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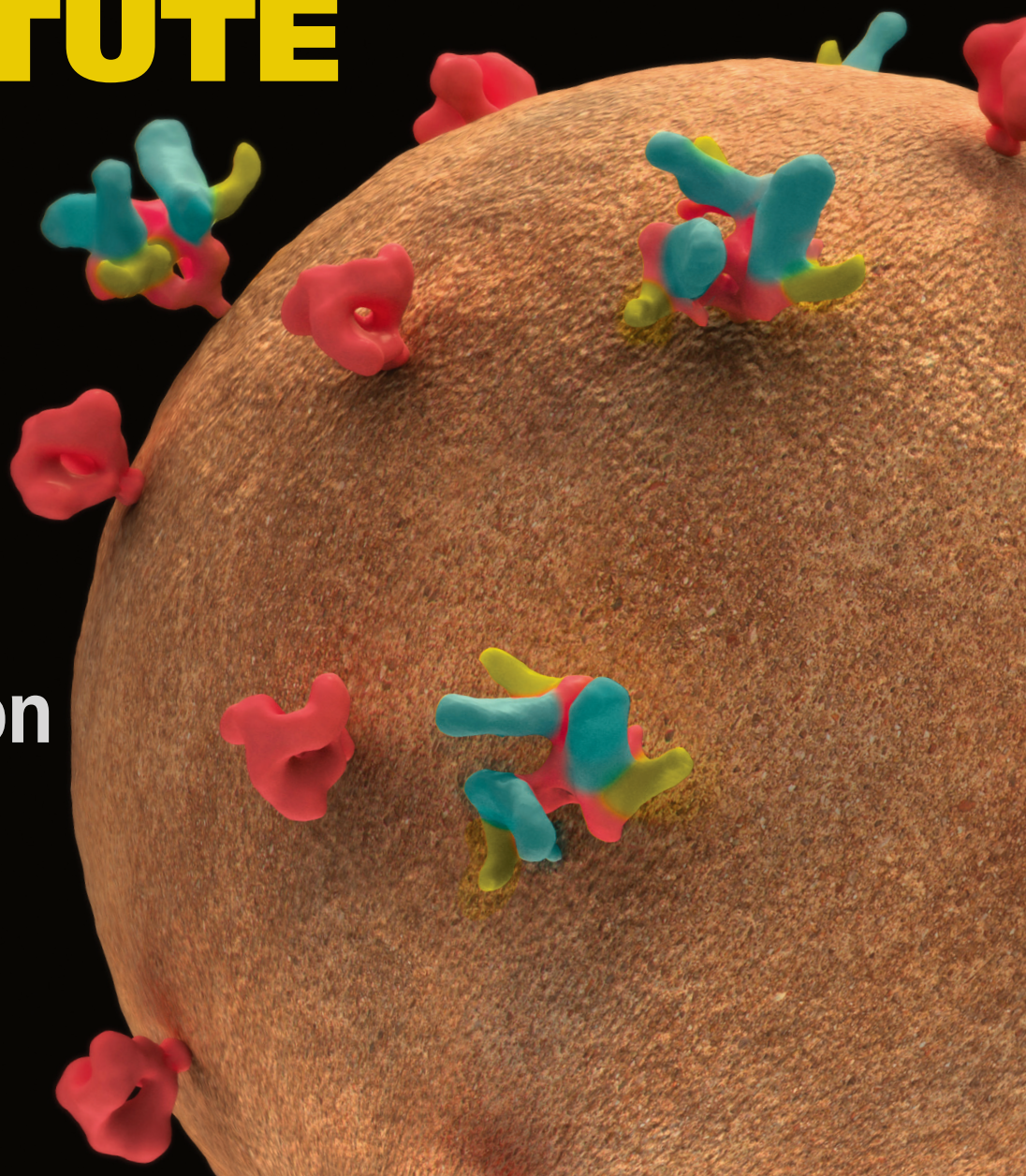
PROFILE

THE RAGON INSTITUTE

ALSO:

Treatment is Prevention

IAS 2011



EDITOR'S LETTER

INNOVATION, COLLABORATION, AND FLEXIBILITY have become buzzwords in the HIV vaccine field. But a two-year-old Boston-based research center is taking these matters to heart. The Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology, and Harvard was formed two years ago after Bruce Walker, the Institute's director, received a US\$100 million gift from technology magnate Phillip "Terry" Ragon and his wife Susan. This gift allowed Walker to build a research team that is focused on trying to overcome some of the most challenging obstacles to the development of an HIV vaccine. The team includes researchers with diverse scientific backgrounds, many of whom are new to studying HIV, which adds a unique perspective to their work.

In this issue, we profile The Ragon Institute, focusing in particular on its formation and some of the research projects underway at its labs in Boston and Cambridge (see page 4).

Also in this issue, we report on the main highlights from the International AIDS Society's Sixth International Conference on HIV Pathogenesis, Treatment and Prevention, which took place July 17-20 (see page 14). Following the release of promising results from trials evaluating the preventive benefits of antiretrovirals (ARVs), the mood at the meeting was jubilant. But given the current economic restraints, there will likely be some difficult and sobering decisions about how to implement earlier treatment of HIV, as well as how to use ARVs as an HIV prevention strategy.

We also feature an interview with IAVI's new Chief Executive Officer Margie McGlynn, who discusses her career in the pharmaceutical industry and her vision for IAVI (see page 12). Finally, we highlight more recent advances in the discovery and characterization of HIV-specific broadly neutralizing antibodies by researchers at Rockefeller University and the Vaccine Research Center (see pages 18 and 19). The advances in isolating broadly neutralizing antibodies keep rolling in. As this issue was headed to press, researchers at The Scripps Research Institute, IAVI, and the biotechnology companies Theraclone Sciences and Monogram Biosciences, reported the isolation of 17 new broadly neutralizing antibodies—most of which are 10 times more potent than the best of the recently isolated antibodies. The study was published online in *Nature*. More information on these recent discoveries will likely come at next month's AIDS Vaccine Conference in Bangkok, which we're gearing up to cover, so follow the *IAVI Report* blog for the latest news and look for full coverage in the next issue.



KRISTEN JILL KRESGE



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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 and operational in 25 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI was founded with the generous support of the Alfred P. Sloan Foundation, The Rockefeller Foundation, The Starr Foundation, and Until There's A Cure Foundation. Other major supporters include the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, The John D. Evans Foundation, The New York Community Trust, the James B. Pendleton Charitable Trust; the Governments of Canada, Denmark, India, Ireland, Japan, The Netherlands, Norway, Spain, Sweden, the United Kingdom, and the United States, the Basque Autonomous Government (Spain), the European Union as well as the National Institute of Allergy and Infectious Diseases and The City of New York, Economic Development Corporation; multilateral organizations such as The World Bank and The OPEC Fund for International Development; corporate donors including BD (Becton, Dickinson & Co.), Bristol-Myers Squibb, Continental Airlines, The Gilead Foundation, GlaxoSmithKline, Google Inc., Pfizer Inc, and Thermo Fisher Scientific Inc.; leading AIDS charities such as Broadway Cares/Equity Fights AIDS; and many generous individuals from around the world. For more information, see www.iavi.org.

IN THIS ISSUE

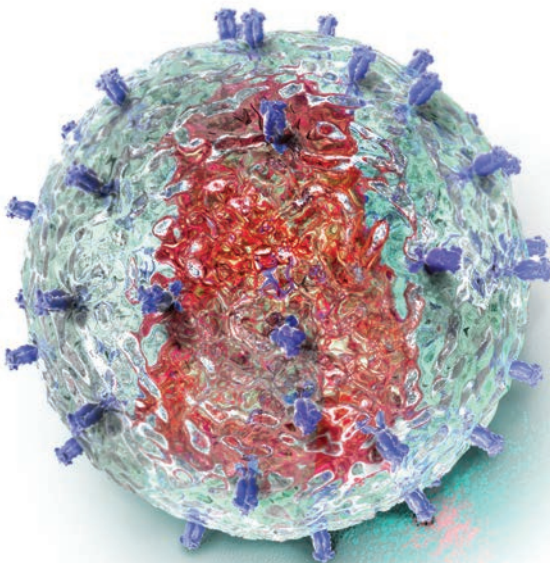
04 **The House That Bruce Built**
A look inside The Ragon Institute at their efforts to tackle the most vexing challenges hindering HIV vaccine research.

12 **An Interview with Margie McGlynn**
The new chief executive officer of IAVI, the second in its history, discusses her career in vaccine development and deployment and her vision for the organization.

