National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Acquired Immune Deficiency Syndrome

AIDS VACCINE RESEARCH WORKING GROUP

Adenoviral Vector Workshop

January 30, 2007
6700-B Rockledge Drive, Bethesda, MD

WORKSHOP SUMMARY

The AIDS Vaccine Research Working Group (AVRWG) met in public session on January 30, 2007, in Conference Room 1205 at 6700-B Fernwood Drive, Bethesda, MD.

AVRWG members present: Scott Hammer (chair), James Bradac (executive secretary), Lawrence Corey (ex officio), Susan Buchbinder, Barton Haynes (ex officio), Eric Hunter, Paul Johnson, Margaret Liu, Juliana McElrath, Bonnie Mathieson (ex officio), Gary Nabel (ex officio), Nina Russell, Jerald Sadoff, David Watkins, and Ian Wilson.

Other NIH personnel participating:
- Carl Dieffenbach, Acting Director, DAIDS, NIAID;
- Peggy Johnston, Director, Vaccine Research Program, DAIDS, NIAID;
- Michael Pensiero, Vaccine Research Program, DAIDS, NIAID

Speakers:
- Dan Barouch, Beth Israel Deaconess Medical Center;
- Lawrence Corey, Fred Hutchinson Cancer Research Center;
- Hildegund Ertl, Wistar Institute;
- Jaap Goudsmit, Crucell Holland B.V.;
- Nicholas Jackson, International AIDS Vaccine Initiative;
- Rick King, GenVec Inc.;
- Marjorie Robert-Guroff, Vaccine Branch, NCI;
- Norman Letvin, Beth Israel Deaconess Medical Center.

Opening remarks and meeting objectives

Session organizer Michael Pensiero welcomed participants and summarized emerging evidence that preexisting immunity to adenovirus-5 (Ad5) in some populations, particularly in sub-Saharan Africa, may limit the effectiveness of the current candidate HIV vaccines, which are based on the recombinant Ad5 (rAd5) vector. The purpose of the workshop is to review data on the various alternative serotype Ad vectors under development, and to provide feedback to DAIDS future funding of Ad vector research. Dr. Pensiero circulated a questionnaire for

AVRWG members to fill out at the end of the session, asking whether additional funding is needed for research and/or development of alternative/novel Ad-based vaccines.

Ongoing and planned clinical trials with Ad5-based HIV vaccines

Larry Corey explained that both of the current HIV-1 vaccine candidates involve a mixture of antigens (Env, Gag, Pol, and Nef) from one or more clades of HIV-1, inserted into an rAd5 vector. However, seroprevalence of Ad5 can be as high as 80 percent in some populations, sometimes with very high antibody (Ab) titers, and this may be a serious limit to current vaccines. Early data indicate that this may be less of a problem in the United States, but more of a problem in Africa. Preliminary data also indicate that resistance may be overcome at higher doses (10^{11} rather than 10^{9} or 10^{10}) or repeated dosing. Purpose and schedule of HIV Vaccine Trial Network (HVTN) trials involving rAd5 vaccines include the following:

- 050 – Phase 1 dose-escalation trial to detect response induced by rAd5-Gag vaccine, interim analysis November 2007;
- 502/503 – Phase 2B proof-of-concept trial using rAd5-Gag/Pol/Nef vaccine, go/no-go decision 2007Q4;
- 052/057 – Phase 1 trial using DNA prime plus Ad4-Env/Gag/Pol(nef) boost;
- 054 – Phase 1 immunogenicity trial using Ad5-Env/Gag/Pol (multiclade);
- 204 – Phase 2 trial in support of PAVE 100 using DNA + Ad5;
- 071 – in development, a step-down trial into adolescents in South Africa.

In addition, three trials are being planned in conjunction with PAVE 100; 068 (kinetics), 069 (routes of administration) and 072 (Ad35 prime plus rAd5-Env(3) boost.

