Phase 1 Clinical Trials of the National Institutes of Health Vaccine Research Center HIV/AIDS Candidate Vaccines

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(See the articles by Catanzaro et al. and by Graham et al., on pages 1638–49 and 1650–60, respectively.)

Nine years ago, in his 1997 Morgan State College commencement address, President Bill Clinton announced a 10-year goal for the development of an HIV/AIDS vaccine. A cornerstone of this plan was the establishment of a vaccine research center on the National Institutes of Health (NIH) campus in Bethesda, Maryland. We are now close to reaching 10 years and are unlikely to realize an effective HIV/AIDS vaccine by 2007. Nevertheless, the NIH Vaccine Research Center (VRC), which opened in 2001, has become a force in vaccine research and development and, in this issue of the Journal, publishes a pair of articles [1, 2] reporting the results of phase 1 human trials for its HIV/AIDS vaccines, which are now well into phase 2 studies. The vaccine strategy uses DNA to prime the immune response and a replication-defective recombinant adenovirus serotype 5 (rAd5) vector to boost responses.

All in all, the development of an HIV/AIDS vaccine has been slow, hard work. Major problems have been the lack of immune correlates for protection, the extensive genetic diversity of the virus, and the inability to elicit neutralizing antibodies for incident isolates [3, 4]. Because of the problem in raising neutralizing antibodies, vaccine efforts have turned to eliciting T cells that, at least in preclinical nonhuman primate models, can protect CD4+ T cells and control infections to the low levels found in successful drug treatment [5, 6].

The 2 articles for the DNA and rAd5 vaccines being developed by the VRC represent the first published reports of the elicitation of anti-HIV T cells in the vast majority of participants in a human trial.

Eighty-six volunteers rolled up their sleeves for the phase 1 testing of the HIV/AIDS candidate vaccines. The vaccine strategy is designed to recognize and hopefully protect against the diversity of isolates present in the worldwide AIDS pandemic. To achieve broad protection, the strategy uses multiple DNAs expressing copies of HIV-1 genes from the 3 dominant genetic subtypes of HIV-1 (clades A, B, and C) to prime immune responses followed by multiple adenovirus vectors, again expressing sequences from the 3 dominant subtypes, to boost responses. In the phase 1 trials reported in this issue, the DNA and rAd5 vaccines were tested separately for their safety and immunogenicity.

The DNA studies are a landmark for DNA-based vaccines in that they are the first to demonstrate a DNA vaccine successfully eliciting immune responses in essentially all vaccinated volunteers (table 1). Four DNA constructs constituted the DNA vaccine: 1 expressing a clade B Gag-Pol-Nef fusion protein, and 3 expressing individual clades A, B, and C Env glycoproteins [7, 8]. Three intramuscular injections of DNA were given with a needle-free biject device at weeks 0, 4, and 8, with a dose escalation from 2 to 8 mg (the highest dose used to date) of total DNA. Both antibody and T cell responses were highest for the Env antigens in the vaccine (table 1). Both the elicited antibody and T cells showed multiclade activity. The 4- and 8-mg doses (but not the 2-mg dose) were, overall, similarly effective in eliciting immune responses.

The rAd5 HIV vaccine had both a higher percentage of responders and, overall, a higher magnitude of responses than did the DNA vaccine, especially for T cell responses (table 1). Four replication-defective rAd5 vectors expressed a clade B Gag-Pol fusion protein (Nef was not included because of problems with vector stability) and the clade A, B, and C Env glycoproteins. A single intramuscular im-
Antibody and CD4+ T cells were elicited are deleted for the proteolytic cleavage site ward [11]. The expressed Env sequences DNA vaccine that the VRC is taking for-place the fusion protein in the “improved” the Gag fusion protein, and 3 separate

rather, it appears to reflect a property of ing and 50% Env-expressing sequences. selecting initial trial in 3 macaques [17], these vectors have been found to provide relatively poor protection in macaques against both chimeras of simian and human immunodeficiency viruses (SHIVs) and sim-ian immunodeficiency viruses (SIVs) [18, 

Table 1. Elicited immune responses.

<table>
<thead>
<tr>
<th>Vaccine, dose</th>
<th>Synopsis</th>
<th>Dose</th>
<th>Elicited immune response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>Elicited Ab, CD4+, and CD8+ T cells; entire 2 mg</td>
<td>0/5</td>
<td>Ab^a CD4+ T cells^b CD8+ T cells^c</td>
</tr>
<tr>
<td></td>
<td>CD8+ response against Env; T cell responses 4 mg</td>
<td>8/20</td>
<td>20/20 (0.07) 7/20 (0.03)</td>
</tr>
<tr>
<td></td>
<td>long lasting 8 mg</td>
<td>12/15</td>
<td>14/15 (0.07) 5/15 (0.02)</td>
</tr>
<tr>
<td>rAd5</td>
<td>Elicited Ab, CD4+, and CD8+ T cells; highest T cell responses to Env; also CD8+ and CD4+ responses to Pol; best persistence of T cells at 10^11 PUs</td>
<td>10^9 PUs</td>
<td>8/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10^10 PUs</td>
<td>10/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10^11 PUs</td>
<td>10/10</td>
</tr>
</tbody>
</table>

NOTE. Data are no. of responders/no. tested (median response). PUs, particle units.

