Walker: bNAbs After Infection and Immunization

OVERVIEW

The development of a safe and effective HIV vaccine is the final missing piece in the complex puzzle of how to attain affordable, durable control of the HIV/AIDS pandemic. At present there are promising leads, but no clear and unequivocal path, to the development of an HIV vaccine. It is likely that the field will have to overcome the key challenge of eliciting a broad neutralizing antibody response in the majority of vaccinated individuals, but so far, candidate HIV vaccines have not elicited any significant levels of broadly neutralizing antibodies (bNAbs). This grant directly addresses the neutralizing antibody problem using innovative technology that may be transformative in the quest for an HIV vaccine.

By stepping back from the problem and taking a comprehensive and unbiased look at how broad neutralizing activity arises in the approximately 25% of HIV-infected individuals who do develop it, this grant proposes to efficiently learn the circumstances under which bNAbs are elicited, and, correspondingly, what vaccines need to do to elicit them. The project will be anchored by technology developed by Atreca, Inc., which represents a powerful, high-throughput, unbiased approach to understanding the antibody response to infection and vaccination. The earliest B-cell responses in HIV infection, including those active just before infection, will be studied and followed prospectively for up to three years in human volunteers who face an exceptionally high rate of HIV infection in KwaZulu-NatalZN, South Africa, along with other cohorts with more immediately available samples. The study in South Africa (called “FRESH”) will be unique in its capacity to enroll and follow volunteers twice-weekly with a finger-stick blood sample, permitting ascertainment of HIV infection as soon as any trace of the virus is detectable in the bloodstream. Evaluation of the status of the B-cell response before infection, during the first days and weeks of infection, and for the next 2-3 years will be enabled, and the follow-up period will allow identification of those who do and do not go on to develop broad neutralizing activity. For this work the researchers have defined broad neutralizing activity as a continuum, ranging from neutralization of only the infecting virus strain (called autologous neutralization) at one end, and equivalent to the very best broadly neutralizing antibodies (bNAbs) at the other, in order to capture all stages of bNAb development. Moreover, the study will include a broader assessment of innate and adaptive immunity, building up a complex of immune data that will provide important context for understanding the factors that support bNAb development. It represents a significant step away from a purely empirical approach to HIV vaccines.

This consortium is led by Bruce Walker, a leading HIV researcher who excels at assembling informative cohorts for studies of immune protection against HIV. A team of investigators from the Ragon Institute of MGH, MIT, and Harvard, will join with investigators from the University of KwaZulu- Natal (SA) and Atreca, to conduct different aspects of the study.

Grant at a Glance

Principal Investigator
Bruce Walker, MD

Grantee Institution
Massachusetts General Hospital, Boston, USA

Project Title
Development of broadly neutralizing antibodies in HIV infection and following immunization

OPPID
1066973

Grant Award
Up to $12.9 Million, awarded in November, 2012

Collaborating Institutions
- ◊ Atreca, USA
- ◊ Jessen-Jessen Medical Practice, Germany
- ◊ University of KwaZulu-Natal, South Africa
- ◊ Umkhuseli Innovation and Research Management

RESEARCH OBJECTIVES

1.) To collect longitudinal samples from individuals with acute HIV-1 infection to investigate the development of broad neutralizing responses

2.) To define the B-cell signatures associated with the induction of HIV-specific neutralizing antibodies using the Atreca technology and other measures of B-cell development and maturation

3.) To define the HIV-specific CD4+ T-cell responses and their relationship to the establishment of broad neutralizing responses

4.) To identify transcriptional signatures of HIV-specific broad neutralizing activity using a systems biology approach applied to relevant cell subsets of the immune system

5.) To obtain large volume blood samples for characterizing the parameters associated with breadth of neutralizing antibodies in HIV controllers with different degrees of antigen load and diversity, and with relatively good preservation of immune function

PROGRESS

The FRESH Cohort (Females Rising through Education, Support and Health) of women at high risk for HIV infection was established in KwaZulu-Natal Province, South Africa, where infection rates of around 9% per year have been documented. The study was originally intended to follow persons with untreated infection, but soon after the study was initiated evidence suggested that early treatment with antiretroviral therapy could improve outcomes. Prior to changes in the South African treatment policies we were given permission to initiate therapy at the initial diagnosis of infection, allowing us to implement therapy before peak viremia. The clinic site is at a shopping mall where each participant is seen twice weekly and given classes designed to empower them by teaching life skills, job skills, and help with obtaining a high school degree. Each time the participants come in they also have a finger prick blood draw looking for acute HIV infection and pre and post-infection blood samples are being obtained for studies of the ontogeny of neutralizing antibodies. The seroconversion rate remained approximately 8% per year, and new infections continue to occure despite implemental of PrEP.

Studies of the earliest immune responses induced, prior to peak viremia, and longitudinal responses in these have been conducted. The immunology studies are being done at the Doris Duke Medical Research Center in Durban, as well as the adjacent Africa Health Research Institute (AHRI, formerly KwaZulu-Natal Research Institute for TB and HIV (K-RITH)). Because of the implementation of ART, we are not able to follow the development of broadly neutralizing antibodies, but instead have turned our attention to assessing the impact of limited antigen exposure on the development of adaptive cellular and humoral immune responses.

Longitudinal and cross-sectional studies of the CD4 T cell and B cell signatures associated with the development of broadly neutralizing antibodies

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have been performed in the HIV Controller cohort, and cell subsets have been isolated for evaluation of transcriptional signatures of HIV specific broadly neutralizing antibodies. The BCR repertoire of both antigen-specific memory B cells and plasmablasts has already been generated by Atreca on eight spontaneous controllers who exhibit broad neutralizing antibody responses. More than 2500 sequences have now been collected, and phylogenetic tress have been constructed per individual as well as for the whole cohort. Preliminary studies on 16 monoclonal antibodies generated from the first three sequenced subjects showed antigen specificity and neutralizing capacity. Seventy antibodies have now been selected from the second batch of five controllers, based on high levels of somatic hypermutation and long CDRH3 lengths, to maximize the likelihood of selecting antibodies with potent antiviral activity. Interestingly, unique patterns of clonal diversification are observable among all sequenced subjects; however, massive diversification of single clonal families appears to be a hallmark of the most potent neutralizers. Additional analyses using sophisticated computational approaches developed by Atreca are underway to gain deeper insights into the pathways and mechanisms by which neutralizing B cell responses are selected.