Current data from HVTN 050 show a strong and durable T cell response: 31.6 percent positive at week 28, and 21.6 percent at week 52 (blinded data including 75 placebo as well as 360 vaccine recipients, so actual response rate is higher), including a number of very high ELISPOT responses at both dates. Preliminary data from HVTN 504 show a strong T cell response, in most cases to more than one antigen and in many cases at very high magnitudes. At present, however, there are no data on how well the results correlate between the Merck and VRC trials.

Julie McElrath summarized the results and lessons learned to date from vaccine-induced T cell responses to Ad5-based HIV vaccines. HVTN 050 demonstrates a strong and durable cross-clade response to clade B Gag, including a good response in clade C areas, which will be important as HVTN 503 moves to South Africa. There is a clear difference in the sensitivity of assays, with Merck's being better than VRC's, so Merck's will be used in all future studies. HVTN 502 recapitulates these results, with an overall response of 95 percent (±15 percent). HVTN 054, using one dose of rAd5 encoding B Gag/Pol and C Nef, also induced a good response, with good correlations between doses at 10^{10} and 10^{11} doses , with most subjects responding to all three antigens and the highest magnitude response to Pol. Epitope mapping indicates that this response includes the same number of epitopes as acute HIV infection. Overall, it would appear that induced T cells are recognizing all peptide pools. McElrath identified three important lessons that should inform the design of large-scale studies in the future:

1. Rapid PBMC processing is vital, preferably in less than 4 hours;
2. Investigators should select assays that examine other, more qualitative responses; and
3. Trials should also follow the qualitative and qualitative responses of long-term nonprogressors.

In the discussion that followed, McElrath clarified that "response," in this context, means something distinguishable from control; the difference is usually clear-cut. In general, it takes a relatively high titer of $Ad5^+$ antibodies to suppress response to the vaccine. In general, the function and breadth of response is better understood in Ad5- subjects than in Ad5+; better validation of assays is still needed, as is further study of durability and the nature of long-term response. Work has just begun on whether these vaccines induce mucosal immune response. It's possible that a heterologous or multiple prime-boost would overcome Ad5 immunity, but this would be far more difficult to manufacture and administer than a single prime-boost.

Adenovirus vectors: key issues for consideration

Jaap Goudsmit reviewed the issues in suitability and producibility in adenovirus vectors. Ad5 is well-understood and has an excellent safety profile, due largely to adequate attenuation of the vector, which renders it replication-deficient. In addition, both Ad5 and Ad2 are nononcogenic, while other Ads are either weakly (Ad3, Ad7) or highly oncogenic (Ad12). In addition, Ad5 vectors are highly infectious and can be produced in large volumes using stable colonies of 293 and 911 cells (human embryonic neuronal cells in kidney-cell cultures). As a result, Ad5 vectors have been the most commonly used for gene therapy and vaccines. However, preexisting Ad5 immunity is fairly common in many populations, often at Ab titers above 1000. Ad5+ neutralizing Abs (NAbs) can hamper the potency of Ad5 vaccines by inactivating the vector, reducing vaccine potency, and interfering with accurate dosing. For this reason, there can be great value in exploring the suitability of other Ad serotypes to circumvent this barrier.

There are 51 human serotypes of Ad, which have been classified into six subgroups based on unique antigenicity and other factors. All of them cause self-limiting disease in healthy individuals, and almost all of them have lower seroprevalence than Ad5, including several that are uncommon enough to be considered "rare" (Ad 11, 26, 35, 48, 49, and 50). Ad35, in particular, has a very low seroprevalence in Africa, as well as Europe and the United States, and for this reason Ad35 emerges as a possible replacement for Ad5 in HIV vaccines. Ad35 is highly immunogenic and producible, and has a proven safety profile. Crucell is already working on Ad35-based vaccines against malaria and tuberculosis, as well as HIV. Unanswered questions about Ad35 and other alternatives to Ad5 include producibility, stability, immunogenicity, and cost per dose, as well as interactions among multiple vaccines based on the same vector. An ideal solution would be a "dual cassette"vaccine in which multiple antigens are included in a single vaccine, as is already done with diphtheria, tetanus and pertussis. Logistics, such as cold chain and administration, will also be a concern once Ad35 vaccines are in the field

