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PERSPECTIVE

HIV Vaccine Research: The Way Forward

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The need to broaden research directed at answering fundamental questions in HIV vaccine discovery through laboratory, nonhuman primate (NHP), and clinical research has recently been emphasized. In addition, the importance of attracting and retaining young researchers, developing better NHP models, and more closely linking NHP and clinical research is being stressed. In an era of a level budget for biomedical research at the U.S. National Institutes of Health (NIH), HIV/AIDS vaccine research efforts will need to be carefully prioritized such that resources to energize HIV vaccine discovery can be identified. This article summarizes progress and challenges in HIV vaccine research, the priorities arising from a recent summit at NIAID, and the actions needed, some already under way, to address those priorities.

With more than 6500 new infections daily, HIV has assumed the dubious distinction of being one of the most catastrophic pandemics to confront mankind. Although the search for an HIV vaccine remains among the highest public health priorities, the identification of a preventive HIV vaccine has thus far eluded the biomedical research community, mainly because of the significant scientific obstacles presented by the virus (1).

A logical first approach to developing an HIV vaccine was to investigate purified recombinant forms of gp120, the outer envelope protein of HIV, as vaccine candidates. Unfortunately, these products failed to protect volunteers in two phase 3 efficacy trials (2, 3), probably because the vaccine failed to induce antibodies that neutralize a broad array of primary isolates of HIV. The development of immunogens that elicit such broadly neutralizing antibodies remains a high priority research goal; their current absence from our vaccine armamentarium represents a major stumbling block in the development of an effective HIV vaccine (1, 4).

As research on the natural history of HIV disease progressed, a greater appreciation of the

role of T cells in the control of HIV disease progression evolved (5, 6). The immune response elicited by a successful vaccine likely will require both antibodies and T cells that recognize diverse strains of HIV and that reach the site of infection very quickly before infection becomes irreversibly established (7, 8). Given the hurdles of eliciting broad neutralizing antibody responses, the focus turned to evaluating whether a T cell vaccine that reduces viral replication after infection might serve as an intermediate step until immunogens that additionally induce broadly functional antibodies that block acquisition are identified. The benefits of such control could include a slower rate of disease progression and/or reduced transmission of HIV from the infected vaccinee to his/her partner. Indeed, several nonhuman primate (NHP) protection studies demonstrated that vaccine candidates that elicited T cell responses enabled animals to better control viral replication after challenge with a pathogenic virus (9–15). However, the inclusion of envelope in some of these vaccines, which leads to antibody induction, and the use of challenge strains that were homologous to the vaccine inserts suggest that most of these studies were not a stringent test of the T cell vaccine concept (16).

The MRKAd5 HIV-1 Gag/Pol/Nef candidate vaccine advanced to a phase 2b test-of-concept trial known as STEP, conducted by Merck & Co., Inc., and the HIV Vaccine Trials Network (HVTN). The vaccine neither prevented infection nor had an impact on early plasma virus levels in those who received the vaccine compared with the placebo recipients (17). In addition, a completely unexpected observation emerged in the STEP trial. Although a strict statistical analysis could not be performed because the data were analyzed in a post hoc manner, there was a trend toward a greater number of vaccine recipients infected, compared with the placebo recipients. Those

who entered the trial with prior immunity to the viral vector [adenovirus serotype 5 (Ad5)], who were also uncircumcised, appeared at increased risk of HIV infection if they received vaccine rather than placebo (18). Those with only one of these risk factors (uncircumcised or prior Ad5 immunity) appeared to exhibit intermediate risk, whereas there was no evident increase in risk among those with neither cofactor. The conclusions from this trial remain tentative given the small numbers of infections observed and the post hoc nature of the analyses.

The STEP trial results pointed to two critical areas for future research. First, did the STEP trial disprove the T cell vaccine concept, or was this a failure of the specific product, perhaps because this particular vaccine candidate did not induce immune responses of sufficient quality or quantity? For example, volunteers who received the MRKAd5 HIV-1 Gag/Pol/Nef vaccine mounted T cell responses to three to five epitopes on average. Perhaps that was insufficient to control the incoming virus. Other qualities of the cellular immune response (such as the balance between HIV-specific CD4⁺ T cell and CD8⁺ T cell responses, or the polyfunctionality, proliferative capacity, specificity, avidity, and the location or kinetics) may also prove important and remain to be examined.

Researchers are now utilizing STEP specimens to explore why this vaccine failed (19). Examining the genomic sequences of infecting HIV strains will demonstrate whether immunization resulted in early immunologic pressure on the incoming virus and may suggest which HIV genes or epitopes should be included in subsequent vaccines. Sequence information will also help elucidate whether infections clustered in social networks at certain trial sites.

