



Spotlight

Industrial strength research

AIDS vaccine field adopts more characteristics of industry.

Like any great scientific challenge, the search for an AIDS vaccine requires money, minds, and collaboration. These first two requirements are closely related, and as new streams of funding flow into the field more interest is being focused on this pursuit. But as the research field broadens, global health leaders are emphasizing the need for cooperation and collaboration among research groups as an equally important component in the discovery process for an AIDS vaccine.

The emphasis on researchers working together more effectively and efficiently has inspired the emergence of several new collaborative efforts, many of which come in the shape of consortia or virtual institutes that are collectives of independent research groups willing to share ideas and resources. And this has inspired the adoption of a new research model, one which stresses coordination of efforts, rapid sharing of positive and negative results, structured decision making, accountability, and consideration of long-term goals. This model has much in common with the way research is done in large biopharmaceutical companies. But precisely how this model is fitted to the evolving field of AIDS vaccine research is currently a subject of discussion.

Industrial approach

The idea of sharing data and results may seem to contradict the way research is done within biopharmaceutical companies. Generally speaking, industry is very protective of its research and closely guards its intellectual property. But within a given company research has long been a collaborative effort where a single product, like a drug or a vaccine, is passed through teams of scientists with different expertise until completion. A new medicine may start out with chemists but will go through teams of biologists, safety assessment specialists, clinical trial coordinators, as well as regulatory groups before it winds up in the hands of marketing professionals.

Conversely, academic scientific research has traditionally been a mostly solitary endeavor, heavily reliant on the specific expertise and interests of the principal investigator. Researchers at universities and institutes tend to work in small groups, sharing their results at conferences and through publication in scientific journals. This academic model means that research teams work on a specific aspect of a project, rather than seeing it through from start to finish.

While this investigator-driven model has thrown up fundamental findings in every scientific discipline, a mission as vast as developing an AIDS vaccine requires extensive coordination. "Focused development programs similar to those within industry are needed so that people can make informed decisions about what is working and what is not," says John Shiver, director of vaccine research at the US-based company Merck.

Over the last few years, support for an industry-like research environment for AIDS vaccines has gained momentum. In 2002 IAVI teamed with a number of academic and government research groups to establish one of the first such research programs, the Neutralizing Antibody Consortium. A collaborative effort involving investigators from across the US, the consortium members share standardized methods. Even more importantly, they share their ideas and discoveries freely and plan some of their experiments collectively.

In June 2003 a group of 24 scientists proposed the creation of a Global HIV Vaccine Enterprise, an "alliance of independent entities" that brings together many of the key players in AIDS vaccine research and calls for the coordination of efforts to improve vaccine discovery. The Enterprise has helped build consensus across the whole field and early last year published its scientific strategic plan (www.hivvaccineenterprise.org/plan/index.html) that outlines the key unanswered questions in AIDS vaccine research.

Just last year the US National Institutes of Health (NIH) awarded

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funds to start the Center for HIV/AIDS Vaccine Immunology (CHAVI), a consortium of largely academic research groups. Additionally, the Bill & Melinda Gates Foundation will grant up to US\$360 million over the next 5 years for the creation of a network of collaborating institutions. Part of the goal is to get people working across disciplines, says José Esparza, who is coordinating the effort. “We would like to bring together complementary expertise that otherwise would not be available.”

The ability to bring together that expertise is just one of the strengths of the industrial approach. Other important aspects are the decision-making process, management, and oversight of a project. Instead of relying on decision making by consensus and committee, industry gives the authority to a project management team that guides vaccine candidates from research to development. A project manager is an asset to any research lab, says David Ho, scientific director of the Aaron Diamond AIDS Research Center, “we have come to appreciate how important that is to keep things on track.”

For early stage research the project manager can help the investigator understand factors outside the researcher’s area of expertise, such as whether a project has the potential to pass regulatory hurdles. This approach ensures that researchers are communicating and goals are being met. “The project manager provides the discipline to march the product through all the phases of its development,” says Gary Nabel, director of the Vaccine Research Center (VRC) at the NIH.

