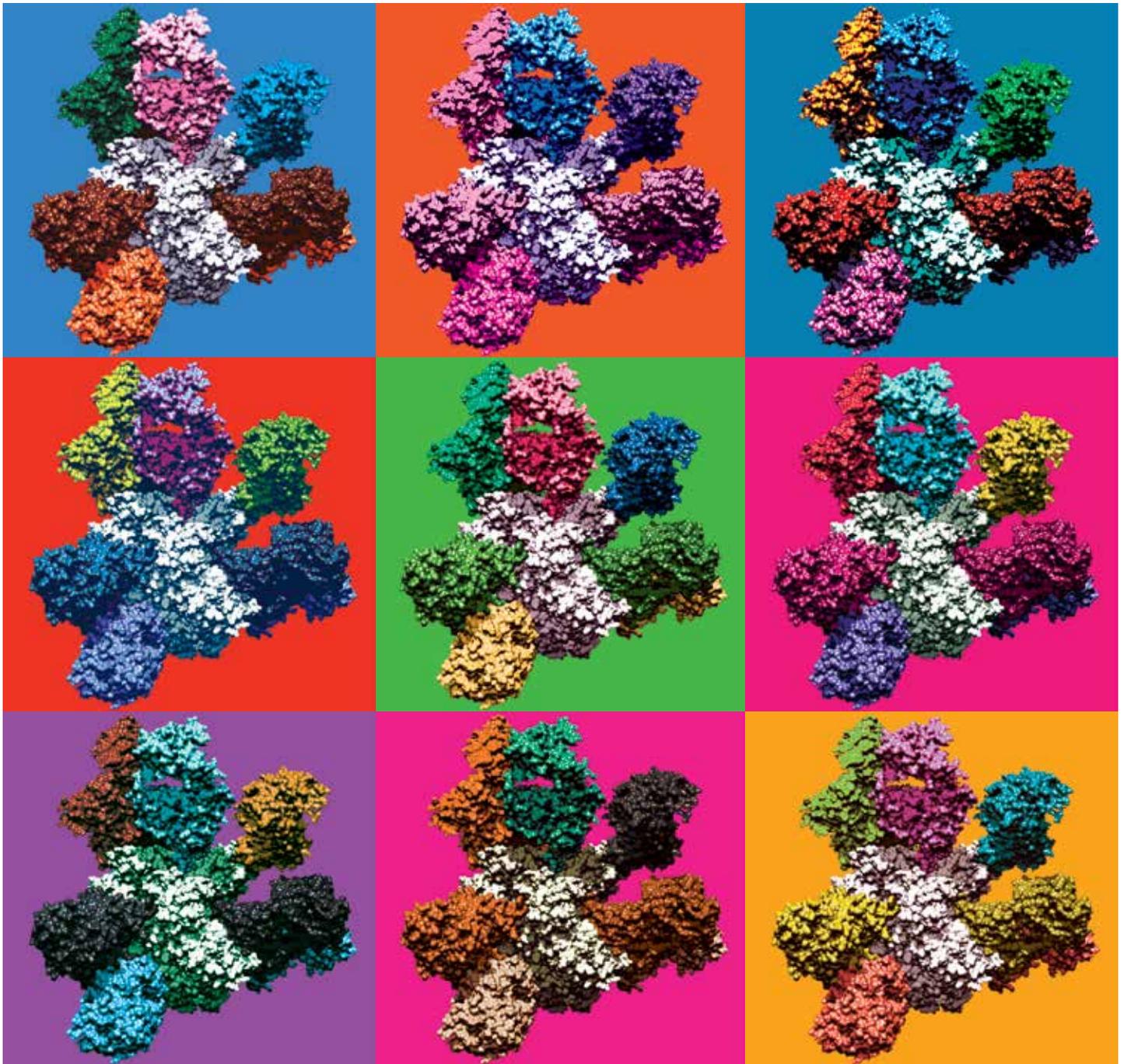


# IAVI Report

The Publication on AIDS Vaccine Research

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## FROM THE EDITOR

**If you are a regular *IAVI Report* reader**, it will come as no surprise that antibodies, particularly those that are both potent and able to neutralize a broad swath of global HIV isolates, are all the rage. Such antibodies have been isolated in droves from HIV-infected people and are now fueling vaccine design efforts. They are also being improved, combined, and tested for their ability to directly prevent, treat, or even cure HIV infection. Meanwhile, researchers continue to isolate additional antibodies, some of which appear to be able to neutralize even more broadly than any others identified to date.

