Kamarck: Clinical Assessment of hCMV-HIV Prototype Vector

OVERVIEW

Vir Biotechnology Inc. (Vir), in collaboration with Oregon Health and Sciences University (OHSU), is developing CMV-VIR2-HIV-001, a novel, first-in-class, prophylactic vaccine for human immunodeficiency virus (HIV). The potential of a cytomegalovirus (CMV)-based vaccine to elicit broad and durable cellular responses, and the central importance of unconventional (MHC-E-restricted and MHC-II-restricted) CD8+ T-cell effector responses, have been shown in published and unpublished work by the Picker group. The concept of immune programming (i.e. the use of CMV-based vectors to elicit CD8+ T-cell responses that are distinct in their epitope recognition and MHC restriction, depending on the genetic modification of the vector) represents a new paradigm in vaccine development. Based on this new paradigm, Vir intends to develop an hCMV vector-based antigen delivery and immune programming platform which can be used as a vaccine for multiple diseases, including HIV.

The prototype of the vaccine contains a live attenuated hCMV derived from clinical isolate TR (Smith 1997). This TR isolate was cloned (Murphy 2003) and genetically modified, introducing the UL97 and US2-7 genes from strain AD169 to provide ganciclovir sensitivity and MHC-I inhibitory activity, respectively. This clone was then attenuated by replacing the gene encoding the tegument pp71 with a genetic sequence encoding the HIV-1 clade A gag transgene derived from the GRIN plasmid (Keefer 2012, Keefer 2010). The CMV-VIR2-HIV-001 vaccine also contains deletions of CMV genes UL128, UL130, UL146, and UL147.

Because the vaccine that Vir proposes to manufacture and test in a first-in-human (FIH) clinical study carries an HIV clade A gag insert only, it is not meant to be a clinical product. This initial vaccine is intended to be used in a proof-of-concept experimental medicine study to determine the safety of the vector backbone and whether the unconventional responses observed in nonhuman primates (NHP) translate to humans. If successful, a vaccine containing an epitope-optimized version of HIV inserts will be used in the next-generation vectors. These new inserts will be sequence-optimized to best match global circulating HIV strains, will include gag, pol, and nef sequences, and will likely focus on universal MHC-E-restricted epitopes (supertopes). The final design of these inserts will be based on ongoing studies at OHSU.

Grant at a Glance

Principal Investigator
Michael Kamarck, Ph.D.

Grantee Institution
Vir Biotechnology Inc., San Francisco, USA

Project Title
Clinical Assessment of Live Attenuated hCMV-HIV Prototype Vector

OPPID
1187970

Grant Award
Up to $12.1 Million, awarded in February 2018

Collaborating Institutions
◊ Oregon Health and Science University

The grant is led by Michael Kamarck at Vir Biotechnology Inc. (San Francisco, CA). The primary scientific collaboration is with the team at OHSU, led by Louis Picker. IDT Biologika (Rockville, MD) is the CRO that will conduct the engineering run, formulation, and stability program, as well as a clinical study material production run, all conducted using Good Manufacturing Practice (GMP). The IAVI VxPDC (New York, NY) assisted in establishing the IDT contract.

RESEARCH OBJECTIVES

1.) Complete the last preclinical pharmacology studies (confirmatory in vitro studies and a GLP toxicology study in rabbits) needed to file an Investigational New Drug (IND) application.

2.) Manufacture clinical study materials.

3.) Conduct an FIH clinical study that will inform whether the vector backbone is safe to use in humans, based on results of physical examinations, clinical laboratory analyses, tolerability assessments, and shedding evaluations.

- ◊ Dose-escalation phase: initially evaluate 4 dose escalation levels of the vaccine in a total of 32 healthy (HIV- hCMV+) adult subjects (24 in the active group and 8 in the placebo group).
- ◊ Dose-expansion phase: gather additional data from 20 subjects (16 in the active group and 4 in the placebo group) on 2 of the dose levels.

4.) Demonstrate proof-of-concept for the CMV platform by evaluating whether the unconventional T-cell response (MHC-II and MHC-E restriction and long-term effector levels) can be elicited in humans.