AIDS Vaccine Research Working Group

Meeting Minutes
August 29, 2006

NIH/NIAID/DAIDS
Amsterdam RAI Centre, Room C/D
Amsterdam, The Netherlands

MEMBERS
Dr. Scott Hammer (Chair)
Dr. James Bradac (Executive Secretary)
Dr. Eric Hunter
Dr. R. Paul Johnson
Dr. Margaret Liu
Dr. M. Juliana McElrath
Dr. Nina Russell
Dr. Jerald Sadoff
Dr. Steven Wakefield
Dr. David Watkins
Dr. Ian Wilson

EX-OFFICIO MEMBERS
Dr. Larry Corey, HVTN
Dr. Barton Haynes, CHAVI
Dr. Bonnie Matheson, OAR
Dr. Timothy Mastro, CDC
Dr. Nelson Michael, USMHRP
Dr. Gary Nabel, VRC

NIH REPRESENTATIVES
Dr. Edmund Tramont
Dr. Carl Dieffenbach
Dr. Peggy Johnston
Dr. Jorge Flores
Dr. Alan Fix

SPEAKERS
Dr. Jorge Flores, DAIDS
Dr. Gary Nabel, VRC
Dr. James Bradac, DAIDS
Dr. M. Juliana McElrath, HVTN

AIDS Vaccine Research Working Group met from 12:00 noon to 3:00 p.m. on August 29, 2006 in a public session. Dr. Scott Hammer chaired the meeting. The agenda included discussions on setting criteria for advancing vaccines into large-scale clinical trials; updates from VRC on their vaccine candidates and future plans; and approaches to obtaining comparative data from clinical trials. The following is a summary of the presentations, key points raised during the meeting, and recommendations for next steps. A consolidated list of action items is provided at the end of this document.

Criteria for Advancing Vaccine Candidates into Large-scale Trials
Presentation by Dr. Jorge Flores

Dr. Jorge Flores exhorted the AVRWG committee to establish criteria that would help DAIDS make decisions on which HIV vaccine candidates should be carried forward into large-scale Phases II, IIb and III trials. The questions before the committee were:

- What data from Phase I trials should be used to establish criteria?
- How high should the bar be set for advancing vaccines further into human trials?
- What data should be presented for the committee's assessment?

Past Criteria (or data):

- Vaxgen gp120 - neutralization of primary isolates

- ALVAC/gp120 Thailand trial RV 144 - 25% cumulative response of CTL., 60% proliferation to ENV, 80% neutralization of B and E laboratory strains
- ALVAC/gp120 trial HVTN 501 - >30% CTL response and/or IFNγ elispot response
- Merck Ad5 trial HVTN 502 – 67%IFNγ elispot response
- Merck Ad5 trial HVTN 503 – ≥30%IFNγ elispot response

Studies to use:

- Natural History – evolution/ acute infection
- Nonhuman primate – immunogenicity/protection and?or acquisition/progression

Data to include:

- Do you need validated assays or not?
- What amount/consistency of data needed? Repeat with or without a trial?
- Analysis of breadth of response? Functional breath?

Bar set for advancing next vaccine candidate

- Different vaccine design?
- Different rational/study design?
- Potential advantages – better protection in NHP? multifunctional response?

Discussion

For at least three vaccines immunogenicity did not necessarily correlate with control. DNA/MVA vaccines and Merck Ad5 Gag, Pol, Nef resulted in a *log* decrease in SIV viral load in macaques. So unless an experimental vaccine performs better than the control in lowering SIVmac 239 or SIVmac251 setpoints by a *log* magnitude or more in Indian rhesus macaques of diverse MHC backgrounds, the candidate may hold no advantage over the vaccines already in testing. Since the immunological correlates of clinical protection remain unknown, Dr. Watkins advocated the use of protection against challenge rather than magnitude of immune response as the yardstick.

Dr. Hammer suggested that the relative merits of animal immunogenicity and challenge data along with safety information from early human clinical trials should be weighed in the decision to move forward into large-scale efficacy trials.