As a result of this progress, scientists are more optimistic than ever that they are on the path to developing HIV vaccines and antibody-based products. The hope is that vaccines and antibody-based prevention, if successfully developed, could finally curb the persistently high HIV incidence rates that have led the Joint United Nations Programme on HIV/AIDS to declare that we are in the midst of an HIV prevention crisis (see page 4).

I've actually never seen more optimism for vaccines than at the recent HIV Research for Preven-

tion (HIVR4P) conference in Madrid, Spain (see page 16). There are now several vaccine candidates in clinical development designed to induce broadly neutralizing antibody responses that several experts at HIVR4P said are most likely to be protective. And nearly a dozen broadly neutralizing antibodies are in development for prophylaxis. In addition, new methods of vaccine delivery, including messenger RNA or mRNA, are in development (see page 7).

There are also two ongoing efficacy trials that are testing vaccine candidates that induce antibodies, which although not broadly neutralizing may still be effective at blocking HIV infection. Janssen Pharmaceutical Companies of Johnson & Johnson is leading one of these efficacy trials, and I recently spoke with Paul Stoffels, vice chair of the executive committee and chief scientific officer at J&J, about this trial and his company's dedication to HIV treatment and prevention research (see page 11).

With all this activity, it is hard not to share in the enthusiasm that is apparent in the HIV prevention field today. We hope you will too.

—KRISTEN JILL KRESGE

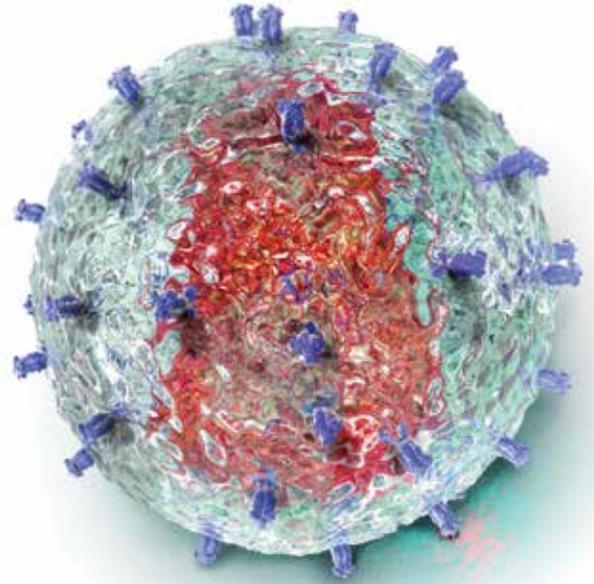


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## ON THE COVER

Taking inspiration from Andy Warhol, this cover image was designed to reflect the various ways researchers are attempting to develop vaccine candidates that can induce broadly neutralizing antibodies against HIV's trimeric Envelope protein. The image we've used as inspiration is the ConMSOSIP trimeric protein (shown in white) developed by researchers at Amsterdam University's Academic Medical Center. This native-like trimer is one of several trimers, and more than a dozen vaccine immunogens that are currently in clinical development, which are designed to induce broadly neutralizing antibodies. The original image was provided by Alba Torrents de la Pena, a PhD student in the lab of Rogier Sanders, a professor of virology at the University of Amsterdam and an adjunct associate professor of research in microbiology and immunology at Weill Cornell Medicine.

# Is there an HIV prevention crisis?

More HIV-infected people than ever before are receiving life-saving treatment. Despite this progress, HIV incidence rates remain virtually static.

BY MICHAEL DUMIAK

The calculus to end the world's HIV epidemic is, once again, proving harder than expected.