Making it happen

Abandoning investigator-led academic research completely is not the solution, but this system has some shortcomings that make it less than ideal for AIDS vaccine development. Some research questions might simply be too difficult or too resource-expensive for a small research group to tackle alone. For example, studying mucosal immunity is prohibitively expensive due to the difficulty in collecting samples (see *VAX* December 2005 *Primer on Understanding Mucosal Immunity*). The

lack of oversight in the academic environment may also mean that major questions can go unanswered, simply because nobody sought out that knowledge.

The new industrial-style collaborations are meant to sidestep pitfalls such as these. CHAVI contains some aspects of the industrial model but retains the committee-based approach common in academia. Their strategic plan includes both a discovery phase and a product development phase, each of which has a team leader, and the teams are organized according to the major unanswered scientific questions put forward

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Mitchell Warren

by the Enterprise. “It is a grand experiment and the key is the interdisciplinary approach, using components of the corporate model, to focus the firepower to solve a very hard problem,” says Barton Haynes, director of CHAVI

This approach will put the focus on successful projects and allow prioritization of vaccine candidates before moving to full-scale clinical trials. For candidates that are ready for further testing, vaccine developers are increasingly interested in the Phase IIb “test of concept” trial, an expanded Phase II trial to evaluate the vaccine candidate’s efficacy (see *VAX* September 2005 *Primer on Understanding Test of Concept Trials*). Merck is taking this approach with a Phase IIb trial of its lead candidate. The goal of these trials is to get answers sooner on whether a vaccine has the potential to work.

IAVI has been active in maintaining that research must adhere to project

guidelines in a timely fashion, often testing a vaccine candidate in several trials simultaneously so the candidate can be evaluated as quickly as possible.

“Products that don’t pass the bar are terminated quickly without waste of resources so that funds are used efficiently,” says Seth Berkley, president and chief executive officer of IAVI.

Secure funding

Some of the drawbacks in traditional academic research stem from researchers having to constantly compete for grant funding, whereas industrial researchers usually know their funding is secure as long as the project is continuing to make progress towards its end goal. One option for meshing the industrial and academic approaches is to fund quality academic researchers with a proven record of achievement for longer periods of time and alter the grant renewal requirements for principal investigators in academia.

A secure source of funding might have another desired effect: luring experienced researchers into the field of AIDS vaccine research. Especially needed are experts in basic immunology, says Bruce Walker, director of Harvard Medical School’s Center for AIDS Research, who explains that few immunologists that helped to explain how the immune system works have transitioned to working on HIV research. “It is not easy to attract people who are successful in other areas to change focus and work on HIV,” says Walker.

But changing the research model alone won’t lead to a vaccine. “We shouldn’t forget that no matter what research model is used, much basic research remains to be done,” says Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition. “I would hate to see people stuck debating about what is the correct model.”

But most global leaders and funding organizations agree that working to harmonize research practices will help ensure that the search for an AIDS vaccine is efficient and takes as little time as possible.

Global News

WHO/UNAIDS convene meeting on AIDS vaccine clinical trial design

The World Health Organization (WHO) and the United Nations Joint Programme on HIV/AIDS (UNAIDS) recently sponsored a technical consultation with experts in the AIDS vaccine field to discuss the design and use of Phase IIb “test of concept” trials in evaluating AIDS vaccine candidates and their implications for approval and licensure (see *VAX* September 2005 *Primer on Understanding Test of Concept Trials*).