14 **Treatment is Prevention**
After results from several trials illustrated the preventive benefits of antiretrovirals, researchers at the annual AIDS conference declare treatment is prevention.

17 **Vaccine Briefs**
HVTN 505 Trial Expanded to See if Vaccine Candidates Can Block HIV Acquisition.

18 **Research Briefs**
Dozens of New Broadly Neutralizing Antibodies Identified; Researchers Gather Clues About How Broadly Neutralizing Antibodies Develop.



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[ON THE COVER]

3D rendering of the surface of HIV displaying the closed conformation of trimeric HIV Envelope glycoprotein spikes (red), and the open conformation of the Env spikes in complex with soluble CD4 (green) and the Fab fragment of the 17b antibody (blue). The 17b antibody recognizes the CCR5 co-receptor binding site on the Env trimer. This site is thought to become exposed as a result of a change of the Env trimer to the open conformation when CD4 binds. The image is based on data generated by electron tomography and shows the trimeric HIV Env spikes in an arrangement that is typical for virions of the HIV-1 strain BaL. Sriram Subramaniam and colleagues at the National Cancer Institute (NCI) at the National Institutes of Health have used this method to look at Env structures in several HIV and SIV strains in native and in antibody-bound states, as well as trimeric Env-based HIV-1 immunogens (see *PLoS Pathog.* **6**, e1001249, 2010; *Proc. Natl. Acad. Sci.* **108**, 11440, 2011).

Image courtesy of Donald Bliss and Sriram Subramaniam, NCI.

Phillip "Terry" Ragon, left, and Bruce Walker at a WhizzKids United event in Durban, South Africa, in 2007.



The House

Photo by Jonas Steengaard,
courtesy of The Ragon Institute

A look inside **The Ragon Institute** at their efforts to tackle the most vexing challenges hindering HIV vaccine research

You could say the “B” in Boston stands for Braniac. After all, the cities of Boston and Cambridge, its neighbor across the Charles River in Massachusetts, encompass the heaviest concentration of engineers, scientists, and researchers in the country, according to *Wired* magazine. And Harvard and the Massachusetts Institute of Technology (MIT), two of the premier universities in the US, are continuously pumping more young scientists into the metropolitan area. If you’ve seen *The Social Network*, you get the idea—it’s the kind of place where today’s computer geek can become tomorrow’s social media giant.

Still, were you to take a stroll around this science and technology hub you might have a hard time finding one of Greater Boston’s newest centers, The Ragon Institute of Massachusetts General Hospital (MGH), MIT, and Harvard. Launched in 2009 with a US\$100 million donation from technology magnate Phillip “Terry” Ragon, and his wife, Susan, who reside in Cambridge, The Ragon Institute represents a collaboration modeled after its neighbor, the Broad Institute of MIT and Harvard, which engages scientists across different disciplines to solve biological problems in a systematic way.

But The Ragon Institute has a more specific mission: melding physicians, basic scientists, and

engineers from MGH, Harvard Medical School, and MIT to study HIV’s interaction with the immune system to try to solve some of the most vexing challenges that have hindered the development of an effective AIDS vaccine.

At the helm of The Ragon Institute sits Bruce Walker, whose office, for now, is housed in the sprawling MGH center in the Charlestown section of Boston. Walker has been working in the field of AIDS since the pandemic began unfolding 30 years ago, but his research has taken new directions since receiving the gift just two years ago, the largest donation in MGH’s history. “This has been the most exhilarating period of my entire career,” says Walker.

When Walker begins describing the Institute, he quickly directs the conversation to South Africa—the country with the highest HIV prevalence in the world. It becomes clear that the devastation wrought by HIV/AIDS is his motivation. He cares deeply about science and harnessing its power to end the pandemic, but he is just as comfortable describing its nearly unparalleled toll on human life.

Another thing about Walker that strikes you almost immediately is his boyish exuberance, which is not that surprising given the golden opportunity The Ragon Institute is providing: a

that Bruce Built

By **Kristen Jill Kresge** and **Regina McEnery**

In the labs

Sylvie Le Gall



Role: Assistant Professor of Medicine

Focus of lab: Studying the mechanisms of viral protein degradation, epitope processing, and presentation to immune cells.

Sylvie Le Gall, an assistant professor of medicine at Harvard Medical School, is interested in how HIV antigens get processed into epitopes and presented to immune cells. “If we better understand how that process occurs, we think that’s going to help us design [vaccine] immunogens,” says Le Gall, whose lab at The Ragon Institute is focused on just that.

Using multiple approaches, Le Gall and colleagues are studying the *in vitro* degradation of HIV proteins in different cells that are infectable by the virus. Then, using high performance liquid chromatography and mass spectrometry, they can determine how fast the protein is degraded by peptidases and what epitopes it’s being chopped into. How fast the proteins are degraded affects how antigens get presented and shapes the overall immune response to HIV. The earlier the presentation occurs, the better it is for the immune system as it tries to mount a defense against the virus. HIV may avoid production and presentation of some epitopes altogether as a means of immune escape. Other epitopes are decoys, distracting the immune system.

Le Gall has observed that there is a big difference in the timing of HIV antigen presentation and she has identified certain motifs that result in better antigen presentation and improved killing by immune cells. When HIV proteins are modified to contain these motifs, the degradation of the protein can be augmented by 10-fold. Le Gall says this work will help inform immunogen design by allowing researchers to specifically present the epitopes that will give good immune responses. “I don’t think there is agreement about what should go into an immunogen right now,” says Le Gall. “Maybe the immunogen is going to be the parts of the virus that elicit good immune responses.”

Le Gall’s lab is currently collaborating with James Mullins, professor of microbiology at the University of Washington, to study what epitopes are produced from HIV immunogens that are based on the conserved regions of the virus. This work could also be extended to understanding the processing of mosaic antigens, which are computationally designed to achieve optimal coverage of the many versions of HIV in circulation.

generous source of flexible funding over 10 years that enables researchers to engage in the kinds of high-risk projects that big grant-making organizations like the US National Institutes of Health (NIH) are less willing to fund. “I think everybody has far greater potential than they think they have,” says Walker. “What we’ve created is an environment where it’s easier for people to realize that potential.”

One of Walker’s guiding principles for The Ragon Institute was to interest researchers whose work was not already focused on HIV to apply their expertise in this area. Two years later, Walker says the institute has brought 40 new scientists to work on HIV, and he thinks this has been a major driver of innovation. “We’re already turning away people with good ideas,” he says.

Walker, who looks younger than his 59 years, has the casual yet classic look that can only be described as Ivy League. In the corner of his office on the seventh floor of MGH is a “stressless” Swedish chair that seems a suitable antidote to his busy schedule, which includes regular teleconferences with Ragon Institute staff and their collaborators at The Scripps Research Institute (TSRI) in California, Oxford University, and the Doris Duke Medical Research Institute in South

Africa and the University of KwaZulu-Natal. He travels to South Africa every month, a journey he notes takes 24 hours door-to-door. And in addition to these hefty administrative and fundraising duties, Walker oversees five post-doctoral candidates in his laboratory at the Institute, which is focused on mechanisms of immune control in HIV infection. Despite all this, Walker insists he gets plenty of sleep. “We have such good people and everyone is taking on so much responsibility that my job has actually gotten so much easier since Ragon got started,” he says.

Plans are now in the works for a building specifically for The Ragon Institute, and the hope is that by August of next year there will be a permanent home. Not all Ragon investigators will work there—it will be up to individual investigators whether they stay in their current location or have a second location at the Institute.

Meanwhile, Walker is working to raise additional money to continue funding innovative, collaborative research projects. “We are talking now about trying to replicate what Terry and Susan have done,” says Walker. “It would be great if we could find a couple of donors who would do that.” As research money gets tighter, Walker thinks it’s important to teach people how



to communicate with donors and how to give them a message that is compelling. The most important thing, he says, is to have a vision. “You can’t be in the position we’re in and in good conscience not ask people for money,” he says. Although, Walker recognizes most researchers are not comfortable asking for money. “It’s not something that any of us are taught to do but I think it’s something we can learn.”

The \$100 million question

By the mid-1980s, Walker began pondering why the immune systems of so many HIV-infected individuals eventually lost the battle against the virus. This question led him to study a small subset of HIV-infected individuals who managed to defy the odds and live with undetectable viral loads for up to 20 years, without the benefit of antiretroviral therapy. Walker is now following a cohort of about 1,600 HIV controllers, in hopes of discovering what genetic or immunological factors contribute to this impressive control. About one in every 300 HIV-infected individuals is thought to be an elite controller.