After marshaling great effort and achieving remarkable results in diagnosing HIV infections and providing life-saving antiretroviral treatment (ART) to those infected, the message from the Joint United Nations Programme on HIV/AIDS (UNAIDS) in recent years seemed to be that the road to ending AIDS was in sight, and could even be achieved by 2030. The idea was that by diagnosing and treating enough HIV-infected people, and making sure their levels of virus were sufficiently suppressed, transmission rates would tail off.

But this strategy, referred to as treatment as prevention, is more complicated than it sounds. "Easy to remember, hard to achieve," says virologist Jeffrey Lazarus, a health systems researcher at the Barcelona Institute for Global Health.

UNAIDS and its partners set goals for treatment as prevention back in 2014 referred to as the 90-90-90 targets. The model works like this: diagnose 90 percent of all HIV-infected people, ensure 90 percent of those people receive ART, and make sure that 90 percent of those on treatment achieve viral suppression. The U.N. goal is to reach those targets by 2020, with the aim of ending HIV as a global health challenge by 2030.

But with just two years to go, only six countries—Cambodia, Denmark, Botswana, Namibia, Eswatini (formerly Swaziland), and the Netherlands—have reached those targets.

Even more concerning is the fact that in some places, HIV infection rates are increasing despite greater access to ART. That's not all. "There are countries that have reached the targets," Lazarus says, "but a surprisingly large percentage of people who are on treatment are not virally suppressed."

UNAIDS officials themselves now doubt the 2020 targets will be reached and are talking about a "prevention crisis." As outlined in a UNAIDS report (<http://www.unaids.org/en/resources/documents/2018/global-aids-update>), there are many contributing factors: In Eastern Europe, Central Asia, the Middle East, and North Africa, HIV incidence is on the rise; there is an ongoing global migration of refugees and asylum seekers, people fleeing both violence and poverty; and if demographic trends in Africa continue, there will be more people aged 15-35 living there by 2050 than ever before. If public health services and prevention efforts do not meet the scale of this demographic wave, new HIV infection rates could balloon.

The progress in HIV treatment is clear. More than half of the world's 36 million people living with the virus are now on life-saving ART, and the number of AIDS-related deaths is declining, dropping 34 percent over the last seven years. In 2017, for the first time, the number of deaths from AIDS is estimated at less than a million.

But the rate of new HIV infections is not falling fast enough. While fluctuating regionally, global incidence has remained fairly steady during the last 15 years. If the number of new infections is not declining quickly enough, the number of people in need of treatment continues to grow every year.

All of these factors place the HIV/AIDS response in a precarious position. Some say an overly optimistic message instilled complacency in the global HIV response. Meanwhile, experts are calling for bolstering HIV prevention efforts and developing newer and better prevention options as a way to finally reverse the trends ([https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(18\)31070-5/full-text](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31070-5/full-text)). "Existing HIV tools and strategies are insufficient to actually end the epidemic," Peter Piot told a large crowd in an auditorium in Amsterdam over the summer, gathered for the International AIDS Society's (IAS) annual meeting. Now director of the London School of Hygiene and Tropical Diseases, Piot was director of UNAIDS during a high-level

meeting 15 years ago in Dublin, when there were already warning signs that Eastern Europe and Central Asia would become the fastest-growing AIDS epidemic in the world.

It did.

This, despite a 53-nation declaration pledging to scale up prevention and treatment efforts in the face of rapid crossover from high-risk groups into the general population. The number of new HIV infections in Eastern Europe was 190,000 in 2016—a 57 percent annual increase over the previous five years.

These statistics once again have the eyes of the global public health community trained on the vast landscape stretching from the Baltic to the Pacific. At the IAS conference this summer, there was a concerted effort to focus on Eastern Europe and Central Asia. Michel Kazatchkine, a onetime U.N. Special Envoy on HIV/AIDS in Eastern Europe and Central Asia, describes a situation in which many people do not know their HIV status, there is little sex education or primary prevention, and where HIV is tightly intertwined with tuberculosis and viral hepatitis. “The whole thing is very fragile,” he says. “With the huge backlog we have and the burden of disease, it will be very difficult to reverse.”