This meeting, hosted by IAVI, was held from January 31 to February 2 in New York City and brought together a diverse range of organizations to consider both the design of test of concept trials and how they should be viewed by vaccine approval agencies in developing countries. Attendees included representatives from the Botswana Harvard AIDS Institute Partnership, Medical Research Council of South Africa, Chinese Center for Disease Control and Prevention, Project San Francisco in Rwanda, HIV Vaccine Trials Network (HVTN), US National Institutes of Health (NIH), US Centers for Disease Control and Prevention, US Food and Drug Administration, IAVI, Johns Hopkins University, as well as other representatives from India, Thailand, and Zambia. The recommendations of this group will be presented as a position paper to the WHO/UNAIDS Vaccine Advisory Committee and will be used to help these organizations develop a set of guidelines on test of concept trials for AIDS vaccines.

Kenya begins enrollment for Phase I vaccine trial

The Kenya AIDS Vaccine Initiative (KAVI) at the University of Nairobi began enrolling volunteers in a Phase I AIDS vaccine trial in January. The trial, IAVI V001, is sponsored by IAVI in collaboration with the Vaccine Research Center (VRC) at the National Institute of Allergies and Infectious Diseases (NIAID). It was initially started in Rwanda and was expected to enroll a total of 64 volunteers in these countries. However after early success in recruiting volunteers the target number for both countries will be increased, pending regu-

latory approval by the local Institutional Review Boards in Kigali and Nairobi.

Sabina Wakasiaka, a nurse counselor from KAVI, credits the successful enrollment rates to outreach programs conducted in the last few years, which have helped to increase the vaccine literacy among many community organizations. The trial staff at KAVI are promoting initiatives to recruit more women for this trial, including holding community seminars within homes or offices targeting only women.

This is one of many ongoing trials testing the safety and immunogenicity induced by a “prime-boost” vaccination regimen with a DNA plasmid vaccine and an adenovirus serotype 5 (Ad5) vector that was developed at the VRC (see *VAX* November 2005 *Global News*).

Trial shows HSV-2 suppression can reduce HIV shedding

Almost a dozen clinical trials are now ongoing to see if drugs to suppress herpes simplex virus-2 (HSV-2) can reduce the risk of HIV transmission and infection (see *VAX* November 2005 *Spotlight* article, *HIV prevention in a pill?*). These studies were initiated because of mounting evidence that there is an association between HSV-2 and HIV infection. Researchers have long thought that HSV-2 infection could increase the amount of HIV in the genital tract and therefore increase both sexual transmission of and infection with HIV. But a relationship between these infections has not been firmly established in a controlled, clinical trial until now. At the 13th Conference on Retroviruses and Opportunistic Infections (CROI) held this February in the US, Nicolas Nagot from the London School of Hygiene and Tropical Medicine (LSHTM) in the UK in collaboration with the Centre Muraz in Bob-Dioulasso, Burkina Faso, presented data from the first “proof of concept” trial verifying the association between HSV-2 infection and HIV.

This study enrolled 140 women infected with both HIV and HSV-2 in Burkina Faso and randomly assigned them to either the treatment or placebo group. Those on treatment received the anti-herpes drug valacyclovir once a day for three months, while those in the placebo group received an inactive substance. The women were followed for a total of

nine months, three months prior to and for three months following treatment. Over 12 visits, researchers measured the levels of HIV and HSV-2 in the genital tract of these women and found that those taking valacyclovir had significantly lower quantities of HIV than those that received placebo. Valacyclovir also significantly reduced the level of HSV-2 in the genital tract of women compared to those in the placebo group.

Although this study does not show a direct link between HSV-2 suppression and HIV transmission, this is the next step for researchers. Several trials are currently ongoing to see if HSV-2 suppressive therapy can lower HIV infection rates.



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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it.

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How can AIDS vaccine trials help build infrastructure and capacity in developing countries?

In order to determine whether an AIDS vaccine candidate is effective it must be tested in the populations that are most affected by the disease. Clinical trials have to take place in communities where there is a high enough incidence of HIV infection for researchers to determine positive benefits from the vaccine. This often requires running trials in developing countries, where there is the highest HIV/AIDS burden. It is also essential that vaccines be evaluated in the communities that need them the most.

