National Institutes of Health (NIH)
AIDS Vaccine Research Working Group (AVRWG)

January 10–11, 2006
6700-B Rockledge Drive
Conference Room 1205
Bethesda, Maryland

Meeting Summary

The NIH AVRWG met on January 10–11, 2005, in Bethesda, Maryland. AVRWG members in attendance were Scott Hammer (Chairperson), James Bradac, Susan Buchbinder, M. Juliana McElrath, Eric Hunter, R. Paul Johnson, Margaret Liu, Nina Russell, Jerald Sadoff, Steven Wakefield, and David Watkins.

Ex officio members Lawrence Corey, Karen Goldenthal, Barton Haynes, Timothy Mastro, Bonnie Mathieson, Nelson Michael, and Gary Nabel also attended. NIH representatives participating in the meeting included Edmund Tramont and Peggy Johnston.

WELCOME

Dr. Edmund Tramont, Director of the Division of Acquired Immunodeficiency Syndrome (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), welcomed the AVRWG members and others in attendance. He expressed his appreciation for the AVRWG's recent support for new trials and reports -- work that has helped to establish priorities for the Institute.

Dr. Tramont expressed his gratitude and presented plaques to Dr. Bette Korber and Dr. Barton Haynes, who were rotating off the working group (Dr. Haynes will remain as an ex officio member). New working group members are M. Juliana McElrath, M.D., Ph.D.; R. Paul Johnson, M.D.; Margaret Liu, Ph.D.; and Nina D. Russell, M.D. Colonel Nelson Michael, M.D., Ph.D., has replaced Deborah Birx, M.D., as an ex officio member. Timothy D. Mastro, M.D., has replaced Alan Greenberg, M.D., as an ex officio member.

OPENING REMARKS

Dr. Scott Hammer, chairperson of the AVRWG, also welcomed the participants and expressed his appreciation for the work of Dr. Haynes, the previous chair. Dr. Hammer reminded the participants that the AVRWG is a working group, not an advisory committee, and reports to the AIDS Research Advisory Committee (ARAC). As a working group, the AVRWG has flexibility in offering advice to DAIDS. AVRWG member, Dr. Susan Buchbinder, who also serves on the ARAC, can act as liaison.

Dr. Hammer presented and described the 2006 AVRWG Annual Report, which is in draft form. The report was fashioned in a bullet-type structure for the purpose of revealing key issues quickly and forcefully. Dr. Hammer asked the working group members to comment on the utility of the report's form and suggest improvements.

The next meeting of the AVRWG will take place May 25–26, 2006, in Bethesda, Maryland. Dr. Hammer asked the members to forward to him ideas for that meeting's agenda—including ideas for a science session.

CHAVI UPDATE

Dr. Haynes provided an update on development of the Center for HIV/AIDS Vaccine Immunology (CHAVI) program. He outlined the program's organization (leadership group and projects), timeline, and activities accomplished so far. The program has contracted for tissue/sample repository, for databases and statistical support, for site management, and more. Some protocols have been drafted.

Dr. Haynes listed the 11 CHAVI Year 1 clinical sites and the members of the CHAVI Advisory Board, which will meet in April 2006. Work on retrospective samples has begun. Other work underway includes sequencing of transmitted viruses, ontogeny of neutralizing antibody responses, ontogeny of T-cell responses, and structural studies of the transmitted HIV-1 trimer.

CHAVI Year 1 features four cores: host genomics and viral genetics, vector development, structural biology, and clinical trials.

The CHAVI Executive Committee will hold a meeting on April 19–20, 2006, in Durham, North Carolina. The CHAVI Web site is at www.chavi.org.

Discussion

Dr. Johnston noted that CHAVI will address the most difficult questions, will change and evolve over time, and will not replace existing programs. As currently planned, CHAVI is 90 percent discovery-driven. The program planners intend to focus on research that has a good chance to answer critical questions.

Dr. Haynes stated that he would describe the CHAVI portfolio in greater detail at the next AVRWG meeting, showing, for example, the development of vaccine platforms. By the end of the first year, the planners hope to establish the best mix of discovery work and development work. Dr. Steve Wakefield encouraged the program planners to be ready to disseminate discovery information to communities. Dr. Korber added that one goal of the program is rapid dissemination of results to the scientific community.

UPDATE ON THE NIAID/USMHRP INTERAGENCY AGREEMENT

Dr. Johnston reported on an agreement between the NIAID and the Military Research and Material Command (MRMC), specifically the U.S. Military HIV Research Program (USMHRP). The agreement recognizes common goals for research on infectious diseases, complementary missions and assets, distinct capabilities, and more.

