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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

In With the New...

The AIDS vaccine field considers ways to encourage innovation and recruit new minds into the effort *By Regina McEneary*

PETER KWONG CLEARLY REMEMBERS the day a seminar helped guide his career path to AIDS vaccine research. It was 1991 and Kwong, working toward a PhD in biology at Columbia University, was among 25 students who gathered to hear pioneering Australian biologist Peter Coleman describe how he had used the relatively new technique of structural biology—a branch of molecular biology that looks at the architecture and shape of molecules—to study the influenza virus.

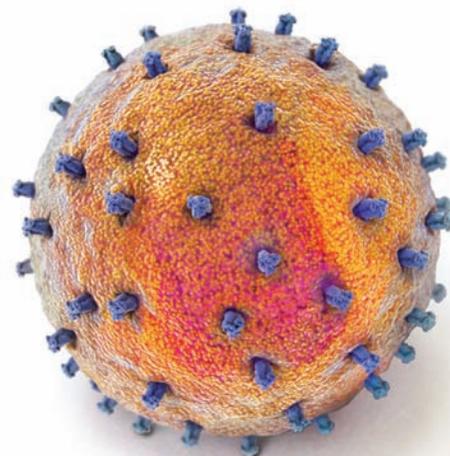
Coleman's pioneering research would eventually lead to a new class of antiviral drugs against influenza, but in the early 1990s it was still conjecture whether crystallography—which primarily relies on X-rays to determine the shape and structure of proteins—was going to be useful for the pharmaceutical industry. Kwong was impressed with the approach and eventually started wondering whether structural biology and crystallography could also be useful in vaccine design, specifically for HIV.

He decided to tackle this question and now, as head of the Structural Biology Section at the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), which is part of the US National Institutes of Health, he is using X-ray crystallography to decipher one of a handful of antibodies—Y-shaped proteins that bind to viruses and prevent

them from infecting human cells—capable of neutralizing a broad variety of HIV variants. The antibody Kwong is studying is known as b12. “We’re basically performing magic,” he says. “But then everything in science is magic until you figure it out.”

Whether or not Kwong's work will lead researchers to be able to design vaccine candidates that could induce this antibody in people remains unknown. But his research is one of the many innovative approaches being utilized to overcome a number of daunting biological challenges in AIDS vaccine development. Following some recent setbacks, most notably the failure of Merck's AIDS vaccine candidate in the STEP trial, the AIDS vaccine field is trying to invigorate research efforts by pursuing new ways to attract more young researchers like Kwong, and encourage more innovative thinking.

But the search for new blood and fresh ideas faces a number of practical hurdles. The percentage of investigators, not just in AIDS vaccine research but throughout academia, competing for their first general research grant—known as an RO1—declined from 35% in 1965 to 25% in 2003. Meanwhile, the average age of principal investigators rose from 35-40 in 1983 to 50 in 2003, according to Jose Esparza, a senior advisor on HIV vaccines at the Bill & Melinda Gates Foundation.



With fewer young, less-established researchers competing for early-career grants, the pace of scientific breakthroughs, such as an AIDS vaccine, will slow considerably, Esparza and others contend. To ensure this doesn't happen, agencies and foundations that fund AIDS vaccine research are creating new ways to encourage young scientists to enter the field and are developing new funding streams to encourage more out-of-the-box thinking.

The hunt for innovation

Leading the charge to spur innovation in the field is NIAID, which devoted US\$497 million of its \$1.5 billion HIV/AIDS budget to vaccine research in 2008 and has made the development of an AIDS vaccine a top priority. Last March, sparked by the results of the STEP trial, NIAID held a day-long summit attended by 200

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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 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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researchers to discuss shifting priorities in AIDS vaccine research and the myriad of challenges still facing vaccine development (see VAX April 2008 *Spotlight on Balancing the AIDS Vaccine Budget*).

