Alter: Signatures of Antibody Responses that Correlate with Protection to Develop Down-Selection Criteria to Guide Vaccine Candidate Selection

OVERVIEW

The goal of this investment is to standardize non-human primate (NHP) assays and to define the non-neutralizing humoral immune correlates of protection from SIV/SHIV infection in NHP vaccine sample sets that have shown a range of protective signals. These results will be used to develop a predictive framework to guide the down-selection of future vaccine candidates that elicit potent non-neutralizing antibody responses.

Since partial protection observed in the RV144 trial was mediated by the induction on non-neutralizing antibodies (nNAbs) and a moderate T cell response, it seems that other immune mechanisms in addition to classical neutralizing antibody responses are required to achieve protection against HIV infection. The functional activity of antibodies extends beyond their variable (Fv) domains. Indeed, the constant domains (Fc) orchestrate a variety of effector functions through the recruitment of an array of innate immune cells. Given that innate immune effector cells are abundantly present at mucosal sites and are armed and prepared to act without the need for prior antigen sensitization, Abs that could recruit these antiviral effectors could provide a robust level of control that could dramatically enhance protection from HIV infection. Non-neutralizing antibodies function in multiple ways, including antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, and antibody-dependent cell-mediated phagocytosis. Several NHP challenge studies support the RV144 findings. Namely, the potential role of Fc-FcγR-mediated innate and adaptive immune functions in HIV-1 protection indicates that the quality rather than the quantity of the antibody response is critical. Therefore, it will be key for HIV-1 vaccine development to understand the Fc-FcγR interaction effector function, including the sequences and functions of the receptors in NHP (which are used readily as a translational HIV/SHIV model).

We have systematically developed high-throughput tools that enable the dissection of humoral immune responses at unprecedented depth. Using these high-throughput 'systems serology' approaches, we have begun to define protective non-neutralizing humoral immune response signatures among vaccinees and naturally infected cohorts. Interestingly, RV144 vaccinees and spontaneous controllers of HIV both elicit polyfunctional Ab responses able to recruit multiple innate immune effector activities, with a critical role for the IgG3 responses and specific antibody glycoprofiles. This points to specific non-neutralizing Ab signatures that may be associated with robust antiviral control if induced with adequate durability.

Grant at a Glance

Principal Investigator
Galit Alter, PhD

Grantee Institution
Ragon Institute of MHG, MIT, and Harvard, USA

Project Title
Signatures of Antibody Responses that Correlate with Protection to Develop Down-Selection Criteria to Guide Vaccine Candidate Selection

OPPID
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Grant Award
Up to $3.1 Million, awarded in November 2014

Collaborating Institutions
◊ Dartmouth College

Ultimately, these studies will (1) define shared and disparate correlates of protection from infection, (2) identify mechanisms of resistance from infection, (3) develop a framework for the down-selection of future vaccine strategies that elicit 'protective humoral signatures,' and (4) develop highly standardized systems to vet novel immunogenicity/protection studies. Together, these findings will lead to the development of a predictive modeling system to identify the most promising new vaccine concepts that warrant accelerated development to clinical testing.

Galit Alter (Ragon Institute) is the principal investigator for this grant. The effort includes extensive collaborative interactions with the laboratories of Margaret Ackerman and Chris Bailey Kellogg (Dartmouth College).

RESEARCH OBJECTIVES

1.) Standardization of Fc effector profiling assays for NHP (including the multiplexed Fc effector array).

2.) Testing of NHP samples to define the signatures of protective immunity against SIV/SHIV infection.

3.) Development and validation of a predictive model by testing samples from emerging NHP efficacy and immunogenicity studies.

4.) Enhancement of the capacity for standardized, high-throughput analyses of vaccine-induced humoral immune profiles, including the establishment of a GCLP laboratory environment.