In 1998, Walker’s research shifted to South Africa when one of his post docs secured a small grant from the Elizabeth Glaser Pediatric AIDS

Foundation. This effort soon led Walker to seek funding from the Doris Duke Foundation in hopes of “building the best biomedical research facility in the middle of the epidemic.”

“We actually did that,” recalls Walker, “but we couldn’t in good conscience let [HIV-infected] people die, so we started a pilot treatment program.” It was this pilot treatment program housed at St. Mary’s Hospital in Durban, South Africa, which ultimately brought Walker and Ragon together. The hospital was using an electronic medical records system known as TrakCare that had been developed by a US company. Walker didn’t know much about the company and was much too busy during his visits to South Africa to meet with the company’s country manager. But then, one day, when Walker was awaiting a flight out of Johannesburg on one of his many trips to South Africa, he finally sat down with the regional manager, who suggested Walker meet with the company’s owner Terry Ragon, who lives in Cambridge.

Ragon, a graduate of MIT, founded the software company InterSystems in 1978. Headquartered in Cambridge, the company now has offices in more than 23 countries and assets totaling \$335 million. Ragon’s interest in international

In the labs

Darrell Irvine



Role: Associate Professor of Materials Science Engineering and Biological Engineering

Focus of lab: Working at the interface of materials science and immunology.

The job of cytotoxic T lymphocytes is clear. But exactly how these killer CD8⁺ T cells execute their targets is a mystery that Maria Foley, a doctoral candidate in the laboratory of Massachusetts Institute of Technology polymer scientist and immunologist Darrell Irvine, is trying to solve using electron microscopy. Foley says this is the first time this technology has been used to study the killing of HIV-infected cells, and the images the lab has been able to capture have been instructive and surprising. The experiments begin with CD8⁺ T-cell clones taken from a cohort of elite controllers that was begun by Ragon Institute Director Bruce Walker. This group of HIV-infected individuals is important in the study of killer T cells because their ability to control the virus for years without the benefit of antiretroviral therapy is speculated to be due in large part to their cellular immune responses.

The CD8⁺ T-cell clones are loaded into a collagen matrix, a simplified model of 3D tissue that allows the cells to engage in a microbiological cat and mouse. Videos show that some of the CD8⁺ T cells annihilate the HIV-infected T cells quickly, while others successfully interact with their target cells, mechanically engaging receptors. However, the target cell eventually escapes, likely because there isn't strong enough T-cell receptor binding

with the target cell. Other cells engage in an "hour-long fight," according to Foley, before they successfully kill their target cells. "The CD8 cell really fights hard to catch and hold on and kill that target cell," she says, speculating that this is something that CD8⁺ T cells from elite controllers might be better at doing. Interestingly, says Foley, the films show that when CD8⁺ T cells do manage to inflict a fatal blow to their targets—usually within 20 minutes—they continue to circle their prey for several more hours. "We think that the CD8 cells are collecting more specific signals from dead targets to turn on genes and secrete factors important for inhibition of the virus," says Foley.

Others in Irvine's lab are focused on ways to improve vaccine delivery. Peter DeMuth, a doctoral candidate, is testing a vaccine delivery platform that employs microneedle arrays—rows and rows of microneedles occupying a space that measures about a centimeter in circumference—to deliver vaccines subcutaneously in a pain-free fashion. Unlike conventional vaccination, this strategy avoids the blood supply and delivers the vaccine components directly to antigen presenting cells, mostly Langerhans cells, which reside just below the skin's surface. Irvine's lab is also developing a nanoparticle vaccine delivery system.

development stems from his childhood. He recalls riding the bus to his exclusive high school in Bogota, Colombia, and seeing children on the street without a stitch of clothing. As he became more successful in business, Ragon was interested in how he could make a difference to these children and others throughout the world.

To connect with possible charities, Ragon asked his regional managers at InterSystems to keep an eye out for any projects they came across that might be interesting. This is how Ragon eventually connected with Walker.

When the two first met, Ragon recalls Walker saying, "I have absolutely no idea why I'm here." Ragon suggested he tell him about the things he was doing in South Africa. After that conversation, it was agreed that Ragon would accompany Walker on his next trip there, which happened to be two weeks later, to see some of the work first hand.

Ragon remembers telling Walker, "I go on a lot of trips like this and I rarely give any money." While in South Africa, Ragon visited patients who were dying of AIDS. "It was quite a shock-

ing event," he recalls. Ragon also toured the research facilities and saw WhizzKids United in action, a non-profit organization that teaches kids leadership skills through football and also delivers HIV prevention and support services. "I don't see how anybody can see what I have seen and not want to get involved," Ragon told Walker. "What do you need?"

Topping Walker's wish list was funding for a collaborative research effort that would bring together researchers from different disciplines to solve the long-standing problems that have prevented the development of an AIDS vaccine. Walker had hoped to tap into the \$300 million, seven-year virtual consortium known as the Center for HIV/AIDS Vaccine Immunology that was awarded in 1995 by the US National Institute of Allergy and Infectious Diseases (NIAID), but his application was rejected.

Ragon agreed that the idea of an institute sounded interesting, but at that time the idea wasn't fully formed and so Ragon agreed to fund one of Walker's vaccine trials.

Three years later, Walker was having lunch with Dennis Burton, professor of immunology and microbial science at TSRI, and Wayne Koff, IAVI's chief science officer, at the 15th Conference on Retroviruses and Opportunistic Infections in Boston when the talk, once again, turned to the idea of doing something bold and innovative.

Walker phoned Ragon and he, Burton, and Koff ended up having a conversation with Ragon that day about the lack of innovation in the HIV vaccine field. "The thing most people don't realize is that scientists don't have flexible funding," says Walker, adding that the constant chase for grants prevents creativity and discourages innovation. "Failure is a no-no."

When Walker returned from the conference, he had an appointment on his calendar with Ragon. Once again they discussed this idea and at the end of that conversation, Ragon said that it sounded like Walker would need \$10 million for 10 years to be able to get this idea off the ground. "My wife and I would like to do that," Walker recalls him saying, likening his initial response to an out-of-body experience. This flexible, unrestricted funding allowed the establishment of the institute, which Walker wanted named after Terry and Susan Ragon.

Nurturing creativity

Researchers affiliated with The Ragon Institute still apply for NIH grants, and Walker says he spends more time than he'd like on fundraising, but the gift from Ragon, in addition to \$14 million donated by Mark and Lisa Schwartz, have created a nurturing research environment for Ragon investigators.

Galit Alter, an assistant professor of medicine at The Ragon Institute, whose laboratory team focuses on innate immunity, primarily natural killer cells, likens The Ragon Institute to a family. "There is just no place like Ragon," she says. "There is a clear path toward developing your own research. The atmosphere is nurturing and supportive, and you have access to cohorts and technology. If you can't succeed here, you can't succeed anywhere."

This nurturing environment is particularly inviting for researchers who've come to Ragon from outside the HIV field, or are early on in their careers. Douglas Kwon, a 39-year-old physician at Ragon whose six-person laboratory is primarily focused on mucosal immunity, is one of those

newer scientists. He says flexible funding is especially important when you are starting out. "If you are new and have an idea you believe in, there are mechanisms in place to get support, even if it is just in the initial stages," says Kwon. "That is something that is unique and great here."

The Ragon Institute has tried to support young investigators by offering innovation awards of up to \$100,000. "When you give young, talented, creative people that flexibility, those sorts of things are transforming," says Walker. "It's incredible."

But others suggest Walker also deserves credit. "There's no question that money helps," says Ragon. "But money alone certainly doesn't do it. It's Bruce's ability to get people working together that makes a difference."

Thumbi Ndung'u, scientific director of the HIV Pathogenesis Programme at the Doris Duke Medical Institute in Durban, South Africa, which Walker helped launch, says The Ragon Institute has helped solidify longstanding academic and research relationships in South Africa. It has also expanded opportunities for young investigators to train at laboratories in Boston and then return to South Africa, or vice versa.

"The model that Ragon has used to do their work in South Africa has very much adhered to the idea that the research should be done locally, usually by South African scientists, even students," says Ndung'u, noting that this model is unusual, even in a middle-income country like South Africa. "A lot of other groups working in the developing world do their research elsewhere and when they publish papers, they are the lead authors." Ndung'u, who met Walker when he was studying at Harvard, says The Ragon Institute director has an "infectious optimism."

