

Spotlight

Balancing the AIDS vaccine budget

Leading AIDS vaccine researchers gather to discuss priorities in AIDS vaccine funding

The US National Institute of Allergy and Infectious Diseases (NIAID), one of the major financial supporters of AIDS vaccine research and development, is reevaluating its funding allocations in light of the recent failure of Merck's vaccine candidate in the Phase IIb test-of-concept trial, known as STEP, as well as pressure from scientists.

The budget for NIAID has remained flat for five years. Without additional money, the question is whether available funds should be shifted away from clinical development—which involves testing vaccine candidates in a series of human trials to determine their safety and efficacy—to basic discovery research, the type that typically takes place in university laboratories or institutes and guides the design of future vaccine candidates. "I think the answer is an overwhelming yes," said Anthony Fauci, director of NIAID, at the conclusion of a day-long summit on HIV Vaccine Research and Development held March 25 in Bethesda, Maryland. "We will make adjustments to existing resources."

Fauci said he would likely start by moving US\$10 million over to discovery research in 2009 to fund a new request for research proposals with the goal of stimulating novel approaches to AIDS vaccine research. "There are so many things we do not know in this field of HIV vaccines," he said.

The US government is the largest financial backer of AIDS vaccine research and NIAID is one of the major recipients. Last year NIAID spent \$1.5 billion on all areas of AIDS-related research. Of this amount, \$497 million funded AIDS vaccine research and development—47% went to basic or discovery research, and 38% funded clinical development. NIAID is also providing an additional \$300 million over seven years, through a separate funding mechanism, to the Center for HIV/AIDS Vaccine Immunology (CHAVI), a virtual consortium of AIDS vaccine researchers.

Responding to a call from one US group to cut government-sponsored funding of AIDS vaccine research altogether, Fauci and the more than 200 researchers who gathered at the summit remained steadfast in their commitment to discovering an AIDS vaccine. "Under no circumstances will we stop AIDS vaccine research," Fauci said. "I'm going to keep fighting like crazy for more money."

Several researchers echoed these sentiments. "There's no better health impact on prevention and disease control than vaccines," said Adel Mahmoud of Princeton University and summit co-chair.

Stepping back

The allocation of funding between discovery and clinical research was called into question recently by a group of outspoken researchers; first in a letter to NIAID and later publicly at the Conference on Retroviruses and Opportunistic Infections, one of the major annual scientific conferences on HIV/AIDS held in the US. They called for NIAID to place a higher priority on

basic discovery research because of the outstanding questions about how best to develop a vaccine against HIV/AIDS.

Some of these questions surfaced when Merck's vaccine candidate, MRKAd5, showed no efficacy in either preventing HIV infection or modulating the amount of virus in the blood (viral load) in volunteers who became HIV infected despite vaccination (see *VAX* October-November 2007 *Spotlight* article, *A STEP back?*). Things went from bad to worse when researchers later reported that among certain sub-groups of individuals—mainly uncircumcised men with pre-existing immunity to the modified cold virus used as the vaccine vector—there was a trend toward more HIV infections occurring among vaccine recipients in the STEP trial (see *VAX* February 2008 *Primer* on *Understanding Biostatistics and the STEP Trial*). This trial was funded in part by NIAID.

There is still no explanation for the candidate's failure or the potential effect vaccination had on HIV infection risk. Yet, in light of these results, researchers in the field began looking critically at the current clinical pipeline and the strategies to stimulate protective immunity against HIV. "The field is clearly at a critical crossroads," said Warner Greene, director of the Gladstone Institute of Virology and Immunology and co-chair of the summit.

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Following the results of the STEP trial, NIAID postponed the start of a large Phase IIb test-of-concept trial, known as PAVE 100, to evaluate a prime-boost regimen with two candidates developed by researchers at NIAID's Vaccine Research Center, one of which uses a similar adenovirus serotype-5 (Ad5) vector (see *VAX* October-November 2007 *Spotlight* article, *A STEP back?*). Discussions about if or how this trial will proceed are ongoing. "Everything is going to be looked at," said Fauci. "We need to look much more carefully at these clinical trials, both in their design and their scope."

One possibility Fauci suggested is moving forward with a scaled-down version of the PAVE 100 trial. This could free up more funding for basic discovery research. "Trials cost more money than grants," he said, adding that conducting that trial in 3,000 volunteers, instead of the 8,000 originally planned for, would save between \$35 million and \$60 million over seven years.