A vaccine generates different responses in humans and primates, but the right responses that provide protection against infection remain undefined. In fact, macaques and humans do not receive the same immunogens in a vaccine rather they are vaccinated with different antigens. The dilemma still remains about the criteria that should be applied to move vaccines forward into efficacy trials, but no vaccine should be propelled into human clinical trials if they fail to achieve a one *log* reduction in control of viremia in monkeys for at least 1 year.

If little ability exists to distinguish among several vaccine candidates, then it will be more important to take a vaccine forward that is different or complements existing vaccines. Normally when no data exists on correlates of immunity, nor ideal animal models, human data is used to obtain hints. If long-term non-progressors respond more to Gag than gp120, then it is a clue that should not be ignored during the design of prophylactic vaccines. If immune responses are directed against certain antigens in primates but not humans, they should be examined further.

Dr. Sadoff argued against venturing into Phase IIb trials, instead favoring smaller trials of 500-1000 people in high incidence populations. In fact, the high incidence regions should conduct Phase I trials too. He advised that in these trials breakthroughs in immune response to non-vaccine antigens should be examined as measure of viral intolerance. Phase IIb trials will not

provide clues about correlates of immunity; only large Phase III trials can provide those answers.

Dr. Hammer proposed that a conference call should be arranged in October to discuss in detail among the committee members on criteria to advance next candidate vaccine into efficacy trial. All of the members agreed to participate in the call.

Update on Phase II trials of VRC vaccines, Timeline for Phase IIb trial
Presentation by Dr. Gary Nabel

Dr. Gary Nabel provided an update on the evaluation of the VRC multiclade candidates. He summarized knowledge gained, information expected, and some of the unique features of this candidate relative to other candidates examined to date.

As an immunogen the platform of DNA priming/Adeno boosting proved immunogenic. They demonstrated reduced peak viremia (0.5-1 *log*) and transient reduction in setpoint (~1 log) in SIVmac251 (10 MID_{50}) model lasting up to day 126 with marked improvement in survival (*Science 312: 1530 Jun 9, 2006***)**. The prime-boost approach not only produced higher magnitude of T cell responses, but also multiple cytokine producing cells that seem to correlate with non-progression and vaccine protection. **The most important predictor of vaccine efficacy and correlate of protection for this vaccine appears to be preservation of central memory $CD4P^+$ T cells ($CD28P^+$, $CD95^+$).**

For expanded human clinical trials, VRC is going to use a 6 plasmid combination that includes Env gene from three different clades (A, B, C), Gag, Pol, and Nef. Earlier studies had used a fusion protein of Gag, Pol and Nef. Lack of robust Gag responses, prompted the decision to place Gag on a separate plasmid. Adenovirus contains Env gene from clades A, B, and C. Under GMP production Nef was found unstable, omitting Nef from the Gag/Pol fusion construct led to clinical grade material.

In Phase I trials DNA priming and adeno boosting resulted 3-5 fold higher immune response than either component alone, but the hierarchy of responses remains same. With the 6 plasmid product responsiveness to Gag is higher. In the VRC 008, the 6-plasmid prime-boost combination approach in the small number of volunteers, revealed no significant association between Ad5 immunity and level of responsiveness at 10^{10} dose levels.

Considerable progress has been made in enrollment for Phase II trials through HVTN (HVTN 204), IAVI (V001), and USMHRP (RV172). HVTN has completed enrollment in US, and are waiting to fill their slots in Caribbean and South America. They have recently begun enrollment in South Africa; currently 44 individuals have been enlisted. IAVI has briskly enrolled their quota at their trial sites in Rwanda and Kenya. USMHRP has recruited 556 out of 908 subjects.

The data emerging from the Phase II trials in early 2007 will drive the decision to move into Phase IIB trial called PAVE 100 through organizations participating in Partnership for AIDS Evaluation (PAVE). A protocol committee has been designated for the trial. In preliminary discussions, the study has been designed as endpoint-driven trial design of 180 infections. The trial will be statistically powered to distinguish vaccine efficacy of 40% for infection acquisition, and 0.4 *log* for viral load endpoint. Data will be stratified by gender, region and Ad5 titer; study number and duration are still under development by PAVE 100 protocol team.

