Update on Progress in HIV Vaccine Development

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The 19th Conference on Retroviruses and Opportunistic Infections heralded the arrival of a new crop of potent, broadly neutralizing antibodies against HIV. This advance has given the entire vaccine field enormous hope that it will be possible one day to develop an antibody-based vaccine for HIV. However, substantial obstacles still exist in the induction of these antibodies by vaccination, given the enormous number of somatic mutations needed to develop these highly efficient antibodies. It is likely that follicular helper T cells will be involved in the development of these antibodies, and this will be a key area of interest in the future. Cellular immune responses will also be an important part of any vaccine regimen. Evidence showed that protection provided by an attenuated vaccine correlated with the frequency of vaccine-induced helper cells and killer cells, underlining the importance of these key immune cells. An alternative approach to the development of potent neutralizing antibodies was presented as part of an update on the Thai Phase III Vaccine Trial RV144. Data were shown suggesting that binding antibodies may play a role in protection from HIV infection.

Neutralizing Antibodies and the Structure of the Envelope Glycoprotein

Burton opened the conference with his delivery of the 17th Bernard Fields lecture, in which he gave a tongue-in-cheek discussion of the state of the development of an antibody-based vaccine (Abstract 15). He used a Tootsie Pop as an example of the envelope spike. To get to the chocolate inside the candy, one has to get through a sugar coating. He used the tongues of several British scientists to demonstrate how a neutralizing antibody might bind to the envelope spike and access the chocolate. Though unorthodox, the demonstration was unquestionably tasteful.

Burton then showed his more serious side with models of the trimeric gp120 structure and its glycan shield. Because of the enormous diversity of the envelope protein, the task of making an antibody-based vaccine will be difficult. However, there have been encouraging developments in the definition of new broadly neutralizing, potent monoclonal antibodies, and Burton showed that we now have a new series of such antibodies. These will be useful tools for understanding the targets of effective neutralizing antibodies and for providing proof that it is possible to make a potent, broadly neutralizing antibody against HIV. However, enormous hurdles still need to be surmounted in the area of inducing such antibodies by vaccination. Most of these neutralizing antibodies have undergone considerable somatic mutation to arrive at the final potent effector molecules. Determining how a vaccine regimen will induce this still remains the holy grail of HIV vaccine development. Sodroski presented new data from single-particle cryoelectron microscopy to further elucidate the prefusion structure of the trimeric HIV envelope glycoprotein (Abstract 76).

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The Emerging Importance of Helper T Cells

Renewed interest in the antibody response to HIV has spawned several new studies of the helper-cell subset that is thought to be crucial in the development of these responses: follicular helper T cells. Koup's group presented preliminary data on the description of this cell type in macaques (Abstract 42). This was followed by a parallel presentation describing these cells in humans by Streeck's group (Abstract 43). Ranasinghe (from Streeck's group) also presented interesting data related to the role of major histocompatibility complex (MHC) class II molecules in viral suppression in humans (Abstract 44). After extensive mapping of the targets of CD4+ cell responses in humans, the group's studies revealed that numerous MHC class II molecules could bind several different HIV-derived peptides. Interestingly, the MHC class II molecules that bound the most HIV-derived peptides were correlated with lower plasma HIV RNA levels. This interesting observation suggests that MHC class II-restricted CD4+ cell responses may play a crucial role in controlling viral replication.

Clues from the Attenuated Vaccine

New data from the Picker group showed that the magnitude of CD8+ and CD4+ Simian Immunodeficiency Virus(SIV)-specific T cells induced by live attenuated virus (LAV) vaccination correlated with a better outcome after pathogenic viral challenge (Abstract 92). Furthermore, the number of these vaccine-induced T cells in the lymph nodes proved to be the best predictor of successful control of the challenge virus. Vaccine-induced lymph node CD8+ T cells had an activated effector phenotype and seemed to be maintained by virus replicating in programmed death-1 (PD-1) high CD4+ memory T cells in the lymph nodes. LAV could be readily detected in PD-1 high CD4+ cells during the vaccine phase. These lymph node T-cell responses, therefore,

appeared to be the key to controlling pathogenic virus replication soon after intravenous challenge.

RV144 Vaccine Trial

In contrast with the notion that neutralizing antibodies are required for protection, the results of the Thai Phase lll Vaccine Trial (RV144) suggest that vaccine-induced antibodies that bind, but do not neutralize, can make a difference in protection against HIV. Michael presented results from the correlation analysis of the RV144 trial (Abstract 167). Six different aspects of the vaccine-induced immune responses in 205 uninfected vaccinated individuals were compared with immune responses from 41 infected vaccinees. The results suggested that antibody responses against the viral envelope may have been involved in the borderline protection observed. Michael presented new monoclonal antibodies that had been isolated from these vaccinees and showed that they had tier 1 neutralizing abilities and antibody-dependent cellular cytotoxicity activity. Future studies will include testing these monoclonal antibodies in passive transfer studies in macaques.

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A list of all cited abstracts appears on pages 87-93.

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