

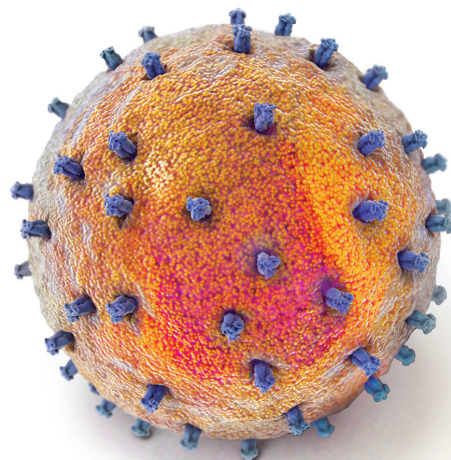
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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

An Interview with Alan Bernstein

At the helm of the Global HIV Vaccine Enterprise *By Kristen Jill Kresge*



Alan Bernstein, PhD, is a renowned researcher whose wide-ranging career has spanned many different areas. Bernstein has authored more than 200 peer-reviewed scientific publications and was the founding president of the Canadian Institutes of Health Research (CIHR), which he helped develop into a leading research agency with an annual budget of US\$1 billion. Prior to that, he was director of research at Mount Sinai Hospital in New York.

In January 2008, Bernstein started the next phase of his career, taking up the helm at the Global HIV Vaccine Enterprise as its inaugural executive director. His appointment came just months after the results of the Phase IIb test-of-concept trial known as STEP showed that Merck's AIDS vaccine candidate failed to provide any protection against HIV. This set off a recalibration of research efforts and Bernstein, as a newcomer, set out to bring his fresh perspective and expertise from other areas of research to bear on the development of an AIDS vaccine.

How did you make the decision to join the Enterprise as its first executive director?

My decision to join the Enterprise was motivated by several factors. One was obviously the size of the problem. HIV/AIDS is the number one health challenge facing the world today and so it's hard to say no to the opportunity to participate. Secondly, the scientific challenges are so great that I was intrigued by the opportunity to contribute whatever I could as an outsider to this field. Also, the uniqueness of the Enterprise model really interests me. I think the opportunity to be involved with an organization that represents a partnership between all the major funders in HIV research around the world, and to convene a conversation on their behalf that hopefully will articulate the fastest way forward to a vaccine, was intriguing, especially given my background.

When I put all that together, and chatted with my wife, it became a no-brainer that I would say yes. Actually, after leaving CIHR, I would have been quite happy to sleep for a year.

What was it like joining the AIDS vaccine field after the STEP trial?

My appointment was announced about two weeks after the STEP trial results were released and it was indeed an interesting time. The scientific community reacted so negatively to those results; there was so much disappointment. It went way beyond what I would have anticipated. I think the expectations in this field have been so high and the pressure to deliver a vaccine as soon as possible has been so great, that every scientist and every funder, whether they were directly involved or not, felt pain over the STEP trial.

I think that speaks to one of the great strengths of this field, which is that everybody wants a vaccine, whether they're the ones who develop it or not, because they understand the humanitarian cost of not having one. At the end of the day, that's what really matters and is what makes this field different. In areas that I know best,

ALSO IN THIS ISSUE

GLOBAL NEWS

- ▶ Two Prime-Boost Regimens Enter Clinical Trials

PRIMER

- ▶ Understanding Innate Immunity and HIV



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VAX is a monthly bulletin from IAVI Report, the publication on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, Spanish, and Portuguese as a downloadable PDF file or an e-mail bulletin.

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 24 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. For more information, go to www.iavi.org.

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like cancer research, most trials don't work. When a cancer trial makes the front page of a newspaper, it is when it works, not when it doesn't. That's what I was used to.

It's been a very interesting time for me to understand what led to the STEP trial and how the science should be framed going forward.

What are some of the other differences between cancer research and the AIDS vaccine field that you've observed?

