IAVI Report

The Publication on AIDS Vaccine Research

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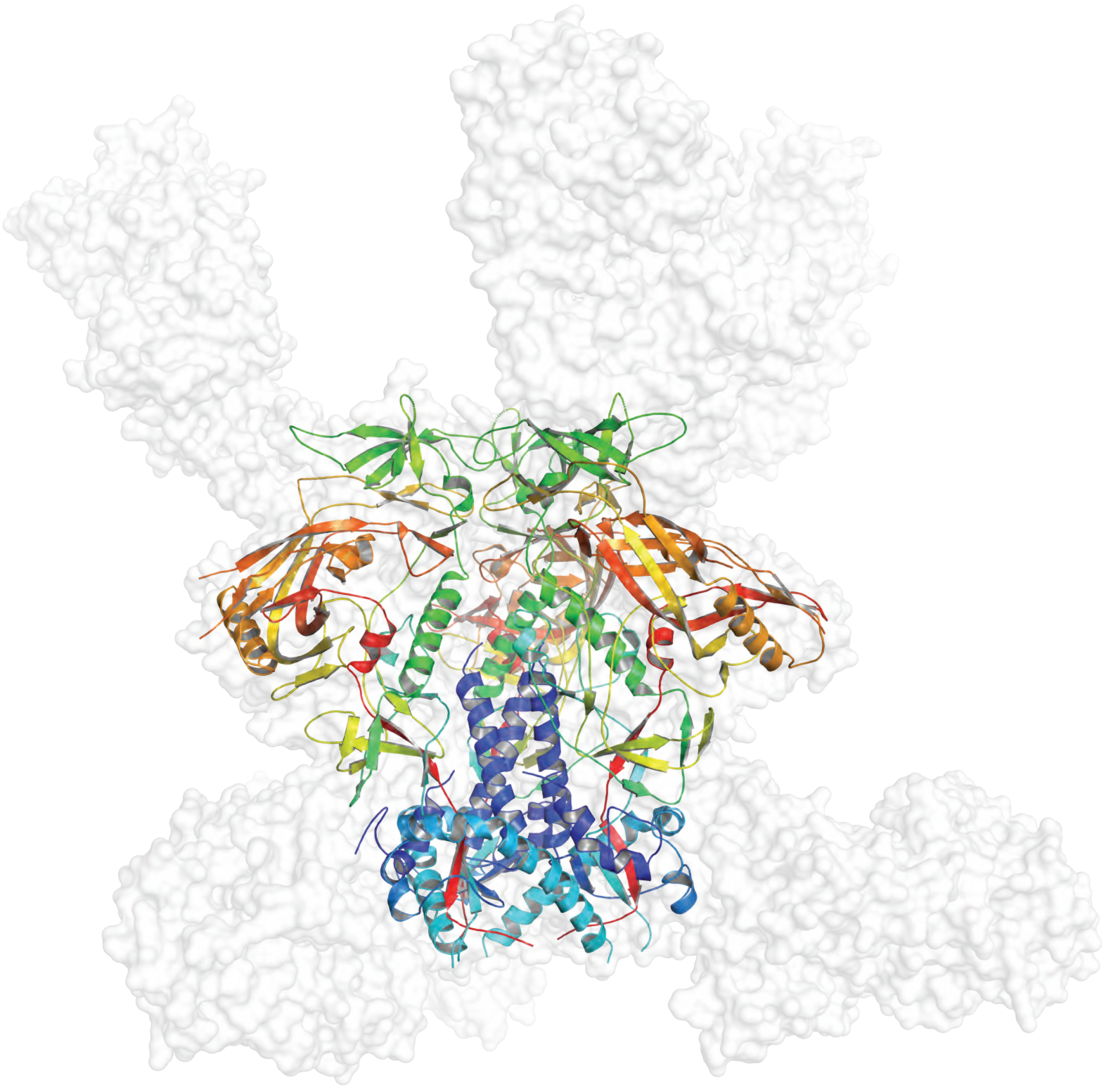

FROM THE EDITOR

In a few weeks, the AIDS 2018 meeting will kick off in Amsterdam. It will be the 22nd annual conference, and remains the largest international gathering focused on a single public health issue. This year, one message that will come out loud and clear is that more than 30 years later, AIDS isn't over.

As International AIDS Society (IAS) President Linda-Gail Bekker said in our recent interview, "We absolutely must subvert the misperception that the AIDS problem is solved" (see page 14).

This misperception could already be inflicting damage, it turns out. Bekker and others say that it is likely one reason that investment in HIV/AIDS prevention has fallen, a trend documented in a recent report by the Institute for Health Metrics and Evaluation (see page 4). Yet in some ways, HIV prevention research has never looked so promising.

While the use of oral pre-exposure prophylaxis—a daily antiretroviral to prevent HIV infection—picks up steam, so-called broadly neutralizing antibodies are revolutionizing vaccine research and HIV prevention efforts more broadly. For the first time, researchers are advancing a new class of vaccine candidates specifically engineered to kickstart the induction of broadly neutralizing antibodies that can face up to the extreme genetic variation of the virus and all its circulating forms. In this issue, we detail this exciting progress as well as the advances in developing the broadly neutralizing antibodies themselves for HIV prevention, an effort referred to as passive administration (see pages 6 and 22).

We also look at the recent grants issued by the Coalition for Epidemic Preparedness Innovations to develop vaccines against three other viral pathogens that are among the top threats to global public health (see page 20), and pay tribute to a great vaccine champion and public health advocate, Adel Mahmoud, who passed away in June (see page 19).

Despite all the talk of ending AIDS, and the well laid-out goals to accomplish this, the rate of new infections on a global scale has continued nearly unabated. And in some places, the epidemic is actually surging. Writing recently in *Science*, Jon Cohen and Jia You profile three places where the response to HIV/AIDS, for a variety of reasons, has been hampered, and as a result, the virus continues to thrive. The places are as disparate politically and economically as they are geographically—Florida, Nigeria, and Russia.

If the upcoming IAS conference sets the tone for the HIV/AIDS response, it will hopefully be that while there is still a long road to ending AIDS, the path is finally becoming clearer.

—KRISTEN JILL KRESGE

The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with partners in 25 countries to research, design and develop AIDS vaccine candidates. In addition, IAVI conducts policy analyses and serves as an advocate for the AIDS vaccine field. IAVI supports a comprehensive approach to addressing HIV and AIDS that balances the expansion and strengthening of existing HIV-prevention and treatment programs with targeted investments in the design and development of new tools to prevent HIV. IAVI is dedicated to ensuring that a future AIDS vaccine will be available and accessible to all who need it. IAVI relies on the generous donations from governments, private individuals, corporations and foundations to carry out its mission. For more information, see www.iavi.org.

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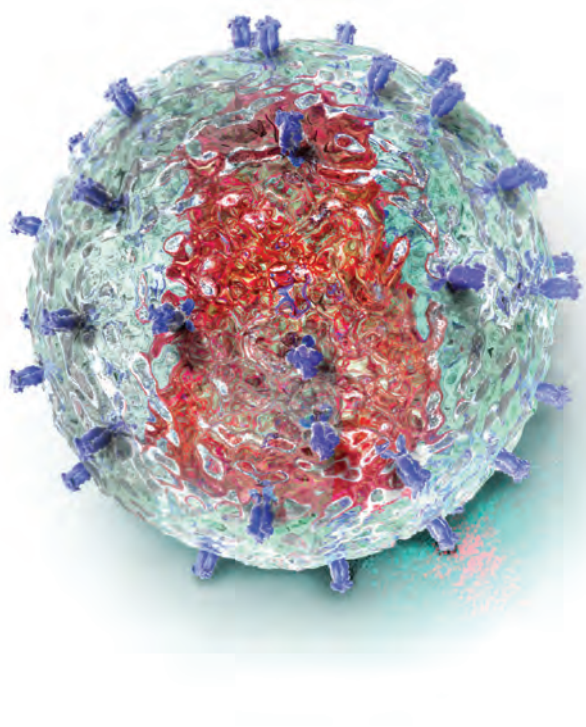

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ON THE COVER
Protein Data Bank entry (PDB ID) 4TVP contains the atomic-level crystal structure of the prefusion closed form of the HIV-1 Envelope trimer (in rainbow-colored ribbon representation) in complex with two neutralizing human antibodies, PGT122 and 35O22 (shown as transparent surfaces). In this orientation the viral membrane would be located towards the bottom of the page. This structure is being used as the basis for a variety of structure-based vaccine approaches.

Image courtesy of Jonathan Stuckey, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

OPENING QUESTION

Could overly optimistic messages be contributing to the drop in global HIV/AIDS spending?

The pandemic isn't over, but that might be what donors are hearing.

BY MARY RUSHTON

A global mission to end AIDS by 2030 has caused a groundswell of optimism. Could it also be, inadvertently, contributing to a recent decline in HIV/AIDS funding?

