Moore: Next generation BG505 SOSIP.664-trimer based lineage HIV vaccines

OVERVIEW

The central goal of the application is to facilitate the development of trimer-based immunogens that are being designed and developed to induce broadly neutralizing antibodies (bNAbs). Recent results from passive antibody transfer studies indicate that virus neutralization assays yield a reasonable measure of a protective response. Our goal, then, is to generate appropriate titers of serum antibodies in vivo that are capable of neutralizing relatively resistant (Tier 2 and 3) viruses in vitro. We believe that the native pre-fusion conformation of the Env trimer is a suitable basis for a vaccine intended to induce bNAbs, particularly now that we and other groups have generated high-resolution structural data to guide the design of trimer immunogens. Native trimers are unique in presenting almost all bNAb epitopes, and do so in an appropriate quaternary context.

We will at present restrict our program to the SOSIP configuration of recombinant trimers that we developed and are highly familiar with, and that we and others have characterized extensively to demonstrate their excellent mimicry of native Env. We are now able to make multiple native-like SOSIP.664 trimers from clades A, B and C, as well as A/C hybrids, by combining protein-engineering techniques with bNAb-purification columns that allow isolation of native structures. We are also using structure-guided design techniques to create improvements to existing trimers, as well as to generate new ones. For example, our overall understanding of structure-function relationships within the trimer has advanced such that we are capable of making native trimers from most env sequences. Thus, we are acquiring the ability to design a large number of hypothesis-based immunization experiments involving multiple variants of native-like SOSIP trimers.

To advance the aforementioned immunization experiments, we have made four different GMP-grade CHO cell lines that express SOSIP.664 trimers of various designs, using a GMP facility available at the Weill Cornell Medical College (WCMC). The lines express next-generation variants of SOSIP.664 trimers that are designed to increase the probability of inducing bNAbs when used as immunogens. Cell lines can be appropriately banked for future GMP production, as well as used for non-GMP, pre-clinical studies of the produced trimers at WCMC and/or the Academic Medical Center (AMC). We will also conduct immunogenicity studies in rabbits and macaques, the goal being to assess which trimers are best suited to the goals of inducing bNAbs by Env vaccination. Those studies will include experiments with the germline targeting GT1.1 trimer developed at the Academic Medical Center (AMC), Amsterdam. This trimer is now in the GMP development program, after the appropriate CHO cell line was made at WCM in this project.

This grant is a collaborative effort led by John Moore, PhD (Weill Cornell Medical College) with the participation of Rogier Sanders (University of Amsterdam) Bali Pulendran (Stanford University) and Francois Villinger (University of Louisiana). The award was received in July, 2015 with an initial agreement length of 2 years.

RESEARCH OBJECTIVES

1.) Develop GMP-grade CHO cell lines expressing SOSIP.664 trimers, down-selected to a choice of four cell lines.

2.) Implement rabbit and macaque studies of next-generation SOSIP.664 trimers.

Grant at a Glance

Principal Investigator
John Moore, PhD

Grantee Institution
Weill Cornell Medical College, New York, USA

Project Title
Next generation BG505 SOSIP.664-trimer based lineage HIV vaccines

OPPID
1132237

Grant Award
Up to $8,723,473, awarded July, 2015

Collaborating Institutions

- Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands
- Kymab Ltd, Cambridge, UK (funded under separate contract)