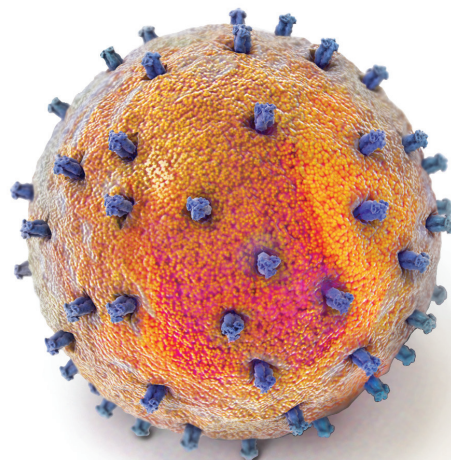


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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

An Interview with Mark Feinberg

The newly appointed president and chief executive officer of IAVI is no stranger to HIV research, having spent more than 30 years of his varied career battling the virus. *By Kristen Jill Kresge*



Mark Feinberg has a broad perspective on vaccine development. He worked in government, serving as a Medical Officer in the Office of AIDS Research at the National Institutes of Health; in academia, as a basic and translational researcher, teacher, clinician, and clinical investigator, including a post as the founder and first Medical Director of the Hope Clinic at the Emory Vaccine Research Center; and for the last 11 years in the pharmaceutical industry, holding

various positions at Merck & Co. working on vaccines and infectious disease therapeutics. His most recent position at the company was Chief Public Health and Science Officer for Merck Vaccines.

Beginning September 8, Feinberg added yet another role to his varied career—President and CEO of IAVI. He succeeds Margie McGlynn, another Merck alum who stepped down after four years as IAVI's head, and becomes the organization's third leader in its nearly 20-year history. Feinberg says the common goal underlying his career is finding a way to “translate science into public health benefit.”

In some way joining IAVI is like returning home. Feinberg was an MD-PhD student at Stanford University when the first cases of a new and deadly disease that would later become known as AIDS were first reported in New York, Los Angeles, and San Francisco. “I finished my thesis research working on HIV and have been involved in one way or another with the disease since then. That's more than 30 years, which is remarkable to reflect on.”

Feinberg joined Merck when the company was actively involved in the initiation of the large Phase IIb STEP and Phambili trials, the first HIV efficacy vaccine trials to test a viral-vector based vaccine candidate designed to induce primarily cellular immune responses against the virus. However, his involvement in vaccine research while there extended far beyond HIV. At Merck he was also involved with the development and licensure of several novel vaccines, including those against human papilloma virus (HPV) and rotavirus, and most recently he led the company's involvement in the public-private partnership to expedite development and testing of a vaccine against Ebola. This candidate, rVSV-ZEBOV, showed great promise in a recent clinical trial in Guinea (see *Primer*, this issue). Despite these varied experiences, Feinberg says his “scientific heart and mind remained committed to doing something about HIV or at least doing my best to help the overall effort be as successful as it possibly can.”

Nelson Michael, director of the US Military HIV Research Program, has known Feinberg since they were classmates at Stanford in 1979. “I was thrilled to learn that Mark was chosen to lead IAVI,” says Michael, who reflected on how both of their lives and careers have been shaped by the HIV pandemic. “Mark and I have become dedicated HIV vaccine developers. We are now in the enviable position, as longtime friends and colleagues, to slay this dragon side by side.”

As Managing Editor, I caught up with Feinberg three weeks after he joined IAVI to discuss his unique perspectives on HIV vaccine research, his broad experiences, and his vision for the organization.

During your time at Merck you were involved in the development and eventual introduction of several novel vaccines. What was that experience like?

Being at Merck was really a wonderful opportunity. When I joined there were vaccines in development that addressed diseases of major global health relevance, including rotavirus, which in the absence of a vaccine will kill around 600,000 children each year, the vast majority of them in low-income countries. There was also the vaccine against human papilloma virus, which is in many countries the leading cause of cancer mortality for women. With HPV too, the health impact occurs disproportionately in low-income countries where screening methodologies for cervical cancer and health-care infrastructure aren't as strong. These vaccines were really very promising technical innovations. It was also really imperative to work to make them available in places where the disease impact was greatest and where the benefit of the vaccines would be most pronounced.