A global report released this year from the Institute for Health Metrics and Evaluation (IHME) shows that after an annualized growth of 20 percent between 2000 and 2012, development assistance for HIV/AIDS has decreased 5.4 percent annually since 2012. This encompasses funding from governments, philanthropic organizations such as the Bill & Melinda Gates Foundation, and individual donors. Development assistance for HIV is now around US$10 billion, well below the $26.2 billion that the Joint United Nations Programme on HIV/AIDS, or UNAIDS, says is needed by 2020 to meet global HIV prevention and treatment targets.

Public policy researchers attribute the drop in HIV/AIDS spending to multiple factors. Refugee and asylum costs and other global health priorities are competing for and winning donor dollars once targeted for HIV/AIDS. Also, several European countries have shifted their bilateral contributions—foreign aid given by one country to another—to multilateral agencies like the Global Fund to Fight AIDS, Malaria and Tuberculosis, while also reducing their level of support.

It is also possible that the rhetoric around ending AIDS may be sending the wrong message to funders. Donors may hear messages like, "we can end AIDS now," or "we have the tools to end AIDS," and think the major hurdles in the epidemic are past us, says Chris Beyrer, professor of epidemiology at the Johns Hopkins School of Public Health and a past president of the International AIDS Society (IAS). "We are not done with AIDS. I think some of the messages out there about achieving epidemic control and ending AIDS as a public health problem have been problematic," says Beyrer. "We have done ourselves a disservice by selling to a policy maker or donor audience that we have this problem solved when we haven't."

Linda-Gail Bekker, deputy director of the Desmond Tutu HIV Centre and current president of IAS concurs. "The decline in HIV funding is deeply disturbing as the epidemic is far from over," says Bekker. "Unfortunately, premature talk of 'ending AIDS' may have caused some to believe erroneously that the epidemic is over. We need to revitalize our activism and emphasize to decision-makers the stakes that are involved in the future of the HIV response. If we fail to strengthen our efforts, we will almost certainly see a resurgence of the epidemic."

Bekker says the scale-up of treatment in recent years has been remarkable, with a turnaround in life expectancy in a number of countries, especially those in southern and East Africa. At the same time, however, almost 2 million people are still becoming infected every year, she said. "As we approach what feels like the second half of the

history of AIDS, the world needs to think about HIV and the AIDS response as a long-term project that needs a long-term plan and sustainable funding, which may require innovative thinking to secure."

The latest report from the IHME, an organization based at the University of Washington, is the group's ninth on global health spending and health financing, and it offers an unusually deep analysis of trends in HIV spending over time, using data provided by 188 countries. The analysis shows, for instance, that prevention programs were hurt most by the reduction in HIV/AIDS spending, while funding for treatment programs remained relatively stable.

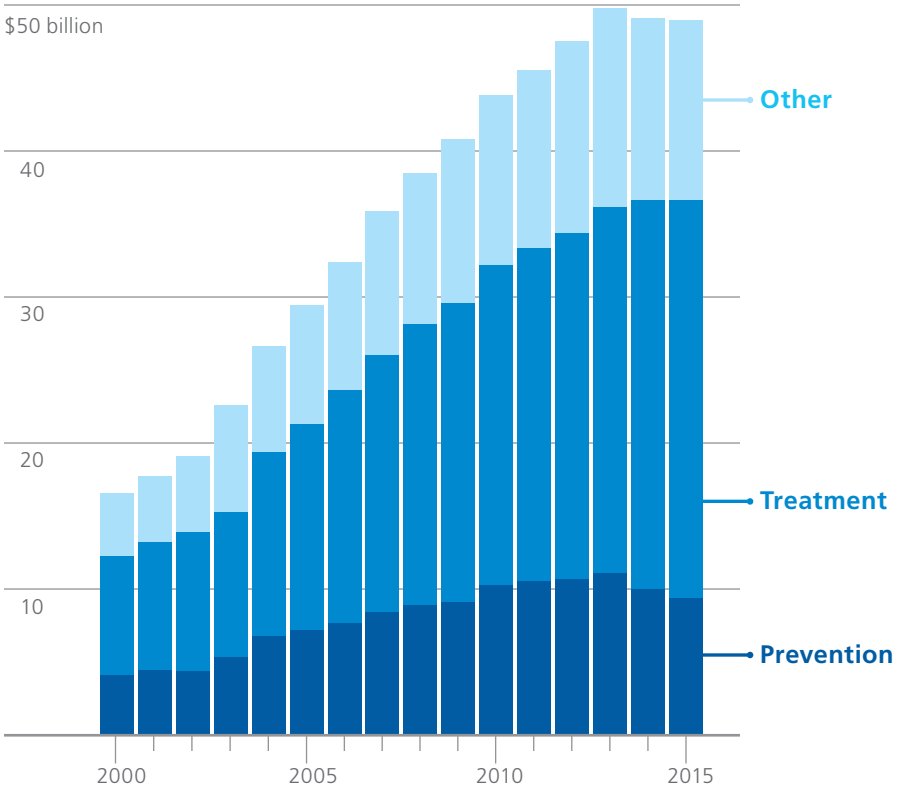
HIV/AIDS has accounted for the largest percentage (26.8 percent) of development assistance health dollars doled out since 2000, the report found. But in the last few years more development assistance has gone to maternal, newborn, and child health program than for HIV/AIDS. Ironically, the success in bolstering maternal and child health programs in sub-Saharan Africa is now one of the biggest threats to sustaining the HIV/AIDS response. As these children enter adolescence, experts warn that HIV infection rates could once again rise, particularly in sub-Saharan Africa.

Though South Africa still has the largest HIV/AIDS epidemic in the world, it will probably not be severely impacted by the reduction in donor funding, says Salim Abdool Karim, Director of the Centre for the AIDS Program of Research in South Africa (CAPRISA). "Since the South African government provides more than 80% of the funding required for the country's AIDS response, the effect of reduced donor funding will likely be minimal."

This is not the case for many other countries burdened by HIV/AIDS that are far more dependent on foreign aid. "It is clear that the lowest income countries cannot pay for their response on their own," says José Antonio Izazola-Licea, Special Advisor for Resource Tracking and Finances at UNAIDS. "These countries must continue to be supported and not be forced to face an epidemic where more people die because of a lack of treatment, and new HIV infections increase due to a lack of resources for HIV prevention efforts." ■

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

Spending on HIV/AIDS by function, 2000-2015



Note: Spending is measured in 2017 purchasing power parity dollars
Source: Financing Global Health Database, 2017

THE ANTIBODY REVOLUTION

A new generation of engineered vaccine candidates enters clinical testing

After decades of work, scientists are now advancing rationally designed vaccine candidates meant to induce a long sought-after broadly neutralizing antibody response.

BY MICHAEL DUMIAK

Armed with an understanding of HIV's structure in minute detail and how antibodies bind to it, scientists are now ushering a new crop of engineered vaccine candidates into clinical trials, all in the hopes of eventually stimulating potent neutralizing antibodies that could block infection with the virus.

Vaccines work by training the immune system to respond to a specific pathogen before an infection ever occurs. The most crucial of these vaccine-induced immune responses are antibodies, typically Y-shaped proteins produced by activated B cells. Antibodies can latch on to and neutralize or inactivate viruses. For HIV, the focus has been on inducing broadly neutralizing antibodies (bNAbs): antibodies that can potently neutralize the many genetically different variants of HIV that are in circulation due to the virus's unprecedented mutation rate.

Many scientists suspect bNAbs will be required to develop a highly effective, preventive HIV vaccine. Yet none of the vaccine candidates developed to date has been able to stimulate them. In fact, the antibodies elicited by current candidates can only neutralize a small fraction of HIV isolates that are typically transmitted from person to person (*Nat. Med.* 2018, doi:10.1038/s41591-018-0042-6).

This is not for lack of effort. Researchers have been exploring ways to develop bNAb-inducing vaccine candidates for decades. Now, thanks to significant scientific progress, these efforts are garnering broad interest and serious investment. About a dozen vaccine candidates designed specifically to initiate the induction of bNAbs are, or soon will be, tested in human volunteers.

These candidates come in different forms. Some are native-like trimers meant to resemble HIV's outermost Envelope (Env) protein spike. Some others are computationally designed immunogens based on the precise epitopes on HIV Env that are targeted by bNAbs. There are also other strategies for invoking antibodies, as well as a slew of antibodies themselves being developed in an effort to protect against HIV infection.

"It's a new era clinically of testing this antibody-based vaccine design concept," says John Mascola, director of the National Institutes of Health's Vaccine Research Center (VRC). "It's certainly a very exciting time."

As remarkable as recent developments in the HIV vaccine field may be, none of these first-generation rational candidates is expected to induce bNAbs right off the bat. Researchers hope to use the early clinical trials to learn, Mascola says, not necessarily to solve. "We're poised to learn a lot, even though the studies are what I would term as early

A trimer up close

Researchers at Amsterdam University's Academic Medical Center designed an HIV vaccine candidate based on the "native-like" ConM SOSIP protein as part of the EU H2020 EAVI2020 program. This native-like ConM SOSIP is shown in white, while the colors depict antibodies binding to it. Green is PGT122 binding to the V3 glycan; orange is 2G12 binding to the outer domain and high mannose cluster; pink is PGT151 binding to gp120-gp41 interface; red is 3bnc117 binding to the CD4-binding site; blue is PGT145 binding to the trimer apex.