The two agencies have signed a memorandum of understanding, which addresses annual reviews, a governance structure, and activities. Through the agreement, the agencies can plan in parallel while being more selective in employing resources.

AIDS VACCINE PRECLINICAL UPDATE

Dr. Bradac provided an update on preclinical vaccine efforts supported by DAIDS, providing the AVRWG members with listings of current programs, cooperative agreements, and grants.

Dr. Bradac reviewed new awards in 2005. The HIV Research and Design (HIVRAD) funded four new programs, led respectively by Christopher Miller at UC Davis, Robert Whalen of Maxygen, David Knipe at Harvard, and Barton Haynes at Duke University. Dr. Bradac reviewed research projects within each of those awards.

The Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) made one new award to Daniel Barouch at Beth Israel Deaconess. The HIV Vaccine Design and Development Teams (HVDDT) made two new awards to Philip Johnson at Children's Research Institute, and Susan Barnett at Chiron Corporation.

FY 2006 initiatives include awards under the Phased Innovation program, HIVRAD, IPCAVD, and the simian vaccine evaluation units.

SCIENTIFIC SESSION: MUCOSAL FRONT LINE—THE PRESERVATION OF MUCOSAL CD4 CELLS AS A DETERMINANT OF VACCINE AND THERAPEUTIC EFFICACY

The Pathogenesis of HIV Infection

Dr. Daniel Douek of the NIH's Vaccine Research Center (VRC) described the well-known pathogenesis of HIV infection, involving a rapid, massive initial depletion of CD4 T-cells, followed by a slow continual depletion. Scientists have proposed two hypotheses for this pattern: (1) HIV causes massive CD4 T-cell death, accompanied by an increase in immune activation, and (2) HIV causes massive immune activation, with CD4 T-cell death as a consequence.

Dr. Ronald Veazey noted in 1998 that the earliest targets of infection in macaques were mucosal cells of the intestine, where the fraction of CD4 T-cells is much higher there than in the peripheral blood. This finding was confirmed in humans. Also, CCR5+ has a

much greater presence in T-cells of the gut and is found to be massively depleted upon HIV infection. Reconstitution of T-cells of the gut is poor in both acute and chronic phases of infection. A conclusion is that peripheral blood CD4 T-cells may not reflect CD4 T-cell dynamics, for example, at major lymphoid sites. Immune activation in the chronic phase is the best predictor of rate of progression to AIDS.

Dr. Douek stated that a vaccine must preserve the numbers of CD4 T-cells in the gut and thereby slow disease progression.

In discussion, Dr. Douek noted that uninfected cells in the gut might be resting or be the result of temperospatial characteristics. Dr. Michael suggested that the results called for an early start of highly active antiretroviral therapy (HAART). How long should therapy be maintained? Dr. Douek proposed that it be maintained as long as the patient can stand it.

Dr. Douek remarked that, despite similarities with gut cells, lung cells do not have lymphoid aggregates and produce a different result regarding preservation of tissue. In HIV infection, the trafficking of cells is disturbed, so that, for example, effector-type T-cells are found in lymph nodes when they should be expected elsewhere. Dr. Haynes suggested that researchers study long-term non-progressors to compare results for T-cell depletion, etc.

Studies of Mucosal CD4+ T-cell Depletion in SIV-infected Macaques

Dr. Ronald Veazey, of Tulane University, cited his work in macaques showing massive depletion of intestinal CD4 T-cells expressing CCR5. This continues in spite of the application of HAART. Studies have found similar depletion of CD4 T-cells in vaginal mucosa. CD4 T-cell depletion is associated with direct viral infection of mucosal cells. HIV might be called a disease of the mucosal immune system. The turnover of viral target cells is a key in progression.

Dr. Veazey noted current studies of mechanisms of depletion, of CD4 T-cell loss in peripheral blood, of depletion during early treatments, and of cytotoxic T-lymphocytes (CTLs). There appears to be no relationship between protection and virus-associated CTLs.

Dr. Veazey concluded that the pathogenesis of HIV and SIV correlates with CD4+ T-cells in the intestinal tract. We need a vaccine that elicits a mucosal response. We need good models of protection (now being developed).

In discussion, Dr. Veazey noted that the characteristics of preserved CD4 T-cells have not been determined. In pre-exposure studies applying prophylaxis, the animal subjects did not become infected. Dr. Sadoff remarked that CD4 T-cells are made elsewhere in the body, so that their depletion may indicate something other than a “gut infection”—that is, gut infection may be a symptom rather than cause.