Arup Chakraborty, a professor of chemistry, chemical engineering, and biological engineering at MIT, was one of the researchers recruited to Ragon from outside the field of HIV. Chakraborty's work involves applying statistical physics to understanding basic immunology. Prior to joining Ragon, this meant working mostly with cell lines and mouse models, but Chakraborty is now spending more and more time focusing his skills on HIV. "I'm really enjoying what I'm doing with HIV," says Chakraborty. "I don't think I've enjoyed science so much. And it's funded by something that allows me a lot of leeway to think about new ideas," he says.

When Walker came to talk to Chakraborty

The Leaders

Bruce Walker, M.D.

The Ragon Institute

Program: Adaptive T Cell Immunity

Marcus Altfeld, M.D., Ph.D.

The Ragon Institute

Program: Innate Immunity

Dan Barouch, M.D., Ph.D.

Beth Israel Deaconess Medical Center

Program: Vaccine/Vector Design

Dennis Burton, Ph.D.

The Scripps Research Institute

Program: Adaptive B Cell Immunity

Arup K. Chakraborty, Ph.D.

Massachusetts Institute of Technology

Program: Computational Biology

Mary Carrington, Ph.D.

National Cancer Institute, SAIC-Frederick

Program: Genetics

Laurie Glimcher, M.D.

Harvard Medical School

Program: Basic Immunology

Darrell J. Irvine, Ph.D.

Massachusetts Institute of Technology

Program: Technology Development

In the labs

J. Christopher Love



Role: Latham Family Career Development Associate Professor of Chemical Engineering

Focus of lab: Developing new processes for analyzing large numbers of individual living cells quantitatively and dynamically.

If you had to guess what the Love Lab at the Massachusetts Institute of Technology (MIT) was working on, you probably wouldn't come close. Rather than matters of the heart, this research group housed in the department of chemical engineering is focused on characterizing the dynamic biological responses of individual cells subjected to defined perturbations. The irresistible name of the lab comes not from its work, but from its leader, J. Christopher Love, an MIT professor of chemical engineering and an investigator with The Ragon Institute.

When researchers try to extract information from biological samples, they are often hindered by the quantity of cells they are able to analyze. Whether peripheral blood mononuclear cells or B and T cells from mucosal tissues, the number of cells available, as well as the number of assays that can be used to determine what these cells are doing, is rather limited. "As engineers, what we're very interested in trying to understand is how to enhance the amount of information you can extract from a given clinical sample," says Love.

To do this, the Love Lab is using nanotechnology to look at populations of cells individually. They've developed a microfabricated slide containing 250,000 wells, each of which can hold a single cell, and a stamping technique that

allows them to transfer the analytes they are interested in from one slide to another. Because this process of stamping can be done serially, you can significantly increase the number of parameters that can be measured from a single cell. This helps eliminate the decisions many researchers face about which assays to run with their precious samples. It also is much faster than the traditional high-throughput screening methods. "We screen tens of thousands of B cells for interesting characteristics in an afternoon," says Love, who is collaborating with both the HIV Vaccine Trials Network and IAVI's Neutralizing Antibody Consortium to develop methods for screening both B and T cells.

Love is even optimistic that this process could eventually be used to develop a "nano-scale neutralization assay," which would be able to identify neutralizing antibodies on a much smaller scale than the current miniaturized system used by Monogram Biosciences that does micro-neutralization assays with 384 well plates.

When Bruce Walker, director of The Ragon Institute, approached Love, he was not working on HIV, but it became clear that their interests overlapped. "There was a certain synergy that made it obvious that we should get involved," recalls Love.

about joining The Ragon Institute, he wasn't interested initially because he was happy with what he was doing, and he felt too many other researchers were studying HIV.

"It seems to me you need to be super bright to contribute something, and I'm not super bright," Chakraborty told Walker. "Why would I do this?"

So Walker asked Chakraborty to travel to South Africa with him. When he returned from his three-day trip, Chakraborty had a different take. "I felt that even if I contribute in some small way it was worth doing."

Two years of progress

Walker believes the 14 laboratories that comprise The Ragon Institute have a chance to do transformational science that will contribute to the development of an AIDS vaccine. "I'm absolutely convinced that this is a viable recipe to speed scientific discovery," he says.

However, not everyone agrees with some of the research approaches The Ragon Institute has

taken. Mark Connors, chief of the HIV-specific immunity section at NIAID, disagrees with some of the conclusions the researchers have drawn using computational immunology. "We need to understand why people don't control the virus and a lot of this basic immunology," says Connors. "But is taking a space shuttle view of the problem and coming up with an attractive answer moving the field forward? I'm not so sure."

Connors cited a few examples. The first was findings published this year in *Science* that suggested the mechanism by which protective human leukocyte antigen (HLA) alleles function is through specific amino acids in the binding groove. But Connors says that these amino acids are the signature for the B57 protective alleles and so are simply a proxy for B57. In another example, control of the virus was associated with having CD8⁺ T cells with certain specificities.

He went on to cite, among other examples, findings published last year in *Nature* from a computational model developed by Chakraborty. The

In the labs

Arup Chakraborty



Role: Robert T. Haslam Professor of Chemical Engineering, Chemistry, and Biological Engineering

Focus of lab: Using computational immunology to understand the adaptive immune response to pathogens, including HIV.

Although immunologists have made strides in understanding how the adaptive immune system is regulated, there are still many unanswered questions. “We still don’t know the principles that lead to the emergence of an immune response,” says Arup Chakraborty, a professor of chemistry and chemical engineering at Massachusetts Institute of Technology (MIT).

To shed light on these immunological mechanisms, Chakraborty began applying theories of statistical physics to immunology, and since he joined The Ragon Institute, he has been using this approach to study HIV. A newcomer to the HIV field, Chakraborty’s lab in collaboration with Bruce Walker’s group, recently published papers in *Nature* and the *Proceedings of the National Academy of Sciences* that focus on HIV. Most recently, they used random matrix theory, a mathematical tool previously applied to high energy physics, economics, and the study of an enzyme family, to identify regions of the HIV proteome that are vulnerable to immunological pressure, what Chakraborty calls the Achilles’ heels of the HIV proteome. For the stock market, random matrix theory identifies groups of companies or sectors for which stock prices fluctuate in a correlated fashion. For example, fluctuations in the stock prices of car manufacturers and car parts companies are typi-

cally correlated. While identification of economic sectors is largely intuitive, the interpretation of the HIV proteome is not.

When Chakraborty and colleagues used this model to analyze the available bank of HIV sequences, they identified groups of amino acids or sectors in the HIV proteome that co-evolve to influence viral fitness, with different groups evolving essentially independently. They then identified sectors in which multiple mutations were less likely to occur, presumably because if they did, the fitness cost for the virus would be too great. The most vulnerable sector they identified was in the p24 protein. Researchers have previously shown that six p24 proteins form hexamers and that these hexamers form the honeycomb shape of the viral capsid. Chakraborty’s lab discovered that the amino acids they identified in the vulnerable sectors were at the interfaces between p24 proteins in the honeycomb structure. If too many mutations occur in p24, the hexamers can’t form and align, hindering formation of the viral capsid. Chakraborty and Walker found that the immune systems of HIV controllers disproportionately target these vulnerable sectors.

Now, Chakraborty and colleagues are trying to develop antigens that would direct the immune response to target these vulnerable sectors.

findings suggest less rigorous thymic selection may explain why people with human leukocyte antigen B57 gene are able to better control HIV, and that people with B57 can better control viral load in part because their CD8⁺ T cells are more likely to recognize a diverse array of HIV peptides presented by major histocompatibility class I molecules on the surface of HIV-infected cells (see *Research Briefs, IAVI Report*, May-June 2010).

Connors says the model runs counter to a considerable body of work and should have been validated to see if the findings held up. “Computational models are an interesting exploratory tool, but the answers that come out of them need testing in additional cohorts and experiments that rigorously test the hypotheses to determine if they are correct,” says Connors.

But others say the work being done by The Ragon Institute enriches the field. David Baltimore, a Nobel Laureate who helped found the Whitehead Institute, thinks Chakraborty’s work is the best example of this. “I think it will be quite

significant because it enables people to think about making a vaccine in new and sophisticated ways,” says Baltimore. “In the spirit of trying every possible avenue to this difficult problem, collaborations between physics, chemistry, and biology are very important.”

“This is one of the rare occasions when what’s occurred has actually exceeded my expectations,” says Ragon. Earlier this year when the second scientific advisory board meeting for the Institute took place, Ragon says the board members were “taken aback by the work that had been done.”