Alba Torrents de la Peña produced this image for an ongoing photo exhibition about EAVI2020's program. The exhibition is currently on display at Paris's Inserm, the French National Institute of Health and Medical Research, and will move in July to the French Alternative Energies and Atomic Energy Commission.

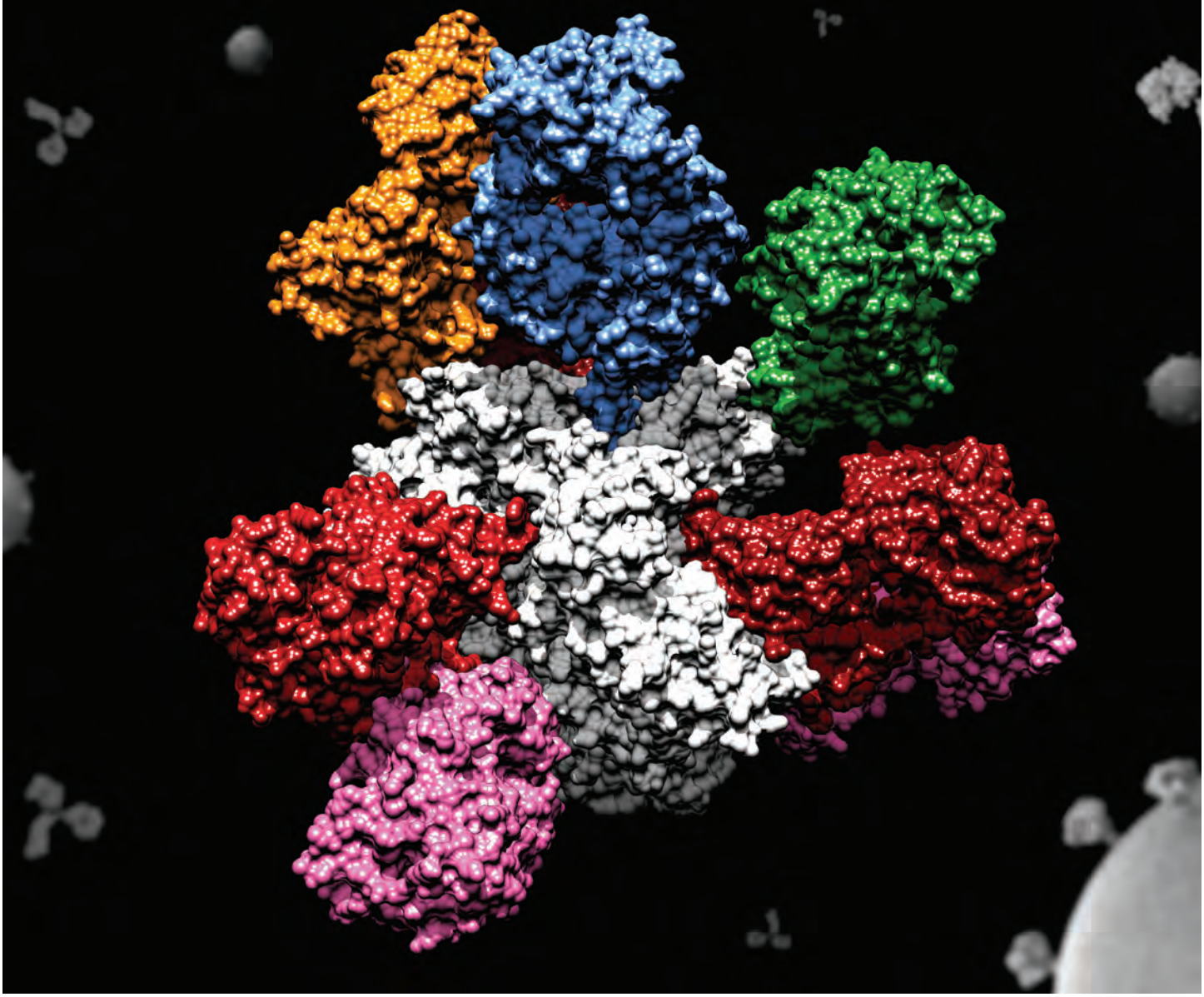


Image prepared by Alba Torrents de la Peña, PhD student in Rogier Sanders' lab, in the department of medical microbiology at the Amsterdam University Medical Center

Awaiting results from efficacy trials

While many in the field are focused on advancing rationally designed, new-generation vaccine candidates, there is also a pair of ongoing efficacy trials that may illuminate additional paths to an HIV vaccine.

One is an efficacy trial in South Africa called HVTN 702, involving 5,400 volunteers. It is the follow-up to the RV144 trial of a canarypox viral vector prime and a gp120 Env protein boost. In the wake of the unexpected efficacy results from RV144, researchers extensively studied the immune responses the experimental vaccine regimen induced. While the vaccine seemed to produce antibodies, they were non-neutralizing. Instead they bound up HIV-infected cells until other parts of the immune system could come to the rescue, an action called antibody-dependent cellular cytotoxicity.

Researchers also reconfigured the candidates and dosing schedule to try to improve the efficacy of the regimen and to prolong the durability of the immune responses it induced. This included basing the candidates around clade C virus, which is most prevalent in South Africa. Results from HVTN 702 are expected by 2020. The trial is being supported by the US National Institutes of Health (NIH), the Bill & Melinda Gates Foundation, the South African Medical Research Council, the HIV Vaccine Trials Network, Sanofi Pasteur, GlaxoSmithKline, and the US Military HIV Research Program.

Another ongoing efficacy trial in South Africa is testing a so-called mosaic immunogen developed by Janssen and Dan

stage. It's still experimental medicine, meaning we need to learn from these studies to really understand the immune response to these vaccines."

Vaccine development over the last century and a half was largely based on empiricism, or experimentation. Its guiding premise is that after conducting experiments in the lab and in animals, the only way to tell if a vaccine will work is to test it in humans. Many, if not most, vaccines were developed this way. But these trials are large and expensive, and in the 30 years that researchers have been trying to develop a vaccine against HIV, only one efficacy trial—the RV144 or so-called Thai trial—showed any efficacy at all. In this trial, the experimental vaccine regimen was 31 percent effective in preventing HIV infection.

"The history of vaccine experiments, and the vaccine experiments in this field, have not been stellar," says John Moore, a professor of microbiology and immunology at the Cornell Weill Medical College. "Lots of immunogens over the years have tended to be put into trials because they exist. We need to understand what antigens are going to work best in animals, and at some point, humans. There are many aspects of these immunogens that remain to be understood."

This is where the rational vaccine development effort comes in. It starts from hypotheses about what type of immune responses are thought to be protective, and then, working from that endpoint, researchers come up with vaccine components or antigens to try to trigger that response. Rational or hypothesis-driven vaccine design efforts are part of a larger vaccine movement against harder-to-combat pathogens for which an empirical approach would take too long and would be too expensive.

An advantage of this approach is that it doesn't require going all the way to an efficacy study to determine if the vaccine candidate is having its desired effect. Researchers can learn this much earlier in the development cycle, allowing them to quickly improve upon the vaccine candidate and test it again, setting up an iterative process. Even though this new generation of rationally designed vaccine candidates will almost surely not deliver the final shot against the virus, researchers are poised to learn how to improve these candidates at a much faster pace than was possible in the past.

In the late 1990s, Moore and Rogier Sanders, now a virologist at the University of Amsterdam's Academic Medical Center, began collaborating on what would be a decades-long effort. Early HIV vaccine trials testing subunits of the HIV Env—

Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconness Medical Center and a member of the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology, and Harvard University. It also carries with it an extensive support infrastructure, from Janssen, which is part of Johnson & Johnson, the Gates Foundation, and the NIH's National Institute of Allergy and Infectious Diseases.

The mosaic antigen is computationally designed to provide maximum coverage against all currently circulating strains of HIV. The Imbokodo, or HVTN 705 trial, is enrolling 2,600 volunteers randomized to received either a four-valent cocktail expressing mosaic Env/Gag/Pol antigens boosted by a clade C gp140 soluble protein, or placebo.

Barouch says the studies leading up to Imbokodo show robust vaccine-induced antibody and T-cell responses: the antibody responses show functional activity, but not broad neutralization.

As for the slew of broadly neutralizing antibody approaches heading into the clinic, Barouch shows some skepticism. "While there are new strategies to trigger neutralizing antibody responses to particular epitope regions, it remains to be seen whether those strategies will be able to induce broadly neutralizing antibodies," he says. "There are a lot of ideas, but not a lot of data, and we're not even talking about human data. There's very little animal data."

which in the wild is a trimeric cluster of three glycoprotein (gp) 120 subunits and three gp41 subunits assembled into a spike—had not gone well.

