# Haynes: Centralized Envelope Phase I Study

## OVERVIEW

This project was aimed at to solving a central problem blocking the development of a successful HIV-1 vaccine—how to design vaccine immunogens from a T-cell epitope perspective to successfully address the broad genetic diversity of HIV-1. The initial goal was to enable acceleration of vaccine development by 'validating' an in silico approach for optimizing HIV-1 T cell immunogens for testing in clinical trials. Over the past two decades, extensive viral sequencing has enabled an in silico approach to immunogen design to be developed, and substantial preclinical progress has been made. Centralized genes have now been identified which, as predicted in silico, have been proven to substantially improve the breadth of T cell reactivity, particularly CD8+ T-cells, in both small animals and non-human primates. This clinical trial, named HVTN 106, sought to determine if the observations in small animals and non-human primates extend to humans.

To test this, the arms of the trial (HVTN 106) included:

1.) Single wildtype transmitted/founder Env (30 subjects + 5 controls)

2.) Single group M consensus Env (30 subjects + 5 controls)

3.) Trivalent mosaic Env (30 subjects + 5 controls)

The vaccines were Env gp160s given as DNAs for priming and boosted with the MVA-CMDR recombinant Env. Three injections of DNA (4 mg) were given at weeks 0, 4 and 8 followed by two injections of MVA-CMDR ($1x10^8$ pfu) at weeks 16 and 32. Placebo controls were given as empty vaccine diluent (saline).

## RESEARCH OBJECTIVES

HVTN106 was a phase I proof-of-concept study initiated to test two centralized approaches (consensus and mosaic Envs) versus single wildtype Env, as a means of enhancing the breadth and coverage of T cell responses to HIV. The critical scientific questions addressed by the clinical trial include:

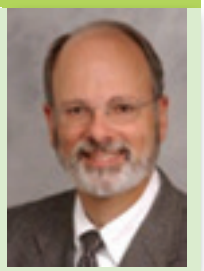
1.) Is consensus Env superior to wildtype transmitted/founder Env for induction of T cell breadth?

2.) Is consensus Env superior to trivalent mosaic Env for induction of T cell breadth?

3.) Can *in silico* predictions of superiority of induced breadth of T cell responses by consensus and mosaic immunogens be validated in humans *in vivo*?

Data analysis to determine the breadth and depth of T cell of responses induced by priming with WT vs. consensus vs. trivalent mosaic Env DNAs is almost complete.

## Grant at a Glance



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**Grantee Institution**
Duke University, Durham, USA

**Project Title**
Centralized Envelope Comparative Immunogenicity (CECI) Study

**OPPID**
52282

**Grant Award**
Up to $7.4 Million, awarded November, 2009

**Collaborating Institutions**
- Beth Israel Deaconess Medical Center, USA
- Fred Hutchinson Cancer Research Center, USA
- IPPOX Foundation, Switzerland
- Los Alamos National Laboratory, USA
- National Institute of Allergy and Infectious Diseases, USA

## PROGRESS

The HVTN106 Phase I clinical trial concluded in September 2016, and the primary CAVD award ended in March 2018. Data analyses are close to completion for all study endpoints. Dr. Nicole Frahm at the FHCRC and Dr. Bette Korber at LANL have been working to measure the magnitude, depth, and breadth of T-cell responses elicited by the HVTN106 vaccine regimens, and Dr. Kevin Saunders at the DHVI has been characterizing the corresponding antibody repertoire.

T cell response rates and response magnitude to the different DNA primes were measured by intracellular cytokine staining (ICS), and the analysis was completed in August 2017. Epitope mapping by ELISpot assay was also performed to characterize the breadth and depth of T cell responses to the different DNA priming immunogens and to assess the impact of the MVA-CMDR boost. Early results indicated that the mosaic DNA induces higher magnitude Env-specific T cell responses compared with natural T/F and could potentially serve as a universal prime. The last round of epitope mapping to quantify response breadth was completed in November 2017. Each DNA prime appeared to target different regions of the HIV-1 gp160. Interestingly, several CD4+ T cell responses clustered the same V2 region as the immunodominant responses seen in the RV144 trial. Dr. Bette Korber has been working with the SCHARP team to extend the analysis to correlate T cell and IgG responses.

Dr. Saunders and team isolated a total of 120 monoclonal antibodies from the final vaccinee samples collected after the last MVA-CMDR boost. Through selective screening for Env-targeted antibodies, they selected 31 mAbs for thorough characterization of epitope specificities and antibody effector functions (ADCC, ADCP, virus capture). Similar to previous studies, they observed a bias toward gp41 reactivity in the HVTN106 vaccinee antibody responses. Several of the gp41-reactive mAbs also exhibited cross-reactivity to human intestine microbiota antigens, and the LLRAIE epitope was required for gp140-reactivity. Additionally, two new V2-specific antibodies, similar to the CH58 and CH59 mAbs from RV144, were isolated and characterized.

A collaborative study with Dr. Suzanne Campion and Dr. Andrew McMichael at Oxford University has been done in parallel with other analyses to assess how the pre-immune CD4+ T-cell repertoire shapes the post-vaccination T cell responses to the HVTN 106 vaccine regimens. This study also aimed to determine whether post-vaccination responses from the naïve or memory precursors pool, how ontogeny affects the persistence and immunodominance of the response, and the influence of the microbiome on post-vaccination T cell responses. The Oxford team has completed epitope mapping for 20 donors against the Con-S peptide set at both the pre-vaccination (visit 2) and post-DNA primes (visit 7) timepoints. Preliminary results suggest that the pre-immune repertoire were often immunodominant in the first responses after vaccination.

Analysis is wrapping up and several manuscripts are in preparation from all of the teams at the HVTN, Duke University and Oxford University.