Certainly, the determination of Walker and the Ragon investigators is unwavering. “I believe that this is a solvable problem,” says Walker. “It’s going to take a lot of people working together. We’re going to do everything we can to contribute to a community effort to solve this problem. Our goal is not that we be the ones to make a vaccine; our goal is that we contribute to making a vaccine.” ■

An Interview with **MARGIE McGLYNN**

The new chief executive officer of IAVI, the second in its history, discusses her career in vaccine development and deployment and her vision for the organization

By Kristen Jill Kresge

What personal experiences have been most influential in shaping the person you are today?

I grew up in a family that owned a retail pharmacy, so I was always very interested in medicines and vaccines. I also grew up in a family that had two children with a rare genetic disease, and so I was very focused as a young child on what new therapies could be developed for my sisters to help keep them alive, which unfortunately did not happen.

I also was told the story as a young child about a brother that I never got to meet because he passed away from measles in the early 1950s. As new vaccines started to come out in the '60s, my parents would bring us to immunization clinics and I asked why I had to get this needle injected in my arm and was told the story about Timmy, and how if the vaccine had been available when he was alive they wouldn't have lost this infant at the age of 18 months. So I grew up with a keen interest in vaccines.

How did this influence your career decisions?

I decided to go to pharmacy school and focus on how I could do what my father did—be involved in helping people through medications and vaccines—but I decided to double major in business because I wanted to make an even bigger impact. I didn't know exactly how I would do it, but I applied for an internship in the

pharmaceutical industry and I was hired by Merck for a summer. It took me about a week to realize that if I wanted to make a really big impact on as broad a population as possible, playing a role in a pharmaceutical company, especially a company like Merck that was focused on unmet medical needs, innovation, and science, but also access programs and philanthropic work, was a great fit for me.

I joined Merck in 1983 and I had many opportunities over a 26-year career there to get very involved in bringing out new medicines and vaccines, as well as making sure that they were accessible to the people who needed them most.

What were the highlights of your long career at Merck?

The most rewarding part of my career was when I ran Merck's global vaccines business my last four years there. To bring out a vaccine to prevent rotavirus-induced gastroenteritis when there were 500,000 infants dying every year of this disease in the developing world brought me great satisfaction. But it was very important to me that we not only introduce this vaccine, but that we do so quickly in the developing world. We worked with the government of Nicaragua to introduce rotavirus vaccine in that country within eight months of the US introduction of the vaccine. We provided the vaccine free for every infant born in Nicaragua over a three-year period, and we



MARGIE McGLYNN

On July 7, Margaret (Margie) McGlynn was appointed president and chief executive officer (CEO) of IAVI, replacing IAVI's founding president and CEO, Seth Berkley, who left at the end of June after 15 years to become CEO of the GAVI Alliance, a Geneva-based organization that works to increase access to immunizations in developing countries.

McGlynn was no stranger to IAVI, having served on its board of directors since July 2010. She has extensive experience in both the vaccine and HIV fields, culled from a 26-year career at Merck. During that time, she held several positions in the company, culminating in the post as head of Merck's global vaccines and infectious diseases business. In this role, she oversaw the launch of four new vaccines, including Gardasil, the first vaccine developed to prevent infection with several of the most prevalent strains of human papilloma virus that can lead to cervical cancer, as well as the first integrase inhibitor to treat HIV. McGlynn also played a pivotal role in ensuring access to these vaccines in developing countries, which typically are introduced many years after they are available in rich countries.

McGlynn describes herself as a "driven but compassionate executive," and looks forward to the challenges of her new role. In her limited free time, the mother of a 20-year-old son and 18-year-old daughter enjoys sailing and skiing with her husband and children.

achieved a higher immunization rate in Nicaragua, over 90%, than we achieved in the US after two years on the market.

I also played a major role in Merck's no-profit pricing strategy for vaccines and HIV therapies in the world's lowest income markets, and in an effort to assure vaccines were developed specifically for the developing world's needs, I worked with others at Merck and the Wellcome Trust to establish a partnership to create a vaccine research center for the developing world in India.

That center is named after the vaccine pioneer, Maurice Hilleman. Did you get to know him well while at Merck?

I did. Maurice was a very inspirational, innovative, and effective scientist. I was fortunate in the last few years of my career to spend more time with him and we would just have fascinating conversations about vaccines. His motto was to always do something useful, and I thought about that when I had the opportunity to take on this role at IAVI.

What was it like inside Merck when the results from the company's Phase IIb AIDS vaccine trial, known as STEP, showed that the candidate was not effective?

I remember waiting for a phone call one particular evening that I knew the data safety monitoring board would be meeting. I expected that most likely the phone call would tell me that the trial was continuing and that there wasn't enough data to make any other decision. We were prepared for the optimistic scenario that we'd have enough evidence to say we have proof of concept. But we knew that was very, very unlikely. And while we had a draft press release ready for what we thought to be the very unlikely scenario that the trial would be stopped, I never imagined that that would be the phone call I would receive. I was devastated. I understood the significance of what this meant, not only to the individuals and countries who were so hopeful that a vaccine would be coming, but also to the entire HIV vaccine field. I spent a lot of time on the communication plans because I knew how important it was that we were fully open and transparent, and especially that we shared information with other scientific partners who could help us comprehensively analyze the data, learn what we could from the

trial, and apply what we learned to any future development.

So how has the transition to being CEO of IAVI gone so far?

There's a lot to accomplish and I don't expect to be fully up to speed immediately, but I'm thrilled with the experience thus far. I've had great mentors and advisors within the organization, on the board of directors, and externally. I really believe IAVI has made a huge impact in the past, and I believe we can make an even bigger impact in the future. I feel like the ultimate goal is in sight.

I look forward to attending the AIDS Vaccine conference in Bangkok, where I think it will all come together and I'll be meeting many external stakeholders and get an even better grasp of the full pipeline of HIV vaccine projects.

As CEO, you will oversee the introduction of a new strategic plan for IAVI. At this point, what can you say about the key elements of that plan?

Our strategic plan is still in development and will be for a number of months as I make sure there is extensive external stakeholder input into the plan, but there are already a few key components. The first is how can IAVI add the greatest value to the field, and how can IAVI be a partner of choice and contribute in whatever way makes the most sense to any HIV vaccine development effort that's underway. A second component is figuring how we can make IAVI's tremendous capabilities in translational research more broadly available for the field. A third component is to ensure that we continue to develop our clinical trials infrastructure in Africa so that we develop the cohorts that are needed and continue to engage the most affected [individuals] so that we someday have an effective vaccine available to those who need it the most.

What do you think will be the biggest obstacles for IAVI in the coming years?

Certainly a major obstacle for any global health organization is funding, given the economic issues that we've had for the past few years and may have for the next few years. The challenge is how we ensure that we're able to secure adequate funding to continue to make adequate progress to achieve our mission. ■

Treatment *is* PREVENTION

After results from several trials illustrated the preventive benefits of antiretrovirals, researchers at the annual International AIDS Society conference declare treatment *is* prevention

By Kristen Jill Kresge

THERE IS NO QUESTION THAT antiretroviral (ARV)-based prevention stole the show at the International AIDS Society's Sixth International Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011). "I've never seen something explode like this," said Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health.

The fervor surrounding ARVs for prevention was fueled by the results of three recent trials, two showing that pre-exposure prophylaxis (PrEP)—the administration of ARVs to uninfected individuals—was 62%-73% effective in reducing HIV transmission, and the third showing that earlier initiation of ARV therapy for HIV-infected individuals results in an overwhelming 96% reduction in HIV transmission. Together, these studies added substantial evidence to support the notion that ARVs may be an effective means by which to curb the spread of HIV. "We are now on solid scientific ground that even without a vaccine or a cure we could turn around the trajectory of the pandemic," said Fauci. "That's huge." The mood in Rome, where

more than 5,000 delegates gathered for the conference from July 17-20, was so ebullient that researchers were comparing it to 1996, the year combination ARV therapy was first shown to be an effective strategy for controlling HIV. "Rome is the watershed for treatment as prevention," said Stefano Vella, a co-chair of IAS 2011.

But as the dust settled in Rome, many researchers and policymakers began asking how PrEP or early treatment will be implemented when funding is tight (see *Snapshot of 2010 Funding*, page 16). "The next steps are trying to figure out how to implement this," said Fauci. "With the resources we have, we can't do everything." Although policymakers will likely face difficult decisions, HIV prevention advocates were happy to be in the position of having new ways to beat back HIV. "These are the challenges we've longed for," said Mitchell Warren, executive director of the HIV prevention advocacy group AVAC. "For many years we've been asking what if. Now we're asking what now." Stefano Bertozzi, director of HIV and tuberculosis at the Bill & Melinda Gates Foundation, said the question is how to capitalize on these results to try to re-energize funding.