I think the image of the HIV vaccine field is that it is simply about product development, as opposed to the need for doing great science, which is the case in cancer research. That's one reason why I think young people don't necessarily see a role for themselves in the AIDS vaccine field. I'm generalizing because there are obviously a lot of young people in the field, but there aren't the numbers that I'm used to in cancer research or in other areas. We need to make sure we renew the current generation of very distinguished scientists, many of whom came into the field back in the mid-1980s when the virus was first discovered.

There's also been a whole slew of new technologies that have been developed due to advances in the field of genomics, which again, we need to make sure are fully incorporated into the search for developing an HIV vaccine, as they are in cancer research.

What is being done to encourage young scientists to pursue AIDS vaccine research?

The Enterprise is putting together a group

of young researchers from around the world and asking them what they need and what's missing for them in the field. There are definitely issues we've identified regarding long-term funding and mentorship.

We're also losing many talented young researchers who are trained in the developed world and then go back to developing countries and don't have the resources there to continue their research, so we need to address that as well.

What are some areas that you think should be more actively investigated in the AIDS vaccine field?

I think we need to better understand a person's immune response to HIV. We have a virus that does very powerful things to the immune system and yet we haven't completely documented the immune responses when someone becomes infected. For example, there are some people who have high levels of virus in their bloodstream, while other people, like elite controllers, have very low levels of virus, and we don't yet understand why. We need to understand the mechanisms behind those differences.

I think we need more overlap between HIV vaccine research and research going on in other areas. We've got to make sure that all new ideas, where relevant, are being applied to developing a vaccine.

What are some of the main areas of focus for the Enterprise?

One of our top priorities over the next year will be to update the existing Scientific Strategic Plan that was created in 2005. This plan is designed to provide a broad framework for the field and it should reflect the profound changes in science that have taken place over the past five years. The new strategic plan will identify opportunities in the field, as well as some of the obstacles with concrete suggestions about how to address them. Then we can renew the scientific plan annually or every two years and see how we are doing. I think that's one way we can add value.

There are currently four areas of focus for the Enterprise: attracting and retaining young and early career investigators, ensuring that systems biology becomes part of HIV vaccine research, closing the gap between preclinical and clinical HIV research, and actively encouraging a culture of knowledge and data sharing. The Enterprise has also formed a Science

An Enterprising Strategy

The Global HIV Vaccine Enterprise is an international alliance of researchers, funders, and advocates committed to accelerating the development of an HIV vaccine. The idea for the Enterprise was originally proposed in a 2003 *Science* article authored by 24 leading AIDS vaccine researchers. They argued that the scale of research at the time was insufficient for solving the major scientific challenges impeding the development of an AIDS vaccine. The approach of the Enterprise, modeled in part on the Human Genome Project, was to attract additional funding to support large-scale, collaborative efforts across multiple organizations and institutions. In 2005, the Enterprise published its Scientific Strategic Plan, laying out a shared vision of the research priorities for the field.

Following this, the Enterprise quickly succeeded in mobilizing significant levels of new funding to the AIDS vaccine effort. The National Institute of Allergy and Infectious Diseases at the US National Institutes of Health awarded US\$300 million over seven years to establish the Center for HIV/AIDS Vaccine Immunology, and the Bill & Melinda Gates Foundation awarded \$287 million to the Collaboration for AIDS Vaccine Discovery. Both of these large-scale, collaborative initiatives fall under the auspices of the Enterprise.

Committee, including 18 of the top HIV and biomedical researchers in the world, which will hold its first meeting in January. Their task will be to identify those areas of HIV vaccine research that require greater attention and resources and those that should be dropped.

Do you think more funding is needed for AIDS vaccine research?

It is hard to say in any area of science whether you need more money or not. What we don't know, and would never know, is if you had more money invested in research, would you speed up the development of a vaccine. I think there are still a lot of good ideas to pursue that aren't being funded at the moment.

Following the STEP trial, there has also

been a lot of discussion about the balance between spending on clinical trials and basic research. I absolutely think we need to be doing more basic research, but I also think we need to do more research to understand the human immune response to HIV and to HIV immunogens.

