

# HIV Vaccine Development

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*Presentations at the 2011 Conference on Retroviruses and Opportunistic Infections reflected the resurging interest in antibody responses against HIV given the encouraging results of the Thai vaccine trial. A plenary talk and an entire symposium were devoted to HIV-specific antibody responses describing newly isolated, potent neutralizing monoclonal antibodies. These antibodies undergo extensive somatic mutation to achieve their remarkable neutralizing properties. Inducing these types of antibodies by vaccination, however, still represents a challenge. New data were presented suggesting that neutralizing antibodies, but not binding antibodies, can provide protection against infection in the nonhuman primate (NHP) model. Several interesting discoveries were also reported showing that cellular immune responses recognizing HLA-C and HLA class II molecules might also be important in control of viral replication. Finally, new vaccine studies in the NHP model showed that electroporated DNA, along with the adjuvant interleukin 12 may be an efficacious vaccine regimen.*

Over the past few years, several new, potent neutralizing antibodies have been described in the HIV vaccine field. These studies have come from many different groups, including those at Rockefeller University, International AIDS Vaccine Initiative (IAVI), and the Vaccine Research Center (VRC). These new studies have shed considerable light on how these critically important antibodies develop. The interesting properties of many of these novel antibodies were discussed at the 2011 Conference on Retroviruses and Opportunistic Infections. Additionally, novel vaccination methods gave the field hope that a vaccine for HIV might eventually be possible.

## Neutralizing Antibodies Against HIV

Nussenzweig gave a plenary talk outlining developments in the discovery of neutralizing antibodies against HIV (Abstract 20). The IAVI Neutralizing Antibody Center at the Scripps Research Institute, the VRC, and now Nussenzweig's group have recently discovered new, highly potent, broadly neutral-

izing antibodies against HIV. Nussenzweig's group sorted gp140-staining, single B cells from HIV-infected individuals and then cloned the antibody genes from these cells. They showed that, after expression, most of these antibodies neutralized tier-1 strains of HIV (ie, strains highly susceptible to neutralization), whereas only a few of them neutralized the more difficult-to-neutralize tier-2 strains (ie, strains moderately susceptible to neutralization). These antibodies had undergone extensive somatic hypermutation, facilitating high-affinity binding to Envelope. Nussenzweig showed that T cells played a crucial role in the maturation of these highly specific antibody responses.

One symposium was devoted entirely to anti-HIV antibodies (Session 18). Mascola initiated the session and reminded attendees that HIV was unusual in that broadly reactive, HIV-specific neutralizing antibodies take more than 2 years to develop in infected individuals (Abstract 62). He then discussed the new neutralizing antibodies from the VRC, highlighting the discovery of a broadly reactive neutralizing antibody, VRC01. He suggested that these broad neutralizing antibodies could be used for passive transfer for prevention of mother-to-child transmission, gene delivery, and micro-

icides. The new VRC01 antibody had undergone extensive somatic mutation and binds to the conserved CD4 binding site of gp120. Indeed, VRC01 differs from the germ line sequences by 30%, and if changes are made so that sequences are reverted to the germ line, the antibody loses its affinity and neutralizing capabilities. This indicates that somatic mutation is crucial to the development of the affinity and neutralizing properties of these broadly neutralizing antibodies. These findings suggest immunization strategies to induce such effective antibodies.

Verkoczy and colleagues discussed the possibility that membrane-proximal external region (MPER)-specific neutralizing antibodies may be under stringent tolerance control (Abstract 63). Sundling and colleagues showed that even if macaques made antibody responses against a vaccine of soluble Env trimers, these antibodies provided moderate protection against a simian HIV (SHIV) challenge (Abstract 64). On behalf of his colleagues, Kim discussed the latest analyses of the results of the RV144 Thai phase III trial (Abstract 65). He also presented ongoing studies showing that there were antibody recognition profiles that were associated with RV144 vaccination.

Moore and colleagues showed that neutralizing antibodies provide protection in a nonhuman primate (NHP) model, whereas nonneutralizing antibodies provided no or partial protection (Abstract 142). The nonneutralizing b6 antibody directed against the CD4 binding site on gp120 did not provide protection in 4 of 4 macaques in 1 study or in 5 of 5 macaques in a second study. Interestingly, topically applied F240 antibody directed against anti-gp41 (nonneutralizing) protected 2 of 5 animals and resulted in relatively low viral loads in 2 of 3 of the infected animals. By contrast, as has been found before,<sup>1</sup> the neutralizing antibody b12 protected all animals in these SHIV-challenge studies.

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Trokla presented data implicating the V1 and V2 loops in protection against antibodies directed against V3 (Rusert et al, Abstract 141LB). With several elegant experimental approaches, the researchers showed that antibodies directed against the V3 loop in 1 peplomer were inhibited from binding by the V1 and V2 loops from the adjacent peplomer on the trimeric Envelope. Thus, the V1 and V2 loops in the quarternary structure of the gp120 trimer may play a crucial role in conferring resistance to neutralizing antibodies directed against the V3 loop.

### HIV-Specific Cellular Responses

Several genome-wide association studies have confirmed that a portion of individuals with HLA-B57 or -B27 control viral replication. However, another polymorphism in the major histocompatibility complex (MHC) region, close to *HLA-C*, was also shown to be associated with control of viral replication. Carrington elegantly demonstrated that this polymorphism may be involved in regulation of *HLA-C* expression (Abstract 105). Whether this polymorphism is exerting its effect through interactions with cytotoxic T lymphocytes or natural killer cells is still unknown.

In the same symposium, Hirsch and colleagues delineated the effects of TRIM5 polymorphism on simian immunodeficiency virus (SIV) replication (Abstract 107). They showed that TRIM5 alleles can have a profound ef-

fect on replication, both in vivo and in vitro, on the SIV<sub>smE543-3</sub> clone. Interestingly, it was more difficult to see these TRIM5 effects on the closely related SIV<sub>smE660</sub> isolate. This may be related to the use of several different stocks of this quasispecies; some stocks may be more sensitive to TRIM5 variation than others. However, the message for the NHP vaccine field is that vaccine and control groups should be typed for these TRIM5 alleles.

Soghoian and colleagues presented intriguing data suggesting that HIV-specific cytolytic CD4+ cells may be involved in control of HIV replication (Abstract 158). They studied 12 acutely infected individuals and divided them into 2 groups: those that exerted a measure of control and those that did not. Even though peak viremia was similar in the 2 groups, those that controlled viral replication exhibited higher levels of HIV-specific CD4+ T cells expressing granzyme, perforin, and CD107a (markers of cytotoxic activity). These data suggest that cytolytic CD4+ T cells may play an important role in the initial control of HIV replication.

### Results From Vaccinated Monkeys After Heterologous Challenge

Vaccination using electroporated DNA along with the adjuvanting cytokine interleukin 12 is among the most exciting breakthroughs in vaccine development recently. Pavlakis and colleagues presented data showing

that DNA vaccination alone or in combination with aldrithiol 2-inactivated SIV resulted in protection after a heterologous low-dose mucosal challenge (Abstract 360). Indeed, of the 24 vaccinated macaques, 2 animals showed no evidence of viral replication, and 9 macaques showed a peak plasma SIV RNA level of 100,000 copies/mL to 1,000,000 copies/mL, followed by complete control of viral replication. By contrast, none of the 8 naive control animals showed this kind of control of viral replication. The authors speculated that a mixture of vaccine-induced antibodies and cellular immune responses were responsible for this control of viral replication.

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**A list of all cited abstracts appears on pages 99–106.**

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### Reference

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