Barouch: Epitope-Modified Env Trimers for Induction of Heterologous Tier 2 NAbs

OVERVIEW

We have recently developed a novel strategy for the generation of HIV-1 Env immunogens aimed at eliciting neutralizing antibodies (NAbs). Signature-based Epitope Targeted (SET) vaccines are designed to incorporate bNAb signatures to optimize key HIV-1 Env epitopes. In our initial studies, the computational approach defined elements associated with bNAb neutralization sensitivity and resistance and resolved common patterns across bNAbs with shared epitope specificities. The bNAb classes evaluated included those that target the V2 region, the V3 region, and the CD4 binding site.

In this proposal, we will evaluate the hypothesis that bioinformatic optimization of HIV-1 Env immunogens will improve the induction of heterologous tier 2 NAb responses. This work will include developing improved immunization regimens with our V2 SET immunogens to increase both the titers and breadth observed in the guinea pig model and increase the fraction of vaccinated animals that develop heterologous tier 2 NAbs. We will examine differing boosting schemes and adjuvants using our existing protein immunogens, as well as examining SOSIP trimers containing the V2 SET sequences of our current vaccines. Simultaneously, we will be generating a second generation of SET designs that will be informed by the recent expansion of data for neutralizing antibodies. We are also exploring new molecular engineering methods to produce the SET immunogens, either for mulitmeric presentation as nanoparticles and nanodiscs, or as improved soluble mimetics of the native Env trimer. These immunogens will also be evaluated in the guinea pig model. All these efforts are slated for the first two years of the program, leading to a Go/No-Go decision for the initiation of a rhesus monkey study in year three.

RESEARCH OBJECTIVES

Outcome 1: Development of Improved Epitope-Modified Env Trimers in Guinea Pigs

1.A.1. Definition of the optimal vaccine regimen in guinea pigsTo manufacture clinical-grade PGT121 and to conduct preclinical toxicology studies;

1.A.2. Comparison of SOSIP vs foldon versions of the WT+Opt+Alt 459C and BG505 gp140 cocktails in guinea pigs

1.A.3. Evaluation of next generation immunogens and immunization strategies in guinea pigs

1.B.1. Second generation bioinformatic design of V2, V3, and CD4bs SET vaccines

1.B.2. Iterative cycle of vaccine design, if warranted, based on outcomes in guinea pig vaccination studies

1.B.3. Statistical analysis of immunological data and modeling to compare vaccine efficacy and the relative importance of different factors and interpretation of serological reactivity patterns

1.C.1. Production and antigenicity of multimerized HIV-1 Env immunogens and soluble Env trimers with the current V2 SET sequences

1.C.2. Production and antigenicity of multimerized HIV-1 Env immunogens and soluble Env trimers with the next generation V2 SET sequences

Outcome 2: Evaluation of Optimized Epitope-Modified Env Trimers in Rhesus Monkeys

2.1. Immunogenicity of epitope-modified vaccines in rhesus monkeys

2.2. Protective efficacy of epitope-modified vaccines in rhesus monkeys

Grant at a Glance

Principal Investigator
Dan H. Barouch, MD, PhD

Grantee Institution
Beth Israel Deaconess Medical Center, Boston, USA

Project Title
Epitope-Modified Env Trimers for Induction of Heterologous Tier 2 NAbs

OPPID
1169339

Grant Award
Up to $4.1 Million, awarded in May, 2017

Collaborating Institutions
- Los Alamos National Laboratories, Los Alamos, USA
- Children's Hospital of Boston, Boston, USA