Adapting Ad5 technologies for development of novel vaccine vectors

Rick King suggested that clinical data from ongoing clinical trials will answer many of the questions about the efficacy of Ad5-based HIV vaccines. Based on his company's experience in developing Ad5 vectors for numerous gene therapies and vaccines, however, he also believes that the experience and techniques used with Ad5 can be adapted for work on alternative and novel vectors. For example, they have learned that vector growth in 293 host cells requires a functional concurrence in the E1 and E4 regions, either Ad5 E1 and E4 or Ad35 E1 and E4. This means that it should be possible to use 293 cells to grow vectors from any serotype. GenVec has also simplified the manipulations that are required to enhance immunogenicity, increase antigen expression, and avoid NAbs. The company has already used these techniques to develop Ad35- and Ad4-based HIV vaccines that are currently in preclinical testing, and only a few modifications in production methods and release assays would be required to bring these and other novel vectors to full production. Stability remains a question mark for Ad35 vaccines, but this far the vaccines have been stable for more than 3 months at -70°C.

Alternative serotypes – rAd35

Gary Nabel suggested that novel vectors could be useful not only for evading natural immunity to Ad5, but also for improving delivery of antigen(s) to presenting cells, reducing reactogenicity (improving safety), and developing novel prime-boost combination. The lower prevalence of Ad35+ NAbs (7 to 25 percent, depending on region) is counterbalanced by possible lower immunogenicity compared with Ad5. The strong immunogenicity of rAd5 is dependent on the virus' fiber shaft; this region is also the target of NAbs and the cause of fever in rabbits injected with rAd5. Ad35 shaft, on the other hand, is not targeted by human NAbs. In addition, Ad35-HIV vector can be grown in the same certified cell line already used to produce rAd5.

Tests conducted by the Virus Research Center (VRC) showed that rAd35 is immunogenic in rhesus monkeys, if only at half the level of rAd5, and that a heterologous boost can increase both T-cell and antibody response, particularly when rAd35 is boosted with rAd5. This may be due to qualitative and quantitative differences in the targeting of dendritic cells by the two Ads; clinical studies in the coming year will provide additional information on rAd5 and rAd35, both alone and in prime-boost combinations. Toxicity testing is complete, and regulatory submissions are in preparation.

Alternative serotypes – Ad26 and chimeric vectors

Dan Barouch reviewed data on the suppressive effect of preexisting Ad5+ immunity on rAd5 HIV-1 vaccines and the desirability of novel vectors, not suppressed by NAbs, to replace or supplement the rAd5 vector. Selection criteria for developing such vectors are seroprevalence, immunogenicity, manufacturability and regulatory issues (safety). Two strategies have been identified: (1) identify a novel serotype Ad vector that combines low seroprevalence with high immunogenicity; or (2) construct a chimeric Ad vector by mapping the targets on Ad5 and replacing them with epitopes of other serotype Ads.

In a comparative evaluation of six rare serotypes (rAd11, 26, 35, 48, 49, and 50), Ad26 was chosen based on its immunogenicity profile (the second-highest immunogenicity (after Ad5) in mice and monkeys) and low seroprevalence (about 5 percent) in sub-Saharan Africa humans. The alternative is to modify the rAd5 vector in such a way as to evade NAbs while retaining this serotype's strong immunogenicity. Epitope mapping reveals that the principal targets of Ad5+ NAbs is the hexon major capsid protein, where most of the variability among serotypes is located in seven highly variable regions (HVRs). Investigators replaced Ad5 hexon HVRs with those from Ad48 and found that the resulting chimeric rAd5HVR48 was highly immunogenic, particularly when primed with DNA, and even in monkeys previously exposed to rAd5. This chimeric vector produced both systemic and mucosal T-cell responses involving both CD4+ and CD8+ cells. Work continues on both rAd26 and chimeric rAd5HVR48 vaccines, with IND submissions due in late 2007.