The HIV Env spike is the only exposed viral protein, and therefore the target of all functional antibodies against the virus. But it is heavily glycosylated, providing multiple sugary decoys that shield the virus from the immune system. It is also notoriously unstable, constantly mutating and changing its shape to enable it to dock to and infect human cells (*Immunol. Rev.*, **275**, 161, 2017). Using monomeric Env subunits as vaccine antigens didn't do the job. They induced plenty of antibodies, but they were not effectively neutralizing. Researchers suspected this was because these protein subunits were inadequate mimics of the native trimeric HIV Env protein (*J. Infect. Dis.*, **173,** 340, 1996; *International Journal of Molecular Sciences,* **19,** 1241, 2018).

Creating a stable form of the Env trimer, the teams hypothesized, might yield a better immunogen. So the researchers engineered an SOS gp140 protein and manipulated it in the lab to try to stabilize it (*J. Virol,* **74,** 627, 2000).

They introduced artificial mutations, including a disulfide bond between the gp120 and gp41 proteins, and made a genetic manipulation to try to prevent conformational changes that caused the trimer to fall apart. By doing so, Sanders and Moore and their colleagues were, by 2002, able to create a stabilized Env trimer. They called it SOSIP gp140 (*J. Virol*, **76,** 8875, 2002).

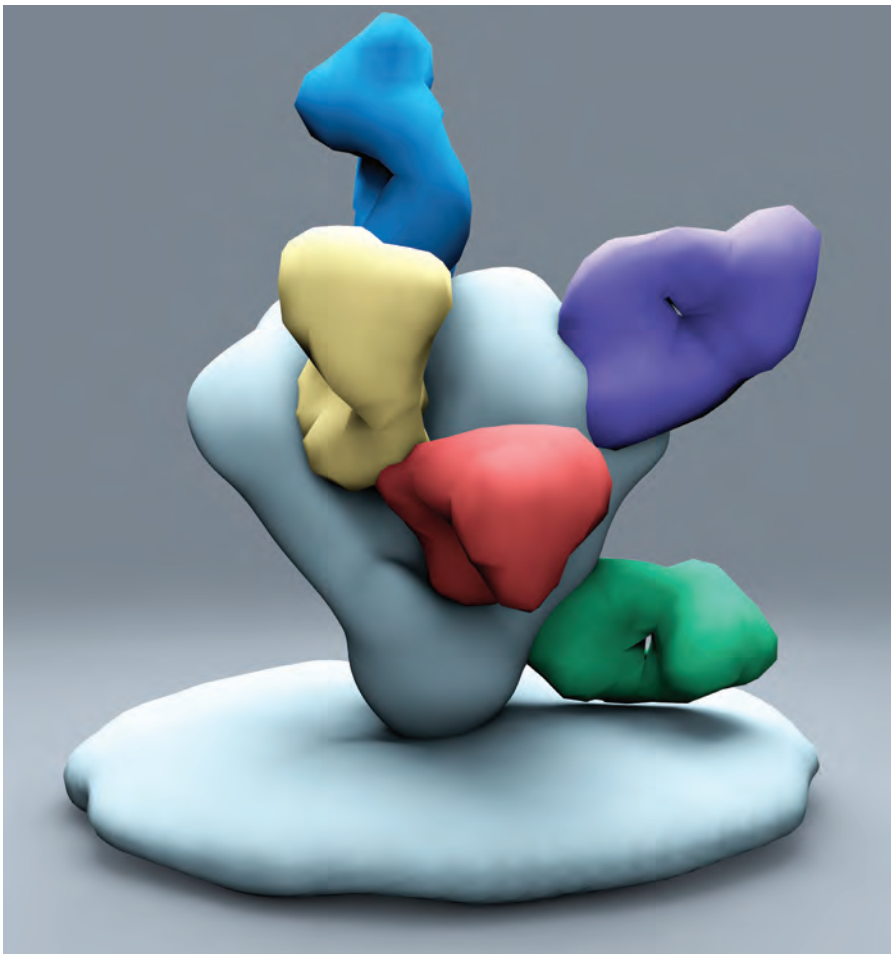
But it turned out the protein wasn't as stable as they'd hoped. "We realized the end product wasn't really what we wanted it to be. It wasn't stable enough and it wasn't kept in the native conformation well enough, for long enough," Sanders says.

The labs went on to work on other projects. Eight years would pass before they returned to the trimer stabilization efforts.

In 2006, a new idea emerged that would greatly influence antibody-based vaccine development. The Neutralizing Antibody Consortium, under the auspices of IAVI and led by Dennis Burton at The Scripps Research Institute, launched a research effort called Protocol G (https://www.iavi.org/what-we-do/partner/the-antibody-project). The protocol's aim was to collect samples from healthy HIV-uninfected volunteers in sub-Saharan Africa, the US, UK, Australia, and Thailand, and screen them for antibodies with the unusual property of being neutralizing against a broad variety of viral strains in the laboratory.

Protocol G showed that a small subset of HIV-infected individuals is able to generate these anti-

Rational vaccine design is part of a larger movement against harder-to-combat pathogens for which an empirical approach would take too long and would be too expensive.



Electron microscopy reconstruction depicting antibodies attached to the HIV Envelope glycoprotein trimer at five sites of vulnerability shown in different colors. These five regions are the conserved epitopes that are currently being used by vaccine researchers as targets to design next-generation vaccine candidates. Image courtesy of Andrew Ward and Christina Corbaci at The Scripps Research Institute.

bodies over time. They are not able to provide much benefit to the infected person, as the virus can quickly mutate around this immune response, but researchers have long figured that it will be bNAbs such as these that, if induced by a vaccine, may be able to prevent HIV infection from ever occurring.

From Protocol G, scientists isolated an antibody called PG9, then another dubbed PG16, which were the first new bNAbs researchers had to work with in many years (*Science,* **326,** 285, 2009). Mascola's VRC soon after published on another broadly neutralizing antibody, VRC01 (*Science,* **329,** 856, 2010).

The number of newly isolated bNAbs soon ran to a dozen, then dozens (*Ann. Rev. Immunol.*, **34,** 635, 2016). Some proved even better at neutralizing a broad swath of HIV isolates in lab tests. By genetically characterizing these antibodies, scientists began to understand precisely where these antibodies bind to HIV. This resulted in a map of antibody targets on the virus that could be exploited by vaccine researchers.

"The actual number of broadly neutralizing antibodies is pretty hard to characterize. But one way to look at it is from the major epitopes on the virus that the antibodies define. There are five major regions and maybe a sixth on the virus that are assigned by broadly neutralizing antibodies. And all of those sites are, in some fashion, a target of vaccine design," Mascola says. These five epitopes comprise HIV's CD4 binding site, the V1 to V2 apex, the V3 glycan super site, the membrane proximal region, and the gp120/gp41 interface region (see Image; *Nat. Comms.,* **6,** 8571, 2015).

With new antibody discovery continuing at an unprecedented pace, researchers returned to trimer stabilization efforts—this time with renewed funding, improved technologies, and a slew of antibodies in hand that allowed them to more easily attack the problem. "What really helped that effort was to have antibodies to the trimer, which allowed investigators to solve the crystal structure of the trimer, and therefore to better understand how to make it and how to stabilize it," says Mascola. "It's not a coincidence that this re-emerged along with the broadly neutralizing antibodies."

In 2013, Moore, Sanders, and their teams were able to successfully stabilize HIV's Env protein in an appropriately native-like conformation. They did this by deleting a string of 15 amino acids from their previous SOSIP construction and screening Env proteins from many isolates.

Moore, Sanders, and their colleagues in New York, Amsterdam, and La Jolla, California, stabilized an HIV gp140 protein called BG505 SOSIP.664 (*PloS Path.* doi.org/10.1371/journal.ppat.1003618). It was derived from a clade A virus isolated from a six-week-old Kenyan infant

Entering the antibody age

As vaccine researchers march new concepts into the clinic, more teams are also advancing multiple monoclonal antibodies for passive administration, which refers to direct injection or infusion of broadly neutralizing antibodies to try to treat, prevent, or possibly even cure HIV infection. This method avoids the need to stimulate the immune system to make these antibodies.

Several of these antibodies are approaching early-phase trials, while one antibody, VRC01, is already in an efficacy trial known as the Antibody Mediated Prevention (AMP) study (*Current Opinion in Immun.*, **41,** 39-46, 2016). VRC01 neutralizes an extensive panel of global HIV strains in the lab and has been shown to protect nonhuman primates against infection with SHIV, a monkey/human hybrid virus. The antibody has also proved to be safe and well tolerated in humans, and passive administration suppressed viral replication transiently in the VRC's Phase I clinical trials VRC601 and VRC602.

A related antibody, VRC01LS, is in a Phase I safety trial evaluating the pharmacokinetics of the antibody in the serum and mucosa of healthy adults. This antibody differs only slightly from VRC01—it has a small amino-acid change designed to extend its half-life. The VRC is also working with Sanofi to advance a "trispecfic" antibody: an artificial antibody created with three "arms," each from a different antibody (*Science,* **358,** 85, 2017).

> "We don't yet understand ... how much of an antibody you need in serum at the time of exposure to block infection."