At the time there was growing interest in accelerating the availability of vaccines in low-income countries, but there wasn't a lot of experience with models or success factors that govern introduction of vaccines. I had the opportunity to lead efforts to help accelerate access to these vaccines in low-income countries in partnership with the governments of those countries. We established a number of partnerships, including one with Nicaragua that led to a national introduction of Merck's rotavirus vaccine RotaTeq in the same year it was licensed in the US and a number of other developed countries. Very quickly after that program was initiated, Nicaragua had the highest rate of rotavirus vaccination of any country in the world, which clearly answered the question about whether you could achieve success in resource-limited settings. Similarly, we established partnerships with the governments of Rwanda and Bhutan early on when Merck's HPV vaccine Gardasil was first

licensed, and those proved to be very successful in getting very high vaccination coverage rates in adolescent females.

I was also fortunate to be provided with the support to lead the development of new partnership models to advance research and development efforts focusing on disease targets that represent major public health concerns, but for which no commercial opportunity exists to recoup a return on the investment in product development. While one example of this is Merck's Ebola vaccine development program, another was our tremendous partnership with the Wellcome Trust to establish the MSD-Wellcome Trust Hilleman Laboratories—a research and development effort, based in New Delhi, that is specifically focused on developing new and improved vaccines to address diseases that disproportionately affect people living in poverty. All of these examples have reinforced my belief that strategic partnerships between organizations that share a common commitment to public health impact can accomplish remarkable things.

Were there any shared lessons for HIV that emerged from the experiences with those vaccines?

One important lesson is that understanding the circumstances under which a vaccine would be utilized is critically important, as is doing your best to tailor the product profile of the vaccine to enable it to be successfully implemented in resource-limited settings. Those are issues that need to be considered very early on in the development of a vaccine candidate. They are not something that can be easily retrofitted in the end. In addition it's very clear that success in public health only comes through creative partnerships of stakeholders who share a common commitment. When that exists, great things can happen, and if it doesn't, then success is much harder to realize.

During your tenure at Merck the company was involved in the STEP and Phambili

trials, the first to test the concept of a T-cell based vaccine candidate. How would you characterize the results of those trials and how they affected the course of vaccine research?

Merck's HIV vaccine program was very influential in my decision to go to work there because I had been involved in the early Phase I clinical trials of a number of the vaccine candidates that Merck was exploring and got to see just how committed the scientists and the company were to advancing that program.

At the time an important research goal was to test the hypothesis about the potential benefits of cell-mediated immunity against HIV as a way of, if not preventing HIV infection, at least enabling an infected person to better control the infection and be less likely to transmit the virus to others, which could help control the spread of the virus in the population.

The STEP and Phambili trials were, at the time, the leading edge of efforts to test this major hypothesis about how you might make an effective HIV vaccine, so when the results came in not only demonstrating a lack of efficacy but also suggesting potential for increased risk of infection, that was deeply disappointing for very many people. It was profoundly disappointing for all of us at Merck who worked on the vaccine, as well as the multitude of wonderful partners and volunteers that we worked with all around the world to make that trial happen. This also had an impact on the field more broadly with respect to rethinking strategies. While the specific approach tested proved unsuccessful, the overall effort was very informative and valuable.

The vaccine field was also influenced by the results of the RV144 trial in Thailand—the first to show any protection against HIV infection. What are your thoughts on the outcome of RV144 and the cadre of follow-up studies that are now ongoing or planned?

I was one of the people who was skeptical of the RV144 study and was an author of an

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with partners in 25 countries to research, design and develop AIDS vaccine candidates. In addition, IAVI conducts policy analyses and serves as an advocate for the AIDS vaccine field. For more information, see www.iavi.org.

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opinion piece in *Science* with many other partners in the HIV vaccine field who expressed concern about that trial. But since then, some very interesting scientific insights and leads have emerged. In particular, the RV144 study provided important clues about what might be a beneficial mechanism of antibody-mediated protection that was previously unappreciated. While additional studies to replicate and extend the RV144 study results are needed, the study investigators have provided the field with important data to frame testable hypotheses. In this regard, the RV144 results will be truly valuable if they can inform new approaches to induce the targeted immune response in the majority of vaccinated individuals, and if this response proves to engender protection from HIV infection in the follow-on studies now being pursued.

Were there any lessons from your experience with an Ebola vaccine candidate that are relevant to HIV?