A potential strategy for the next generation of HIV vaccines would be based on heterologous rAd prime-boost. DNA/rAd5 has already been shown to be more immunogenic than rAd5 alone, and mouse studies suggest that heterologous rAd26/rAd5 could be comparably immunogenic to DNA/rAd5. The optimal prime-boost regime might employ rAd26 prime plus rAd5 or chimeric rAd5HVN48. In monkeys, all of these combinations induce polyfunctional central memory CD8+ T-cell lymphocytic response.

In response to questions, Barouch said that rare serotype vectors grow at higher titer than chimera, but both are manufacturable. Chimeric vectors outperform rare serotypes in mice, but less so in rhesus monkeys. The goal is to find out which works best in Ad5+ humans.

Novel rAd- and mycobacterium-based vaccines for HIV-1

Norm Letvin described other efforts to create chimera that evade preexisting Ad5 immunity, for example by moving the Ad5 fiber or fiber-knob region to rAd35, or by adding the RGD and LYS targeting motifs to rAd35. In addition, it is known that Ad41 induces disease only in the gastrointestinal tract and might become the basis for a mucosal vaccine; in mice, Ad41 has proven more resistant to acid and pepsin exposure than Ad5. Ad41 has the downside of causing diarrhea, but GenVec is working on a replication-incompetent variant. Others are working on oral-perenteral-intramuscular combinations.

Alternative serotypes – novel rAd35 and NHP Ad7 vectors

Nick Jackson described IAVI's "mid-term" strategy to develop low-seroprevalence HIV vaccines, which focuses on doing the hard production work now on the HER96 cell line and 20-liter scale batches. This program employs Gag, Pol, Nef, and Env antigens from circulating strains of Clade A. The immediate target is based on replication-defective rAd35, with rAd11 as a backup. Testing in rhesus monkeys showed that the rAd35 vaccine is immunogenic, with dose range response, and homologous boost increases strength and breadth of response. Pre-IND is complete, and Phase 1 trials are scheduled to begin in 2007Q1. In the longer term, IAVI is also working on a vector based on nonhuman primate adenovirus type 7 (C7).

Alternative serotypes – chimpanzee adenoviruses

Hildegund Ertl explained that considerable work has been done on a number of chimpanzee adenoviruses (AdCs) and on chimera that incorporate features of both AdCs and human Ad5. Much remains to be learned about AdCs. Prevalence and titer of NAbs to AdCs is low, although they do occasionally jump species. Studies in NHPs shows that preexisting Ad5+ immunity suppresses and alters the response to AdC68 prime plus AdC1 or Ad5 boost, especially T cell response and impacts on the spleen. In the end, however, in vitro neutralization assays fail to accurately predict neutralization in vivo. In addition, AdCs lead to higher levels of inflammation in mice, and may also have higher toxicity. Nevertheless, AdCs may prove to be a useful adjunct to human Ads because of their extremely low seroprevalence.

Replication-competent Ad vectors

Marjorie Robert-Guroff described work on developing a replication-competent rAd4 vector carrying Clade C Env antigen, which is seen as a good vehicle for inducing mucosal immunization. The wild-type virus has a good safety record and limited seroprevalence (immunization ended in 1966). Ad4 does not replicate in NHPs, but studies using rAd5-SIV Env, Rev, Gag, and or Nef showed that immunization to the upper respiratory tract elicited potent, persistent immune responses and strong, durable protection against SIV(mac251). Strategies for enhancing the efficacy of such vaccines include heterologous primes and adjuvants, different routes of administration, and changes in the viral gene targets.

