HIV Vaccine Development

David I. Watkins, PhD

Updates on the Thai clinical vaccine trial, the discovery of additional neutralizing antibodies, and several new, nonhuman primate vaccine studies were presented at the 17th Conference on Retroviruses and Opportunistic Infections this year. Interestingly, the vaccine effect observed in the Thai trial diminished with time and was most effective in individuals who reported low-risk behavior. Two new neutralizing monoclonal antibodies were reported that were more potent and broadly reactive than the previously described monoclonal antibodies, giving the neutralization field an important boost. New studies were presented in macaques showing that a DNA prime modified vaccinia virus Ankara boost regimen can reduce acquisition of infection after a low-dose mucosal challenge with a heterologous pathogenic simian immunodeficiency virus (SIV) strain. Data suggesting that attenuated SIV vaccines can induce cellular immune responses that control viral replication were also discussed. Finally, and perhaps most encouragingly, vaccination with cytomegalovirus-expressing SIV antigens provided robust levels of protection against the highly pathogenic SIVmac239 viral isolate. All of these promising results should serve to energize the HIV vaccine field.

Most classic vaccines induce neutralizing antibodies that prevent or control viral replication. However, given the diversity of the HIV envelope and its glycan shield, it has been difficult to develop neutralizing antibodies against this virus. Many investigators have therefore been trying to develop alternative strategies to induce effective HIV-specific immune responses by vaccination. Encouraging results from antibody studies were expanded upon at the 17th Conference on Retroviruses and Opportunistic Infections this year, and new data from nonhuman primates gave the field hope that it might indeed be possible to make a vaccine against HIV.

Human Vaccine Trials

Michael described new post hoc analyses from the Thai clinical vaccine trial (Abstract 74). He urged that these post hoc analyses be treated with caution, however. Despite a paucity of vaccine-induced cellular immune responses, vaccinees acquired HIV at a lower rate (31%) than individuals given placebo, but the vaccine had no effect on viral load or CD4+ counts in vaccinees once they became infected. Interestingly, Michael presented data showing that vaccine efficacy dropped over time. Although most vaccinees had binding antibodies, titers collapsed after 24 weeks.

Fauci discussed the Thai vaccine trial results, urging researchers to try to understand the correlates of protection in vaccinated individuals who avoided infection in this trial (Abstract 19). He suggested that new vaccines should be designed to try to prevent acquisition rather than control viral replication after infection. Furthermore, in future HIV vaccine trials, researchers should strive for an efficacy rate higher than 60%. Both Fauci and Michael urged further studies with this vaccine approach.

In a follow-up to the Step (HIV Vaccine Trials Network/Merck 023) trial, Rolland tested whether adenovirus serotype 5 (Ad5)-induced T cells can affect viral evolution in infected vaccinees (Abstract 75). She presented data from the Step Trial Study Group showing that vaccinees exerted statistically significant selective pressure on cytotoxic T-lymphocyte (CTL) epitopes, largely in Nef sequences. In viral proteins that were not used in the vaccine, there was no evidence for selection. These results suggest that the vaccine-induced CTLs exerted some measure of selection on the regions of the virus that encoded CTL epitopes.

HIV Pathogenesis Studies With Relevance to Vaccine Studies

Alter discussed the possible role of natural killer (NK) cells in controlling HIV replication (Abstract 178). It has previously been shown that certain NK cell receptors paired with particular HLA types can affect the rate of progression to AIDS after HIV infection.[1] Individuals with the activating killer immunoglobulinlike receptor (KIR) allele 3DS1 paired with HLA-Bw4 progress to AIDS more slowly than individuals without the 3DS1 allele. Alter presented data showing that during early infection, 50% of peripheral blood mononuclear NK cells secreted cytokines. Furthermore, individuals who express KIR3DS1 and HLA-B48 suppressed viral replication better than others. Alter also showed emerging data suggesting that NK cells can select for mutations in several different regions of HIV. Thus, it is possible that vaccination to induce NK cells might prove to be a novel and useful avenue for exploration in HIV vaccine development.

Burton presented encouraging data from the field of neutralizing monoclonal antibodies (Abstract 67). Before 2009, only 4 neutralizing antibodies had been isolated from HIV-infected individuals. Burton described 2 new antibodies, PG9 and PG16, that were more potent and of higher affinity than those previously described. He also reiterated that lower concentrations of these neutralizing antibodies in vivo might be required to achieve neutralization than described earlier. Overall, he painted a hopeful scenario for the field.

Dr Watkins is professor in the Department of Pathology and a member of the AIDS Vaccine Research Laboratory at the University of Wisconsin Madison.