Following the summit, NIAID announced two new grants to spark creative approaches to vaccine discovery and

development. The Basic HIV Vaccine Discovery Research grant program will commit \$10 million to fund 20-30 applications, while the Highly Innovative Tactics to Interrupt Transmission of HIV program, or HIT-IT for short, will commit \$4.5 million for 5-10 applications. Both grant programs, which will be funded this year, were created to address some of the most pressing questions facing vaccine researchers today, including improving our understanding of how the immune system responds to natural infection and vaccination, new mechanisms and pathways that could be targeted by vaccines, and developing better animal models for evaluating AIDS vaccine candidates, as well as many other areas.

Last year the Gates Foundation, the largest private funder of HIV/AIDS research, awarded \$100,000 grants over five years to 105 researchers through its Grand Challenges Explorations program. These grants will be awarded to individuals with novel ideas that cross a number of areas, including AIDS vaccine research and, like HIT-IT, target high-risk, outside-the-box proposals that traditionally would have a hard time attracting private and public funding.

IAVI, meanwhile, has a two-year-old Innovation Fund that provides seed money to help bring novel, early-stage technologies to the field of AIDS vaccine research. The Innovation Fund, which is partially supported by a grant from the Gates Foundation, has awarded six grants since its creation in August 2007 and nine more are expected over the next two years.

While the Innovation Fund does entertain and fund projects from academic researchers, the program is primarily directed at identifying novel technologies within industry, says Kalpana Gupta, IAVI's director of new alliances and initiatives.

However, this new roadmap toward innovation is being laid out during a time of great economic uncertainty. A sharp slow-

down in the global economy and prospects of what could be a deep and lengthy recession have cast a cloud over a research environment already struggling with flat budgets and increased competition for grant dollars. While NIAID's director, Anthony Fauci, does not expect any cutbacks in AIDS spending in the near future, he also isn't anticipating any new funding. Still, he said the \$14.5 million recently pledged for the HIT-IT and Vaccine Discovery Research programs is secure. Moreover, he said the agency is "committed to not only maintaining but increasing HIV vaccine research," particularly in basic science. Fauci says that means redirecting money from other areas of NIAID's AIDS budget considered "less pressing."

"There is obviously a lot of interest in HIV vaccine research," says Fauci. "A lot of that is coming from philanthropic groups. But with the economy in free fall, the question remains whether people will be more reluctant to give money to philanthropic groups." Also of concern is whether the economic downturn will dampen philanthropic support for high-risk projects that are likely to deliver more blanks than magic bullets.

The next generation

Another way to stimulate innovation is to encourage more early career investigators to pursue AIDS vaccine research. Because young researchers tend to have a certain naive curiosity that fosters exploration, they are often more willing to adopt novel approaches to addressing questions that have confounded their mentors.

The Global HIV Vaccine Enterprise, an international alliance of researchers and funders, is focusing on identifying potential solutions for how best to attract and retain young scientists to AIDS vaccine research through its Young and Early Career Investigators (YECI) Initiative.

"We are not a funder," says Alan Bernstein, executive director of the Enterprise. "It is not our responsibility or mission to mandate those things directly, but I think our job in this case is to highlight a problem or opportunity and come up with possible ways of addressing it and then present that to funders."

Dan Barouch, associate professor of medicine at Beth Israel Deaconess Medical Center in Boston, and Thumbi Ndung'u, associate professor in HIV/AIDS Research

The field of investigators has come to the realization that they will have to pass the torch to the next generation. The scientific problems are there, and it will need young, talented, and creative investigators to solve them.

— Dan Barouch

at the University of KwaZulu Natal in Durban, South Africa, were appointed to chair the YECI Committee established by the Enterprise.

The Center for HIV/AIDS Vaccine Immunology (CHAVI) and the HIV Vaccine Trials Network (HVTN), both funded by NIAID, are also reaching out to early career scientists, most notably those interested in non-human primate research. Last year CHAVI and HVTN began soliciting pilot study proposals from young researchers that “strengthen bridges between non-human primate studies and human research by addressing key questions in the search for a safe and effective vaccine.”

Barouch said the STEP trial findings, ironically, have given young researchers a huge opportunity. “The future has never looked more promising because the failure of the Merck [candidate] shows there is a lot more research to be done,” says Barouch, a molecular immunologist who is studying T-cell based vaccines. “The field of investi-

gators has come to the realization that they will have to pass the torch to the next generation. The scientific problems are there, and it will need young, talented, and creative investigators to solve them.”