The second critical research area pertains to a biological basis for the enhanced acquisition observed in certain subsets of volunteers. HIV cases did not appear to cluster around vaccination times, which suggests that the volunteers did not have enhanced susceptibility to HIV infection immediately after receiving the vaccine (18). Also, no differences in activated circulating T cells between vaccine and placebo recipients have been found (20). Additional studies with mucosal and biopsy specimens will be required to explore whether activation of cells at the mucosal sites were different between vaccine and placebo recipients. Whole-genome studies may reveal associations between host genetic background, baseline Ad5 titer, and HIV acquisition. Targeted studies are under way to determine whether a relation exists between human lymphocyte antigen (HLA) type or KIR (killer cell immunoglobulin-like receptor) genotypes and HIV acquisition and immune responses. Investigators are also working to determine whether the Ad5 vaccine elicited T cell or antibody-mediated responses that could have enhanced HIV acquisition.

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Table 1. Highest research priorities identified at the NIAID HIV Vaccine Summit, March 2008.

- Further define the first events leading to HIV and SIV's entering the gut-associated lymphoid tissue
- Determine the rate and mechanisms by which immune cells are mobilized to the site of infection and whether innate responses can alter the course of infection
- Characterize the cellular and humoral immune responses needed to control viral replication through modulation and/or elimination of specific cell subsets in the SIV model and studies of HIV-infected populations
- Determine the three-dimensional structure of HIV envelope trimer
- Determine why broadly neutralizing antibodies are uncommon and how they can be elicited
- Define the specificities of antibodies that neutralize diverse primary isolates
- Develop more relevant animal models (and challenge viruses) to explore protection or enhancement of infection or disease, especially heterologous challenge models
- Determine why SIV is apathogenic in some NHP species
- Identify correlates of vaccine-induced immune protection, especially the mechanisms whereby nonpathogenic (e.g., attenuated) SIVs prevent infection by pathogenic virus



Additional information on the summit, including the Webcast, can be found at the URL in (21).

Although the vaccine in the STEP trial failed to show efficacy, the trial unequivocally demonstrated that the current simian-human immunodeficiency virus (SHIV) NHP challenge model is not appropriate for evaluating T cell vaccines; that the SIV NHP challenge model is more predictive; that immunity to vectors, including at the tissue level, should be evaluated in future clinical studies; and that this smaller efficacy trial design can yield valuable information to help guide future efforts.

After the disappointing results in the STEP study, the National Institute of Allergy and Infectious Diseases (NIAID) held a scientific summit in March 2008 (21, 22) to solicit input on how best to reinvigorate and advance the field of HIV vaccine discovery research. The need to broaden research directed at answering fundamental questions in HIV vaccine discovery through laboratory, NHP, and clinical research was emphasized (Table 1). In addition, the importance of attracting and retaining young researchers, developing better NHP models, and more closely linking NHP models and clinical research was stressed.

Shortly after the summit, NIAID solicited additional input on how HIV vaccine discovery should be broadened and supported (23). Information from the summit and this solicitation will be used to help craft broad initiatives to stimulate HIV vaccine discovery research in 2009 and beyond.

The summit provided no clear consensus on whether a vaccine should demonstrate efficacy in a NHP model of AIDS as a criterion for entering clinical trials (the "gatekeeper" role). Yet it was clear that expansion of NHP vaccine studies

could contribute to vaccine discovery research (Table 1). NIAID is partnering with the National Center for Research Resources, the directors of the U.S. National Institutes of Health Regional Primate Centers, and others to examine how best to ensure the availability of sufficient numbers of NHPs and the appropriate infrastructure to support vaccine discovery research. Expansion of center capabilities is being explored. A workshop to further explore research needs and approaches in more detail is planned for the fall of 2008.

One area in particular that requires attention is the design of parallel NHP and clinical studies so that results from these studies are more directly comparable. The HVTN in collaboration with NHP researchers is launching a pilot program to support the exchange of researchers, including young investigators, between the clinic and NHP facilities so that common questions in HIV vaccine discovery can be identified and addressed using common tools. For example, does a specific vaccine such as Ad5 induce the same immune responses and degree of cell activation at mucosal sites in NHPs and in humans? Can the use of heterologous gene inserts increase the breadth of immune responses? Does electroporation of DNA alter the qualitative or quantitative nature of induced immune responses? Data from human and NHP studies that are more directly comparable will help identify and validate the most predictive NHP model(s).

Some empiric evaluation of candidates in humans that appear most promising in NHP studies should continue, with cost-benefit carefully evaluated. One needed change is the expansion

of immune-monitoring tools to make such assessments. Elispot assays and intracellular cytokine analysis should no longer be the only tools used to evaluate immunogenicity. The development and validation of additional assays that measure proliferative capacity, mucosal recruitment, cytotoxic capacity, or other immune functions may provide a more robust indication of functional antiviral activity.

NIAID, with input from the extramural community, will support test-of-concept trials if a candidate vaccine is considerably improved and has reasonable potential for moving the field forward relative to candidates that preceded it in the clinical pipeline. Thus, the bar that a candidate vaccine needs to pass will be raised on the basis of accumulated knowledge from prior trials, NHP studies, and fundamental research.