Several other antibodies have been in or will be entering Phase I trials shortly. Some of these include the VRC's VRC07-523LS, 10E8VLS, and N6LS, and Rockefeller University's 3BNC117 and 10-1074.

The Rockefeller antibodies have been through Phase I trials and have shown some suppression of viral rebound in HIV-infected volunteers, following interruption of antiretroviral treatment (*Science,* **352,** 997, 2016). Now, they are being tested together in a Phase I trial, and researchers are also creating longer-lasting versions of these two antibodies. The antibody PGT121 is also slated for clinical trials, while many others are also in various stages of development.

Marina Caskey, an immunologist and associate professor of clinical investigation at Rockefeller University, is enthused by the many advances in developing vaccine immunogens. At least for now, she thinks the way ahead is clearer for passive administration.

"There's proof of concept that it will work," she says. But there is still much to learn about this approach as well. "We don't yet understand the relationship with how much of an antibody you need in serum at the time of exposure in order to block infection from occurring," she says. "We hope we will learn a lot about that in the AMP study."

born in Nairobi, who had developed a bNAb response to HIV after being infected for two years.

They then collected immunogenicity data in rabbits and nonhuman primates for the BG505 SOSIP.664 trimer, as well as another native-like trimer called B41 SOSIP.664, which was based on a clade B founder virus from an HIV-infected adult (*Science,* **349,** 6244, 2015). The SOSIP trimers were each only able to induce neutralizing antibody responses against autologous virus, that is viruses from same strain as the sequence used to make the native-like SOSIP trimer. Even so, this was the first time an antigen showed an ability to provoke a strong and consistent neutralizing antibody response against an autologous virus with properties matching those of a transmitted virus. According to Sanders, it made an excellent starting point for iterative vaccine design.

"We're trying to make immunogens that induce neutralizing antibodies against resistant viruses and to deal with the problem of diversity," Moore says. " If it were an easy thing to do, it would have been done a long time ago."

Researchers then focused even more on how to optimize native-like trimers. The increasing use of cryo-electron microscopy and vastly more detailed modeling yielded unprecedented atomic-level resolution of HIV. "Those have been instrumental in designing further improved trimers, as

Highly mutated bNAbs are typically not able to bind to native HIV, which creates yet another challenge for vaccine scientists.

well as imitations that made the technology applicable to envelope sequences from other viral strains," Sanders says.

Now there are hundreds of these stable trimers, some of which are already in, or are being readied for, clinical trials. A vaccine candidate employing the BG505 SOSIP.664 gp140 protein as the antigen insert, with a GlaxoSmithKline adjuvant made up of a monophosphoryl lipid and the proprietary immune booster QS-21 combined in a liposome solution, will enter Phase I trials in the US and Kenya this summer.

Robin Shattock, head of mucosal infection and immunity within the department of medicine at Imperial College London, has long called for faster-moving, iterative, early-phase clinical studies, and that is what he is coordinating with the European AIDS Vaccine Initiative (EAVI 2020). The program is working to advance a total of seven SOSIP native-like trimer candidates into the clinic, as well as a single-chain construct based on a consensus sequence. Two stabilized SOSIPs are due to enter Phase I trials in early 2019, with another six candidates to follow later that year and in early 2020.

Seven of these eight candidates are coming from Sanders's lab in Amsterdam, the other from Shattock's (*Immunol. Rev.*, **275**, 161, 2017). "We're looking at two different stabilization approaches to see which is the best," Shattock says. "We've stabilized them molecularly, and we are taking a further step and stabilizing them chemically. We have made it almost like a rock and we want to know which of these gives us a flavor of antibody response that we have not seen before."

As is often the case, HIV presents unique challenges, and the development of bNAbs is no exception. First of all they develop rarely—only in about 20 percent of infected individuals—and even then, only after years of exposure to the ever-mutating virus. Broadly neutralizing antibodies to HIV are also highly mutated as a result of undergoing multiple rounds of a process called somatic hypermutation. It is through this process that antibodies accrue the mutations that allow them to better bind to and neutralize HIV.

But highly mutated bNAbs are typically not able to bind to native HIV, which creates yet another challenge for vaccine scientists. The challenge is how to stimulate so-called germline antibodies that can bind to native HIV and then shepherd them through the mutation processes required to become bNAbs. Current thinking is that this may require vaccinating with a series of immunogens, each meant to facilitate the evolution of germline antibodies to those that are broadly neutralizing, and hopefully do so faster than what happens in natural infection.

Barton Haynes, director of the Duke Human Vaccine Institute in North Carolina and of the Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID), and colleagues are attempting to recreate the process of bNAb development by sequentially immunizing volunteers with four HIV gp120 Env proteins isolated from an HIV-infected individual who eventually developed bNAbs, along with the lipid adjuvant GLA-SE. A Phase I trial, known as HVTN 115, is currently enrolling volunteers to receive this multi-Env candidate that goes by the name of CH505 or EnvSeq-1. The first part of the study is meant to find the optimal dose of the first Env protein. In the second part of the study, researchers will administer the entire set of sequential Envs to see if they can kickstart the process of bNAb development in uninfected volunteers, and whether adding a DNA vaccine candidate, DNA Mosaic-Tre Env, can further improve the immune response.

"We've learned an awful lot about what happens, from an immunologic standpoint, when broadly neutralizing antibodies are made. We've also learned what happens when they are not made, when they are disfavored," says Haynes. "Now we're moving into a phase where we are combining the new structural knowledge we've gained with what has to happen immunologically."

The Duke CHAVI-ID group is also running trials comparing CH505 produced from stable transfection with that produced by transient transfection to see if transient transfection, which is a faster method of manufacturing vaccine, delivers similar immune responses. "We're trying to get to iterative Phase I trials," Haynes says.

He and others are also developing a peptide lipo-

some vaccine candidate based on the membrane-proximal external region (MPER) on HIV's gp41 glycoprotein subunit. "It's been very difficult to make, but we've now succeeded in making it and we've had a successful engineering run," Haynes says. Toxicity studies are due to finish at the end of the year, and the researchers have an eye toward testing the MPER liposome in clinical trials in late 2019 or early 2020.

"A lot of these efforts are categorized as what Dennis Burton years ago called reverse vaccinology," Mascola says. "The premise is, if you have an antibody that works pretty well, meaning it neutralizes the virus, you can design your vaccine to elicit that antibody."

This is the goal of work by CHAVI-ID-backed researchers at The Scripps Research Institute in La Jolla. They, in partnership with IAVI, are advancing a vaccine candidate structurally designed to induce germline precursors to bNAbs. The Scripps group, including William Schief, Dennis Burton, Ian Wilson, and others, have employed computation-guided *in-vitro* screening to engineer a germline-targeting immunogen based on the outer domain region of HIV gp120.

This approach is referred to as structure-based vaccine design, and it is being applied to other vaccine development efforts as well, including against respiratory syncytial virus (RSV; *Clinical and Vaccine Immunology,* **23,** 189, 2016, and **23,** 243, 2016).

Scripps researchers took this "engineered outer domain," or eOD, and figured out how to manufacture and deliver it in a cluster of multiple copies arranged on nanoparticles that are "self-assembling," making the antigen look more like a virus. The resulting vaccine immunogen, eOD-GT8 60 mer, is now ready for Phase I trials. These trials will evaluate the ability of the candidate to expand the pool of B cells capable of making germline antibodies against the CD4 binding site.

The idea is that once germline antibodies are stimulated, perhaps researchers could then use the eOD candidate as the first in a sequence of immunogens, the others being more and more native-like synthetic trimers, to encourage the mutation and evolution of the induced antibodies to the point where they are broadly neutralizing.

> "We're moving into a phase where we are combining the new structural knowledge with what has to happen immunologically."

Other structure-based vaccine candidates are also in development by researchers at the VRC. One candidate, FP-KLH, is based on the exposed epitope on the N-terminal region of HIV's fusion peptide (FP) that is targeted by the antibody N123-VRC34.01. Recently published data show that immunizing with FP-KLH combined with a native-like trimer induced antibodies with promising neutralization breadth in mice, guinea pigs, and nonhuman primates (*Nat. Med.* 2018, doi:10.1038/s41591-018-0042-6). This work provides proof of principle for this epitope-based vaccine design and suggests the exposed N terminus of FP is a site of "exceptional HIV-1 vaccine promise," the study's authors conclude.

While the field largely rallies around this new crop of rationally designed vaccine candidates, there are still those that see the appeal of a more empirical approach. Burt Dorman, an 80-year-old biophysical chemist, argues in a recent profile by Adam Rogers in Wired that a classical, empirical approach to HIV vaccine development is still the best path forward (https://www.wired.com/story/search-for-aids-vaccine/). Dorman has also published, along with Haynes Sheppard at Global Solutions for Infectious Diseases, an essay calling for a systematic look at inactivated HIV vaccines (*AIDS,* **29,** 125, 2015).