The Tat protein, in particular, is highly conserved and cross-reactive, and anti-Tat Abs are associated with slow progression in AIDS. Animal studies have shown that Ad5-HIV Tat+Env prime, with a Tat+Env protein boost, provides higher Ab titers and lower viremia (both acute and chronic) that a multigenic regime that also includes SIV Gag and Nef. The explanation appears to be that extracellular Tat can facilitate the binding of HIV, so higher anti-Tat titers actually block HIV infection. Further study of the synergy between Tat and Env immunogens is under way.

In answer to questions, Guroff added that the oral route presents fewer safety problems than nasal. The vector is shed in stool for several weeks, but there is no transmission through casual contact. Wild-type Ad4 isn't seen as a huge problem, but several participants raised concerns about the impact of this vector on a population that was malnourished, diarrhetic and immunocompromised.

Discussion

In the discussion that followed, one participant urged the group to "respect the pathogen" – if the candidates currently in clinical trials aren't adequate, then it makes sense to support a diversity of vectors, inserts and combinations. But we already have a pretty good "tool kit" – there was consensus that we have plenty of candidates. If different Ads produce different kinds of immunity, then we should identify them; if they're all pretty much the same, then go with the best and drop the rest. This calls for a systematic comparison of the existing candidates and alternatives, preferably a standardized comparison that uses a single animal model and a single

immunological assay. In the end, this is a question of portfolio management: we may need a better understanding of why one vector is a better prime than another, but the task is to move an effective vaccine into production, and get it into the populations that need it. This suggests that the funding balance should be 80 percent for development of current candidates, 20 percent for further discovery.

Several participants pointed out that we still don't know the correlates of immunity for HIV, so we don't necessarily know what kind of vaccine we need. In addition, NIH will get the biggest bang for its buck by supporting basic science rather than advanced development. Consequently, the next phase in the process will be a challenge for the Enterprise. Each candidate has a champion who's made a large investment; how does the community now decide which candidate to pursue? This will require the various players to sit down and compare notes. It will also require a collection of investors, including DAIDS, but the majority of the money will have to come from elsewhere.

There seems to be pretty good agreement that there is no one best candidate, although clearly Ad5 would win if not for preexisting immunity. Nevertheless, there is a lot that the teams can learn from one another. Several participants also pointed to the need for better communication among teams, in order to share information and cross-fertilize the various approaches. Accelerated clinical trials would be useful, since human data will make many of these questions disappear.

National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Acquired Immune Deficiency Syndrome

AIDS VACCINE RESEARCH WORKING GROUP

January 31, 2007
6700-B Rockledge Drive, Bethesda, MD

MEETING SUMMARY

The AIDS Vaccine Research Working Group (AVRWG) met in public session on January 31, 2007, in Conference Room 1205 at 6700-B Fernwood Drive, Bethesda, MD.

AVRWG members present: Scott Hammer (chair), James Bradac (executive secretary), Susan Buchbinder, Barton Haynes (ex officio), Eric Hunter, Paul Johnson, Margaret Liu, Juliana McElrath, Bonnie Mathieson (ex officio), Gary Nabel (ex officio), Nina Russell, Jerald Sadoff, David Watkins, Ian Wilson.

Other NIH personnel participating:
- Carl Dieffenbach, Acting Director, DAIDS, NIAID;
- Peggy Johnston, Director, Vaccine and Prevention Research Program, DAIDS, NIAID;
- Alan Fix, Vaccine Clinical Research Branch, DAIDS, NIAID.

Speakers:
- Lawrence Corey, Fred Hutchinson Cancer Research Center;
- Richard Koup, Vaccine Research Center, NIAID;
- Scott Hammer

Session to discuss PAVE 100 protocol

Peggy Johnston called the meeting to order and explained that AVRWG members had asked Nina Russell to chair the session on the proposal by the Partnership for AIDS Vaccine Evaluation (PAVE) to conduct a PAVE 100 clinical study. Johnston asked other members of AVRWG to state their own real or perceived conflicts of interest on this subject. Most members had some perceived conflict, either as consultants, collaborators or grantees of IAVI or HVTN, and Gary Nabel joined chair Scott Hammer in recusing himself from the group's deliberations.

