Pantaleo: Optimization of the LN02 Anti-HIV Broadly Neutralizing Antibody

OVERVIEW

This grant will be used to improve the potency and breadth of LN02-derived antibodies, while maintaining or improving properties such as stability and production yield that will facilitate their preclinical and clinical evaluation. We recently identified several broadly neutralizing antibodies (bNAbs) targeting HIV 1 Env that were isolated using sorted lymph node B cells from viremic HIV-1-infected donors. LN02 is one of the most advanced bNAbs from this effort; it has both potent and broadly neutralizing activity against a diverse panel of ~200 Tier 1 and Tier 2 viruses. However, there remains a need to improve the potency and breadth of this bNAb to facilitate its advancement for preclinical and clinical evaluation.

Under this award, LN02 will undergo mutational optimization to improve its neutralization potency and to identify antibody variants with properties consistent with a clinical development candidate. Site-directed mutagenesis will be performed on the heavy and light chain CDR regions of LN02. Five separate rounds of mutational analysis will focus on individual mutations and/or mutation combinations that generate improved potency, increased breadth, and other desirable drug-like properties. A streamlined decision tree will eliminate unsuitable variants, and through this iterative process it is anticipated that >220 LN02 Ab variants will be produced and tested.

Primary investments will be limited to the following: 1) generation of bNAb mutations; 2) Ab production and purification; 3) Ab characterization and Env-binding analyses; 4) bNAb profiling against a panel of viruses in neutralization assays; and 5) structural studies and modeling to predict substitutions leading to improved Ab properties and potency. Structural studies of LN02 in complex with an Env trimer could provide binding insights that will help in the design of bNAb variants with improved neutralization breadth.

A comprehensive characterization strategy is planned for bNAb development candidates. Production yields, preliminary stability, biophysical properties, and polyreactivity will be tested. This enhanced characterization will ensure that efforts focus on bNAbs with clinical development potential. From this characterization, one or two LN02-derived candidates will be tested for neutralization activity against a global panel of 200 Tier 1 and Tier 2 viruses. Profiling each candidate's in vivo pharmacokinetics using huFcRn transgenic mice will also occur.

Grant at a Glance

Principal Investigator
Giuseppe Pantaleo, MD

Grantee Institution
Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Project Title
Optimization of the LN02 Anti-HIV Broadly Neutralizing Antibody

OPPID
OPP1190237

Grant Award
Up to $749,000 awarded in April 2018

Collaborating Institutions
- Institute for Research in Biomedicine, Bellinzona, Switzerland
- Institut de Biologie Structurale Grenoble, France

The grant is led by Giuseppe Pantaleo at Centre Hospitalier Universitaire Vaudois, Lausanne. Partner investigators include Dr. Antonio Lanzavecchia (Institute for Research in Biomedicine, Bellinzona) and Dr. Winfried Weissenhorn (Institut de Biologie Structurale, Grenoble). Dr. Lanzavecchia will design, produce, and test antibodies to improve affinity and breadth. Dr. Weissenhorn will characterize the structure of LN02 in complex with a native Env trimer to help with the selection of mutational variants.

RESEARCH OBJECTIVES

1.) Generate LN02 variants with a minimum 5-fold improvement in neutralizing activity (median IC50 of <0.02 μg/ml and IC80 <0.08 μg/ml).

2.) Improve the overall breadth of LN02 variants.

3.) Achieve production yields >50 mg/L.

4.) Show polyreactivity consistent with bNAbs already advanced to the clinic.

5.) Demonstrate adequate or improved Ab stability.