Walker: Implications for vaccine design from T and B cell mechanisms of HIV control

OVERVIEW

Efforts under this grant will characterize the ontogeny and immunologic signatures of neutralization breadth in unique cohorts of HIV infected persons, thematic elements initiated under a prior CAVD award. One of the main outcomes from this branch of the program will be the identification and characterization of new bnAbs in HIV controllers, for potential clinical development. A secondary objective for this new grant is to define the phenotype, specificity, and function of early T and B cell responses generated in peripheral blood and lymph nodes following early treatment in acute infection.

For bnAb discovery, the program will make use of the HIV Controllers cohort, individuals who maintain viral loads of less than 2000 RNA copies/ml plasma without the need for combination antiretroviral therapy (cART). The HIV Controllers cohort was used to previously identify 3BNC117, a broad and potent CD4-binding site bnAb where proof of concept studies have established clinical anti-viral activity. In collaboration with the CAVIMC, the neutralization breadth has already been characterized in over 600 HIV controllers, and the ongoing work will define the antibody repertoires generated in those with the most potent neutralization breadth. The latter effort includes the expression of a refined set of B cell receptors (BCR) selected from the 17,000 BCRs already sequenced from this controller cohort. Selection of this set will use an evolutionary profiling analytical algorithm developed by Tom Kepler. In addition, next-generation native-like trimers that omit binding of non-neutralizing antibodies (e.g. SOSIP, fold-on trimer, etc.) will be used to pull out additional rare, memory B cells from samples of the top broadly neutralizing controllers, utilizing multiple tissues, including lymph nodes and bone marrow.

Under the secondary objective, investigations will endeavor to define the phenotype, specificity, and function of early T and B cell responses generated in peripheral blood and lymph nodes following early treatment in acute infection. By focusing on this period of infection before peak viremia, and by initiating immediate therapy in these persons, it will be possible to define the phenotype, function and specificity of the earliest T and B cell responses that occur in blood and lymph nodes in the absence of ongoing viremia, CD4+ T cell depletion and T cell exhaustion. This research component will engage the FRESH cohort (“Females Rising through Education, Support and Health”, Umzali Township, Durban, see https://youtu.be/D8SY98CZiYY), a cohort of South African women identified at the time of “hyperacute infection”, defined as the period from first detectable viremia to peak viremia.

Grant at a Glance

Principal Investigator
Bruce Walker, MD

Grantee Institution
Massachusetts General Hospital, Boston, USA

Project Title
Identification of new bNAbs in Elite Controllers and implications of early ARV on acute infection in a clade C cohort

OPPID
1146433

Grant Award
Up to $4.8 million, awarded in June 2016

Collaborating Institutions
- KwaZulu Natal Research Institute for TB and HIV, Durban ZA
- The Doris Duke Medical Research Institute, Durban ZA

Grant Leadership
The grant is led by Bruce Walker, MD at the Massachusetts General Hospital. The investigative team includes participants from the Ragon Institute of MGH, MIT and Harvard, from the Doris Duke Medical Research Institute, and the Africa Health Research Institute (AHRI, formerly K-RITH). The work will include extensive engagement of the CAVIMC for viral neutralization assays, and BCR characterization will be performed in collaboration via Atreca, to be secured via the GH-VAP. The award was made in June 2016 with an anticipated duration of 24 months, and is now in a no-cost extension.

RESEARCH OBJECTIVES

1.) To identify and clone novel broadly neutralizing antibodies (bNAbs) of unique specificity in HIV controllers for clinical development.

2.) To define the phenotype, specificity and function of the earliest T and B cell responses generated in the peripheral blood and in lymph nodes following treatment-limited antigen exposure in acute HIV infection.