Ackerman/Alter: Leveraging Antibody Effector Function

OVERVIEW

Neutralizing antibodies are the holy grail of HIV vaccine development but attempts to elicit them with vaccines have yielded little in the way of success. The field is gradually opening up to a broader view, with more attention paid to antibodies that protect by mechanisms other than neutralization. The successes of the RV144 trial and non-human primate (NHP) studies of passively transferred antibodies have provided new enthusiasm for the extra-neutralizing antiviral properties of antibodies.

Two obstacles are encountered in attempting to monitor and improve upon these non-traditional effector functions of antibodies elicited by new vaccine regimens. First, the methods currently used to determine the innate immune-recruiting properties of antibodies are not compatible with the scale and standardization of analysis necessary to properly evaluate the potential role of this mechanism of protection in pre-clinical and clinical vaccine trials. Second, the signals responsible for driving B cells to produce potent innate immune-recruiting antibodies are not known. New technologies coupled to a better understanding of underlying signals that induce these types of immune responses are critically needed to improve upon the current vaccine approaches.

The consortium led by Drs. Margaret Ackerman of Thayer School of Engineering at Dartmouth and Galit Alter of Massachusetts General Hospital seeks to define, induce, and evaluate protection afforded by potent innate immune-recruiting antibodies. These are antibodies that form a bridge between the adaptive and innate immune systems. This may be particularly important in the case of HIV, where a narrow window of time soon after the virus enters the body may represent the best opportunity to prevent infection. Innate effector mechanisms are designed in part to contain pathogens until the adaptive immune system can respond, and this proposal will attempt to harness the capacity of antibodies to recruit innate immunity in the crucial early days following HIV transmission.

These studies will develop enabling technology for monitoring of Ab effector functions, as well as define the signals required to induce such protective Abs in vivo, providing new approaches aimed at harnessing the antiviral activity of the Ab-Fc domain to provide sterilizing protection from HIV infection.

Grant at a Glance

Principal Investigator
Margaret Ackerman, PhD
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Grantee Institution
Massachusetts General Hospital, Boston, USA

Project Title
High-throughput Technology for Assessing Antibody Effector Function

OPPID
1032817

Grant Award
Up to $8 Million, awarded in October, 2011

Collaborating Institutions
◊ Beth Israel Deaconess Medical Center

RESEARCH OBJECTIVES

1.) To develop a high-throughput proteomic-based microarray approach to quantify the spectrum of innate immune-recruiting antibody effector functions.

2.) To develop a high-throughput in vitro system to define the innate immune inflammatory signals required for the induction of innate immune-recruiting antibody effector functions.

3.) To develop a robust computational prediction model and scoring system to apply to microarray output.

4.) To apply the proteomic microarray and in vitro screening system to define the top innate immune signals that result in the induction of the most potent innate immune-recruiting antibody functions.

5.) To define whether in vitro innate immune signals coupled to gp140 clade C trimers induce innate immune-recruiting antibodies in vivo, and to define their protective efficacy in a SHIV challenge model.

6.) To determine if specific stimulatory signals can durably programmed antibody glycosylation and if antibody glycosylation can be recalled following subsequent antigenic exposure.

PROGRESS

The goal of the Ackerman/Alter CAVD is to define, induce, and evaluate protection afforded by potent innate immune-recruiting antibodies through the development of (a) robust, high-throughput array technology to predict Fc-effector function and (b) an in vitro–screening approach to define the signals in B cells that result in the targeted production of innate immune–recruiting antibodies. Objectives 1 and 3 have generated a remarkable platform to define the spectrum of biophysical antibody features that reliably predict specific effector functions. This platform now provides a comprehensive set of standardized (and some qualified) tools that objectively and deeply interrogate the polyclonal humoral immune response following infection and/or vaccination in both humans and non-human primates. Moreover, linked to unsupervised and supervised systems level machine learning analyses, vaccine profiles and correlates analyses can be defined for HIV and beyond.

In parallel, in Objective 2, we developed a robust in vitro B cell-screening approach, using single cell RNA sequencing and ATAC sequencing, to specifically define the molecular programs that control Fc-effector function. Specifically, a set of innate immune inflammatory signals have been identified that specifically and selectively skew antibody function via glycosylation. Through studies performed in vitro, in mice, and in non-human primates, it has become clear that adjuvants can selectively skew Fc-antibody profiles. Interestingly, profound shifts towards highly cytolytic, low-fucosylated glycans were observed with viral TLR agonists including TLR7/8/9, whereas more phagocytic antibodies were observed with bacterial TLR agonists including TLR2/4/5. These data point to the evolutionary programming of distinct effector functions based on pathogen-type. However, how these particular adjuvants mediate these differences and/or how vaccine-regimens may be customized to drive enhanced protective functional antibody profiles remains unknown. Thus in the final phase of this grant, we propose to take 2 of our most potent adjuvants: a bacterial and a viral adjuvant and examine their capacity to: 1) induce potent and distinct functional antibody profiles, 2) program long-lived functional B cell responses, and 3) provide protection from SHIV challenge in NHPs through distinct functional mechanisms. This experiment will test the hypothesis whether ADCC or phagocytic antibodies provide enhanced protection from SHIV infection and will provide the first proof-of-concept that vaccines may selectively program long-lived innate immune– recruiting antibody activity that may prevent SHIV infection.