But to meet these challenges, particularly in countries hardest hit by the epidemic, it will require a long-term investment to prevent the kind of brain drain that has prevented many African countries from developing their own research infrastructure and holding onto their scientists, says Ndung’u, a Harvard-trained virologist whose research institute in Durban was built primarily with funds from the Doris Duke Foundation.

“It takes time to build a good research institution,” says Ndung’u. “A lot of the grants that have been given to investigators to do work in Africa, I don’t think those grantees were held to the fire in terms of making sure there is a pathway that is developed and sustained.”

In developed countries with good research infrastructure, the money is sim-

ply getting tighter. “It is getting tougher and tougher to get into the big laboratories because they don’t have the money,” acknowledges Galit Alter, who was mentored by Harvard immunologist Marcus Altfeld, director of the innate immunity program at Partners AIDS Research Center, and now has her own research laboratory there.

“The most important thing that the NIAID summit did, I think, was encourage investigators not to give up,” says Alter. “Even though funding is tight there really is a reason to stay in it. It’s survival of the fittest. Those who survive will be the creators.”

Bernstein says he hopes that the recommendations of the YECI Committee will provide traction in the AIDS vaccine arena and beyond. “These issues are not unique to HIV vaccine research,” says Bernstein. “Young people have particular challenges these days in biomedical research. If we don’t renew ourselves as a scientific community, we will be in trouble.” ■

GLOBAL NEWS *by Regina McEnergy*

CDC, PEPFAR, and UNAIDS to Have New Leaders

A FLURRY OF PERSONNEL and policy switches impacting global health and HIV/AIDS were rolled out recently, including many political appointments within US government agencies which coincided with President Barack Obama taking office on January 20.

Obama’s administration named Richard Besser, a pediatrician and leading authority on disaster preparedness, to be acting director of the US government’s leading public health agency, the Centers for Disease Control and Prevention (CDC). A permanent director will be chosen by Obama’s Secretary of Health and Human Services. Besser replaces Julie Gerberding, a longtime AIDS physician who resigned January 20 after six years as director of the CDC.

Another key shift in US public health administration occurred this month with the resignation of Mark Dybul, the US Global AIDS Coordinator who spearheaded the President’s Emergency Plan for AIDS Relief (PEPFAR) for former President George W. Bush. The US State Department, which has authority over the Global AIDS Coordinator, confirmed that Dybul was asked to submit his resignation. A State Department representative said they did not know how long it would be before Dybul’s replacement is named. PEPFAR, which won widespread praise, has sup-

ported the provision of life-saving antiretroviral (ARV) treatment for 1.7 million HIV-infected people in developing countries. The program, which was first announced in 2002 by Bush, was reauthorized last year for US\$45 billion, including \$9 billion in funding for malaria and tuberculosis programs (see *VAX* Aug. 2008 *Global News* on *Passage of PEPFAR*).

These changes within US agencies and departments coincide with a recent shift in leadership at the Joint United Nations Programme on HIV/AIDS (UNAIDS). In early December, the agency named its Deputy Executive Director of Programmes, Michel Sidibé, to lead UNAIDS, replacing Peter Piot, a Belgian physician who helped create UNAIDS and had been its director since 1995. Sidibé, a native of Mali, has a long tenure within the United Nations system, including 14 years with UNICEF.

Piot is now President of the Board of Directors at the Global HIV Vaccine Enterprise and is also spending five months as a top health advisor with the Bill & Melinda Gates Foundation. He then plans to launch a global health institute at Imperial College London that will be dedicated to combating AIDS, tuberculosis, malaria and other deadly diseases afflicting poor countries. ■

Understanding the Conundrum of Immune Activation in HIV/AIDS

Why is it that chronic activation of the immune system during HIV infection actually leads to disease progression?