Earlier is better

Because effective ARV therapy can suppress HIV replication, in many cases to levels below detection by all but the most sensitive single copy assays, researchers have long speculated that starting HIV-infected individuals on ARVs earlier would likely have the fringe benefit of making them less infectious. This was borne out in several observational studies, and served as the basis for the controversial test and treat strategy that calls for universal HIV testing and immediate treatment for those found to be infected (see *IAVI Report* July-Aug. 2009, *Test and Treat on Trial*). The most outspoken proponent for test and treat was Julio Montaner, former IAS president, who in Rome was recognized by many researchers for his work in this area.

But until the results from a trial known as HPTN052 were released in May showing that earlier ARV treatment reduced HIV transmission by 96% among a cohort of 1,763 serodiscordant couples, there was never a randomized, controlled clinical trial demonstrating the prevention benefits of starting ARVs earlier. “As we put people on treatment we render them less infectious,” said Myron Cohen, principal investigator of HPTN052. “That’s a given now.” Montaner called treatment as prevention a “double hat trick”—ask a Canadian if you’re not sure what that means—and called for it to be implemented immediately.

The US\$73 million Phase III trial, conducted at 13 clinical research centers in Africa, Asia, and North and South America, was launched in April 2005, or as the white-haired Cohen joked, back when he was in high school. In May, the study’s independent data safety monitoring board (DSMB) recommended stopping the delayed treatment arm four years ahead of the study’s scheduled completion date based on the overwhelmingly clear benefit of starting treatment earlier. At IAS 2011, several investigators presented for the first time the full analysis of the trial, which was published simultaneously (*N. Engl. J. Med.* 365, 493, 2011).

The early treatment group in HPTN052 started therapy when their CD4⁺ T-cell counts were between 350 and 500, while treatment was delayed for the other half of HIV-infected individuals until their CD4⁺ T-cell counts dropped to 250 or they developed an AIDS-defining illness. Of the 39 new infections that occurred during

the trial, phylogenetic analysis of the HIV *pol* sequence or deep pyrosequencing was used to confirm that 29 of the new infections were genetically linked to the infected partner, seven were unlinked, while three are still being classified. Of the 29 linked transmissions, only one occurred in the early treatment group, and Cohen said data suggests this transmission likely occurred before the individual’s viral load was fully suppressed.

Based on an analysis of 28 linked infections (one was confirmed to be linked just before the conference but not included in the published article), 64% occurred when the infected partner’s CD4⁺ T-cell count was above 350, the point at which current guidelines from the World Health Organization call for treatment to be initiated. Of note were the regional differences in the new infections: 23 of 28 (82%) of the linked transmissions occurred in sub-Saharan Africa, even though couples there accounted for only 54% of the volunteers enrolled in the trial. Mina Hosseinipour, an HPTN052 site investigator, said differences in baseline viral load might contribute to this difference. And, as the study investigators note in the paper, clade CHIV, the dominant type in southern Africa, may have transmission advantages as well. Hosseinipour also noted that there were “markedly different” behavioral characteristics among the African volunteers, with 9% of volunteers at African sites reporting unprotected sex compared to 4% at the Asian/American sites.

Beatriz Grinsztejn, another HPTN052 investigator, reported earlier treatment in the trial was also associated with a 41% reduction in HIV-related clinical events, suggesting earlier treatment has a clinical as well as a prevention benefit. This difference was largely due to the discrepancy in the number of cases of extrapulmonary tuberculosis in the early and delayed treatment arms (three versus 17 cases respectively).

Based on these results, Cohen concluded “this tool should be applied aggressively in the population we studied.” And although he and his colleagues acknowledge that serodiscordant couples may not be representative of the general population, they say that the HPTN052 results support the use of ARVs as a strategy to reduce the spread of HIV.

Even in serodiscordant couples alone, earlier treatment could have an impact, based on mathematical models developed by John Stover of the

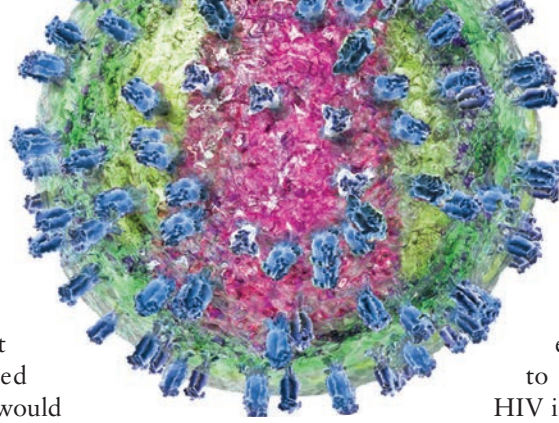
[VACCINE UPDATE]

With all the pomp surrounding antiretroviral-based prevention at IAS 2011, it was easy for other strategies, including vaccine research, to be overshadowed. But at a satellite symposium before the start of the conference, researchers gathered to discuss progress and prospects in HIV vaccine research and development.

Nelson Michael, director of the US Military HIV Research Program, reported that the eagerly anticipated results of the search for immune correlates of protection from the RV144 vaccine trial, the first to show any efficacy, will be released at the AIDS vaccine meeting in September, though he warned that even if correlates are identified, they may not be at all applicable to other vaccine approaches.

Meanwhile, a promising avenue of pre-clinical research has been the isolation of numerous new broadly neutralizing antibodies from chronically HIV-infected individuals (see *Research Briefs*, page 18). But given that researchers don’t yet know how to elicit these antibodies, many are suggesting other approaches must move forward in the meantime. “We’re still at the point where we don’t know how to make neutralizing antibodies and nobody wants to wait until we’re able to do an efficacy trial with neutralizing antibodies,” said Robin Shattock, professor of mucosal infection and immunity at Imperial College, London. “The presumption is that antibody-based vaccines is the way to go without any proof that it’s a correlate,” he added.

Speaking a few days later at a special session to commemorate 30 years of AIDS, Anthony Fauci, director of the US National Institutes of Allergy and Infectious Diseases, said, “an effective vaccine is going to require multiple immunological components.” —KJK



[SNAPSHOT OF 2010 FUNDING]

Funding for HIV vaccine research and development declined by 1% in 2010 from the previous year and by 11% from its peak in 2007, according to the annual report by the HIV Vaccines and Microbicides Resource Tracking Working Group. The report, which was compiled by IAVI, the HIV prevention advocacy group AVAC, the International Partnership for Microbicides, and the Joint United Nations Programme on HIV/AIDS, was released at the IAS 2011 conference in Rome (www.hivresourcetracking.org). The funding drop is due in part to the expiration of the two-year economic stimulus package that was passed in 2009 by the US Congress and funneled millions of dollars toward large grant-making institutions like the US National Institutes of Health, some of which went to support HIV-related projects.

Funding for HIV vaccine research totaled US\$859 million in 2010, with the bulk of the money—\$726 million—coming from the public sector, according to the report. Total investments for research and development of other HIV prevention strategies were as follows: microbicides (\$247 million), pre-exposure prophylaxis (PrEP; \$58.3 million), adult male circumcision (\$21.7 million). For the first time, the report also included an estimated annual investment of \$19.6 million for treatment as prevention in HIV-infected individuals. In 2010, funders invested \$1.19 billion in research and development for preventive HIV vaccines, microbicides, PrEP, and adult male circumcision, which the report's authors note approached the previous historical high of \$1.23 billion reached in 2007 for these four strategies. —RM

Futures Institute. Although earlier initiation of ARV therapy would raise treatment costs by an estimated 6%-9%, Stover said it would be a good investment in the long run. The question, he said, is “are we willing to pay the money now to avert having to pay more in the future?” The World Health Organization (WHO) originally planned to release guidelines on studies involving serodiscordant couples at IAS 2011, but delayed the release based on the influx of new data. Now, the WHO hopes guidelines will be available by the end of the year.

More positive results on PrEP

The other ARV-based prevention strategy to show efficacy is PrEP. Results from two PrEP studies were released the week before the opening of IAS 2011 and researchers scrambled to pull together data to make it available at the conference. The first trial, known as Partners PrEP, showed that a daily dose of tenofovir (TDF) reduced the risk of HIV infection by 62% in a cohort of 4,758 serodiscordant couples in Kenya and Uganda, while a daily dose of Truvada (the single pill combination of TDF and the ARV emtricitabine, or FTC) reduced HIV infection risk by 73%, a difference that was not statistically significant. “Both drugs work to prevent HIV acquisition,” said Jared Baeten, associate professor of global health at the University of Washington who presented the Partners PrEP results. These results spurred the trial’s DSMB to recommend discontinuation of the placebo arm of the trial 18 months before its scheduled end date. The study, which was funded by the Bill & Melinda Gates Foundation, is the largest PrEP study conducted thus far.