Anthony Fauci, head of the US National Institute of Allergy and Infectious Diseases, argues there is a role for both rational and empirical approaches in one of his commentaries (*Science,* **349,** 386, 2015). "These approaches are coalescing into concomitant paths toward a safe and effective HIV vaccine." ■

Michael Dumiak, based in Berlin, reports on global science, public health and technology.

INTERVIEW

Igniting passion for the long haul

Linda-Gail Bekker talks about how she came to work on HIV and shares her thoughts on an evolving field.

BY KRISTEN JILL KRESGE

The story of HIV/AIDS is still being written, but it is already a page turner. "I have a 16-year-old son, and I am constantly telling him that his generation will marvel at what has been done and what has been learned. It has been a historic story," says Linda-Gail Bekker, deputy director of the Desmond Tutu HIV Centre at the University of Cape Town in South Africa.

A significant part of that historic story has played out in Bekker's home country. South Africa remains the epicenter of the HIV/AIDS pandemic. It is where 19 percent of the globe's HIV-infected individuals live and where 15 percent of the new HIV infections occur on an annual basis, according to data from the Joint United Nations Programme on HIV/AIDS or UNAIDS. It is also home to the world's largest HIV treatment program, 80 percent of which is funded by the South African government.

This was not always the case. The picture in South Africa was much more dire before the 13th International AIDS Conference took place in Durban, South Africa, in 2000. This conference marked a turning point in the global response to HIV, and particularly changed the landscape for treating and preventing HIV in South Africa. This also happens to be the year Bekker returned to Cape Town after finishing her PhD studies.

From that momentous time point on, she used her training both as a physician and as a researcher to confront the country's epidemic. She helped fight for, and then was able to witness first-hand, the life-saving benefits of antiretroviral treatment as it reached more and more of the nation's HIV-infected individuals.

In 2004, Bekker and her then husband Robin Wood joined their efforts and created the Desmond Tutu HIV Centre, of which he is now the director. They have worked side by side since then in diverse communities, in HIV prevention and treatment, as well as in other infectious diseases, including tuberculosis (TB).

Bekker remains a steadfast advocate for the need for an HIV vaccine. She has chaired vaccine trial protocols and recently joined IAVI's Board of Directors. Since 2017, Bekker has also served as the President of the International AIDS Society, the first African woman to hold the post.

As she prepares to open the upcoming AIDS conference in Amsterdam this July, she reflects on how important it is that a new generation of young doctors and researchers pick up the fight that she and countless others have engaged in for decades. "We are here for the long haul," she says. "We need a new generation to engage, not only as activists and as clinicians, but also as researchers." She hopes that the upcoming conference will help ignite some enthusiasm and excitement among younger generations of scientists to pursue new and better ways to prevent HIV infection and also to help find a cure for HIV/AIDS. Perhaps most importantly, she hopes the conference will help dispel the misperception that AIDS is over, which she says threatens to undo the hard-won progress she and so many others have fought for. It is hard to imagine anyone could deliver a more impassioned plea for these changes than Bekker.

Below is an edited version of our recent conversation.

Linda-Gail Bekker addresses the staff of the Desmond Tutu HIV Centre at the University of Cape Town on the Centre's values.

How did you first become involved in HIV/AIDS?

It goes back to me being posted to Northern KwaZulu-Natal as a very young doctor. I went off to do my internship and then my first medical officer job just as the AIDS epidemic was really breaking. This was in the late 1980s, and a few things about this experience struck me very hard. The first was that young people were dying, and I seemed to be incapable of helping, despite the fact that I had just finished seven years of medical school. That was the first very humbling experience. The second was that I felt like I needed to know more. So I went back to medical school four years later to specialize, in the hope that I could learn something more and try and stop this. The other thing that I recognized was that I wanted to be a researcher—I had this insatiable curiosity—so I finished my specialization training at the University of Cape Town and then, even before I completely qualified, I managed to get myself into a PhD program because I realized I really wanted to be able to answer the questions, not only ask them.

When I finished my PhD in 2000, which I did partially at the Rockefeller University in New York City, I came back to Cape Town ready to start a career. By then I also had met and fallen in love with Robin Wood, who was running a research organization here. I started to set up my own research, and then Robin and I realized we were aligned in more ways than one, so we decided to join the two research organizations together. That's when the Desmond Tutu HIV Foundation was born. Since then we've been very blessed and lucky to go from strength to strength.

What is the focus of your work at the foundation?

Well, we have a prevention center, a youth center, and a treatment center. We also have a couple of clinical trial sites and a mobile unit, so we have footprints in a number of different communities and are working on a variety of different projects. One of my other quirks, which may or may not be a strength, is that I have an inability to focus on one thing.

That's called multitasking, right?

Well that's the nice way of putting it! But it does mean we literally do work in TB, HIV, HPV [human papilloma virus], and are working with men who have sex with men, young women and girls, pregnant women, and straight men. We go wherever there is a question that seems to need a solution. That's how we like to operate.

It must have been an amazing experience to return to South Africa in 2000 and to witness the turning point in the government's response to HIV/AIDS that took place after that.

Absolutely. I think it was a huge privilege and wonderful opportunity to be here at that time, but obviously hard as well. It was just an amazing thing to see things shift from a point where everybody was dying to a place where everybody is actually surviving, and living healthfully into adulthood and beyond. That has been extraordinary.

The fantastic thing at that time was that you were a clinician, a scientist, and an activist all at the same time. Robin and I both were working for the Treatment Action Campaign in their early efforts to bring ARVs to the fore. We were also very involved in the initial mother-to-child prevention programs. We were able to really be out-and-out activists as well, which I think in many ways shaped our passion for the future. I recall often thinking we were fighting forces way beyond the virus, which seemed such a shame because it kind of forced us to waste energy on things that shouldn't have been taking our energy. But at the same time, we were driven by this incredible sense that you had to do something. It didn't matter even if a politician was in the way; you had to work around it. You had to move beyond the obstruction.

I think that is a great lesson. You have to have passion, and then you can usually work around difficulties to get to where you need to go. That has been our mantra from the get-go. Very rarely do I talk myself out of something that I want to do on the basis that it's too hard or there just seem to be too many obstructions.

Despite the sense of optimism around treatment and that more and more people are able to access it, there is still an alarmingly high number of people who are becoming HIV infected every year, particularly in sub-Saharan Africa. What more can be done to really reverse that trend?

I think prevention has been more challenging in many ways. I don't think we've completely figured out what is necessary. But we are definitely getting some very clear indications of what the key ingredients are, and it is obviously not to hand out condoms or hand out PrEP [pre-exposure prophylaxis]. For most young people, it's about providing them with hope for the future, making sure that they actually do have a way to accomplish their goals, and then opening a discussion about how they can keep themselves free of infection.

I think one thing that we need to continue to shine a very strong light on is the fact that we will not treat our way out of this epidemic. Treatment will definitely reduce morbidity and mortality, and there's no doubt we have to do it to the best of our ability, but we also have to promote prevention.

I also think we need targets for prevention, and we have to be very explicit about what those are. Those targets should be regionally focused and take into consideration key populations.

Then, we need to look at getting more resources for prevention. Obviously, countries have to put money into treatment first of all. You must treat those who are already infected. But if you don't prevent new infections, your pool of people who need treatment is going to get bigger and bigger and, ultimately, you're going to lose the war. It's

> I think prevention has been more challenging in many ways. I don't think we've completely figured out what is necessary. But we are definitely getting some very clear indications of what the key ingredients are.

very important that we also find ways to either bring in new money or help countries, either through donor funding or whatever, to be able to actually have a prevention budget. I think that is really key.

I also think we need a very tailored and strategic approach to prevention so we can use resources wisely. We need to get quite granular in how we approach prevention as a one-approach-fits-all is certainly not the best strategy.

It also behooves us to keep working on other prevention options, including a vaccine.

How are things going with the use of oral PrEP in South Africa?

A little bit slow. On the other hand, one could argue, it is going safely and wisely because obviously it is a new intervention. I think there is great interest in PrEP, but I do think we have to face the fact that for some people, a daily intervention is very hard. Some people take it on easily, while others really struggle. Clearly, having other options down the pike is going to be very good for those individuals.

What has the experience of serving as President of IAS been like?

It has been a wonderful, wonderful opportunity. There is something very special about HIV stakeholders, whether they're doctors, researchers, community workers, or activists. They exude passion. It doesn't matter who you speak to or where you are—they are there because they believe in it. To be constantly engaged with this community has been such an amazing adventure and really a privilege.

In this role, I have also learned a lot. We are a community that speaks its mind and there are often many personalities and opinions, but I think that's our strength as well. It moves the field forward in ways that would take 100 years in other areas. Being in a position where I've been able to watch all this from sort of a birds-eye view, but also get very involved, and to a certain extent to influence the field, has been just amazing.

> I think one thing that we need to continue to shine a very strong light on is the fact that we will not treat our way out of this epidemic.

The AIDS 2018 meeting will open in a few weeks in Amsterdam. What themes do you expect to emerge there?

We set out wanting to really shine a spotlight on the Eastern Europe/Central Asia region and the worsening situation there. I think this is a region that urgently needs the world's focus and attention, as it is lacking resources and political leadership all while the region is seeing an alarming increase in infections. That's the first point.