The impact of pre-existing Ad5 immunity on vaccine efficacy remains undetermined. In preliminary studies no major impact has been observed. If Phase II studies suggest a minor or modest impact of Ad5 immunity, then PAVE 100 will proceed as roughly outlined. However, if a major impact is observed, then high Ad5 titers volunteers may be eliminated or it will be a US only trial.

Discussion

Dr. Sadoff recommended that Gag/Pol/Nef responses from VRC and Merck vaccines should be compared. One of the criteria the committee set up was that every succeeding vaccine should be better than the preceding candidates. In the VRC data Gag responses hover around 100-400 ELISPOT responses. Merck responses seemed better but the variations could be attributed to assay differences. Comparative data will allow the group to compare the two candidates.

Dr. McElrath confirmed that in the HVTN trials of the Merck and VRC products the same assays will be performed that will yield a comparison of the two vaccines. Dr. Koup added that VRC has compared the Ad5 titer assays used by Merck and VRC, which are based on the same protocol but with minor differences. VRC titers are 2-3 fold higher than Merck titers. An Ad5 neut titer of 100-200 in Merck assay equals 100-500 in VRC assay.

As part of the contingency in the Product Development Plan, VRC has begun work on second generation products based on other adeno-serotypes. VRC currently has under GMP production a prototype Ad35 vector expressing clade A Env, which is under analysis for lot release criteria. Most likely, the product will be ready for testing in Q1 2007. VRC and HVTN are developing protocols to test priming and boosting combinations of DNA/Ad35 and Ad5/Ad35. As Ad35 uses the same packaging lines as Ad5, it will be easy to move into trials in a two-year time frame, if necessary.

Dr. Sadoff mentioned that Ad35 based malaria and TB vaccine are going into human clinical trials in 2 months, so data accumulated with those vaccines should help the HIV field.

Dr. Johnston suggested that one potential topic for the May workshop could be alternatives to circumventing immunity to Ad5, if necessary, to give guidance to future investment of NIAID resources. Dr. Johnston reiterated that the committee should give feedback on the kind of data they would like the presenters to show to give their assessment. Copies of the trial design of PAVE 100 will be distributed to the committee.

Approaches to obtain comparative data from vaccine trials: Standard reagents, standard assays, standard vaccine gene inserts
Presentation I by Dr. James Bradac

Dr. Bradac asked the committee if DAIDS should require all investigators requesting NIH support for vaccine design, development and production to utilize standard HIV gene inserts to facilitate comparison of the vaccines, or if standardized assays and reagents will suffice for judging the relative merits of the candidates.

In two instances standard gene inserts will not be required by NIH.

- Investigator has designed HIV vaccine using unique gene inserts designed to improve breadth or immunogenicity of the vaccine.
- HIV vaccine has been tested in humans and financial backing sought to make cGMP lot for Phase II/III clinical trials.

The early and mid stages of vaccine development may be more appropriate for requesting insertion of standard genes.

- When researchers have considerable proof of principle studies with SIV or SHIV constructs, and request support for HIV vaccine design.
- Proof of principle has been established as above, but HIV constructs have already been designed using the investigator's choice of insert. Funding is required for cGMP production for clinical testing.

A University of Capetown group led by Carolyn Williamson in 2003 designed standard genes (Gag,Pol, Env) using South African clade C consensus sequence, and provided their genes to several vaccine makers. NIAID supported SAAVI's efforts to insert the genes into DNA/MVA platform, while AlphaVax and Targeted Genetics with support of IAVI put the genes into VEE and AAV respectively. These latter two products are in early clinical trials and comparative data is just becoming available on these platforms. Recently DAIDS requested two investigators to insert VRC's clade B Gag/Pol and clade A env genes as standards into their platforms. Merck used Gag as a standard gene to compare Ad5 and MVA vectors. Using ELISPOT assay, Merck found Adeno performed better in macaques, so they decided to go forward with Ad5. But other MVA constructs have shown better immunogenicity with Gag gene than seen in the Merck study. Thus not every gene may prove stable or immunogenic in every vector. **Dr. Bradac petitioned the panel to discuss the feasibility of using standard genes as test of platform inserts.**

