Feinberg: IAVI Neutralizing Antibody Consortium (NAC)

OVERVIEW

Thirty years since the identification of HIV as the cause of AIDS, the development of a safe and effective HIV vaccine remains a global health priority. There is a growing body of literature to suggest that a broadly neutralizing antibodies (bnAb)-based vaccine against HIV may be achievable. The PRIMARY OUTCOME of this proposal is the demonstration that an HIV ENV based immunogen(s) can be designed to elicit bnAbs in humans.

Classical approaches to vaccine discovery have thus far failed to identify immunogen(s) capable of eliciting HIV bnAbs. Using rational vaccine design, this CAVD grant investigates the interaction of HIV and bnAbs at the molecular level, takes this information for immunogen design and advances candidate immunogens through an iterative pipeline towards human clinical testing. We aim to develop at least one vaccine approach (immunogen(s), immunization strategy) that induces in humans, nAbs against 50% of HIV primary isolates at a titer of at least 1:100. We employ detailed antibody response analysis in our efforts to iteratively design, improve and evaluate immunogen candidates.

RESEARCH OBJECTIVES / PROGRESS

We have achieved significant progress during the first four years of this CAVD program, including but not limited to:

- Development of the germline-targeting concept and design of the first germline-targeting immunogen (eOD-GT8), evaluated in knock-in mice, transgenic mice and entering Phase I clinical trials this year (2018). In addition to eOD-GT8, we have designed germline-targeting immunogens for HCDR3-dependent bnAbs to three major sites of vulnerability on the HIV trimer: V3-glycan, V2-apex, and MPER, that are in various stages of pre-clinical testing. Our germline-targeting immunogen for the V3-glycan (N332-GT5) has been selected for manufacture and clinical testing.

- Development of an immunofocusing strategy to initiate V2 apex bnAb responses using the V1V2 epitope transplanted onto different trimer backgrounds.

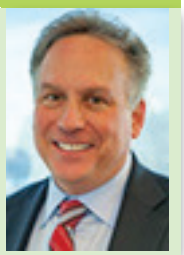
- Improvements in the yield, antigenic profile, thermal and structural stability of well-ordered trimer immunogens. In addition to selecting BG505 SOIP.664 for clinical manufacturing, we developed a stabilization platform for the HIV trimer (MD39 and descendants) that improves significantly in several dimensions on the original native-like Env trimer BG505 SOSIP. Capitalizing on the MD39 improvements, we also developed trimer-nanoparticles being used for various prime and boosting immunogens. We also developed an alternative to SOSIP as a platform for native-like trimers; the NFL (native flexibly linked) trimer platform.

- Establishment of an antibody response analysis core for evaluation of antibody responses to candidate immunogens and vaccine regimens.

- Establishment and application of approaches for site-specific analysis of glycosylation to a number of immunogens, including eOD-GT8, CD4 binding site shepherding immunogens and V2 apex germline-targeting and immunofocusing immunogens.

- The first high-resolution structure of a V2 apex bnAb bound to a native-like HIV-1 Env trimer and the structures of a series of antibodies from longitudinal studies on bnAb evolution.

Grant at a Glance



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Project Title
IAVI Neutralizing Antibody

OPPID
1084519

Grant Award
Up to $50 Million, awarded November, 2013