Then, I think everybody has been a little bit concerned about the notion—particularly in Europe—that AIDS is done. That has implications on two fronts. One is that we then take our foot off the gas pedal. Secondly, it puts funding, much of which comes from Europe and North America, in jeopardy. We absolutely must subvert the misperception that the AIDS problem is solved. I would go so far as to say that given recent anxieties about funding, this misperception has put the HIV response in more jeopardy than it ever has been before. Not only should we not be complacent, I think we have reason to be quite concerned and anxious. We need to redouble our efforts in terms of passion and enthusiasm. Yes, we have come an amazing distance—we've got half the world's population who need treatment on treatment—but we have to keep that half on treatment, and we have to find the other half. Then we also have to make headway in prevention.

We need to change the narrative and figure out how to sustain the response going forward. We also need to integrate HIV/AIDS into the broader healthcare agenda. I think that is an important conversation to start. I don't think we can resolve it in four days in Amsterdam, but it is the beginning of a conversation that must happen.

And as if you didn't have enough to do, you joined IAVI's Board of Directors this past January. How you would characterize the importance of HIV vaccine research and the energy and optimism about some of the current research approaches?

Truly getting on top of this epidemic is going to mean we need a vaccine. I have always been a believer, even through the dark days following the results of the STEP and Phambili studies, but I am feeling a real sense of optimism now. Thirty years into the epidemic, I think we are beginning to make amazing inroads. I am so privileged to be in this country where at least three major trials are underway, including two vaccine efficacy trials (HVTN 702 and HVTN 705), and then also the antibody-mediated prevention, or AMP, study that is testing monoclonal antibodies for HIV prevention. In addition to these candidates, there is also very exquisite and incredibly innovative work going on to strengthen both the passive and the active immunization components.

All of this makes me unbelievably optimistic. ■

IN MEMORIAM

Remembering Adel Mahmoud, a giant in the vaccine world

BY KRISTEN JILL KRESGE

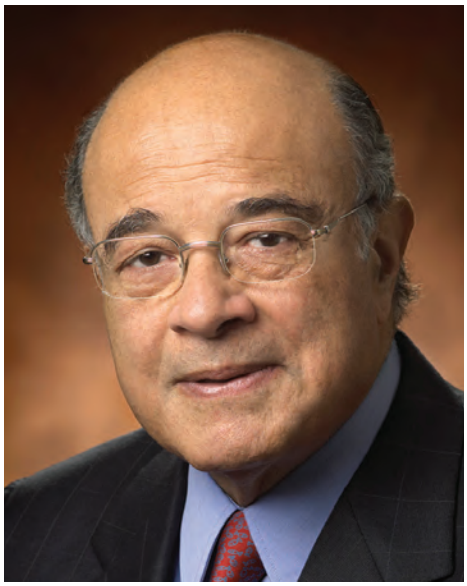
The vaccine world lost another of its great leaders recently with the passing of Adel Mahmoud, a physician, scientist, and professor who played a critical role in the development of many innovative and lifesaving vaccines during his long and successful career. He is remembered by his friends and colleagues as a tireless champion of public health and a warm, generous, and compassionate person.

"Dr. Mahmoud used the force of his magnetic personality and humanitarian values to drive the development and use of innovative vaccines—especially in places where they were most needed," says Julie Gerberding, Executive Vice President and Chief Patient Officer at Merck. Gerberding was previously president of Merck Vaccines, the same post held by Mahmoud from 1998-2006.

During this time, Mahmoud led the development and introduction of several new vaccines. These include the combination vaccine against measles, mumps, rubella, and varicella-zoster virus, the cause of chickenpox, as well as the shingles vaccine, known as Zostavax, which helps prevent the painful infection caused when the chickenpox virus re-emerges.

He also oversaw introduction of two new vaccines that have played a pivotal role in global public health. These vaccines are effective against rotavirus, a diarrheal disease that can be fatal in infants, and human papilloma virus (HPV), which is the cause of cervical, vulvar, and vaginal cancer in females, and anal cancer and genital warts in both males and females.

"His work has contributed to saving countless lives around the world," says Mark Feinberg, President and CEO of IAVI, who also held a position at Merck Vaccines as Chief Public Health and Science Officer prior to joining IAVI. "Adel was also an important advocate for a global focus on vaccine development and equitable access, including the importance of advancing HIV R&D."



Adel Mahmoud led the development of several new vaccines and "contributed to saving countless lives around the world."

Mahmoud served on IAVI's Board of Directors since 2012. He was a highly respected voice in the HIV vaccine field and was even tapped to become the inaugural head of the Global HIV Vaccine Enterprise in 2006 before he and the Enterprise's organizers decided their visions were not aligned (*Science,* Aug. 15, 2006).

Instead, he went on to become a professor at the Woodrow Wilson School of Public and International Affairs and the department of molecular biology at Princeton University, which is where he worked until his death on June 11th at age 76. While in this post, he became a vocal proponent for vaccines to prevent the many infectious disease threats facing the world today.

In 2015, following the largest and deadliest Ebola outbreak to date, Mahmoud was one of three prominent vaccine and infectious disease experts to author an article calling for the establishment of a global vaccine development fund (*N. Engl. J. Med.*, **2015**, 373, 297). In this commentary, Mahmoud, along with veteran vaccine developer Stanley Plotkin and Wellcome Trust Director Jeremy Farrar, argued that vaccine development was in crisis, owing to the complexity of existing infectious disease targets vaccinologists are facing, the declining number of manufacturers capable of making vaccines, and the current business model for the vaccine industry that emphasizes market potential.

"We consider an international vaccine-development fund to be urgently needed to provide the resources and the momentum to carry vaccines from their conception in academic and government laboratories and small biotechnology firms to development and licensure by industry," they wrote.

One such effort to usher new vaccines into development, the Coalition for Epidemic Preparedness Innovations (CEPI), did form partly in response to the 2014 Ebola crisis and is now funding vaccine research for its three initial priority pathogens (see page 20). If successful, CEPI may go part of the way to making Mahmoud's vision a reality, saving lives in the process.

In the meantime, those close to him mourn the loss of this great mind and person. "For those of us who were fortunate to have Adel as a friend, we know how much joy and positive energy he shared with us and how much we will miss his very special presence," recalls Feinberg. ■

RESEARCH NEWS

A fast track for vaccine development

Coalition awards US$174 million in grants for research targeting Nipah virus, Lassa fever, and MERS.

BY MICHAEL DUMIAK

The Coalition for Epidemic Preparedness Innovations (CEPI) has issued grants to a half-dozen biotech firms and non-profit organizations in its bid to accelerate vaccine development for priority pathogens. CEPI, which launched at the World Economic Forum in Davos last year with US$500 million in funding (see *IAVI Report*, vol 21, No.1, p.4), announced its first grants in March, April, and May of this year. The grants, totalling up to US$174 million, will go toward the development of vaccine candidates against Nipah virus infection, Lassa fever, and MERS, Middle East Respiratory Syndrome.

All of these conditions are potentially fatal, and there have been outbreaks this year of all three, says Richard Hatchett, CEPI's chief executive. Along with a current outbreak in Liberia, Nigeria had 400-plus confirmed cases and 100 fatalities due to Lassa fever as of April. There are currently small outbreaks of MERS in Saudi Arabia and the United Arab Emirates, as well as a Nipah outbreak in Kerala state in India. Each outbreak carries with it a small death toll but is nonetheless worrisome to public health officials. "It's underlined the unpredictable nature of these outbreaks and the importance of vaccines as a weapon in our armory," says Hatchett. "We want to advance the development of rapid-response platforms that would speed the development and manufacturing of vaccines," he says.

Profectus Biosciences and Emergent Biosolutions will be working together to advance a vaccine candidate to prevent infection with Nipah virus that was first developed 17 years ago by Christopher Broder, director of the Uniformed Services University. Broder says the only reason the Nipah vaccine candidate was never tested in humans was a lack of financial support. The CEPI-backed effort will be supported by the Jackson Foundation, the Uniformed Services University of the Health Sciences, and the international nonprofit PATH.

Efforts to develop vaccines against Lassa fever and MERS will be the purview of three organizations, including IAVI, which is pursuing development of a replicating vesicular stomatitis virus (VSV) vector-based Lassa vaccine candidate. CEPI's partnership with IAVI aims to not only advance the candidate but—in line with CEPI's mission to prepare against future pandemics—create a stockpile of effective vaccine. Initial funding for the project provides $10.4 million in support, with options to invest a total of $54.9 million over five years.

The vaccine candidate employs the same VSV vector used in Merck's Ebola vaccine with a Lassa virus glycoprotein insert. Merck's Ebola vaccine is not licensed yet, but was found safe and effective in humans when tested during the 2014-2015 Ebola outbreak. Health workers recently deployed this experimental vaccine in the Congo to guard against another potential outbreak of the Ebola virus.

