# Basic HIV Vaccine Development

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*The highlight of the 2008 Conference on Retroviruses and Opportunistic Infections was a sober assessment of the HIV vaccine field by one of its pioneers. Desrosiers delivered a plenary session in which he called for refocusing our HIV vaccine effort. He suggested that none of the current vaccine candidates in human clinical trials stands a chance against HIV. Thus, we need to redirect our efforts to basic vaccine research. This call for a sea change in how we carry out HIV vaccine research has already had an impact, prompting a recent HIV vaccine summit in Bethesda, MD. This will likely herald a new era in HIV vaccine research, resulting in a redoubling of effort to uncover innovative new ways of making an HIV vaccine.*

Desrosiers delivered a candid, and to some a controversial, assessment of the HIV vaccine field, providing the sobering highlight of the recent 15th Conference on Retroviruses and Opportunistic Infections in Boston. He suggested that we do not have a viable HIV vaccine candidate in development currently and that we need to return to basic research. Only a creative idea would solve the enormous barriers to an effective vaccine.

### HIV Vaccine Development: The Problems

The enormity of the problems posed by this virus to the vaccine field was delineated by Desrosiers (Abstract 91). He began by posing 3 questions: where are we, where are going, and where should we be going? He then discussed whether a vaccine for HIV was feasible at this time. He pointed out that the natural response to HIV neither controls viral replication nor prevents superinfection. The enormous sequence diversity and the fact that we do not know what a protective immune response is against this virus make it unlikely that we have the necessary information to make a vaccine at this stage. Furthermore, our best vaccine results to date in monkeys afford only a 1.0- to 1.5-$\log_{10}$ copies/mL reduction in viral replication—and these trials were conducted under highly idealized conditions with homologous viral challenges. We are 0 for 3 in clinical vaccine trials, and we have no idea how to elicit a broadly reactive neutralizing antibody response.

Desrosiers asked whether we should be surprised by the failure of the STEP trial vaccine. He referred to monkey studies using a trivalent adenovirus type 5 (Ad5) vaccine (Merck & Co, Inc) that afforded little or no reduction in viral load after challenge with a monkey virus that was exactly matched in sequence to the vaccine. He went further to ask whether any of the products in the vaccine pipeline had a reasonable chance of showing efficacy, especially against nonhomolgous challenges, and again was pessimistic about the likelihood of success with these products.

Finally, Desrosiers suggested that we rethink the way in which the National Institutes of Health (NIH) spends its HIV vaccine budget. Given the paucity of good vaccine candidates currently, we should probably refocus our research efforts on basic discovery.

Desrosiers suggested several topics that should be high priority for discovery research. How do we elicit broadly reactive neutralizing antibodies? We need novel vaccine and preventive concepts. We need to understand what is responsible in those rare cases in which virus replication is controlled: in elite controller humans and in macaques vaccinated with attenuated simian immunodeficiency viruses (SIVs) that subsequently control replication of highly pathogenic challenge viruses. We also need to understand why sooty mangabys and African green monkeys have high levels of viral replication but show no signs of disease. Desrosiers also called for comparative testing of vaccines in macaques and humans.

Nathanson (Abstract 92) then gave the second plenary presentation of the session and discussed vaccine approaches and animal models. Many of his points supported and expanded those of Desrosiers. Nathanson emphasized the need to get honest answers from the nonhuman primate challenge models and wondered if a refocusing of the vaccine field is necessary.

### Pathogenesis Studies with Relevance to Basic Vaccine Research

In the conference session titled "Viral Pathogenesis and Immune Surveillance," several oral presentations addressed T-cell responses to SIV and HIV that might be relevant to vaccine development. Loffredo (Abstract 18) suggested that broad CD8+ T-cell responses might play a role in control of SIV replication in macaques that expressed protective major histocompatibility complex types. Streeck (Abstract 22) presented interesting data from the Altfeld group suggesting that "polyfunctional" CD8+ T-cell responses were a result of antigen load and sequence diversification. Should this prove to be correct, it will have implications for assessing CD8+ T-cell responses in vaccines.

### Vaccines in Phase I and II Studies and Therapeutic Vaccines

Robinson (Abstract 85) presented her group's safety and immunogenicity data for the clade-B DNA-priming and modified vaccinia virus Ankara (MVA) product (GeoVax Labs, Inc). Volunteers were vaccinated with low and high

*Note: The STEP vaccine trial results are summarized in the accompanying report by Susan Buchbinder, MD.*

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doses of DNA and MVA expressing the Gag, Pol, and Env proteins. The vaccine was well tolerated, and the majority of volunteers responded to the vaccine in the CD4+ (82%) and CD8+ (67%) T-cell compartments when given the highest dose. Although it was not clear whether this vaccine induced T-cell responses that were significantly different from those induced by the Ad5 Gag, Pol, and Nef product (Merck), planning for a phase II trial is underway.