For me, there were a number of very important lessons from the Ebola vaccine development experience. It was an unprecedented effort, not only in terms of the speed with which the candidate advanced through various stages of clinical trials—progressing from the first-in-human studies to evidence of vaccine efficacy in only 10 months—but also with respect to the number of independent studies done by different partners as part of the development program. It was really impressive to see so many private and public sector partners stepping up to address this pressing public health need and finding ways to align complementary expertise to get the job done in an accelerated way. That was not only what happened with the Merck program but also with other collaborations advancing alternative vaccine candidates. The clinical investigators in the various countries and their partners did a remarkable job launching complicated and high quality clinical trials in a very short period of time.

We now need to find ways to foster even more effective multi-sector partnerships to address established public health threats like HIV and to proactively prepare for other infectious disease threats that will emerge in the future. I believe that we can do this, and that we must take the opportunity and responsibility to do so very seriously.

Unfortunately, public attention focused on HIV has waned because the pandemic has

been around for so long—almost 35 years. Yet more people die each week from AIDS than have died of Ebola in the 2014 outbreak overall. The urgency to enable all HIV-infected people to get effective therapy and to develop effective approaches to protect at-risk individuals so that they don't become infected remain major imperatives.

After such a broad and varied experience at Merck, why return to HIV, and IAVI in particular?

While I have worked on a number of diseases and that has been tremendously exciting from a scientific, public health, and personal perspective, my scientific heart and mind remained committed to doing something about HIV, or at least doing my best to help the overall effort be as successful as it possibly can. Contributing to HIV control and hopefully elimination is really what I've always wanted to focus my career on.

My interest in coming to IAVI really grew out of what I have seen working in academia, government, and industry, and that is that I believe there are major opportunities for more effective collaborations between sectors than many people can imagine if they only work in one sector. There is all too often a misunderstanding between the different sectors and I think people don't fully appreciate the good intentions or the real constraints that exist in each sector. I believe that is a solvable issue, but one that will require innovative approaches to partnership and collaboration. IAVI worked hard under Margie McGlynn's leadership to become an ever more effective partner and I think there are opportunities to take that to an even more significant level if we understand how we can play the most effective, collaborative, enabling role for the field overall. That to me is a really exciting opportunity. I think there are opportunities to fill gaps, imagine new models of collaboration, and work in close partnership with others to set some powerful precedents in the HIV vaccine field.

My impression, having now been at IAVI for three weeks, is that everything I hoped would be true about the promise of IAVI to be that positive, collaborative presence in the field is true. The people who work here are incredibly dedicated to the goal of HIV vaccine development. They are people who want to be the most effective partners and collaborators that they can be and I feel fortunate to have them as colleagues.

I also feel fortunate to be able to work with really great partners at USAID [United States Agency for International Development], the Bill & Melinda Gates Foundation, the National Institutes of Health, academic and government laboratories, and a number of other partners including private sector entities and governments that IAVI works with. All of these organizations share a common commitment and collectively we have the opportunity to figure out how we can best advance progress across the HIV vaccine field.

So what then is your vision for IAVI?

When you have a disease like HIV or Ebola, for which either the commercial incentive doesn't exist or the scientific complexity or risk is too great, it's really going to depend upon models of collaboration between public and private stakeholders to achieve success. And that means we need to find ways of collaborating effectively and linking different sectors with each other in the most effective ways. And if there are opportunities for organizations like IAVI or others to help facilitate those collaborations that would be a really important contribution. In addition, we hope to make valuable contributions to advance and enable basic, translational, and clinical HIV vaccine research—ideally in collaboration with others and in ways that establish platforms for broader research benefit—and to strengthen research capacity in countries heavily impacted by AIDS in innovative and sustainable ways.

Likewise, a lot of great science is taking place in academic and government laboratories, but the people doing the science don't necessarily have experience in product development so they don't always have the vision of the end-to-end framework within which successful vaccine programs are developed in private sector entities. Similarly, they don't often have expertise in bioprocess, scale-up manufacturing, or regulatory issues. That is an area where IAVI has begun to play a positive role—enabling the work of others to be translated from concept to hopefully proof of concept. I think that is an important contribution and an area where we can do even more. We can work to achieve the vision of being the facilitators of progress for different partners in the field and can hopefully help connect the dots between different stages and partners in the vaccine development process. ■

New Global Goals and Guidelines Aim to Eliminate AIDS

In less than a week's time, three organizations took bold steps intended to slow the spread of AIDS, if not end it entirely.