Identifying research priorities

Throughout the summit researchers discussed several of the still largely uncharted territories in AIDS vaccine discovery. Among these, were the need to more fully understand mucosal immunity and its role in protecting against HIV infection (see *VAX* January 2008 *Primer* on *Understanding HIV Transmission*); the ability of certain nonhuman primate species to effectively control infection with the related monkey version of HIV, known as simian immunodeficiency virus (SIV); the early events in HIV/SIV transmission and infection; and how to induce broadly neutralizing antibodies against HIV (see *VAX* February 2007 *Primer* on *Understanding Neutralizing Antibodies*).

"The biggest challenge is what is a promising vaccine," said Rafi Ahmed, an immunologist from Emory University. He emphasized the importance of developing vaccine candidates that can stimulate neutralizing antibodies against HIV, a task that has stumped researchers for many years. Candidates like MRKAd5 and those developed by the VRC induce primarily, if not exclusively, T-cell responses against HIV (see *Primer*, this issue). Ahmed suggests that only candidates that induce both T-cell and neutralizing antibody responses should be advanced into efficacy trials.

"Vaccine concepts that test only one arm of the immune system are doomed for failure," he added.

But this does not mean that clinical development should be stopped entirely. Almost everyone agreed that Phase I and II clinical trials are still necessary. "We have a lot to learn from clinical investigation," said Alan Bernstein, who was recently appointed executive director of the Global HIV Vaccine Enterprise. Several participants spoke instead about more carefully bridging discovery and clinical research to ensure that each was informing the other. To achieve this,

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Rafi Ahmed

Scott Hammer of Columbia University, said a "nimble, collaborative clinical trial system" is required. "There needs to be more emphasis on discovery," said Ahmed, but "this should not come at the expense of jeopardizing the clinical infrastructure."

Between mice and men

In a session devoted to the strength and limitations of the current animal models for HIV infection and their role in vaccine discovery, Louis Picker of Oregon Health and Sciences University said any rational approach to AIDS vaccine development would have to involve full exploitation of the nonhuman primate model.

Some researchers called for extensive pre-clinical testing of AIDS vaccine candidates using SIV in nonhuman primates to prioritize the best candidates for advancement into clinical trials (see *VAX* October 2006 *Primer* on *Understanding AIDS Vaccine Pre-clinical Development*). But

others were reluctant to endorse the nonhuman primate model as the "gate-keeper." Julie Overbaugh of the Fred Hutchinson Cancer Research Center argued that none of the monkey models have been validated in their ability to predict vaccine efficacy in humans. "It [the nonhuman primate model] shouldn't be used solely as a go no-go," said Seth Berkley, president and chief executive officer of IAVI.

Influx of ideas

If there was one point on which there was almost unanimous agreement, it was the need for more creative approaches to vaccine discovery. Carl Dieffenbach, director of the Division of AIDS at NIAID, said that in 2007, NIAID funded all "meritorious" discovery grants on HIV vaccine research that were solicited. He said this was not a comment on the amount of funding available, but rather the "dearth of ideas."

"The easy things have been done," said James Hoxie of the University of Pennsylvania. There are several innovation programs currently operating in the field, including those from IAVI and the Bill & Melinda Gates Foundation, but other mechanisms for supporting novel research are still required, according to many summit attendees. Bruce Walker of Harvard University said coming up with innovative ideas isn't the problem, it is actually having the money to test them.

Some ideas for encouraging innovation were recruiting young scientists into AIDS vaccine research and also collaborating with researchers from outside but related disciplines. The hope is that young scientists would bring fresh perspective to this now 25-year-old problem. "The real next step is going to come from outside this room," said Mahmoud.

And although this point was mentioned repeatedly throughout the day, the question of just how to recruit young researchers remained largely unanswered. "We have to find mechanisms to recruit young people into the field and not just talk about it," said Dennis Burton of the Scripps Research Institute. More guidance on this issue may come from future sessions—Fauci said this meeting was just the initial step and that finding the right balance between discovery and clinical research would be an iterative process. "We're just getting started," added Hoxie.

HIV Vaccines: Progress and Prospects

Just a few days after many of the leading researchers in the AIDS vaccine field gathered for the HIV Vaccine Summit (see *Spotlight*, this issue), they reconvened in vastly different environs for the annual joint Keystone Symposia on HIV Vaccines and HIV Pathogenesis. This year's meeting took place from March 26 to April 1 in Banff, Canada, and like the field itself, was more focused on fundamental immunology and discovery research.

