Jolicoeur: A new class of immunogens for raising broadly neutralizing antibodies

OVERVIEW

This grant is based on the hypothesis that it should be possible to exploit anti-idiotype monoclonal antibodies (mAbs) as a tool to obtain mirror image representations of the HIV-1 Env neutralizing paratopes on anti-Env broadly neutralizing Abs (bnAbs), and then to use these anti-idiotypic Abs as immunogens. Such an anti-idiotypic Abs should mimic the Env conserved region targeted by the cognate anti-Env bnAb and, when used for immunization would be expected to generate a bnAb against HIV-1 Env in a single step. This approach could overcome the long maturation process and other problems when Env is used as an immunogen. The application originated from the Foundation's Grand Challenges program.

The program will generate anti-idiotypic Abs in llama immunized with anti-Env bnAbs. The choice of llama was based on the unique class of natural antibodies found in camelids. These antibodies have no light chain and are made of a single heavy chain whose short variable domain, designated VHH, is sufficient for antigenic recognition. VHH are very small and are capable of penetrating into small pockets of molecules, thus enhancing the chance to recognize the paratope 3D structure of the human anti-Env bnAb.

Anti-idiotypic llama VHH Ab will first be screened for the capacity to inhibit the neutralization of their cognate bnAb. For this initial screen, the program will take advantage of robust, established methods to generate libraries of VHH cDNA clones using RNA from PBMCs harvested from bnAb vaccinated animals. The cDNA clones are constructed in a GST expression context, with the VHH-GST protein readily produced in a semi-automated manner for ensuing assessment in a standardized in vitro neutralization competition assay against their cognate bnAb. VHH proteins passing this first screen will then be assessed for function in vivo (i.e. for their capacity as immunogen to generate anti-HIV neutralizing antibodies). For this latter stage, mice and guinea pigs will be immunized with anti-idiotypic VHH mAb proteins to generate anti-HIV bnAbs. Overall, the approach apprehends a broad diversity in the VHH libraries and funnels the anti-idiotype antibodies through a stringent screen.

Grant at a Glance

Principal Investigator
Paul Jolicoeur, MD, PhD

Grantee Institution
Institut de Recherches Cliniques de Montréal, Montréal, Québec CA

Project Title
Development of a new class of immunogens for raising broadly neutralizing antibodies

OPPID
1146356

Grant Award
Up to $698,000, awarded in May 2016

The program is led by Paul Jolicoeur, MD, PhD at the Institut de Recherches Cliniques de Montréal, an affiliate of the Université de Montréal. The award was made in May 2016 with an estimated duration of 23 months.

RESEARCH OBJECTIVES

1.) Generating cDNA libraries of VHH clones, and producing VHH proteins from two cDNA libraries.

2.) Screening VHH candidates capable of competing the neutralizing activity of their cognate bnAb *in vitro*.

3.) *In vivo* screening of pre-selected VHH candidates for their capacity to elicit an anti-HIV nAb activity.