Michael Krone, executive coordinator of the Berlin-based HIV nonprofit AIDS Action Europe, sees it acutely in social terms. “The value of the lives of drug users, sex workers, gay men and other men who have sex with men, trans people, and other minorities is not estimated to be as much as those of other citizens,” he says. Data compiled by UNAIDS shows that of the 30 percent increase in new HIV infections in the region since 2010, nearly 40 percent were among injection drug users and 97 percent were among sex workers, prisoners, sexual partners or clients of sex workers, and men who have sex with men. Consistently reaching these individuals with public health or prevention and harm reduction services—needle exchange, testing and counseling, hepatitis B vaccination, treatment for tuberculosis, and HIV treatment—is difficult, and is made even more difficult because of stigma, state actions that limit access to health care services and information, and broader social pressure.

“The emerging data really call for immediate action to link and integrate HIV services with other services, particularly for people who inject

drugs in the region,” says Chris Beyrer, a Johns Hopkins epidemiologist and a former IAS president. “All of this is going to be crucial for Eastern Europe and Central Asia. The work that is ahead of us is trying to do better delivering essential services to those people who need them most.”

Without a substantial investment in primary HIV prevention, particularly for key populations, young adults, and adolescents, it will be impossible to control the epidemic, analysts at the Joep Lange Institute in Amsterdam argue. “We don’t have a vaccine. But we have most of the tools: we have highly efficacious treatment, rapid HIV tests, syringe exchange, condoms, and PrEP [pre-exposure prophylaxis],” Lazarus says. “The question is, do we have the tools in Tajikistan. Do we have the tools in middle America?”

Eastern Europe is not the only obstacle to ending HIV. Sub-Saharan Africa is still home to two-thirds of the 37 million people living with HIV around the globe. Even there, where rates of new infections are falling, experts warn the situation is likely to worsen in coming years. Sub-Saharan Africa will soon have more young people than ever entering adolescence and young adulthood, Piot says. Aleya Khalifa, statistics officer for HIV/AIDS at UNICEF, has compiled data and is running models suggesting the region will be unlikely to reduce new infections in people aged 15-24 because this youth bulge will double the adolescent population by 2050. Khalifa’s modeling suggests new infections in those aged 15-19 will still be about 200,000 annually by 2030, the year targeted for ending the epidemic.

Harvard virologist Max Essex, who chairs the Botswana Harvard AIDS Institute Partnership, argues the math behind 90/90/90 makes sense and that it may just be taking time for this strategy to have its desired effect. “I’m very optimistic for places like Botswana, Namibia, South Africa, and Swaziland (now called Eswatini),” Essex says. He and a large team surveyed Botswana’s progress in achieving the 90/90/90 targets (*Lancet HIV* 3, e221, 2016). “The very imperfect estimates I’ve seen are compatible with incidence going down there,” he says. “Many critics misinterpret and think we should see major, statistically significant reductions in incidence within a year or two. I think this is unrealistic. I’m not a fan of the phrase ‘ending AIDS.’ It is so confusing to many.”

Reuben Granich, a Geneva-based public health consultant and former chief technical officer at the International Association of Providers of AIDS Care, worked on launching the “Fast Track Cities” program, which hinges on the 90/90/90 targets. He doesn’t think much of the “HIV response is faltering” narrative. “The recent wave of pessimism from HIV experts is a bit odd given the successes that we have seen,” he says. “We can reduce the epidemic to more manageable proportions that will then be amenable to last-mile tactics and strategies.”

Meg Doherty, the World Health Organization’s treatment and care coordinator for HIV and hepatitis, points to countries with declining HIV incidence. “Even South Africa is showing declines in incidence,” she says. But the epidemic is variable. “What we can see is there is a slowdown in [declines in] mortality and that we have to redouble our efforts and figure out why people are still dying,” she says. “It’s going to be about a few regions and a few countries. It is likely to be in more marginalized populations.”