The shift in research focus to less product evaluation and more vaccine discovery research will require a more nimble, robust, expandable (and contractible) clinical research infrastructure, which will be achieved through linking funding of sites to clinical research activity that is ongoing and planned for each site. It will also require new ideas. NIAID leadership has been working to help new investigators obtain their first grants. The broad HIV/AIDS innovation grant program often serves as an entry point for new investigators who lack the preliminary data required to successfully compete for an R01 grant. In addition, NIAID's current policy for unsolicited grant applications favors new investigators. NIAID is committed to exploring new avenues to attract new and young investigators into this area and maintain their involvement.

Unfortunately, the need to focus additional resources on HIV vaccine discovery comes at a time when the NIH budget remains flat. When the biomedical research and development price index is considered, the purchasing power of research dollars has decreased by >13% since 2003. In the immediate future, all current HIV product development activities may feel the effect in order to yield the funds necessary for new initiatives aimed at stimulating HIV vaccine discovery research. Underutilized HIV vaccine clinical trial sites will be encouraged to participate in other types of prevention or treatment research. Funds from contracts that do not meet milestones and unexpended balances from initiatives that do not attract high-quality applications will be redirected. Certain development contracts will either be discontinued or opened to new competitors less frequently. Should growth in the NIH budget be reinstated in future years, one of the highest priorities will be to target those additional resources to HIV vaccine programs, particularly vaccine discovery research.

Given the extraordinary genetic diversity of HIV, the many features of the envelope glycoprotein that shield the virus from antibody-mediated neutralization, and the speed at which viral replica-

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tion occurs and latency is established, design of a vaccine that blocks HIV infection will require enormous intellectual leaps beyond present day knowledge. Despite the obstacles that HIV presents to vaccine researchers, the historic success of vaccines argues that HIV vaccine research must be continued and accelerated. There should be no doubt about our commitment in this regard. Furthermore, pursuit of new avenues and cross-fertilization from such fields as genetics, structural biology, systems biology, cell biology, and peptide chemistry (among others) could yield new approaches for tackling these major obstacles and generate knowledge useful in vaccine design and evaluation.

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PERSPECTIVE

Whither or Wither Microbicides?

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After disappointing results from all efficacy trials conducted to date, the field of microbicides research now faces substantial challenges. Poor coordination among interested parties and the choice of nonvalidated scientific targets for phase III studies have hampered progress and created mistrust about the use of microbicides as a method to prevent HIV-1 sexual transmission. Although new promising strategies are available, there will need to be serious reappraisals of how decisions are made to advance the next generations of candidates into clinical trials, and the use of appropriate animal models in this process will be critical.

The vaginal microbicide field faces yet another of its all-too-frequent crises after the outcome of the Carraguard efficacy trial, conducted by the Population Council in

South Africa. This compound, a sulfated polysaccharide (polyanion), failed to demonstrate efficacy against HIV-1 vaginal transmission.

Almost simultaneously, the U.K. Microbicide Development Program reported that the high-dose arm of the efficacy trial of another polyanion, PRO-2000, would be terminated immediately because there was no hope for demonstrating efficacy (1). It is a sign of the state of the field that there were sighs of relief when it became clear that Carraguard had not enhanced HIV-1 transmission rates, for this was the apparent outcome of the efficacy trial of Ushercell (cellulose sulfate), yet another polyanion, last year (2). With enhanced transmission occurring in the first ever microbicide efficacy trial, that of the detergent nonoxynol-9 (3), and probably at one of the trial sites of another detergent, Savvy (4), the track record of microbicide products in large-scale trials has been extremely poor. The failure of polyanions is not surprising because these compounds have limited

potency in vitro, particularly against the most commonly transmitted strains of HIV-1, those that use the chemokine receptor CCR5 to enter cells (5, 6). Moreover, evidence is now emerging that cellulose sulfate can enhance HIV-1 infection in vitro, particularly of CCR5-using viruses (7). Because similar observations of polyanion-mediated enhancement of such viruses, both in vitro and in vivo, were made 15 to 20 years ago (8, 9), the subsequent testing of the polyanions in thousands of women raises concerns about the preclinical research that was performed on these microbicide candidates. Yet another detergent, sodium lauryl sulfate, is still being evaluated; the rationale for continuing this study is unclear. Questions must now be asked about the past and future directions of the microbicide field; the answers should help to frame the next phase of microbicide development.

Why were detergents and polyanions selected for efficacy trials? The simple, and probably correct, answer is that decisions were based on the belief that preventing HIV-1 sexual transmission would be much easier to accomplish than turned out to be the case. Detergents disrupt HIV-1 efficiently in the test tube, and the polyanions have at least some antiviral activity in vitro (3, 5, 6). Moreover, these compounds were cheap, available, and thought to be safe on the basis of in vitro studies. Phase 1 trials also revealed no major safety problems, although inflammation was observed in early tests of nonoxynol-9 (3, 10, 11). Given the need to generate "momentum," and the lack, several years ago, of alternatives, key decision-makers in the microbicide field presumably believed that these products should be fast-tracked. Duplication of effort was an inevitable consequence when multiple funding agencies or institutions each felt the need to adopt its own polyanion candidate. Rather than comparing the different products in an

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