Presentation II by Dr. M. Juliana McElrath

Dr. McElrath described a new peptide reagent set developed by HVTN to perform comparative analysis of CTL-based vaccine candidates. Steve Self and Fusheng Li developed a biometric approach to define potential T cell epitopes (PTE). The PTE panel consists of 15 amino acid peptides whose sequences span all possible 10 amino acid T cell epitopes in HIV-1 that occur at a frequency of greater than 15%, an arbitrarily chosen cutoff point. These sequences include all the circulating strains annotated in the Los Alamos Database (~100-150 strains per subtype), and reagent panels can be devised to be clade-specific or global.

HVTN conducted a pilot study comparing the usability of PTE panel and clade B consensus peptide panel in detecting Nef-specific CTL responses in PBMCs from 12 US HIV-1 infected individuals and 12 US HIV-1-uninfected donors. The clade B consensus peptide set contained a total of 49 peptides with 15 mer peptides that overlap by 11 amino acids, while the PTE peptide set of 88 peptides covered greater than 70% of clade B Nef sequences in the Los Alamos database. With the PTE set IFN –γ ELISPOT assay picked up 44 Nef-specific epitopes of which 12 were unpublished, while the consensus set recognized 26 epitopes including only 6 unpublished regions. Thus, the PTE set picked up more epitopic domains.

The global PTE peptide set of 1458 peptides, which is 2.3 times greater than an overlapping peptide set, was validated in HVTN054, a Phase I trial of the VRC recombinant Ad5 vector expressing clade B Gag/Pol/Nef/ and Env from clades A, B, and C. For this purpose an expanded global PTE set was generated. This peptide set covered epitopes across all clades, with 160 peptides per pool containing 3 Env pools, 2 Gag Pools, 3 Pol pools that were also pooled by frequency of PTE coverage. The PTE panel detected robust HIV-specific CTL responses and performed satisfactorily.

Studies have been planned to compare responses with PTE *versus* VRC vaccine strain peptides in conjunction with Dr. Rick Koup in the VRC. The global PTE can be used as a universal set to compare various vaccine candidates in HVTN portfolio. Other networks can also avail of the global PTE set for use in their studies. HVTN plans to use the PTE panel in

Phase II studies conducted with VRC, and in PAVE100. A PTE C panel has been designed for use in Merck protocol 502 and 503 trials.

Discussion

Most members of the group were averse to the idea of using a standardized insert as a "gold standard" as imposing this criterion may throttle innovation. Instead most members favored the use of standardized reagents and assays. Although Dr. Sadoff suggested that Gag may be used as a standard insert as a large body of data exists on this gene, but costs and ease of development and manufacture should determine the decision.

The members also cautioned that while standardization of assays constitutes a step forward in the right direction, the IFN-γ ELISPOT responses may not be readouts for correlates of protection. Some concern was expressed that the evolving nature of HIV could render the PTE set obsolete in two years, but Dr. Steve Self reassured the committee that that evolving viral subtypes are continually evaluated, and the PTE set will be enriched with new viral peptides as needed. A comparison was made with Dr. McCutchan's database of sequences of acute HIV infection isolates, and surprisingly the PTE set covered all epitopes.

The committee recommended that DAIDS should be flexible, and the decision of standard insert depends on the hypothesis of the study. If a study uses a new vector, then standardized insert may be useful.

Action Items

1. **Set up conference call in October to get more input on criteria to advance next candidate vaccine into efficacy trial.**
2. **Decision on standard insert should not strict, rather dependent on whether an insert or vector is under scrutiny.**
3. **A potential topic for AVRWG May workshop is how to maximize T cell immunity. Information on Ad35 based malaria and TB vaccines should be included.**
4. **Encourage HVTN to compare Gag-Pol responses in trials of Merck and VRC products.**
5. **Evaluate impact of prior immunity to Ad5 on immune responses.**