A few years ago the infectious disease modeler David Wilson in “A Reality Check for Aspirational Targets to End HIV,” warned that if diagnosis rates and prevalence

remain constant, as they have in many settings, then prevalence and incidence could actually increase while pursuing the 90-90-90 targets. “Increasing numbers of case reports and overall increases in numbers of new infections do not mean the test-and-treat strategy is failing, but simply that the strategy and targets are not consistent with large reductions in absolute numbers of new infections,” Wilson wrote (*Lancet HIV*, DOI:[https://doi.org/10.1016/S2352-3018\(14\)00038-1](https://doi.org/10.1016/S2352-3018(14)00038-1)). His view today is the same. “It is just not surprising that the global impact has not quite met what was optimistically hoped for,” Wilson says. “That there are hot and cold spots of epidemics and targeted responses is hugely important.”

Piot recognizes the need after four decades of HIV for a long-term view. “Tens of millions of people will require access to ART for decades. *Decades*. So, this is not going to stop in 2030,” he says. “Let’s not fool ourselves. The end of AIDS will not be possible without a vaccine. In the meantime, we will do as well as we can. The good news is that there is exciting news in terms of vaccine development, so let’s continue that effort.” ■

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

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## On the move

A sharp increase in the scope and reach of human migration is affecting the HIV epidemic and the public health response to it. The Joint United Nations Programme on HIV/AIDS (UNAIDS) says migration places people in situations that increase their risk of acquiring infection. Irregular immigration status, language and cultural barriers, out-of-pocket health care costs, difficult-to-access health services, and policies that exclude migrants pose additional hurdles. As a result, migrants diagnosed with HIV are more likely to present late for treatment and care. Ana Tavares and her colleagues at the New University of Lisbon reviewed dozens of epidemiological studies and found migrant populations are also disproportionately affected by HIV and tuberculosis co-infection (*PLoS One* 12(9), 2017).

In Western Europe and Germany, recent focus has been on migration from the Middle East and sub-Saharan Africa via Libya and Greece. In Eastern Europe the migratory flows are different but just as strong, if not more so. Central Asia and the Russian Federation now show significant intra-regional migration, becoming one of the largest labor corridors in the world, according to reporting from the United Nations Population Fund presented in Kazakhstan earlier this year. Hundreds of thousands of migrant workers are setting out from Central Asia into Russia.

“People on the move in Western Europe are a different group as to labor migrants in Russia and Central Asia,” says Ljuba Böttger, communications coordinator for AIDS Action Europe. In the European Union, asylum seekers may not want to get regis-

tered until they arrive at their intended destination. If they are unregistered, though, they cannot gain state-sponsored health-care services. “In Russia, labor migrants may want to stay until their work is done and then they move along or go back to their origin countries and again migrate to another place. In this case, some people are legal, but they do not have free access to health care,” Böttger adds. Michel Kazatchkine, former director of the Global Fund to Fight AIDS, Tuberculosis and Malaria and onetime U.N. Special Envoy on HIV/AIDS in Eastern Europe and Central Asia, cites figures from newly diagnosed HIV infections in Armenia: 65 percent are among people who have gone to Russia for work. In Uzbekistan the figure is 30 percent. “Clearly, we have a factor of vulnerability,” he says.

# Coding for protection

Although challenges remain, the growing field of mRNA-based vaccine development seems to have a bright future, with potential for preventing cancer, flu, and HIV.

BY MICHAEL DUMIAK

Proteins are what make living creatures what they are. They form the building blocks and spark the molecular reactions fundamental to life, including the creation and management of the immune system, which keeps us protected from disease. The production of proteins hinges on single molecular strands of nucleic acids called messenger RNA, or mRNA. Strands of mRNA in cells act as couriers—hence messengers—carrying instructions, a recipe of sorts, to the ribosomes, where proteins are actually made.

What if you could make mRNA instruct ribosomes to make whatever protein you wanted? This is the concept driving a growing number of researchers who are working on mRNA as a potential therapy or vaccine strategy.

Vaccines typically work by introducing a foreign substance, a non-harmful virus or bacteria, into the body to stimulate an immune response against it. Then, due to immunological memory, if that same pathogen is encountered again, the body can mount a quick and powerful immune response against it. If researchers could introduce custom-made mRNA into cells, the hope is they could direct the body to make specific kinds of proteins, thereby prompting an ongoing immune response against the cancer or pathogen of choice.

