid substitutions (the LS mutation) were introduced in the Fc region of the parental antibodies to extend their half-lives. Both the parental and LS-modified antibodies provide broad coverage of diverse HIV-1 strains, and the parental antibodies showed favorable safety profiles in phase I trials. The LS mutation alters the binding properties of the antibodies for the neonatal Fc receptor (FcRN). It thereby enhances antibody re-cycling and prolongs the half-lives by 3- to 4-fold. The increased half-lives should be dose sparing and allow for quarterly or biannual dosing.

This proposal builds on the research performed under OPP1092074 (awarded to M. Nussenzweig, Rockefeller University), and enables the development and evaluation of a combination of 3NBC117-LS and 10-1074-LS for passive immunoprophylaxis in sub-Saharan Africa. It includes phase 1 studies in the US and in sub-Saharan Africa, as well as overall management and oversight of product development. Data generated from these studies will support phase 2b efficacy studies in sub-Saharan Africa. Two studies will be conducted at the Rockefeller University, and the other will be conducted in four sub-Saharan African sites. The ultimate goal is to develop a commercially viable product for sub-Saharan African countries that can be delivered subcutaneously once every 3-6 months.

Grant at a Glance

Principal Investigator
Michel Nussenzweig, MD, PhD

Grantee Institution
The Rockefeller University, New York, USA

Project Title
Phase 1 studies of the pharmacokinetics, safety, and bioactivity of 3BNC117-LS and 10-1074-LS among adults in the US and sub-Saharan Africa

OPPID
1168933

Grant Award
Up to $13.1 million, awarded in October, 2017

Collaborating Institutions
- International AIDS Vaccine Initiative, New York
- University of Washington, Seattle
- Fred Hutchinson Cancer Research Center, Seattle

The grant is led by Michel Nussenzweig at Rockefeller University. Drs. Connie Celum (University of Washington, Seattle) and Julie McElrath (Fred Hutchinson Cancer Research Center, Seattle) are partner investigators for the proposed phase 1b study in Africa. The Product Development Center at the International AIDS Vaccine Initiative (IAVI) will manage the production of 10-1074-LS and will assist with regulatory submissions in the US and Africa; these activities are funded under separate awards to IAVI.

RESEARCH OBJECTIVES

1.) **Phase 1a: First-in-Human Studies in the US.** Two phase 1, dose-escalation studies to assess the safety, pharmacokinetics, and antiretroviral activity of 10-1074-LS alone and in combination with 3BNC117-LS in HIV-uninfected and HIV-infected individuals will be conducted. The antibodies will be administered intravenously or subcutaneously.

2.) **Phase 1b: Study in sub-Saharan African Sites.** This will be a phase 1b, placebo-controlled study of the safety, tolerability, and pharmacokinetics/pharmacodynamics of 10-1074-LS and 3BNC117-LS administered in combination subcutaneously to HIV-uninfected individuals in Kenya, Uganda, and South Africa.