What is your overall impression of the AIDS vaccine field and what thoughts do you have about what should be done differently?

I have been very impressed with the quality of the individuals working in the field as well as the different teams and networks. The challenge for me is how to add value given the talent that's already out there. I

know I made the right decision to come into this field because of how warmly I have been received by everybody in the scientific community, as well as by the funders.

What I do think we need to do differently is to urgently move away from the expectation that the next trial will be a home run. We shouldn't be thrown off because one or two trials have failed or are not going ahead, that's just not the way science advances.

We've become spoiled in the AIDS field because treatment has worked so spectacularly well. But it is important to remember that these drugs have side effects, they're expensive, and they don't cure anybody of the disease, so we haven't really solved the treatment problem until we solve prevention. ■

GLOBAL NEWS *by Regina McEnergy*

Two Prime-Boost Regimens Enter Clinical Trials

GeoVax launches Phase IIa trial

A Phase IIa trial testing the safety and immunogenicity of a prime-boost regimen of two vaccine candidates developed by US-based GeoVax is now enrolling volunteers in the US and Peru. This trial, known as HVTN 205, launched on December 1, World AIDS Day, and will involve 225 volunteers.

Those randomly selected to receive the vaccine candidates will receive a prime-boost regimen of two doses of a DNA candidate carrying three HIV fragments or immunogens, followed by two doses of a modified vaccinia Ankara (MVA) virus vector carrying the same immunogens. The MVA vector cannot cause disease, and neither of the vaccine candidates can cause HIV infection.

Harriet Robinson, vice president of research and development at GeoVax, says the vaccine candidates showed "fabulous control" of infection with a hybrid virus that combines parts of HIV and simian immunodeficiency virus (SIV), the monkey equivalent of HIV, in preclinical studies in non-human primates. The candidates did not fare as well against SIV challenge but still showed a 10-fold reduction in viral load after six months compared to unvaccinated control animals, says Robinson.

Vaccinations begin in IAVI's Phase I trial

IAVI, in conjunction with St. Stephen's AIDS Trust and Westminster Hospital in the UK, has launched a Phase I clinical trial involving 32 volunteers in London to evaluate the safety and immune responses induced by two AIDS vaccine candidates administered in a prime-boost regimen.

One of these candidates, called TBC-M4, utilizes an MVA vector to deliver non-infectious HIV fragments in the hope of

inducing an immune response against HIV. This candidate, developed in collaboration with the National Institute of Cholera and Enteric Diseases in India, was tested previously in a Phase I trial conducted in Chennai, India. In this new trial, administration of TBC-M4 will be preceded by a DNA-based vaccine candidate called ADVAX, which was developed at the Aaron Diamond AIDS Research Center in New York City in collaboration with Rockefeller University and IAVI. The ADVAX vaccinations will be administered with a needle-free device called Biojector 2000 to see if this delivery system induces stronger immune responses than a regular syringe injection.

This UK trial will also allow researchers to assess the merits of a new laboratory test known as a viral suppression assay to determine whether the CD8⁺ T cells, produced in response to the vaccine candidates, that are isolated from volunteers in the vaccine trial are capable of inhibiting HIV in the lab. "What we would like to do is see if the CD8⁺ T cells after vaccination stop the virus from growing," says Jill Gilmour, senior director of clinical research at IAVI.

The assay being used in this trial is an optimized version of one developed by Bruce Walker, director of the Partners AIDS Research Center at Massachusetts General Hospital, who has long advocated for researchers to use this type of assay to measure the function of immune cells produced in response to vaccination. Most often the immune responses induced by candidate vaccines in clinical trials are assessed using an ELISPOT assay. This assay detects the number of CD8⁺ T cells that are excreting specific proteins known as cytokines but does not measure the ability of these cells to actually inhibit HIV (see *VAX August 2007 Primer on Understanding Immunogenicity*).

