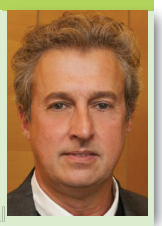
OVERVIEW

Transgenic mice expressing human immunoglobulin genes encoding inferred germline precursors to known broadly neutralizing antibodies (bNAbs) will be used to evaluate the ability of novel HIV immunogens to elicit protective immune responses. The premise of vaccine strategies to induce bNAbs in humans is the determination that a small percentage of HIV-infected patients naturally produce high titers of bNAbs capable of neutralizing several strains of HIV. These bNAbs also protect macaques against simian/human immunodeficiency virus (SHIV) when used for passive immunization prior to challenge. These observations suggest that engineered immunogens against specific HIV epitopes could potentially stimulate the generation of bNAbs in the HIV-free human population for protection against HIV infection. However, at present, testing of immunogens on human subjects is both impractical and unsafe. Therefore, to drive HIV vaccine development, animal studies using sophisticated knock-in (KI) mouse models are essential in order to determine: (i) how B cell precursors corresponding to the most promising bNAbs respond to various HIV immunogens; (ii) whether these B cell precursors mature into B cells with desirable qualities, such as adequate somatic hypermutation; and (iii) whether these immunogens induce a rapid and robust memory response capable of neutralizing a wide number of HIV strains. Our laboratory has developed a highly efficient technique for generating such KI mouse models using a one-step CRISPR/Cas9-induced homology-directed recombination approach, via direct injection of a donor plasmid, guide RNA, and Cas9 protein into mouse oocytes. The goal of this grant is to (i) use germline-targeting KI mouse models to determine whether a given immunogen will be able to bind to precursor B cells and elicit a desired immune response (thereby making the immunogen a viable clinical trial vaccine candidate); and (ii) use KI models to advance the clinical testing of eOD-GT8 and BG505.SOSIP-derived (GT1.1 and GT1.2) germline-targeting immunogens.

The work includes ad hoc collaborations with the academic research labs of Rogier Sanders, Ph.D. (University of Amsterdam and Weill Cornell Medical College, New York), William Schief, Ph.D. (The Scripps Research Institute, La Jolla), and Fred Alt, Ph.D. (Children's Hospital, Boston).

Grant at a Glance



Principal Investigator
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Grantee Institution
Massachusetts General Hospital Corporation – Ragon Institute of MGH, MIT, and Harvard (Cambridge, MA) USA

Project Title
Accelerating Vaccine Design through Interrogation of Physiologically Relevant Mouse Modelsr

OPPID
1185467

Grant Award
Up to $2.9 Million, awarded in February 2018

RESEARCH OBJECTIVES

1.) Generation of new KI mouse models bearing human germline-reverted sequences of three heavy chain and three light chain bNAb sequences. Sub-efforts include:

- ◊ Perform immunocharacterization experiments on KI mice
- ◊ Immunization of KI mice using eOD-GT8 and BG505.SOSIP-derived immunogens

2.) Assess the potential of human Ig precursors to mature into bNAbs in KI mice by rigorously testing the effects of antigen design, dose, timing, adjuvant, and whether sequential or combinatorial challenge with immunogens results in the best immune outcome.

3.) Test the capacity of verified immunogens to stimulate B cell responses in vivo by immunizing KI mice. Sub-efforts include:

- ◊ Before antigen challenge, the B cell development and maturation of KI mice will be compared with wild-type mice by examining key B cell markers
- ◊ Conduct similar immunization experiments in wild-type mice into which low numbers of KI B cells will be adoptively transferred prior to immunization
- ◊ Examine the functionality of antibodies that are produced upon immunogen stimulation