Dr. Hammer stressed that the CD4 T-cell count tracks disease progression. Despite the strong effects in the mucosal area of the gut, measurement of CD4 T-cells in the peripheral blood accurately indicates disease progression. Therapy today is conservative, in that it allows the peripheral CD4 T-cell counts to fall significantly before applying a next round of toxic medication.

Vaccination Preserves Memory CD4 T-cells During Acute SIV Infection

Dr. Joseph Mattapallil, of the VRC, focused on the fact that the mucosal CD4 T-cells are memory T-cells. Other tissues feature a mix of CD4 T-cell types. In all tissues, HIV leads to depletion of the memory type. Therefore, memory T-cell dynamics accurately discriminates the effects of viral infection. Again, a vaccine must target the mucosal cells, which are the primary target of the virus.

Dr. Mattapallil and his co-workers applied Dr. Gary Nabel's vaccine to rhesus macaques and challenged them with SIV. As a result, fewer memory CD4 T-cells were infected, although the improvement was modest. The level of vaccine was high. It appeared to create neutralizing antibodies against primary isolates. The researchers plan to repeat the experiment challenging with lower doses of SIV.

Dr. Mattapallil concluded that vaccine can preserve memory CD4 T-cells in all tissues. A reduction in the loss from 80 percent to 20 percent would be very helpful.

Virologic and Immune Correlates of Survival in Vaccinated Rhesus Monkeys Challenged with SIVmac251

Dr. Norman Letvin, of the VRC, described experiments in which immunogens (plasmid DNA followed by rAd boost) were applied to groups of monkeys and cellular response to SIV measured. The vaccinated monkeys experienced only a transient reduction in viremia. At 800 days, plasma SIV RNA levels remained lower in the vaccinated monkeys. Over the long-term, the vaccinated monkeys displayed a statistically significant survival advantage. Long-term clinical outcome correlated with plasma SIV RNA level.

Early trends did not predict long-term survival, and Dr. Letvin's group performed additional research to determine what does. One finding was that central memory CD4 T-cells (not other memory T-cells) were predictive. Dr. Letvin concluded that the research results suggest immune correlates for evaluating CTL-based vaccines in humans.

Vaccine-Induced Cellular Immune Responses in Rhesus Macaques Challenged with SIVmac239

Dr. David Watkins, of the Wisconsin Regional Primate Research Center, described the Merck-supported DNA Ad5 vaccine trial, which produced a transient decrease in viral replication and a reduction in T-cell loss in the initial acute phase of infection. The trial

employed gag, tet, rev, and nef proteins as immunogens and found a strong and broad immune response to the virus SIVmac239. The vaccine and challenge virus were matched. Dr. Watkins concluded that vaccine-induced cellular immune responses can control replication. Memory cells can be preserved to some extent.

CLINICAL TRIALS UPDATE

Dr. Joseph Chiu, of NIAID's Division of AIDS, provided an update on the Institute's clinical research program. He reported that the HIV Vaccine Trials Network (HVTN) added five new sites, in Philadelphia, Chicago, Peru, Jamaica, and South Africa. He listed other ongoing trials/protocols, 11 of which were open for enrollment during 2005. Two large trials begun in 2005 were the Merck Phase II trial (discussed below) and the VRC Phase II trial. Two additional Phase II trials will begin in 2006–2007.

The Thai Phase III trial was fully enrolled (16,403 persons) in November 2005. The Data and Safety Monitoring Board (DSMB) recommended continuation of the trial in October 2005, and the trial's set point was elevated.

PLANS FOR THE MERCK IIb TRIAL (503) IN AFRICA

Dr. Hunter chaired a session on the proposed Merck Phase IIb trial, planned for South Africa. He began by asking the participants to disclose potential conflicts of interest. Dr. Hammer cited his own research. Dr. McElrath stated that she is director of the HVTN lab program. Dr. Wakefield stated that he is an employee of the HVTN, and Dr. Buchbinder stated that she is an investigator in the HVTN. Dr. Sadoff stated that he is a former Merck employee. Dr. Liu stated that she is a former Merck employee and holds stock in the company. Dr. Haynes stated that he is recipient of a grant from Wyeth.

Introduction

Dr. Corey introduced the session by citing unresolved issues. Will vaccines work? If they control viremia, what will be the pattern? What if the response is a wide spectrum? Will the use of the Ad5 vaccine be affected by preexisting immunity effects?

Immunogenicity and Safety Data of MRK Gag-Pol-Nef Vaccine

Dr. John Shiver, of Merck & Company, described aspects of the trial's vaccine development strategy, including selecting the best vectors for eliciting cellular immunity, identifying antigens most likely to be cross-reactive, obtaining preclinical proof-of-concept (in clade B) for the impact of cellular immunity on viral infection, and developing backup vaccine candidates that address shortcomings of current vectors.