Results From Nonhuman Primate Vaccine Studies

Robinson presented encouraging results from a DNA prime/modified vaccinia virus Ankara (MVA) boost vaccination regimen in which they used granulocyte macrophage colony-stimulating factor (GM-CSF) as an adjuvant in half of the vaccinated animals (Abstract 79LB). The vaccine constructs expressed the proteins Gag, protease (PR), reverse transcriptase (RT), and envelope (Env) of the simian immunodeficiency virus strain mac239 (SIVmac239) and prevented infection in 5 of 7 vaccinated animals (using the adjuvant GM-CSF) from a repeated low-dose heterologous mucosal challenge. In the group of animals that did not receive the adjuvant, 4 of 7 were protected. By contrast, all 9 naive control animals became infected after 12 low-dose weekly challenges with the heterologous challenge isolate SIVsmE660. Robinson noted that the GM-CSF group had developed antibodies with enhanced neutralizing titers against a neutralization-sensitive variant of SIVsmE660.

Johnson presented a comprehensive overview of the state of knowledge regarding vaccine protection induced by attenuated live SIV (Abstract 179). Vaccination of macaques with SIVmac239 from which the *nef* region was deleted (SIVmac239Δnef) confers sterilizing immunity against challenge by the highly pathogenic homologous SIVmac239. However, protection against heterologous intravenous challenge has proved to be less robust. Johnson presented new results from Reynolds showing that the attenuated vaccine can prevent acquisition of a heterologous low-dose mucosal challenge. These data suggested that attenuated SIV might indeed be effective against a heterologous isolate using a challenge that more closely mimicked human HIV exposure. Johnson then presented new data from Schmitz indicating that B-cell depletion does not affect protection after challenge with SIVmac239.

Similarly one of Johnson's colleagues, Desrosiers, who first described the protection induced by SIVmac239Δnef, showed that manipulating the envelope in the vaccine had little effect on protection. The majority of animals vaccinated with SIVmac239Δnef expressing the envelope (Env) protein of SIVsmE543 were protected from SIVmac239 challenge, suggesting that Env-specific antibodies were not playing a role in control of viral replication because the envelopes of these 2 viruses are very different. Johnson also presented data suggesting that ongoing viral replication likely plays a role in this protection. Vaccination of animals with single-cycle SIVmac239 that undergoes only a single round of replication is not as effective as with SIVmac239Δnef. Finally, Johnson presented data showing that if animals are challenged vaginally 5 weeks after vaccination with SIVmac239Δnef, they reduce viral replication by 1 $\log_{10}$ in the acute infection phase, but no protection is noted in the chronic phase. These results confirm earlier studies suggesting that SIVmac239Δnef–induced protection needs time to develop.

Picker presented follow-up studies (Abstract 181) to his previously published work.[2] Here the researchers used a cytomegalovirus (CMV)-vectored vaccine to induce immune responses that afforded protection in 4 of 12 vaccinees after repeated mucosal challenge with the highly pathogenic SIVmac239 clone. Interestingly, these 4 monkeys showed small "blips" of viral replication and subsequently developed T-cell responses against Vif, a region of the virus that was not used in the vaccine phase. Thus, these animals had clearly been infected with the challenge virus but had effectively controlled replication. Picker credited this remarkable protection in the 4 vaccinees to the effector memory CD8+ T cells induced by the chronic CMV vector.

Picker described a new study in which 6 of 12 animals vaccinated with CMV showed the same type of control as previously reported.[2] One animal had a peak of 40 million copies/mL, after which viral replication was controlled to undetectable levels. Half of the CMV-vaccinated animals showed no control of SIVmac239 replication, and their viral loads were indistinguishable from those of the naive, unvaccinated animals. Picker also presented a new correlative analysis showing that peak frequency of SIV-specific CD8+ T cells in the vaccine phase was the only factor that correlated with the ability to withstand challenge. Importantly, 33 weeks after infection, 12 of 24 vaccinees were still controlling viral replication, with only 1 animal having lost control. Picker also presented data showing that 7 years after CMV-Gag vaccination, high frequencies of effector memory T cells were still present in the liver, spleen, and bone marrow. Finally, Picker suggested that there may be 3 levels of protection—antibodies, effector memory T cells, and central memory T cells. Understanding why this CMV vector is so efficient at controlling replication of the highly pathogenic SIVmac239 challenge should give important insights into how to make an effective HIV vaccine.

Financial Disclosure: Dr Watkins has served as a consultant to Pfizer Inc.

A list of all cited abstracts appears on pages 93-99.

Additional References

1. Martin MP, Qi Y, Gao X, et al. Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. *Nat Genet*. 2007;39:733-740.

2. Hansen SG, Vieville C, Whizin N, et al. Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. *Nat Med*. 2009;15:293-299.

Top HIV Med. 2010;18(2):35-36