Many speakers remarked in some way on the results of the STEP trial and its repercussions. Larry Corey of the University of Washington said during his opening keynote presentation that the STEP trial has "recalibrated" the HIV vaccine field, but he dismissed the notion that nothing positive has come out of it and made it clear that in his estimation, the results from the STEP trial do not mark the end for vaccine candidates that stimulate T-cell responses and not neutralizing antibodies (see *Primer*, this issue). "The ability to make such vaccines may be more approachable than getting effective neutralizing antibody vaccines," Corey said.

Researchers presented some updated data from the ongoing analyses of the trial. Susan Buchbinder of the San Francisco Department of Public Health, and a principle investigator on the STEP trial, said there was a two- to three-and-a-half-fold increase in risk of HIV infection in the vaccine group as the level of antibodies against adenovirus serotype-5 (Ad5), which was the modified cold virus used as the vaccine vector, increased. Corey and Buchbinder addressed possible explanations for this observation. The majority of volunteers in the trial were men who have sex with men and so one possible mechanism is that more Ad5-specific CD4⁺ T cells were present in the rectal mucosal tissues, creating more targets for HIV, according to Corey. He also said an indirect biological mechanism could be at play and that perhaps the vaccine candidate interfered with the body's innate or natural immune responses against HIV. Buchbinder said analyses of other potential confounding factors—including sexual networks, clusters of

infections, and changes in sexual behavior—which may also help explain this observation are still ongoing (see *VAX* February 2008 *Primer* on *Understanding Biostatistics and the STEP Trial*).

Efforts to more fully understand mucosal immunology (see *VAX* January 2008 *Primer* on *Understanding HIV Transmission*), the types of T-cell responses a vaccine should induce (see *Primer*, this issue), and the mysteries of individuals who are HIV infected but are able to control the virus (long-term nonprogressors), all figured prominently at this meeting and remain clear priorities for the field. "There isn't one way forward or one simple way forward," said Alan Bernstein, executive director of the Global HIV Vaccine Enterprise. "If anyone says there is they've got a crystal ball that I don't have."

First Phase I trial of Ad26 vector begins

Dan Barouch and colleagues at the Beth Israel Deaconess Medical Center in Boston began enrolling volunteers in April for a Phase I clinical trial to evaluate the safety of an adenovirus serotype-26 (Ad26) vector-based vaccine candidate compared to an inactive placebo. The trial is being conducted at the Brigham and Women's Hospital, also in Boston, and will involve 48 volunteers randomly assigned to receive either two or three doses of the vaccine candidate. The Ad26 vector is used to carry an HIV fragment in the hope that it will trigger immune responses against HIV. The vaccine candidate itself can not cause HIV infection.

There are several serotypes of adenovirus, which is one cause of the common cold, and AIDS vaccine candidates based on adenovirus serotype-5 (Ad5) have already been tested in clinical trials. Merck's vaccine candidate, which was tested in the Phase IIb test-of-concept trial known as STEP, used an Ad5 vector, but this is the first time an Ad26-based vaccine candidate is being analyzed in human volunteers. Ad26 was chosen because fewer people are naturally exposed to this serotype of adenovirus and therefore levels of pre-existing immunity to Ad26 are much lower throughout the world. Pre-existing antibody immunity to the vaccine vector could potentially limit an individual's immune responses against HIV.

In preclinical studies in nonhuman primates, Barouch and colleagues also found that the Ad26 vaccine candidate was more

effective than an Ad5 candidate at protecting against infection with the monkey equivalent of HIV, known as simian immunodeficiency virus (SIV). This Ad26 vector "outperforms Ad5 vectors in rhesus macaques," said Barouch. The vaccine candidate is manufactured by the Dutch biotechnology company, Crucell.

Correction: The February 2008 *VAX* *Spotlight* article, *Small loans: Big hopes*, incorrectly attributed a statement to Grace Sebageni of World Vision. The statement was made by Annabel Erulkar of the Population Council.



Managing Editor

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What is known about cellular immune responses against HIV?

The human immune system uses both innate and adaptive immune responses to combat pathogens such as viruses and bacteria (see *VAX* March 2004 *Primer on Understanding the Immune System, Part II*). Innate immune responses are always on standby and can act quickly, usually within hours, to either snuff out or help limit an initial infection. If more help is needed, adaptive immune responses—which include both antibodies and cellular immune responses—kick in. These take longer to activate because they are designed to target a specific pathogen. The immune system generates HIV-specific antibodies and cellular immune responses against the virus, both of which are critical in either preventing or controlling the infection, and are therefore of great interest to AIDS vaccine researchers.