Johnston laid out the assignment to AVRWG: provide DAIDS with a technical assessment of the rationale, supporting data, trial design, and proposed timeline for PAVE 100, and comment on whether this trial would be a good use of public funds. Potential sources of funds include savings from contracts, implementation funds from the Clinical Trials Network (which assigned PAVE 100 a high priority), allowances for solicited programs, and other (outside) sources. Funding PAVE 100 will not affect the DAIDS payline. PAVE 100 will cost DAIDS an

estimated $100 million to $130 million over 6 or 7 years; other funds would come from IAVI and CDC.

Preclinical and clinical data in support of the PAVE 100 Phase 2B trial

Gary Nabel explained the concept behind the VRC multiclade vaccine, which addresses viral diversity by combining both envelope (Env), structural and regulatory proteins (Gag, Nef, Pol) from three of the six globally prevalent strains of HIV-1 (clades A, B and C). The hypothesis is that such a vaccine can control or prevent replication of diverse HIV isolates through CD4+ and/or CD8+ T-cell responses; the regime calls for DNA prime at months 0, 1 and 2 followed by rAd5 boost at month 6. Preliminary data shows that DNA+rAd5 immunization reduces early viral replication of SIVmac251 in nonhuman primate infection; that prime-boost does not diversify the $CD8^+$ response but does increase its magnitude; and that prime-boost does diversify the $CD4^+$ response but without increasing its magnitude. DNA plus rAd5 produces better results than DNA or rAd5 alone, or rAd5 plus rAd5, including mucosal responses. These results have been replicated in mice, hamsters and nonhuman primates (NHPs), and the vaccine now needs to be tested in humans.

Rick Koup reported the preliminary human immunogenicity data in support of PAVE 100. Immune response to Ad5 has been measured by multiple labs in several previous trials, using fully validated assays (ELISPOT, ICS and protein ELISA). It shows that one or more of the vaccine components is immunogenic in about 80 percent of population, and the suppressive impact of preexisting Ad5 immunity is seen only at high titers (>1000). In addition, the DNA prime plus rAd5 boost appears to increase the number of polyfunctional T cells, which is known from previous research to be correlated with nonprogression. Phenotype testing determined that the responding T cells have a "central memory" phenotype. Epitope mapping revealed a hierarchy of immunodominance, with more and stronger responses to Env protein, perhaps reflecting conserved regions, and fewer and weaker responses to Gag, Nef and Pol. In response to questions, Koup said that – setting aside the general differences in cytokine profiles between macaques and humans – these results closely mirror those found in NHPs. The proposed protocol may be more complex than necessary, and available data indicate that there is no increase in immunogenicity with three primes rather than two; the team will look more closely at this and revise the protocol as indicated. Better modeling will also be needed to determine a meaningful definition of a "high" Ad5+ NAb titer.

Scott Hammer outlined the protocol for PAVE 100, a Phase 2B (proof of concept), double-blind, placebo-controlled trial of the VRC multiclade, multigene DNA prime plus rAd5 boost preventative vaccine against HIV-1. If all milestones are met, the study will open in North America in July 2007. Primary objective is to evaluate the efficacy of vaccine in preventing infection and viremia diagnosed 26 weeks or later post-randomization. Secondary objectives include:

- Determine whether CD8+ T cell response is an immune correlate of protection;
- Determine the immunogenicity of the vaccine regimen;
- Compare efficacy, safety and immunogenicity for participants with high and low Ad5 antibody titers;

- Compare efficacy, safety and immunogenicity in male and female participants;
- Compare efficacy, safety and immunogenicity in participants from three regions (Eastern Africa, Southern Africa and the Americas) with different predominant HIV-1 serotypes;
- Evaluate efficacy endpoints for all participants by intent-to-treat analysis.