Many organizations involved in AIDS vaccine research, including the Global HIV/AIDS Vaccine Enterprise and the European & Developing Countries Clinical Trials Partnership (EDCTP), have recently published reports emphasizing the importance of developing both the physical infrastructure and the human resources at clinical trial sites in developing countries. This is the strategy used by organizations like Walter Reed Army Institute of Research, the US Centers for Disease Control and Prevention, and IAVI that have been running vaccine trials in Africa and Asia. The idea of building trial site capacity involves both establishing clinics and laboratories and training medical professionals. Both of these steps help ensure that the research site is sustainable over the long term and can be used for future clinical trials. Developing these sites also benefits the community by providing career opportunities for healthcare workers that can serve the community long after the trial ends or by attracting other medical services to the area, such as HIV treatment programs (see *VAX* February 2006 *Primer on Understanding the Benefits and Risks of Participating in Clinical Research*).

Infrastructure

The first step in building an AIDS vaccine clinical trial site involves constructing the actual buildings that will serve

as clinics and laboratories or modifying those that already exist. These facilities are then equipped with the instruments necessary to process laboratory samples obtained from volunteers during the trial and preparing these specimens for storage or shipment. Some sites may even develop sophisticated HIV immunology and virology laboratories that can analyze samples and process the data from the trial in the country where it takes place.

India recently started an AIDS vaccine trial sponsored by IAVI in partnership with the Indian Council of Medical Research and the National AIDS Control Organization at the Tuberculosis Research Center (TRC) in Chennai. The TRC, a newly-established center of excellence for the clinical evaluation of vaccines in the country, features a safety and immunology laboratory where all laboratory tests will be run.

Human capacity

Once the clinics and laboratories are established it is also important to build human capacity at AIDS vaccine trial sites. Sponsor organizations spend significant amounts of time hiring and training medical professionals in developing countries to handle the activities associated with the trial.

This occurs through a series of instructional workshops that cover all aspects of the clinical trial process, from screening and enrolling volunteers to collecting and analyzing data, and are based on a set of work practices developed specifically for each site. All trials are certified according to a set of international guidelines, known as Good Clinical Practice (GCP). Compliance with GCP guidelines ensures that the trial is run properly, that the rights and needs of the volunteers are protected, and that the data collected during the trial is of high quality.

Counselors and nurses are trained to work with potential volunteers and to administer the informed consent process (see *VAX* June 2005 *Primer on Understanding Informed Consent*). These individuals may also receive specialized training on enrolling women in AIDS

vaccine trials and other gender-related issues.

For the staff working in the laboratories the training includes how to handle and process the laboratory samples and the procedures for data management. All tests run in the laboratories are verified by quality control processes to ensure that the results of the trial are meaningful.

The process of site development continues even after the trial has started. Many organizations continue working to enhance the site's ability to deliver HIV prevention and treatment services and to provide referrals to other clinics in the community. This can involve additional training sessions or meetings arranged with the staff from other AIDS vaccine clinical trial sites in order to learn from shared experiences.

Providing the site staff with such extensive training helps strengthen the human resources in that community. Once the trial is complete, these medical professionals can work in many other areas, including research, nursing, or in conducting other clinical trials.

Sustainable trial sites

Developing both the physical infrastructure and human capacity at a site are necessary steps for conducting an AIDS vaccine clinical trial in developing countries, but once established these sites can continue to function well beyond the end of the current trial. The staff's expertise in HIV could make the site suitable for other types of HIV prevention trials, including trials of microbicides, or for clinical research studies that contribute to the understanding of the HIV/AIDS epidemic in that country. These sites may also attract HIV treatment programs or other healthcare services that can continue adding benefit to the community. Keeping these sites active is also of great interest to organizations sponsoring AIDS vaccine trials, since many vaccine candidates will need to be evaluated in the future and these trials will require experienced sites and surrounding communities that have successfully conducted past trials.