Pantaleo: Generation/Isolation of Novel bnAbs from Lymph Node B cells

OVERVIEW

Generation of potent broad neutralizing antibodies (bnAbs) occurs only in a minority (<5%) of HIV infected subjects. The mechanisms preventing the generation of bnAbs remain mostly unknown. Recent advances in the development of methods for supporting proliferation and differentiation of single Env-specific B-cells have led to the isolation of potent bnAbs targeting different regions of HIV envelope. The currently available bnAbs have been derived from cloning memory B cells isolated from the blood, however it is unknown whether circu- lating B cells are quantitatively and qualitatively reflective of the overall B cell repertoire. Studies of the B cell repertoire in humans have been limited to blood B cells and no information is available on the B cell repertoire in B cells isolated from lymphoid tissues. The differences in the composition of B cell populations isolated from blood and lymph nodes (LNs) in humans are substantial. In particular, the germinal center (GC) B cell population is virtually absent in blood. The study of this population may be particularly relevant in HIV infection since >50% of total B cells in LNs of viremic subjects are composed of GC B cells. It is also highly likely that GC B cells are the precursors of memory B cells and/or plasma cells producing the type of antibodies with features typical of bnAbs, i.e. marked somatic hypermutation or long CDR H3.

The analysis of Env-specific B cells isolated from LNs will allow us to address a series of unresolved questions regarding the generation of bnAbs. These include:

a.) The frequency of Env-specific B cells in blood and LNs,

b.) The distribution/enrichment of Env-specific B cells within the different B cell populations in blood and LNs,

c.) The identification of the B cell population enriched in precursors of B cells producing bnAbs,

d.) The diversity of the B cell repertoire of Env-specific B cells,

e.) Block in the maturation of the B cells producing bnAbs and

f.) Defective retention for B cells producing high affinity antibodies. If the central hypothesis of the proposed research project is correct and the frequency of B cells producing bnAbs is much higher in LN as compared to the blood and the quality of B cells (GC B cells) is crucial, the isolation and cloning of LN B cells will lead to more efficient generation of novel bnAbs.

Based on the initial results, Pantaleo/CHUV was awarded with the 2nd award focusing on the optimization of the LN02 bNabs.

RESEARCH OBJECTIVES

The overall primary goal of the project is to generate novel broadly neutralizing antibodies. The specific objectives include:

1.) Isolation and characterization of novel bnAbs from lymph nodes B-cells

2.) Determination if generation of rare bnAbs is due to a block of B cell maturation or defective retention of B-cell producing high affinity antibody

3.) Development of a computational framework to analyze the phenotype, function, signaling, gene expression profile of different B cell populations and B cell repertoire in lymph node B cells, the functional profile of Tfh cells and their association with bnAbs production

4.) Improve the potency and breadth of LN02 and facilitate the advancement for preclinical and clinical evaluation

PROGRESS

Major advances have been made in all the different areas of the project and include:

1.) Identified two lead candidates LN01 (an MPER antibody) and LN02 (an gp120-gp41 interface Ab), both demonstrating great neutralization potency in terms of breadth and magnitude;

2.) Demonstration that the frequency of HIV-specific B cells is significantly higher in lymph nodes and particularly in germinal centers B cells;

3.) Identification of distinct phenotypic and functional profiles in lymph nodes versus blood B cells;

4.) Identification of unique phenotypic and functional profiles of Tfh and B cells associated with HIV infection.

Grant at a Glance

Principal Investigator
Giuseppe Pantaleo, MD

Grantee Institution
Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Project Title
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OPPID
OPP1114725

Grant Award
Up to $4.3 million, awarded in November, 2014

Collaborating Institutions
- ◊ Institute for Research in Biomedicine, Bellinzona, CH
- ◊ Fred Hutchinson Cancer Research Center, Seattle, USA
- ◊ University of Regensburg, Regensburg, DE
- ◊ Sacco Hospital – University of Milan, Milan, IT

Funded under separate contract:
- ◊ Atreca, Redwood City, USA