Understanding Innate Immunity and HIV

What role do innate immune responses play in defending against HIV infection? *By Regina McEnery*

HUMANS ARE REPEATEDLY EXPOSED to various pathogens, including viruses and bacteria. The body defends itself against these pathogens using a complex network of cells, tissues, and organs, which together form the human immune system (see VAX July 2008 *Special Issue, Understanding the Immune System and AIDS Vaccine Strategies*). There are two branches of the immune system, innate and adaptive, that play a critical role in eliminating invading pathogens.

The innate immune system is the first line of defense against viruses and bacteria. The cells of the innate immune system both detect the invading virus and try to control or eliminate it. Dendritic cells and macrophages are among the most important in recognizing invading viruses like HIV and are found in mucosal tissues, as well as at other sites. These cells are like the body's 24-hour security force and are constantly patrolling for foreign invaders. Once they come in contact with viruses, they grab hold of the warring particles with the help of finger-like projections. The dendritic cells then cut the virus into small fragments called epitopes that are displayed on the cell's surface. When these dendritic cells travel to the lymph nodes, which are the communication hubs of the immune system, the HIV fragments on their surfaces act as warning flags, alerting other immune cells of the invading virus.

Innate immune responses are activated soon after an infection occurs but they are not specific, so whether the enemy is a cold virus or HIV, the innate immune system responds in the same way.

If the innate immune response is not capable of eliminating the virus

or bacteria, or if these responses are evaded by the pathogen, the adaptive branch of the immune system kicks in. The adaptive immune responses, which include cellular immune responses (CD4⁺ and CD8⁺ T cells) and antibodies (Y-shaped proteins that work primarily by latching onto viruses and preventing them from infecting their target cells), are pathogen-specific and therefore take longer to become activated—typically several days.

Studying immune responses

The adaptive immune responses produced following HIV infection have been well studied and are still being fully characterized. AIDS vaccine researchers are also able to detect and measure the cellular and antibody responses induced in individuals that have received various vaccine candidates in clinical trials.

However, even though innate immunity is widely considered to be critical in shaping the body's immune response to HIV, this type of response is much more difficult to study. Innate immune responses are only active for about six to seven days following HIV transmission, and so newly HIV-infected individuals would have to be identified very soon after they become infected for researchers to study innate responses. Also, HIV is most often a sexually transmitted infection and so the innate immune responses, which may play a key role at or very soon after transmission, may be hidden at mucosal sites that are difficult to study. Despite these complications, efforts are underway to identify infected individuals as soon as possible after HIV transmission and to better classify the very early interactions between the virus and the innate immune system.

It is also likely that the innate immune system plays an important role in the

response to AIDS vaccine candidates, but this is not very well understood. Investigators involved with the Phase IIb test-of-concept trial known as STEP are currently analyzing the types of innate immune responses induced in volunteers who received Merck's vaccine candidate. These analyses may offer new clues about the role of innate immunity following vaccination.

A wily virus

HIV has several tricks it uses to evade the immune responses mounted against it. One of the virus's advantages is that it primarily targets and infects CD4⁺ T cells, a vital component of the adaptive immune response against HIV. HIV's ability to constantly mutate also allows it to evade antibody responses.

But scientists still do not completely understand how HIV manipulates the innate immune system. It is possible that macrophages and dendritic cells may unwittingly be helping HIV by delivering virus particles directly to target CD4⁺ T cells, which the virus then infects. HIV is also thought to disrupt other functions of the innate immune system, including the functional capacity of a subset of cells called natural killer (NK) cells, which would otherwise recognize and destroy HIV-infected cells.

Ongoing study

To help clarify the murky role that innate immunity plays in HIV infection, researchers are studying different groups of individuals. One group of interest is highly exposed seronegatives—individuals who remain uninfected for years despite known and often repeat exposure to the virus. Past studies have found that some women inexplicably resist HIV infection despite participating in commercial sex work and having been repeatedly exposed to the virus. Some scientists have theorized that innate immunity may explain their apparent ability to avoid HIV infection. ■

Innate immunity is widely considered to be critical in shaping the body's immune response to HIV.