Additional, exploratory objectives include sieve analysis (HIV genomics), details of disease progression, long-term durability of protection, the role of central memory Cd4+ cells in progression, and the full suite of immune responses. Investigators estimate that 180 endpoints will provide 90-percent power for detecting differences in acquisition and viremia; if statistical significance is achieved for either primary endpoint, follow-up will continue until 140 infections have occurred in vaccinees.

Vaccination schedule calls for three DNA primes four weeks apart, followed by the VRC multiclade rAd5 vector at week 24. Study population includes 8,500 health, HIV-negative males and females age 18-45, at risk for HIV-1 through sexual exposure, from three regions with different circulating serotypes (clades A, B and C). The goal is to cast a broad net for exposure; inclusion criteria include unprotected vaginal or anal sex with HIV-positive or anonymous partners, or in exchange for money, goods or services, or with three or more partners. Projected incidence is 2 to 3 percent, or about 376 infections. Investigators have made a commitment to provide infected volunteers with long-term follow-up and access to care or rollover to a therapeutic trial (RV152 or HVTN802). Important externalities will include circumcision, pre-exposure prophylaxis and concurrent microbicide trials.

Larry Corey offered a brief comparison of PAVE 100 with the ongoing HVTN 204 trial of the Merck candidate vaccine. HVTN 204 also involves a DNA prime plus rAd5 boost in 480 at-risk volunteers, 240 vaccinees and 240 controls. Preliminary efficacy data will be available in 4 to 5 weeks, with full data analysis to follow in 12 months. Immunogenicity data show a 74-percent response rate, including good response and low and medium titers of Ad5+ NAbs and a 50-percent response even at high titers. Investigators have achieved good process quality in the handling of PBMCs and assays. Corey said that the two trials actually complement each other – PAVE 100 may better address the diversity of the epidemic in East Africa, but even better results if the data from the two trials could be combined through the use of a single, validated assay.

Gary Nabel summarized the morning's presentations. Preexisting Ad5 immunity may have a suppressive effect on the efficacy of an rAd5 vaccine vector. Preliminary data suggest that DNA plus rAd5 may have a unique immune effect. Safety and immunogenicity data from the United States support the decision to proceed in East Africa. Under these conditions, there are at least three things that can be learned from PAVE 100:

1. It will provide the first evaluation of DNA prime plus rAd5 boost, which induces potent and consistent immune responses that are quantitatively different from rAd5 alone.
2. It will analyze the breadth of immune response against globally relevant isolates, which the multiclade and multigene components of the VRC vaccine are designed to induce.
3. It is designed to define the immune correlates of protection against acquisition, reduction in viremia, and/or disease progression/survival.

Discussion

Discussion began with the question of what the future will be after PAVE 100. Participants said that this would depend on what's learned from trial, whether it succeeds or fails. Ideally, if this Phase 2B trial succeeds, the community would move expeditiously to a full Phase 3 trial. At this point it would be appropriate to consider different Ad vectors and more or new inserts. With regard to Ad5+ immunity, the differences between Ad5 + Ad5 and DNA + Ad5 are unlikely to be zero, although both will probably be somewhat dampened at high titers. We'll need a big data set to halt Ad5, and we still need to understand why some vaccinees still respond at high titers. If the differences between Ad5 + Ad5 and DNA + Ad5 really are zero, then the PAVE 100 investigators merely need to screen a baseline and adjust the inclusion criteria.