The Merck trial will test vectors expressing Gag, Pol, and Nef genes, measuring T-cell responses and cross-reactivity. An earlier protocol testing various doses and endpoints, revealed good immunogenicity with little difference among the doses. Phase I safety studies found the vaccine to be well tolerated. In general, the researchers have found

significant cross reactivity of the anti-HIV T-cell response (that is clade B vaccine with viruses of the same or different clades), primarily because of the Gag and Pol components.

Study Design of HVTN Protocol 503—Phase IIb Trial of MRK Ad5 Gag-Pol-Nef Vaccine in the Republic of South Africa

Dr. Steven Self described the structural and statistical features of the proposed Merck 503 protocol that will lead to a test-of-concept. The trial will provide a profile of frequency of viral subtypes in the population. The efficacy of the Merck antigen currently is uncertain, yet it offers very good coverage of T-cell epitopes known to exist in high frequency in the population. It also offers fair coverage of epitopes with intermediate frequencies.

The Merck trial is multicenter, randomized, double-blind, and placebo-controlled. Endpoints will include infection and viral load. The concept being tested in the trial is not simply efficacy, but robust efficacy—and in a varied setting.

Overview of the NIH Epidemic and Community Preparedness for the Trial

Dr. James Kublin provided a brief overview of HIV in South Africa. Overall prevalence is about 10 percent. The prevalence for young women has increased sharply in recent years—for females aged 25–29, the prevalence now is greater than 30 percent. Dr. Kublin presented a map of South African provinces, showing the distribution of HIV prevalence and target populations. Populations for the Merck trial are being drawn from five regions of the country, with the largest cohort from Soweto (1.1 million).

Dr. Glenda Gray described the capacities of the South African sites to engage in the trial. Most regulatory preparations have been completed. Dr. Gray outlined plans to address adolescents, who are disproportionately affected by the South African AIDS epidemic. Community advisory boards targeting adolescents have been established, and a Phase I trial to evaluate the safety and tolerability of the administration of the MRKAd5 vaccine has been proposed. Various legal factors make the development of a separate adolescent Phase I trial necessary.

Timeline, Costs, and Wrap Up

Dr. Corey stated that the Merck trial will cost more than $32 million. This includes the five sites and 3,000 enrollees. The HVTN SSC has ranked the trial highly. The trial will require expanding the HVTN sites in Soweto, Cape Town, and elsewhere. It will feature enhanced buy-in by the SAAVs and will break the adolescent barrier. The enhanced recruiting will help to increase enrollment for the VRC trial.

Discussion

There was considerable discussion about the plusses and minuses of the proposed 503 trial. All members were asked to write down their opinions concerning the trial.

The plusses included:

- It will be critical to have non-clade B data from a developing country with the Merck product close on the heels of the 502 data both to answer the clade question and to have data to compare with the VRC products.
- Non-clade B data will be critical both scientifically and politically for introducing potentially partially effective T cell vaccine in the developing world.
- Additional efficacy data will move the field forward.
- Population, behavior differences from 502 enhance rationale for doing 503.
- Arguments for improving the infrastructure rather than inhibiting other trials is important.
- Only way to address "mismatched" issue at this time with highly immunogenic vaccine.
- Importance of testing in MSW, female population.

Minuses included:

- Concerned about the low frequency of responses in the earlier Merck trial. One or two responses per gene will not be very informative with regard to the impact of clades if we can develop vaccine protocols that allow greater number of responses.
- Lack of clade match coupled with difference in study population and routes of transmission will complicate comparison with 502.
- Need to minimize effect of the cost of these studies on other HVTN trials and AIDS vaccine basic research.
- This study is premature. 502 and VRC phase I/II studies need to be completed and data cross-analyzed prior to launching a $32M trial that extends, but does not transcend, the scientific questions raised in 502.
- Should go forward only if it does not interfere with the VRC and other trials.
- Given the enormous expense of the 503 trial in this time of NIH fiscal woes, it seems more reasonable to make a decision about 503 after the 502 results are available.

Suggestions should the trial go forward:

- Initial immunogenicity assays should be carried out on clade C peptides to assess in a realistic way the true immunogenicity.
- Re-look at a number of patients for determination of who are infected vs. the epitopes/match since otherwise less will be learned about why vaccine fails.
- Ensure expectations are established and managed as this is being billed as "efficacy."
- Address central memory vs effector memory in the trial.
- Recommend that Merck consider making a matched clade C rAd for comparison in immunogenicity in this population.

ADJOURNMENT