Baker: Testing the Nearest Neighbor Approach to Active Vaccination for HIV-1 bNAbs

OVERVIEW

This program seeks to develop improved HIV-1 envelope glycoprotein (Env) immunogens based on the engineered SOSIP HIV glycoprotein trimer constructs developed by the Moore/Sanders/Ward labs. The original premise of the approach is the observation by Dr. Garnett Kelsoe's group at Duke that the generation of some broadly neutralizing antibodies (bNAbs) to Env appears to be restricted by host epitope mimicry. Hence deletion of many responsive B cell clones, either during B cell development or in germinal centers, may be the basis for sub-optimal immune responses to current HIV-1 Env vaccines. Therefore the goal of this grant is to arrive at next generation "Nearest Neighbor (NN)" SOSIP Env immunogens that avoid restriction by such tolerance mechanisms that may underlie the sub-optimal immune responses to current Env vaccines. NN immunogens may be produced either as soluble antigens or via multivalent display on designed protein nanoparticles based on technology developed in the King and Baker labs.

This goal remains the same but now follows a more broadly-defined hypothesis that the difficulty in generating a broadly neutralizing immune response to the virus arises not from mimicry of specific host proteins but from a more general similarity in properties of the HIV Env surface to those of host proteins (e.g., the surface of Env is nearly completely covered by glycans, so antibodies against Env often interact with glycan and hence may cross-react with host proteins). To test this hypothesis, the team is testing variants of Env with substitutions that alter residues at which there is strong selective pressure in strains isolated from patients that (1) cannot be explained by computational modeling based on the structure and (2) are not conserved in laboratory virus passaging experiments. To increase the extent to which these NN variants can rescue anergic B cells producing precursors to HIV Nabs that weakly cross-react with self and drive them toward germinal centers, the designed NN immunogens will be displayed with high multivalency on nanoparticles.

In the final year of the grant, the PI team will be pursuing two parallel tracks. Track 1 (King, Moore, Sanders, Ward) focuses on a systematic exploration of the Env antigen-nanoparticle display platform including epitope accessibility of Env trimers on nanoparticles and the relationship between nanoparticle geometry/valency and immunogenicity. Track 2 (Baker, Bloom, Sanders, Goodnow) will focus on the design of NN immunogens as described above.

The work is a collaborative effort between the academic research labs of David Baker, PhD (University of Washington - Seattle), Neil King, PhD (University of Washington – Seattle), Jesse Bloom, PhD (Fred Hutchinson Cancer Research Center), John Moore, PhD (Weill Cornell Medical College), Rogier Sanders (University of Amsterdam), Andrew Ward, PhD (The Scripps Research Institute), and Christopher Goodnow, PhD (Garvan Institute of Medical Research).

Grant at a Glance

Principal Investigator
David Baker, PhD

Grantee Institution
University of Washington, Seattle, USA

Project Title
Testing the Nearest Neighbor Approach to Active Vaccination for HIV-1 bNAbs

OPPID
1111923

Grant Award
Up to $7.5 million, awarded in November, 2014

Collaborating Institutions
- Weill Cornell Medical College, New York, USA
- Academic Medical Center, Amsterdam, The Netherlands
- Duke University, Durham, USA
- The Scripps Research Institute (funded under a separate analytics grant), La Jolla, USA
- Fred Hutchinson Cancer Research Center, Seattle, WA
- Garvan Institute of Medical Research, Darlinghurst, Australia

RESEARCH OBJECTIVES

1.) Systematic investigation of the relationship between particulate antigen presentation and immunogenicity (King, Moore, Sanders, Ward).
   - Computational design of protein nanoparticles (King)
   - Expression, purification and biophysical characterization of SOSIP trimer on protein nanoparticles (King, Ward, Sanders, Moore)
   - *In vitro* antigenicity studies, rabbit immunogenicity studies and serological analysis (Moore, Sanders)

2.) Identification of naïve B cell bNAb precursors using designed NN immunogens (Baker, Bloom, Sanders, Goodnow). Sub efforts include:
   - Computational design and viral fitness studies/deep mutational scanning to identify NN immunogens (Baker/Bloom)
   - Expression and structural validation of NN-mutant trimers and NN-mutant trimers expressed on self-assembling protein nanoparticles. The NN Env mutants will be elected based on the NN design protocol of the Bloom and Baker labs (Sanders)
   - Identify NN Env constructs with conserved epitopes specifically bound to cell surface antibodies carried by circulating B cells present in most healthy people (via multi-color flow cytometry). Each NN immunogen will be tested by two complementary flow cytometric platforms to cover the full range of possible BCR affinities and the likelihood that cross-reactivity with self-antigens will downregulate surface IgM resulting in low binding (Goodnow)