Similarly, Schuetz (Abstract 86) presented immunogenicity data from 20 volunteers vaccinated with the Vaccine Research Center (VRC) DNA prime/Ad5 boost expressing Env proteins from clades A, B, and C along with clade B expressing Gag, Pol, and Nef proteins. T-cell responses were predominantly against Env (16/20 responders), whereas weaker responses were generated against Nef (5/20) and Pol (3/20). Unfortunately Gag-specific responses were not assessed. Again, it was difficult to assess whether this VRC vaccine induced better immune responses than those induced by the failed Ad5-only Gag, Pol, and Nef vaccine (Merck).

Data from a therapeutic trial of an Ad5 vaccine expressing Gag were presented by Schooley (Abstract 87). Even though the vaccine was generally safe and well tolerated, no significant reductions in viral replication were seen in vaccines compared with placebo after analytical treatment interruption.

Finally, efficacy results from the STEP trial (Abstracts 88LB and 89LB) of the Ad5 vaccine (Merck) were presented. These are covered in greater detail in Buchbinder's article, "HIV Testing and Prevention Strategies," on pages 9–14.

## Frontiers in Vaccine Research

### Antibody Responses

Inducing a broadly reactive antibody response to the envelope glycoprotein (Env) is probably the most important goal of HIV vaccine research. This has been difficult to achieve for a variety of reasons, including the fact that the conserved sites are difficult to access by antibody and Env is covered by sugars and is highly variable. In the final session on vaccine research, Wyatt (Abstract 152) discussed the biophysical and antigenic properties of the Env. He showed that stabilization of the CD4-induced coreceptor binding site enhances elicited immune responses to this region. He also analyzed antibody responses generated in animal models to the soluble trimers.

### The First Infecting Viruses

Understanding the nature of the first infecting virus is central to vaccine development. Are people infected by a diverse swarm or by a single virus? Are these viruses sensitive to immune responses? Shaw (Abstract 153) presented evidence of infection by 1 to 2 viruses by sampling very early after infection. By making a few assumptions, he and his colleagues could predict the nature of the starting virus from the diversity of the viral sequence at sampling. They found that in 78 of 102 patients infected with HIV-1, clade B had evidence of infection by only a single virus. The others were infected by a minimum of 3 to 5 viruses. The virus population seemed to evolve randomly until CD8+ T cells exerted pressure and antibodies subsequently also exerted selective pressure. Interestingly, there was no evidence for adaptation to cell-specific replication. Thus, most (80%) of the infections examined appeared to have been caused by a single virus that then diversifies. It is thus likely that the majority of HIV-1 clade-B infection is not caused by a swarm of several viruses, one of which is then selected. Interestingly, all viruses used CCR5, and transmitted Envs were typical of primary isolates, that is, not easily neutralizable.

## A New Attenuated SIV for Understanding the Correlates of Protection

Currently, only 1 vaccine confers complete protection from homologous challenge of nonhuman primates. Delineating the immune responses that account for this control in macaques vaccinated with attenuated SIV will be very important in vaccine design. Hoxie (Abstract 154) presented his group's data describing a new attenuated SIV termed ΔGY, which contains a mutation in the cytoplasmic tail of Env. This mutant in the Env trafficking signal had no effect on peak viral replication, but in the chronic phase, virus replication was undetectable. It offered complete protection from challenge with the homologous SIV isolate SIVmac239 and afforded some measure of protection from disease after heterologous E660 challenge. Indeed, 2 out of 3 pigtailed macaques controlled E660 viral replication. After depletion of CD8+ T cells in vivo, the challenge virus replicated, suggesting that CD8+ T cells were involved in control of replication. The animals were then challenged with SIVmac239, and nothing happened.

After a subsequent E660 challenge, 1 animal had a blip of viral replication and the other had 1000 copies/mL of E660, and later, low levels (100 copies/mL) of E660. Three more animals were vaccinated with ΔGY, and 2 of 3 completely controlled the vaccine strain in the chronic phase, the other to less than 1000 copies/mL. Anti-CD16 antibody was administered with no viral replication. The animals were then challenged with additional E660. Two of 3 had a peak of viral replication and then controlled viral replication to less than 1000 copies/mL. After anti-CD8 antibody administration in vivo, SIVmac239 replicated in 1 animal. In the second animal, E660 returned. In the third animal, E660 replicated to 10 million copies/mL, and the animal subsequently died. Thus, this model of attenuated virus vaccination may prove informative in our understanding of how attenuated live vaccines might provide protection against heterologous challenge.

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**A list of all cited abstracts appears on pages 69-77.**

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