By Regina McEnery and Kristen Jill Kresge

IN MOST CIRCUMSTANCES, the body's deployment of the immune system (both the innate and adaptive arms) allows it to conquer an invading pathogen (see VAX July 2008 *Special Issue, Understanding the Immune System and AIDS Vaccine Strategies*). But HIV is unique in that it directly attacks the cells of the immune system, slowly breaking down the body's defenses. Once the adaptive immune system is alerted to an HIV infection, it responds by producing HIV-specific CD4⁺ T cells, which orchestrate the function of CD8⁺ T cells, also known as killer T cells because of their ability to kill virus-infected cells. While these T cells are beneficial in suppressing HIV, they are also preferentially targeted and destroyed by the virus. As more CD4⁺ T cells are generated in response to HIV, there are also more cells for the virus to infect and kill, setting off a destructive cycle.

Once the virus destroys a critical number of these immune cells, the body's ability to control HIV is severely compromised. A person is diagnosed with AIDS once their number of CD4⁺ T cells declines below a certain level (fewer than 200 cells in a milliliter of blood). When the immune system is compromised to this degree, a person also becomes susceptible to many other bacterial and viral infections. In a person with AIDS, these are referred to as opportunistic infections.

Many T cells are lost during the course of HIV infection because they are directly infected and killed by the virus. However researchers suspect that HIV also uses

other mechanisms to induce immune dysfunction. These mechanisms are not fully understood but some scientists believe that the presence of HIV overstimulates the immune system. HIV

is a chronic infection and there is little or no evidence that any HIV-infected individual has ever been able to clear the virus from their body. As long as HIV is present, the immune system is in a constant state of activation or high alert—struggling to produce immune responses that could control the rapid spread of the virus. There is a broad consensus among researchers that this chronic state of immune activation contributes to the virus's ability to cause disease, an idea referred to as pathogenesis. However, while there are some hypotheses about how HIV causes chronic immune activation, the precise mechanisms are still under investigation.

Clues from nonhuman primates

Studies in nonhuman primates infected with simian immunodeficiency virus (SIV), the monkey equivalent of HIV, suggest that chronic immune activation may play a crucial role in pathogenesis. Rhesus macaques, which are most often used in AIDS vaccine research, develop an AIDS-like disease following SIV infection. However there are some species of nonhuman primates, including sooty mangabeys and African green monkeys, which do not develop AIDS-like symptoms or any deleterious consequences following SIV infection (see VAX Sept. 2008 *Primer on Understanding Control of Virus Replication*). Although SIV-infected sooty mangabeys have high levels of virus circulating in their blood, they are able to maintain normal levels of CD4⁺ T cells. Interestingly, researchers have also observed that the immune systems of SIV-infected sooty mangabeys are not chronically activated, as they are in SIV-infected rhesus macaques or HIV-infected individuals. This may be partly why they are able to avoid developing AIDS. Researchers plan to do additional studies to see if artificially increasing the level of immune activation in these animals will trigger disease progression.

Causes of immune activation

Studies in HIV-infected humans have shown that during the very early stages of infection, the virus rapidly infects and kills T cells in mucosal tissues, with the greatest depletion of CD4⁺ T cells occurring in the intestine, or gut (see VAX April 2006 *Primer on Understanding the Early Stages of HIV Infection*). In most people, the numerous immune cells in the gut that are lost early in infection are never restored, even following initiation of highly active antiretroviral therapy. Some researchers propose that this massive depletion of T cells in the gut allows disease-causing bacteria that normally live in the intestine to leak out and circulate more widely in the body, further burdening the immune system. This is one factor that researchers think may contribute to the high level of immune activation in HIV-infected individuals.

HIV may also interfere with a subset of T cells that are responsible for dampening immune responses and keeping the immune system in check. These so-called regulatory T cells play an important role in suppressing immune responses once an infection is eliminated, and also prevent the immune system from becoming overzealous and attacking the body's own cells. Little is known about the function of regulatory T cells in HIV infection, but this is an active area of investigation and may provide additional insights about the role of immune activation in HIV pathogenesis.

Although the ideal goal is to develop an AIDS vaccine that could prevent HIV infection entirely, a partially effective vaccine that could control the virus in the early days of infection might help prevent severe damage to the immune system and allow the body to better control HIV. This could alleviate some of the causes of chronic immune activation and might help delay disease progression in individuals who may become HIV infected through natural exposure to the virus, despite vaccination. ■