On September 25, the United Nations General Assembly (UNGA) adopted a sweeping set of 17 Sustainable Development Goals (SDGs), one of which relates to health and aims to end AIDS, tuberculosis, malaria, and neglected tropical diseases by 2030. These broad and ambitious goals, which also aim to end hunger and poverty and combat climate change, replace the soon-to-expire millennium development goals (MDGs) that were adopted in 2000.

Two days after the SDGs were endorsed by the UNGA, US President Barack Obama urged world leaders to support the SDGs and announced plans to expand the HIV/AIDS treatment and prevention goals for the President's Emergency Plan for AIDS Relief (PEPFAR). The US government has already invested US\$65 billion in PEPFAR, which now supports antiretroviral therapy (ARV) for about 7.7 million HIV-infected individuals in developing countries. By the end of 2017, PEPFAR plans to support ARV therapy for nearly 13 million HIV-infected individuals in its target countries—almost double the current number. PEPFAR also plans to provide 13 million adult male circumcisions to prevent new HIV infections, and to reduce HIV incidence by 40% among adolescent girls and young women in 10 sub-Saharan African countries with the greatest HIV infection rates by reallocating \$300 million of current funding.

Capping these announcements, the World Health Organization (WHO) issued revised guidelines on September 30 for HIV treatment and prevention. The updated guidelines call for all HIV-infected individuals to start ARV therapy as soon as possible after their infection is discovered. The guidelines also recommend that high-risk, HIV-uninfected individuals be offered ARVs as a means of HIV prevention, a practice known as pre-exposure prophylaxis (PrEP). Previous guidelines were more lim-

ited; viral load determined who received ARV therapy, and PrEP was recommended only for men who have sex with men.

Chris Beyrer, a professor at Johns Hopkins Bloomberg School of Public Health and President of the International AIDS Society, considers the SDGs bold and visionary. "My only concern is that on health, they are very broad, and it may prove that they are too broad and general to serve as foci for advocacy, including around HIV/AIDS," said Beyrer. "The power of the MDGs was at least in part their specificity. The SDGs may be harder to advocate around."

And advocacy will likely be key, given the high price tag that accompanies achieving these goals. Governments, foundations, and public-private partnerships are already investing around \$19 billion a year in programs that provide ARVs in developing countries, and a recent report released by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and *The Lancet* Commission estimates it will cost \$36 billion annually to end AIDS by 2030.

If anything, the HIV-related MDGs, which called for halting the spread of HIV/AIDS by 2015 and achieving universal access to ARV treatment for all in need by 2010, illustrate how difficult it can be to reach the finish line. Earlier this year, UNAIDS reported that new infections have declined 35% and 15 million people in developing countries are now receiving ARV therapy. Yet ARV coverage still only accounted for about 41% of the 36 million people estimated to be living with HIV/AIDS.

Mitchell Warren, executive director of the global AIDS advocacy organization AVAC, remains optimistic. He recalls the 2000 International AIDS Conference in Durban, South Africa, when doubts remained about whether there was enough money to fund ARV treatment outside the US and Europe. "Look what happened," he said. "Fifteen years later we have 15 million people on ARVs. The world can change." —*Mary Rushton*



Source: UN in collaboration with Project Everyone

Understanding Ebola Vaccine Development

What are the strategies scientists are using to develop vaccines to prevent Ebola? *By Mary Rushton*

Last year an unprecedented outbreak of the highly lethal Ebola virus occurred in the West African countries of Guinea, Liberia, Nigeria, and Sierra Leone. This epidemic, which started in 2013, led to over 28,000 infections and has killed more than 11,000 people, making it the largest outbreak of Ebola ever. The number of new cases of Ebola infection declined dramatically since the height of the outbreak, with Liberia recently being declared Ebola-free. But the World Health Organization (WHO) continues to receive reports of new infections and fatalities in Guinea and Sierra Leone.

The most recent Ebola epidemic created a humanitarian crisis as it spread through highly populated corridors of these West African countries. The urgency of responding to the outbreak spurred public health officials, research institutions, and pharmaceutical companies to rapidly accelerate the development and testing of new drugs to treat and vaccines to prevent Ebola infection—none of which currently exist.