Budget decisions on whether to support one or the other vaccine can't be made without efficacy data. Perhaps the funding community should see itself as a hedge fund, making enough of an investment to move quickly on a new vaccine, if necessary, and trying to preserve those parts of the research that could be used for other vaccines. In any event, this will be an Enterprise decision, not (merely) a DAIDS decision. One participant pointed to the high cost of PAVE 100 as a Phase 2B trials and asked how much more it would cost to run it as Phase 3, thereby saving time (5 to 7 years) and money in moving ahead in the case of success. Some participants thought that the FDA might accelerate approval based on a successful Phase 2B trial, as they did for antiretrovirals, but others thought there would be regulatory questions that would require a full Phase 3 trial. A few participants questioned this approach, saying that the need for speed would be better served by opening and enrolling the trial as rapidly as possible. Others questioned the length of the followup period, suggesting that the same data could be generated with a shorter followup and a long-term registry. Investigators responded that the 144-week followup was for safety reasons and was a compromise on the 5 years that was originally proposed.

Several participants suggested that PAVE 100 needs clearer prospective definitions and criteria, for example in how to make a go/no-go decision. There is no substitute for data in humans, but would immunogenicity data for Southern Africa provide a threshold for go/no-go? Would they drop one region and continue with others, or merely adjust the inclusion criteria? The design does set minimum immunogenicity, and the breadth of response may be more important that the raw response rate. The go/no-go decision will be made 2Q2007 in the United States and 3Q or 4Q2008 in other regions. Several members pointed out that AVRWG is not in a position to set benchmarks; they must trust the protocol team to set criteria and the DSMB to adjust them. The protocol team will take a hard look at the Triad data and will report back to AVRWG in the future.

In response to a question about the community response to prescreening for Ad5+ NAb titers, investigators said that their African colleagues were not enthusiastic. They would prefer a vaccine that can be used in all of their population, and the preliminary data indicate that Ad5 immunity will not be a major problem. Certainly prescreening would a practical problem, slowing accrual and increasing costs.

Others questioned the true breadth of the vaccine and asked why more or different epitopes could be included. Investigators responded that there were practical limits on the size and complexity of the vaccine particle, beyond which it becomes unmanageable and unstable. They screened epitopes for inclusion and chose the top responders. Env, for example, may be the most polymorphic part of the virus, but it does have several highly conserved regions. They don't yet have full data on how many epitopes are being seen by vaccinees who receive the 6-plasmid product, but it's more than are recognized following the 4-plasmid vaccine, including one individual who is recognizing 19 epitopes. There will be an opportunity in the future to learn more about immunodominance.

Although there was no single specific recommendation formed by the AVRWG as a whole, many members suggested revisiting the extensive duration of follow up, exploring a mechanism to decrease the cost, and/or revisiting the power calculation around the correlates analysis. Suggestions were made to shorten follow-up for safety and instead develop a registry for long-term follow-up for safety with placebo recipients included. This will also shorten the length of the trial. The paucity of immunogenicity data from Africa was of concern to the AVRWG members. PAVE partners will need to follow up and develop clear, prospectively defined analysis that will need to be considered in making a decision as to whether to open the trial outside the Americas. In that regard, AVRWG was very clear in its belief that NIAID should not support a phase 2B trial in Africa that requires screening for Ad serology. In addition, they expressed that the critical read outs be based on assays that utilize epitopes that reflect HIV that is circulating rather than vaccine specific epitopes. Finally, the AVRWG requested an update on TRIAD results at the May meeting.

Program updates

Jim Bradac announced that AVRWG would next meet on 22-23 May. AVRWG will also meet for a full day on 20 August, in connection with the AIDS Vaccine 2007 Conference in Seattle. Bradac also reviewed DAIDS program milestones. CHAVI in particular has been making tremendous progress and will give a complete update at the May meeting.

Alan Fix reviewed the status of HIV vaccine clinical trials. Seven products are currently in trials or will begin trials this year. Efficacy data will be available from RV 144 in 2Q2009 and from HVTN 502 in 1Q2010, with HVTN 503 and PAVE 100 in mid-2011. Additional new products are under development by UPenn-Wyeth, SAAVI and others.

The meeting was adjourned at 1:00 p.m.