The other PrEP results presented at IAS 2011 were from the TDF2 trial, sponsored by BOT-USA, a partnership of the US Centers for Disease Control and Prevention and the government of Botswana. The study showed that a daily dose of Truvada reduced the risk of HIV infection in a cohort of 1,219 sexually active men and women in Botswana by approximately 63%. If individuals who interrupted PrEP at any point during the study were excluded from the analysis, the efficacy reached 78%.

TDF2 was originally planned as a Phase III efficacy trial but was scaled back to an expanded safety

study when investigators concluded they would need to double enrollment in the trial due to a lower than expected HIV incidence in the country.

Despite this, the TDF2 study did yield statistically significant results.

Although these trials are not the first to show PrEP is effective (results released last year from the iPrEx trial showed that daily Truvada was 44% effective in preventing HIV among nearly 2,500 men and transgendered women who have sex with men), they are the first trials to indicate this strategy is effective in heterosexuals. Earlier this year, doubts were raised about PrEP efficacy in heterosexuals when the Phase III FEM-PrEP trial, involving 1,951 high-risk heterosexual women in Africa, was stopped early because the DSMB concluded that it was highly unlikely the trial would be able to show efficacy given the HIV infections that had occurred so far were equally split between PrEP and placebo recipients. But given the results from TDF2 and Partners PrEP, these concerns were largely alleviated. “There’s little doubt about the power of ARV-based prevention strategies among heterosexuals,” said Michael Thigpen, a TDF2 study investigator.

However, data from the TDF2 trial do suggest there may be a difference in the protective efficacy in men and women. Although Thigpen did note that the study was not powered to determine efficacy by gender, based on the 33 new HIV infections that occurred during the trial, the protective efficacy among men was 80%, while among women it was 49%. For the Partners PrEP study, Baeten said, “Our results are robust for both women and men,” though he didn’t share the breakdown.

The evidence from these two studies were strong enough for Fauci to suggest the FEM-PrEP trial was likely a fluke, but others like Helen Rees, executive director of the Wits Reproductive Health and HIV Institute at the University of the Witwatersrand in Johannesburg, South Africa, were not fully convinced. She suggested that the field wait until the results of the VOICE study—which is testing oral Truvada and TDF, as well as a TDF microbicide gel in 5,029 women in Uganda, South Africa, and Zimbabwe—before any guidelines about PrEP use are crafted. Results from the VOICE study aren’t expected until early 2013. ■

Vaccine BRIEFS

HVTN 505 Trial Expanded to See if Vaccine Candidates Can Block HIV Acquisition

THE US NATIONAL INSTITUTE OF ALLERGY and Infectious Diseases (NIAID) is expanding a Phase II trial, known as HVTN 505, testing the safety and efficacy of a DNA/Ad5 prime-boost regimen to determine whether the two vaccine candidates developed at the Vaccine Research Center (VRC) at NIAID are capable of protecting against HIV infection.

The trial, which was launched in 2009, was initially designed based on a single endpoint—whether the prime-boost regimen was able to decrease set point viral load in volunteers who became HIV infected despite vaccination (see *Vaccine Briefs, IAVI Report*, July-Aug. 2009). Adding protection against infection as an additional endpoint will result in significant change in enrollment in the HVTN 505 trial. The trial was originally designed to enroll 1,350 circumcised, HIV-uninfected men who have sex with men (MSM) or transgendered women who have sex with men with no pre-existing immunity to adenovirus serotype 5 (Ad5), a commonly circulating strain of the cold virus that is used as a vector in one of the two vaccine candidates. Now investigators aim to enroll 2,200 participants—the number of volunteers that is estimated to be needed in order to determine whether the vaccine regimen is at least 50% effective at preventing HIV acquisition 18 months following immunization—at 15 sites in 12 US cities at an expected overall cost of between US\$75million and \$80 million. So far, investigators have already enrolled more than 1,173 volunteers.

The prime-boost regimen being tested in HVTN 505 involves three vaccinations with DNA encoding HIV clade B Gag, Pol, and Nef, and Env from HIV clades A, B, and C, followed by an Ad5 vector-based vaccine candidate encoding clade B Gag and Pol, and Env from clades A, B, and C.

Carl Dieffenbach, director of the Division of AIDS (DAIDS) at NIAID, says the expanded trial is a positive step for the field, but he cautioned observers to keep the scope of the trial and where it might lead in perspective. “We have to be careful that we continue to put this forward without trying to over-promise,” he says.

The evolution of the HVTN 505 trial reflects a dizzying series of changes that have largely been driven by the outcomes of two other efficacy trials: the STEP trial of Merck’s MRKAd5 candidate, another Ad5 vector-based vaccine that produced a disappointing outcome in the fall of 2007, and the RV144 trial that tested a canarypox vector-based candidate in combination with a protein boost and energized the AIDS vaccine field two years later when it yielded the first evidence of

vaccine-induced protection against HIV.

A much earlier version of HVTN 505 known as PAVE 100 was slated to begin enrolling 8,500 HIV-uninfected men and women at multiple study sites in the Americas and southern and eastern Africa just a week after results showed that MRKAd5 failed to show any efficacy in the STEP trial. Further analysis of the STEP trial indicated that male volunteers who received the vaccine candidate had a higher risk of acquiring HIV if they were uncircumcised and had pre-existing immunity to the Ad5 vector. This prompted NIAID to shelve the original PAVE 100 design in favor of a smaller trial focused only on viral load set point, and to only enroll circumcised men with no pre-existing Ad5 immunity (see *PAVEing the Way to a Smaller Trial, IAVI Report*, July-Aug. 2008).

This trial, which became known as HVTN 505, faced additional challenges, however. Despite a much smaller enrollment target, the study struggled to find volunteers, prompting investigators to turn to social media sites and online classified sites such as craigslist to try and attract participants (see *Vaccine Briefs, IAVI Report*, Mar.-Apr. 2010).

Then, when the RV144 trial, jointly funded by NIAID and the US Army, delivered unexpectedly encouraging results, NIAID decided to take a closer look at the immune responses elicited by its other HIV vaccine candidates in clinical trials.

Results from a series of nonhuman primate studies influenced the decision to expand the HVTN 505 trial, says Dieffenbach. Animal data showed that about half of rhesus macaques given a simian immunodeficiency virus (SIV) vaccine regimen similar to the HIV vaccine regimen used in the HVTN 505 trial were protected against SIV following SIVsmE660 challenge, and that a low level of neutralizing antibodies to Env, and an Env-specific CD4⁺ T-cell response correlated with this protective effect (see *Research Briefs, IAVI Report*, May-June 2011).

Dieffenbach says the large number of animals (129 macaques) used in the study, and the fact that the protection occurred in the presence of robust cellular responses and low levels of SIV-neutralizing antibodies, suggested that the HVTN 505 regimen could have the capacity to prevent HIV acquisition in people. “You are only as good as the data you have in front of you,” says Dieffenbach, reflecting on the expansion of the HVTN 505 trial. “We [haven’t had] many efficacy trials and if we have the opportunity and there is plausibility, we need as a field to take a chance.” —Regina McEnery

Research BRIEFS

Dozens of New Broadly Neutralizing Antibodies Identified

In the last two years, many potent, HIV-specific broadly neutralizing antibodies (bNAbs) have been isolated from chronically HIV-infected individuals. Now, a study led by Michel Nussenzweig, a professor of molecular immunology and a Howard Hughes Medical Institute investigator at Rockefeller University, adds dozens of new CD4 binding site specific bNAbs (isolated from four chronically HIV-infected individuals who have high levels of bNAbs to HIV in their serum) to the collection (*Science* 2011, doi: 10.1126/science.1207227).

The new bNAbs recognize the CD4 binding site on Env that is also the target of other known bNAbs including VRC01, which was isolated last year by researchers at the Vaccine Research Center (VRC) and is one of the most potent bNAbs identified so far. According to Nussenzweig, some of the best of the newly isolated bNAbs are broader and more potent than VRC01, while others are equivalent.

