Überla: Antibodies without HIV T helper cells

OVERVIEW

The HIV vaccine field has shifted over the years from focusing on vaccines that primarily induce neutralizing antibodies to those focusing on T cell responses (i.e. Merck STEP trial) to ones that attempt to elicit both humoral and cellular immune responses. The failed Merck T-cell vaccine was both disappointing and surprising in that not only did the vaccine fail to protect but an ad hoc analysis showed that there was an increase in the risk of acquisition of infection in some subjects. The favored hypothesis is that the vaccine may have increased the risk of acquisition of infection in some individuals by increasing the number of HIV specific activated CD4 T cells, which are the target of HIV replication, at the time of natural infection or during the early stages of viral infection in the face of non-sterilizing immunity. Understanding the mechanism(s) of increased risk of infection in the STEP study is of the utmost importance as several new HIV vaccine candidates are presently moving into the clinic in the form of “adeno vector prime/boost” vaccines. Identifying approaches that avoid the issues observed in the STEP trail has the potential to significantly impact vaccine design.

The experimental vaccine proposed by Dr. Klaus Überla from University Hospital Erlangen employs a prime/boost strategy of vaccination - Ad5 expressing a heterologous (non-HIV or non-SIV in the case of a SIV or SHIV challenge model) retroviral Gag (intrastructural) antigen to prime CD4 T cells followed by boosting with the same heterologous Gag protein encapsulated in an Env virus like particle (VLP). Since the Gag proteins in the VLP are not physically linked to Env it is expected that the native Env structure is preserved. Immunization against the non-HIV Gag proteins provided heterologous “intra-structural” T cell help for Env-specific antibody responses improving the magnitude and the quality of anti-Env antibodies in mice. Non-human primate studies will reveal, whether avoiding HIV specific CD4 T cells that may have contributed to the findings of the STEP trial indeed improve vaccine efficacy.

These experiments will generate information that addresses two key issues in HIV vaccinology: 1) does boosting HIV specific CD4 T helper cell responses required for producing protective antibodies detract from vaccine efficacy and 2) what immunological parameters are associated with the risk of acquisition of infection observed after immunization in humans with an adenoviral vector 5 (Ad5) non-structural protein T cell vaccine (STEP trial). The outcome of this work will be to inform more rational HIV vaccine design.

The studies will be performed at Virology Institute of the University Hospital Erlangen in close collaboration with Dr. Christiane Stahl-Hennig´s team from the German Primate Center.

RESEARCH OBJECTIVES

1.) Induce affinity-matured antibodies to the Env trimer by recruitment of T-helper cells specific for heterologous vaccine antigens

2.) Assess the efficacy of the heterologous intra-structural help vaccine in a low dose NHP challenge model

3.) Characterize the type of vaccine-induced immune responses that are associated with enhanced acquisition of infection

Grant at a Glance

Principal Investigator
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Grantee Institution
University Hospital Erlangen, Germany

Project Title
Induction of affinity matured HIV Env antibodies in the absence of HIV specific T helper cells

OPPID
1040727

Grant Award
Up to $2.4 Million, awarded September, 2012

Collaborating Institutions
◊ German Primate Center, Göttingen, DE