Antibody responses are Y-shaped molecules that primarily latch on to viruses and prevent them from infecting cells (see *VAX* February 2007 *Primer on Understanding Neutralizing Antibodies*). Once cells are already infected, cellular immune responses come into play. These responses involve a subset of immune cells known as CD4⁺ T helper cells that orchestrate the activities of activated CD8⁺ T cells, known as cytotoxic T lymphocytes (CTLs), which can kill cells already infected by the virus.

The role of cellular immune responses in HIV infection is complicated because the very cells that play a role in limiting infection are under attack—the virus preferentially targets and infects CD4⁺ T cells, severely hampering the immune system's ability to fight back. However, both CD4⁺ and CD8⁺ T cells still play a critical role in the control of HIV infection and are also likely to be important to the development of an AIDS vaccine. Researchers are now studying the ideal types of antibodies and cellular immune responses that a vaccine should induce to best prevent or control HIV infection.

Inducing T-cell responses

Developing AIDS vaccine candidates that are capable of inducing neutralizing antibody responses against HIV is

challenging and so far the strategies tested have been unsuccessful. However, several AIDS vaccine candidates have been identified that can induce cellular immune responses, both CD4⁺ and CD8⁺ T cells, against HIV. Many of these have been evaluated in clinical trials, including Merck's MRKAd5 vaccine candidate that was recently tested in the STEP trial (see *VAX* September 2007 *Special Report*).

Typically, researchers measure the size of the cellular immune responses that are induced by different candidates, as well as the ability of these cells to secrete cytokines, which are proteins produced by immune cells in response to viruses or bacteria (see *VAX* August 2007 *Primer on Understanding Immunogenicity*). Merck's MRKAd5 candidate induced T cells secreting a cytokine known as interferon- γ (IFN- γ) in more individuals than any candidate tested in Phase I clinical trials, prior to it being advanced to a Phase IIb test-of-concept trial. In Phase I trials, 80% of MRKAd5 recipients, who did not have high levels of pre-existing immunity to the cold virus used as a vector, developed T cells that secreted IFN- γ .

The majority of vaccine recipients in the STEP trial also developed both CD4⁺ and CD8⁺ T-cell responses against HIV after receiving MRKAd5. But these immune responses were not sufficient to protect against infection. Researchers have not observed any correlation so far between the size of HIV-specific immune responses in vaccine recipients and whether or not they subsequently became infected with HIV through risk behaviors, such as unprotected sex with an HIV-infected partner or injection-drug use.

Researchers have also found that the quantity of T-cell responses does not seem to correlate with control of the virus in some HIV-infected individuals, known as elite controllers, either. Elite controllers are a group of long-term nonprogressors who are HIV infected yet have very low levels of virus (viral loads) and do not progress to AIDS in the usual time, even without the aid of antiretroviral therapy (see *VAX* September 2006 *Primer on Understanding Long-term Nonprogressors*). The magnitude

of HIV-specific cellular immune responses are actually lower in elite controllers than those seen in individuals with typical viral loads who have normal disease progression.

Quantity vs. quality

Together these findings indicate that the size of the T-cell response may not be the key factor in either preventing or controlling HIV infection. Instead, the capability of the T cells to perform a particular function may be more important. Some immunologists suggest that it is not the size of the initial T-cell response to vaccination that matters, but the ability of these T cells to multiply later on, when the individual encounters the pathogen they were vaccinated against, that is most critical.

Other researchers are studying the direct ability of the T cells induced by an AIDS vaccine candidate to kill virus-infected cells. Researchers can extract T cells from volunteers in an AIDS vaccine clinical trial through blood samples and test them in a laboratory against HIV to see if they are actually capable of killing virus-infected cells. This method is now being used by some researchers to prioritize vaccine candidates in Phase I clinical trials.

Another approach is to study different viral and bacterial vectors that may be used for AIDS vaccine candidates to see if they induce different types of T-cell responses. Researchers have conducted preclinical experiments in mice to compare the T cells induced by different viral vectors. The results indicate that the choice of vector does affect the type of T cells that are induced upon vaccination.

Researchers are also currently studying the characteristics of effective T-cell responses in other viral infections, in which cellular immune responses are at least partly responsible for protection, to determine what types of T cells an AIDS vaccine candidate should ideally induce. More research on T-cell responses to HIV, as well as other pathogens, will shed light on these questions and help researchers design more effective AIDS vaccine candidates.