Nussenzweig and colleagues isolated single memory B cells from the blood of the HIV-infected individuals using protein baits that consist of parts of the HIV Env protein. They then used polymerase chain reaction (PCR) to amplify the variable regions of the light and heavy chains of the antibody genes that are expressed in these memory B cells to make monoclonal antibodies (mAbs).

The study is a follow up to a 2009 study in which Nussenzweig and colleagues used a similar approach to isolate HIV-specific mAbs from six HIV-infected individuals with high titers of broadly neutralizing sera against different HIV strains (*Nature* 458, 636, 2009). In the 2009 study, recombining some of the HIV-specific mAbs they isolated could reconstitute the broad neutralizing activity of the

serum in two of the individuals. Still, the neutralizing activity of any single antibody alone was less broad than the sera, suggesting that mixtures of antibody were responsible for the neutralizing activity in those two patients. They did not isolate single bNAbs in the 2009 study.

Nussenzweig says they were likely able to isolate single bNAbs in the most recent study because they took into account that HIV-specific bNAbs typically show a high degree of somatic hypermutation that makes them different from the germline genes they are derived from. Nussenzweig and colleagues used different primers that were designed to PCR amplify even highly mutated antibody genes from B cells by binding to less mutated parts of the antibody sequences.

When Nussenzweig and colleagues tested the same gp140 bait they used in their 2009 study together with the new primers, they could isolate VRC01 and VRC01-like bNAbs from the same individual from whom VRC01 was isolated last year, as well as many CD4 binding site specific bNAbs from two of the same individuals from whom they did not isolate bNAbs in their 2009 study. This suggests that the primers, and not the bait, account for the difference in the success in isolating bNAbs between their 2009 and their 2011 studies, Nussenzweig says. However, they did find that using the new primers in these two individuals with a bait designed to more specifically identify CD4 binding site specific antibodies resulted in isolation of an even larger fraction of CD4 binding site specific bNAbs.

Peter Kwong, chief of the structural biology section at the VRC, who was not involved in Nussenzweig's study, says "it's really exciting that they have many new

broadly neutralizing HIV antibodies." And because the antibodies were amplified from single cells, they represent true pairs of heavy and light chains of the antibodies. "I think that that is a big strength of this paper," says Kwong.

For the first time, Nussenzweig and colleagues also showed that some of the newly identified CD4 binding site specific bNAbs are expressed in the HIV-infected individuals' antibody-producing plasma cells, and that some of the corresponding secreted antibodies were in their serum.

"I think this study represents a landmark in the field," says Davide Corti, director of the antibody discovery unit at the company Humabs BioMed, who was involved in isolating another CD4 binding site specific bNAb, known as HJ16, last year (see *Research Briefs, IAVI Report*, Jan.-Feb. 2010). Corti, who was not involved in the isolation of the latest bNAbs, says the study shows that at least in chronically infected people with high levels of bNAbs in their serum, which make up only a few percent of HIV-infected people, broad and potent antibodies are "not a gold nugget."

Like other recently described HIV-specific bNAbs, the most potent new bNAbs Nussenzweig and colleagues identified show an unusually high degree of somatic hypermutation. But, to their surprise, they found that the variable portions of the heavy chain of the most potent new bNAbs and VRC01 have about 68% of their amino acid sequence in common and also share a common origin in that they are derived from two related germline genes, IgVH1-2 or IgVH1-46.

The most potent new bNAbs are also similar to VRC01 in that their binding to gp140 induces a similar conformation

change in gp140 as does binding of CD4. In addition, the crystal structure of the Fab region of one of the new bNAbs, 3BNC60, was similar to VRC01, suggesting that it binds gp120 in a similar way.

This suggests that despite the high degree of somatic hypermutation of the CD4 binding site specific bNAbs Nussenzweig and colleagues identified, they are surprisingly similar in structure and sequence.

“The path to achieve this particular type of antibodies seems to be fairly narrow,” says Johannes Scheid, a graduate student in Nussenzweig’s lab and first author of the study. —*Andreas von Bubnoff*

Researchers Gather Clues About How Broadly Neutralizing Antibodies Develop

THERE HAS BEEN AN INCREASING INTEREST in trying to understand how HIV-specific broadly neutralizing antibodies (bNAbs) develop in HIV-infected individuals (see *Vaccines to Antibodies: Grow Up!*, *IAVI Report*, July-Aug. 2010). Now, a new study adds significantly to the understanding of this process. In the study, led by Peter Kwong and John Mascola of the Vaccine Research Center (VRC), researchers for the first time combined deep sequencing technology with bioinformatics to identify bNAb sequences from millions of variable heavy chain sequences in HIV-infected individuals (*Science* 2011, doi: 10.1126/science.1207532). They also identified the likely precursors from which these antibodies develop through affinity maturation—a process through which an antibody’s variable region becomes different from its germline precursor as the result of somatic hypermutation—which increases the affinity of the antibody to its targets.

To isolate the new VRC01-like antibodies, the researchers used the same CD4 binding site specific bait that was used last year to isolate three bNAbs (VRC01, 02, and 03) from a chronically HIV-infected individual called donor 45. Using this bait, they isolated seven new VRC01-like antibodies from two additional chronically HIV-infected individuals—donor 74 from IAVI’s Protocol G cohort of chronically infected individuals, and donor 0219 from the Center for HIV/AIDS Vaccine Immunology’s 001 cohort.

All of these VRC01-like antibodies—which included the bNAb VRCPG04 isolated from donor 74 and VRC-CH31 from donor 0219—are similar to VRC01 in their breadth and potency, and in that they are CD4 binding site specific, highly affinity matured, and derived from the germline gene IgVH1-2. In addition, the crystal structure of gp120 bound to VRC03 and VRCPG04 showed that they bind gp120 similarly to the way VRC01 binds gp120. Despite this, the sequences of the variable regions of these VRC01-like antibodies were not more similar to each other than to completely unrelated antibodies. “From analysis of sequence identities, we were unable to determine if a particular sequence was a VRC01-like antibody or not,” says Kwong, who is chief of the structural biology section at the VRC.

In an attempt to identify VRC01-like antibodies just by deep sequencing analysis, the researchers also determined the sequences for hundreds of thousands of variable heavy chains expressed by B cells from donors 45 and 74 with 454 pyrosequencing, a next-generation sequencing technology.

Because just comparing sequences would likely miss VRC01-like antibodies that differ in sequence but not in structure, they selected sequences that were derived from the germline gene IgVH1-2, highly affinity matured, and related to known VRC01-like antibodies pre-

viously isolated from these donors. They also made the assumption that antibodies with different sequences but similar structures probably share a similar precursor or intermediate along their affinity maturation pathway. To find such intermediates, they did a phylogenetic analysis of the variable heavy chain sequences from donors 45 and 74, using them to construct an evolutionary tree.

To calibrate the trees, they included the variable heavy chain sequences that came from known VRC01-like antibodies from different donors, and found that these known VRC01-like antibodies shared the same precursor sequences with each other, and with certain unknown antibody sequences from the donors. This suggested that these unknown sequences encoded VRC01-like antibodies that could neutralize HIV. And, indeed, when they tested the neutralization capabilities of these sequences—by combining the encoded antibodies with light chain sequences from known VRC01-like bNAbs—they found that the resulting antibodies could neutralize HIV, some quite potently, whereas antibodies encoded by sequences that didn’t share common precursors with known VRC01-like antibodies could not neutralize HIV.

The researchers also used the sequence of CDRH3, one of the most variable parts of the heavy chain variable region of the antibodies, as a unique marker for antibodies that are likely derived from the same B cell in the germline to reconstruct how they accumulate somatic hypermutations on their way to the fully affinity-matured bNAb. This identified several maturation lineages of VRC01-like neutralizing antibodies within donor 74, suggesting that VRC01-like antibodies are not that rare, even within the same individual.

“The unique feature of this study is the deep sequencing analysis of the HIV Env-specific B-cell receptors from multiple HIV infected subjects, combined with their functional characterization,” says Leo Stamatatos, director of the viral vaccine program at Seattle BioMed, who was not involved in the study. “The amount of work it involves is out of this world.”

Kwong says the common precursors of VRC01-like antibodies identified by this phylogenetic analysis could be used to guide development of a vaccine that stimulates the immune system to generate these precursors. The B-cell sequences of vaccinees could then also be checked for these precursors to see if the vaccine-induced affinity maturation goes in the right direction, he adds.

“We now have come up with tools that will actually give us the entire maturation pathway for every single antibody that we choose to examine with this deep sequencing method,” Kwong says. “[The] next step [is] to make immunogens that will be effective in eliciting or producing these maturation series.” —*Andreas von Bubnoff*

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