Now these efforts are bearing fruit. The first efficacy trial of an Ebola vaccine tested in 4,000 high-risk volunteers from Guinea who had recently been in close contact with Ebola-infected individuals shows a single dose of one vaccine candidate was safe and highly effective—in some cases 100% effective—in preventing Ebola infection.

The culprit

Ebola is a type of virus called a filovirus and is named after the river where it was discovered in 1976 in the central African country of Zaire, now the Democratic Republic of the Congo. Since then, 19 major and 14 minor Ebola outbreaks have occurred, primarily in Africa, and four additional species of the virus have been identified. Ebola has a wormlike structure that can infect and quickly overwhelm nearly every cell and organ in the human body. As a result, it is highly fatal. Of the 318 people diagnosed with Ebola during the first outbreak, 288 died—a case fatality rate of 88%. The virus is transmitted through direct contact with infected blood or bodily fluids.

Circle of protection

The first efficacy trial of an Ebola vaccine candidate provided results earlier this year. The candidate, known as rVSV-ZEBOV, was first developed by the Public Health Agency of Canada and is now manufactured by the pharmaceutical company Merck. The VSV in the candidate's name stands for vesicular stomatitis virus. This virus, which primarily infects cattle, is disabled and used as what researchers call a viral vector to shuttle a gene from the Ebola virus into the body so that the immune system can create an immune response against it, without an actual Ebola infection occurring.

Scientists are using various viral vectors in HIV vaccine candidates as well, including VSV. Viral vectors are a promising strategy for pathogens like Ebola or HIV, for which a killed or weakened version of the pathogen is not feasible to use in a vaccine.

The efficacy trial of rVSV-ZEBOV in Guinea utilized a strategy called ring vaccination. Ring vaccination is so-named because the close contacts of an infected individual are immunized to create a ring of protection that can control the spread of the virus. Ring vaccination was used to contain the spread of smallpox in developing countries during a highly successful eradication campaign in the 1970s, but it is an unusual approach for testing the efficacy of a vaccine candidate.

In the Guinea trial, some rings of susceptible individuals were vaccinated immediately after the newly Ebola-infected person was identified, while other rings were vaccinated three weeks later, when the period of Ebola infectiousness was ending. This strategy allowed researchers to compare the efficacy between these different rings. It also enabled researchers to forego use of a placebo group.

The interim data published in July showed that none of the individuals in the immediately vaccinated rings contracted Ebola, while in the delayed rings, 16 Ebola infections were reported.

The WHO, with the approval of the Guinea government, plans to continue the trial to gather more conclusive evidence of

how well the vaccine candidate induces herd immunity—when a high enough percentage of people are immunized that the chain of infection for contagious diseases is broken and the spread of disease within the community is contained (see *VAX March 2015 Primer on Understanding Community Immunity*).

Other vaccine candidates

Other Ebola vaccines are also in clinical development. Scientists from the US National Institute of Allergy and Infectious Diseases' Vaccine Research Center and pharmaceutical company GlaxoSmithKline (GSK) recently conducted a Phase II clinical trial in Liberia comparing another viral vector-based vaccine candidate with rVSV-ZEBOV. Both candidates were found to be safe, but a dramatic drop in Ebola incidence in this country is impeding the ability to compare the efficacy of the two vaccines.

Johnson & Johnson and Bavarian Nordic are also developing a two-dose vaccine candidate that employs two different viral vectors. Phase II trials of these candidates are planned for later this year in Uganda, Kenya, and Tanzania. Other trials are also underway.

Many of the current Ebola vaccine candidates were developed years ago, but the relative rarity of Ebola prevented researchers from conducting large efficacy trials. This all changed with the scale of the latest outbreak and researchers reacted quickly. Some candidates received regulatory approval to advance from Phase I to Phase III trials in less than a year. And now that one vaccine candidate appears effective, there are calls from public health organizations to make it available, even as researchers collect more conclusive data on the vaccine's efficacy.

What scientists ultimately learn from these vaccine candidates could affect other viral diseases, such as AIDS, for which scientists are developing and testing a range of viral vector-based vaccine candidates. ■

Mary Rushton is a freelance writer based in Cambridge, Massachusetts.