"IAVI has been working for a number of years on the VSV platform and vector system for HIV vaccine development," says Mark Feinberg, President and CEO of IAVI. "In the effort to advance HIV vaccine development, we have built partnerships, technical expertise, and platforms that have the potential to contribute to broader public health that goes beyond HIV. To ensure the maximum contribution and the sustainability of that network, there's value in looking outward."

As former Merck chief public health and science

officer, Feinberg helped lead the effort to develop Merck's Ebola vaccine candidate. And it was the deadly Ebola outbreak in west Africa that spurred the development of CEPI itself, with the idea to act as a kind of insurance system against emerging pathogens in the event of future outbreaks.

Two life sciences firms will be lending their expertise to developing candidates against both Lassa fever and MERS, including two candidates that employ an antigen built using gene transcription. Inovio, a US-based infectious disease and cancer biotech, has a candidate against MERS that has gone through Phase I clinical trials, and a candidate against Lassa that has shown promise in nonhuman primate studies. Both candidates are DNA vaccines.

Austrian company Themis will bring its proprietary platform to bear in advancing vaccine candidates against Lassa and MERS through Phase II development. The Lassa fever vaccine candidate was originally developed at the Institut Pasteur, while the MERS candidate comes from the Paul Ehrlich Institut. The platform is essentially a measles vaccine vector that can be genetically modified to express proteins for a variety of pathogens.

Themis chief executive Erich Tauber says the measles vector has the capacity to incorporate large recombinant genes, and that both the Lassa and MERS candidates deliver their antigens to macrophages and dendritic cells. "They are the most potent antigen-presenting cells and trigger a specific immune response," Tauber says. "The measles vector can continuously replicate within the cell and express antigens even after immunization," which is why Tauber says the candidates are expected to confer long-term immunity.

"Emerging diseases pose a rapidly increasing threat to developing and developed countries alike. Climate change and mass tourism are fueling this raise in outbreaks worldwide."

Themis is also developing a Chikungunya vaccine candidate, which is currently in Phase II testing.

"Emerging diseases pose a rapidly increasing threat to developing and developed countries alike. Climate change and mass tourism are fueling this raise in outbreaks worldwide, which are no longer confined to tropical regions of the world," Tauber says. "There are no effective treatments or vaccinations available yet for many diseases, and vaccines are one of the most important, safe, and efficient interventions to protect people. We see it as an important mission."

Hatchett says CEPI has raised $630 million so far to support these efforts and is looking to continue raising more money and developing new partnerships. He says he expects that CEPI will have close to 20 vaccine candidates under development against priority pathogens by the end of the year. ■

Michael Dumiak, based in Berlin, reports on global science, public health and technology.

COMMENTARY

HIV vaccine efforts herald a new era of vaccinology

Mark Feinberg is President and CEO of the International AIDS Vaccine Initiative.

BY MARK FEINBERG, MD, PhD

We are at a defining moment in the history of HIV vaccine research. It is not an exaggeration to also propose that, thanks to the fruits of decades of HIV vaccine research and development efforts, we are entering a new era of vaccinology more broadly.

A new generation of HIV vaccine candidates is poised to enter clinical trials in the coming weeks and months, and these candidates are fundamentally different from those developed and tested in the past. These candidates are the result of a decades-long effort to understand the biology of HIV transmission and the nature of the immune responses mounted against the virus. While empiric-based approaches have dominated HIV vaccine development in the past, the vaccine candidates now entering human trials are designed based on hypotheses about how best to elicit specific immune responses, particularly broadly neutralizing antibodies. Scientists widely agree that inducing these broad and potent antibodies would be the best means of conferring protection against this virus and are pursuing multiple paths to achieve this goal.

The road to designing these vaccine candidates started with two key milestones—successfully engineering stable proteins that mimic the trimeric structure of HIV Envelope (and that enabled solving for the three-dimensional structure of the native HIV Envelope trimer), which is the target of all broadly neutralizing antibodies, and the identification of potent, broadly neutralizing antibodies in a small subset of infected individuals.

IAVI and our partners were one of the global collaborative teams that played a leading role in the identification of new broadly neutralizing antibodies and in describing how they develop in infected people. These antibodies are able to block infection with a wide range of genetically diverse variants of HIV in the laboratory, and have been shown to protect monkeys against a hybrid simian/human immunodeficiency virus (SHIV). This provides strong support that these are the types of immune responses we want to recapitulate with a vaccine.

Detailed structural analyses of how these antibodies interact with the virus unveiled multiple targets on the HIV Envelope for vaccine researchers to exploit. By applying cutting-edge technologies and methods in protein engineering, scientists are designing vaccine immunogens using a structure-based vaccine design approach. Through a detailed understanding of how such broadly neutralizing antibodies develop over time in infected individuals, the importance of engaging the initial B-cell populations expressing germline antigen receptors became clear. These germline B-cells represent the precursors from which broadly neutralizing antibody responses can eventually develop, and researchers are attempting to elicit them via specifically designed HIV vaccine immunogens. This work is the most sophisticated, elegant, and insightful vaccine science that has ever been done. And now, the first of these structure-based vaccine candidates, predicated on so-called "germline-targeting" approaches, as well as some of the native-like trimeric proteins, will soon be tested for the first time in human volunteers. Stepping back from a specific focus on HIV vaccine

development, it is clear that these studies represent the start of a new era for how vaccine immunogen design and development programs will be rationally approached for a wide range of infectious disease targets in the future.

While these first-generation candidates are unlikely to induce broadly neutralizing antibodies by themselves, we will be able to get a clear indication of whether they are on the right track early on in clinical development. This is another promising aspect of these hypothesis-driven approaches. Even in Phase I studies, the earliest studies of the safety and immunogenicity of a vaccine candidate, we will be able to tell whether the vaccine is achieving its intended goal. With empirical vaccine approaches—especially when a clear correlate of protection is not available from preclinical studies—it was only when a vaccine candidate advanced to large-scale efficacy trials involving thousands of people that we would find out whether or not it worked. The goal with this new generation of candidates is to utilize data from the initial clinical trials to not only determine if the approach being pursued is working as intended, but to also inform how to refine and improve the candidates much faster and much earlier in the development process.

Meanwhile, researchers are exploring whether the crop of recently identified broadly neutralizing antibodies can be used directly to either prevent or treat HIV infection. There are already studies testing the efficacy of passively administered broadly neutralizing antibodies to prevent HIV infection, and several other antibodies with greater breadth and potency and longer half-lifes are also in development. While we work to develop an efficacious vaccine, these antibodies may provide an additional tool to help reduce infection rates, and one that could be available sooner.

While the effort to develop an HIV vaccine has yielded many disappointing results, tremendous scientific progress has been made and will continue to be made as these rationally designed vaccine candidates enter clinical trials. This is not to say a vaccine is right around the corner. The path is still going to be long and likely complicated, and there will probably be surprises and disappointments along the way, but we now have a much better understanding of what it will take to make an HIV vaccine.

Success can't come soon enough. We need new ways to stop the spread of HIV if we are going to successfully end this epidemic. There has been tremendous progress in making treatment more widely available, but unfortunately, the rates of new infections have not fallen appreciably. Only about half of the people who need treatment are currently receiving it, and there are still about two million people becoming infected each year who will need treatment for the rest of their lives. We need to do everything we can to make sure that as many people as possible are able to access life-saving antiretrovirals, but treatment alone is not going to end this epidemic. Ending it will require maximizing treatment availability and developing and providing broad and affordable access to new innovations to prevent HIV infection. The only way an epidemic has ever been eliminated or eradicated in human history is with a vaccine. We will need one to end AIDS. ■

This work is the most sophisticated, elegant, and insightful vaccine science that has ever been done.

Upcoming HIV-related meetings

JULY 2018

10th International Workshop on HIV Pediatrics
July 20-21; Amsterdam, Netherlands
http://www.virology-education.com/event/upcoming/10th-workshop-hiv-pediatrics

22nd International AIDS Conference
July 23-27; Amsterdam, Netherlands
https://www.aids2018.org

SEPTEMBER 2018

21st Annual United States Conference on AIDS (USCA)
September 6-9; Orlando, Florida
http://2018usca.org

Australasian HIV & AIDS Conference 2018
September 24-26; Sydney, Australia
http://www.ashm.org.au/Conferences/conferences-we-organise/the-hiv-aids-conference

OCTOBER 2018

4th Central and Eastern European Meeting on Viral Hepatitis and Co-Infection with HIV
October 11-12; Prague, Czech Republic
http://www.virology-education.com/event/upcoming/4th-central-eastern-european-meeting-viral-hepatitis-co-infection-hiv

9th HIV & Aging Workshop 2018
October 1-2; New York, NY
http://www.virology-education.com/event/upcoming/9th-international-workshop-hiv-aging-2018

20th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV
October 13-14; New York, NY
https://www.intmedpress.com/comorbidities

2nd International Conference on Sexually Transmitted Diseases, Infections and AIDS
October 17-18; Las Vegas, Nevada
https://www.poz.com/event/2nd-international-conference-on-sexually-transmitted-diseases-infections-aids

For a full list of meetings and their descriptions, go to *www.iavireport.org/meetings.*