

HIV Vaccine Development

David I. Watkins, PhD

Several interesting new vaccine-related studies were presented at the 16th Conference on Retroviruses and Opportunistic Infections this year. Transmitted viruses appear to be derived from cell-free virus rather than cell-associated virus, at least in men who have sex with men. Follow-up studies from the Step (HIV Vaccine Trials Network 502) trial indicated that if individuals mounted certain vaccine-induced responses, they may control viral replication after infection. Finally, adeno-associated-virus-derived neutralizing antibodies completely protected macaques from infection, suggesting novel mechanisms of viral control.

Transmission

One of the highlights of the 2008 (15th) Conference on Retroviruses and Opportunistic Infections was the discovery that only a few HIV variants cross the mucosa to initiate viral infection. At the 2009 (16th) conference this year, data were presented suggesting that the origin of the infecting virus in semen is cell-free virus rather than viral DNA present in cells (Abstract 49LB). Four transmission pairs of men who have sex with men (MSM) were studied; sequences of the virus present in plasma of the infected recipient clustered with donor cell-free virus from semen rather than viral DNA in lymphocytes from semen. It will now be important to assess the origin of the transmitted virus in heterosexual transmission pairs and in men infected by genital secretions. Nonetheless, this result suggests that vaccines should target cell-free virus rather than cell-associated virus. Furthermore, the cell-free viral challenges employed in macaque challenge studies may be relevant to HIV transmission.

Step Trial Follow-Up

In a symposium on “Learning from Negative Trials,” Hunter discussed possible reasons for the failure of the Step

trial (HIV Vaccine Trials Network 502 study) (Abstract 119). It was suggested that despite relatively robust vaccine-induced T-cell responses, the breadth of these responses may not have been sufficient to protect against HIV infection or reduce postinfection viral loads in the majority of vaccinees. New T-cell vaccine approaches may, therefore, have to be qualitatively different or include an antibody component in the future.

In an attempt to explain why vaccinees in the Step trial with high adenovirus serotype 5 (Ad5) neutralizing antibodies were more susceptible to HIV infection, the immune response to Ad5 was monitored in individuals participating in phase I studies (Abstract 85). Approximately 73% of individuals already had Ad-specific T cells before receiving the vaccine. Only individuals given 3 injections of 3×10^{10} viral particles showed a statistically significant increase in the percentage of Ad-specific CD4+ and CD8+ T cells. These CD4+, Ad5-specific cells exhibited macrophage inhibitory protein (MIP)-1 alpha activity, which the authors speculated might make them resistant to HIV infection.

In a follow-up study of the Step trial, data suggest that if vaccinees show a response to a “good” epitope after vaccination, they will likely exert some measure of control over viral replication after infection (Abstract 86LB). Although this would be expected for epitopes bound by the “protective” alleles HLA-B*57 and -B*27, there were 9 individuals who showed a response

to the HLA-A*02-bound epitope Nef LV10. The vaccinees who showed a response to this epitope before infection did better than those that did not.

Further evidence for the concept that CD8+ T-cell recognition of good epitopes results in control of viral replication was presented by Streeck and colleagues (Abstract 112). The authors showed that if individuals recognized frequently targeted immunodominant epitopes during the acute infection phase, they would control viral replication later. Preservation of this recognition pattern into the chronic infection phase also correlated with a slower CD4+ decline.

Finally, 2 studies (Abstracts 90aLB, 90bLB) presented the effects of interleukin-2 on clinical outcomes. Despite evidence of preservation of CD4+ cells and increases in some patients, there was no reduction in the rate of opportunistic infections or death.

Monkey Vaccine Studies Using Attenuated Simian Immunodeficiency Virus

Two studies (Abstracts 116, 117) shed light on protection induced by live attenuated simian immunodeficiency virus (SIV) SIV_{mac239ANef}. The first study examined the expansion of natural killer (NK) cells (CD3-, CD8+, NKG2A+) after vaccination and challenge. NK cells expanded by as much as 8-fold in 70% of the vaccinated animals. Similarly, NK expansion was observed in challenged vaccinated monkeys, in the absence of obvious anamnestic responses, implying that these NK cells may play a role in vaccine-induced protection.

The second monkey study involving SIV_{mac239ANef} showed that depletion of B cells had little effect on vaccine-induced protection. Although not all of the vaccinated macaques exhibited adequate B-cell depletion, 5 of 10 anti-CD20-antibody-treated animals had no SIV-specific antibody at time of challenge. Of these, 4 of 5 showed no evidence of

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

replication of the challenge virus, and the other showed only limited viral replication and subsequent control. Thus, B-cell responses likely play only a marginal role in vaccine protection induced by SIV_{mac239ΔNef}.

Vaccine Development

In a symposium titled “Vaccines—Back to Basics,” several elegant antibody studies were described. The first presented an analysis looking at the first antibodies present after detection of virus (Abstract 162). At 8 days postinfection, antibody-virion complexes were present, followed by antibody to gp41 at 13 days. Anti-gp120-specific antibodies appeared at 28 days post-viral detection. Mathematical modeling suggested that these antibodies had little effect on reducing acute-phase viremia given the timing of their appearance during natural infection.

Mascola discussed approaches to generate broadly reactive neutralizing antibodies (brNAbs) (Abstract 163). These antibodies may be more common than previously thought, and new methods for developing additional brNAbs were described. This involved sorting of B cells from infected individ-

uals with subsequent cloning of the immunoglobulin heavy and light chains. After transfection of these heavy and light chains, it was possible to produce neutralizing antibodies.

One of the most interesting and novel discoveries reported at this year’s conference involved the use of adeno-associated virus as a gene therapy agent to express an SIV-specific neutralizing monoclonal antibody (Abstract 164). Three monkeys treated in this way resisted challenge with SIV_{mac316}, whereas 6 naive macaques became infected and developed sustained viral replication out to 12 months postinfection. This novel approach may well hold substantial promise as a method of controlling the HIV epidemic.

Encouraging news from the T-cell vaccine field closed this symposium (Abstract 165). Vaccination with a DNA/Ad5 regimen encoding all of the SIV proteins except Env induced high-frequency and broad T-cell responses in 8 macaques. Repeated low-dose mucosal challenge with a heterologous virus demonstrated that these vaccine-induced T-cell responses controlled replication of the challenge virus in 6 of 8 vaccinees. These data suggest that both acute- and chronic-phase viral

replication can be controlled by T cells alone, in the absence of Env-specific antibody responses.

New HIV Vaccine Testing

Finally, encouraging immune responses were engendered in a safety trial of a protein vaccine adjuvanted (with AS01) and consisting of a recombinant fusion protein containing p17, p24 Gag, reverse transcriptase, and Nef (Abstract 87LB). Additionally, there were no vaccine-related serious adverse effects. At the highest doses of this vaccine, 80% of the human volunteers showed recognition of all 4 antigens in the vaccine, with a mean CD4+ cell reactivity of 1.2%. Interestingly, few CD8+ T-cell responses were seen in the vaccinees. Further human testing is planned for this vaccine approach.

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A list of all cited abstracts appears on pages 89-95.

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