^a Anti-Env antibody (Ab), as measured by immunoprecipitation followed by Western blotting.

^b Elicited CD4+ and CD8+ T cells against EnvA (for the DNA vaccine) or total vaccine antigens (for the replication-defective recombinant adenovirus serotype 5 [rAd5] vaccine), as measured by intracellular cytokine staining assay after stimulation with peptide pools. The median values for the magnitude of elicited T cells are the percentages of total CD4+ or total CD8+ T cells. Median responses are estimated from figures.

munization was given, with a dose escalation from 10^9 to 10^11 particle units (PUs). Antibody and CD4+ T cells were elicited in essentially all vaccine recipients, and CD8+ T cell responses were elicited in 50%–70% of the volunteers (table 1). The highest rAd5 dose was accompanied by transient systemic adverse effects in some volunteers; however, it also elicited the best persistence of responses. Preexisting immunity to endemic adenovirus infections can limit the effectiveness of rAd5 vaccines. In this study, preexisting immunity to rAd5 was present in 32% of the volunteers and reduced the magnitude of the vaccine-elicited T cell response by slightly more than 3-fold.

Both the DNA and Ad5 candidate vac-cines elicited higher responses against Env than against Gag. Natural HIV infections eliciting higher T cell responses against Gag than against Env, and anti-Gag CD8+ T cell responses show a better correlation with protection than do anti-Env CD8+ T cell responses [9, 10]. The bias against the elicitation of anti-Gag T cells was not due to dose, because the vaccine mixtures were constituted to contain 50% Gag-expressing and 50% Env-expressing sequences. Rather, it appears to reflect a property of the Gag fusion protein, and 3 separate constructs for Gag, Pol, and Nef now replace the fusion protein in the “improved” DNA vaccine that the VRC is taking forward [11]. The expressed Env sequences are deleted for the proteolytic cleavage site that gives rise to the gp120 and gp41 forms of Env, as well as functional regions within gp41 [7]. These Env immunogens elicit good binding antibody but fail to elicit the hoped-for neutralizing antibody for incident isolates.

Recent studies being reported at meet-ings show excellent boosting of the DNA-primed response by the rAd5 component of the vaccine strategy [12]. Rollover of volunteers receiving 4 or 8 mg of DNA into a trial testing the rAd5 boost (10^10 PUs) demonstrated >5-fold increases in T cell responses and >1000-fold increases in the levels of anti-Env binding antibody. These increases in immune responses occurred for boosts given 9 months to 2 years after the DNA prime.

On the basis of these findings, phase 2 studies have been undertaken in the Amer-icas, South Africa, and East Africa to pre-pare for efficacy studies testing for multiclad protection. The immunogens are 4 mg of a 6-component DNA vaccine (clade B Gag, Pol, Nef, and Env plus clade A and C Env DNAs) and 10^10 PUs of the 4-com-ponent rAd5 vaccine. Volunteers are being typed for preexisting immunity to ade-novirus serotypes 5 and 35, to determine the extent to which preexisting immunity will affect immune responses to the vaccine in different regions of the world.

The rAd5-vectored vaccine that is most advanced in human trials is the one de-veloped by Merck [13]. This vaccine uses 3 separate clade B Gag, Pol, and Nef vec-tors to both prime and boost the immune response in a 3-dose regimen [14]. A proof-of-concept trial for this vaccine, which does not have a component de-signed to elicit protective antibody, was initiated in December 2004 in 1500 ade-novirus serotype 5–seronegative volun-teers in the Americas, where clade B pre-dominates, and then extended to include 1500 adenovirus serotype 5–seropositive volunteers. Merck has decided to discontinue a DNA prime for its rAd5-vectored vaccine.

The rAd5-vectored vaccines represent the third major vaccine concept to pro-gress to extensive testing in human trials. The first was VaxGen’s alum-adjuvanted gp120 protein, which elicited anti-gp120 binding antibody but failed to provide protective immunity [15]. The second, an Aventis Pasteur replication-defective can-narypox vector (ALVAC) boosted with the VaxGen alum-adjuvanted B/E gp120 pro-tein, is currently in efficacy trials in Thai-land [16]. In phase 2 trials, this vaccine elicited antiviral T cells in <30% of the participants. In contrast to these earlier vaccines, the rAd5 vaccines successfully elicit T cells in the vast majority of vol-unteers. However, despite a highly prom-ising initial trial in 3 macaques [17], these vectors have been found to provide relatively poor protection in macaques against both chimeras of simian and human immunodeficiency viruses (SHIVs) and sim-ian immunodeficiency viruses (SIVs) [18,
Other concepts that have shown higher protective potential in preclinical macaque models are presently in phase 1 human trials [20]. If the ALVAC prime and VaxGen gp120 boost were to work, or if the Merck proof-of-concept trial were to give favorable results, we could possibly identify an efficacious vaccine by 2008 or 2009—only 1 or 2 years past the 2007 goal. However, if these candidate vaccines are not protective, there are solid candidates waiting in the wings that give us a real chance to have an HIV/AIDS vaccine by 2017. Whether it will be the constructs of the NIH VRC or those of others that prove to be the most effective, the VRC will have played a dynamic role in spurring the development of a much-needed HIV/AIDS vaccine.

References