Kublin: HVTN 100

OVERVIEW

The need for a preventive HIV-1 vaccine is acute, especially in southern Africa, the world region most heavily burdened by the HIV epidemic. This grant provides funding for initial testing in South Africa of a vaccine regimen based on the regimen shown to be modestly efficacious in preventing HIV infection by the RV144 clinical trial in Thailand. Under the aegis of the Pox-Protein Public Private Partnership (P5), a vaccine regimen has been developed that is similar to the regimen in the RV144 trial, but adapted to the clade C strains of HIV circulating in southern Africa and modified (in vaccination schedule and certain product components) to enhance the magnitude and durability of the immune responses elicited by this regimen. This investment will support the implementation of HVTN 100, a phase 1-2 randomized, double-blind, placebo-controlled clinical trial of clade C ALVAC-HIV (vCP2438) and Bivalent Subtype C gp120/MF59® in HIV-uninfected adults in South Africa, who are at low risk of HIV infection. Results from this trial will determine whether the ALVAC-HIV (vCP2438) / Bivalent Subtype C gp120/MF59® prime-boost vaccine regimen qualifies for advancement to phase 3 efficacy testing in the Republic of South Africa. This determination will be based on evaluation of vaccine safety/tolerability and peak immunogenicity following the primary immunization schedule (i.e., Month 6.5). Rates and magnitudes of vaccine-generated immune responses will be evaluated against preset criteria, designed to ensure immunogenicity sufficient to support testing the hypothesis that the presence of binding antibodies to the V1V2 region of HIV Env is a vaccine correlate of reduced risk of HIV-1 infection.

Based on interim safety and immunogenicity data for the primary vaccination series (i.e. Months 0, 1, 3, and 6), a decision has been made to advance the HVTN 100 vaccine regimen to a pivotal efficacy trial in South Africa (HVTN 702). In this context, understanding the durability of vaccine-elicited immune responses and the extent to which those responses can be maintained or enhanced by subsequent booster vaccinations has assumed great importance. Part B of HVTN 100 seeks to provide this understanding by characterizing the immune responses elicited by different booster vaccinations at Month 24 and also to explore differences between boosting at 1 year and 2 year intervals.

Participants in Part B will receive vaccinations at Month 24 with ALVAC-HIV (vCP2438) plus Bivalent Subtype C gp120/MF59, with Bivalent Subtype C gp120/MF59 alone, or placebo. Participants in the three subgroups will also receive booster vaccinations at Month 36. Participants in subgroups that received Month 24 booster vaccinations with ALVAC-HIV (vCP2438) plus Bivalent Subtype C gp120/MF59 or with Bivalent Subtype C gp120/MF59 alone will receive the same booster vaccinations at Month 36. Part A vaccinees who received placebo injections at Month 24 will receive boosts of ALVAC-HIV (vCP2438) plus Bivalent Subtype C gp120/MF59 at Month 36.

Grant at a Glance

Principal Investigator
James Kublin, MD, MPH

Grantee Institution
Fred Hutchinson Cancer Research Center, Seattle, USA

Project Title
HVTN 100 A phase 1-2 randomized, double-blind, placebo-controlled clinical trial of clade C ALVAC-HIV® (vCP2438) and Bivalent Subtype C gp120/MF59® in HIV-uninfected adults at low risk of HIV infection

OPPID
1110792

Grant Award
Up to $4.8 million, awarded in November, 2014

Collaborating Institutions
- Hutchinson Center Research Institute of South Africa, Cape Town, South Africa
- Centre Hospitalier de l'Universite de Montreal, Montreal, Canada

Part B of HVTN 100 thus provides an opportunity to characterize the immune responses elicited by booster vaccinations at Months 24 and/or 36 and, importantly, in the event that vaccine-induced immune correlates of risk or protection are identified in the planned HVTN 702 trial, samples from Part B of HVTN 100 can be evaluated to determine whether booster vaccinations can maintain or even enhance those correlates. This information may inform investigation of boost strategies should the vaccine regimen be advanced toward an application for marketing authorization.

The program also includes development of next-generation CD4+ T cell laboratory evaluations that will be conducted through collaboration with Dr. Daniel Kaufmann at McGill University using microfluidic qRT-PCR arrays (90 gene panels, Fluidigm platform) on sorted HIV-specific CD4+ T cells expressing CD40L and through evaluation of single-cell expression of 40 immunological markers using the CyTOF technology. These data sets will be analyzed and compared with the validated ICS and cytokine bead array HVTN endpoint assays from the same participants to extend the functional profile of CD4+ T cell responses and to determine if the exploratory studies provide additional signatures that may merit analysis in the future phase 3 trial.

This grant is a collaborative effort led by James Kublin, MD, MPH (HIV Vaccine Trials Network (HVTN), Fred Hutchinson Cancer Research Center (FHCRC)), with the participation of M. Juliana McElrath, PhD (FHCRC, HVTN, and the Hutchinson Center Research Institute of South Africa (HCRISA)), and of Daniel Kaufmann, MD (Centre Hospitalier de l'Universite de Montreal). The CAVD award was received in November 2014, with an initial agreement length of 2.4 years; HVTN 100 derives additional support from NIAID.

RESEARCH OBJECTIVES

1.) To evaluate the safety and tolerability of 2 doses of ALVAC-HIV (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59® in HIV-seronegative low risk South African adults

2.) To evaluate the immunogenicity of ALVAC-HIV® (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59® in HIV-seronegative South African adults at the month 6.5 time point (2 weeks after completion of the primary immunization series)

Additional Objectives for Part B include:

3.) To evaluate the safety and tolerability of Bivalent Subtype C gp120/MF59 and of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 when given as boosts in participants previously vaccinated in Part A

4.) To evaluate the immunogenicity of Bivalent Subtype C gp120/MF59 and of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 when given as boosts at Month 30 in participants previously vaccinated in Part A at 2 weeks following each vaccination