University of Pennsylvania immunologist Drew Weissman is compelled by the possibilities for mRNA, particularly when it comes to using this approach as a type of production engine for delivering vaccine immunogens. “We’ve got about 15 different pathogens currently under study,” he

says. “We think this is going to be the vaccine platform of the future.”

**Researchers have been** directly injecting mRNA into mice in an attempt to influence protein production since at least 1990, if not earlier. The most active branch of mRNA research started in a hallway in Philadelphia 20 years ago. There, at the University of Pennsylvania, the Hungarian biochemist Katalin Karikó, who was working in neurosurgery, met Weissman at the Xerox machine. She was working with mRNA, while he was working with dendritic cells and their role in stimulating immune responses by presenting antigens. “A couple of months later, we wrote our first proposal to the U.S. National Institutes of Health for immunization with mRNA encoding HIV-specific antigens,” Karikó says.

By 2010 the Harvard stem cell researcher Derrick Rossi and his team, drawing on the techniques developed by Karikó and Weissman, produced something remarkable—a glowing dot on a mouse leg. What was remarkable was that they made this glowing dot by engineering mRNA to code for a protein expressed in fireflies that produces the bioluminescence in the insect’s light-producing abdominal organ. Then they injected the mRNA directly into a mouse. The result, a glowing dot on the mouse’s leg, signaled that the animal was producing the bioluminescent protein as a result of its cells taking up the mRNA code.

The group then published research using modified mRNA to generate human pluripotent stem cells, which was one of *Time* magazine’s top 10

We think this is going to be the vaccine platform of the future.

scientific discoveries in 2010. It led Rossi to co-found the biotechnology company Moderna Therapeutics, where he remained on the scientific advisory board for the company's first four years. The company is now valued at US\$7 billion, with \$1.6 billion in capital.

What began with photocopies and fireflies is now a growing field that includes efforts in different stages of development targeting influenza, melanoma, prostate cancer, lung cancer, herpes, Zika, Ebola, respiratory syncytial virus, rabies, *Toxoplasma gondii*, and HIV, according to a review article by Norbert Pardi, a University of Pennsylvania research associate and medical professor (*Nat. Rev. Drug Discov.* 17, 261, 2018). It is still a nascent field but different systems are developing for different pathogens, and now researchers are focusing on optimizing techniques to boost safety and consistency. Most mRNA candidates so far are in preclinical development, but data is emerging from a few early-stage clinical safety studies.

**The process of introducing** engineered mRNA into the body starts with getting it into cells. Pardi, in his review, describes several methods of introducing mRNA solutions into the body, among them are nose drops; intradermal, intramuscular, subcutaneous, and intravenous injection; or injection directly into lymph nodes or the spleen. At the outset, researchers employed injections of naked mRNA. But naked mRNA, Pardi says, gets degraded by extracellular RNases, nucleases outside the cell that chop RNA into smaller components.

While naked mRNA still offers a potential avenue of inquiry, researchers are now much further along in developing what's called complexed mRNA, which is mRNA encapsulated in nanoparticles that protects it from degradation. Researchers are employing different solutions for different targets: negatively charged nanoemulsion or lipid nanoparticles for flu, hepatitis C, rabies, and HIV; or liposomes in a solution mixed with a protein called protamine for complexing mRNA for cancer therapies, for instance. Although scientists still do not fully understand the molecular mechanics involved, complexing does seem to aid in shielding the mRNA from the body's defenses and increasing cellular uptake.

Once inside cells, the magic happens. "The cells translate the RNA to protein, and the proteins do what they are supposed to do," Pardi says. If for instance the mRNA is introduced into dendritic cells, the intermediaries of the body's innate and adaptive immune systems, the information carried by the mRNAs could facilitate the production of proteins that would act as antigens and prompt an immune response.

Chemical and nanomaterials engineer Omar Khan, a former Massachusetts Institute of Technology researcher and now chief scientist at Tiba Biotech in Boston, sees broad applications for this approach. "It is neither a vector nor an antigen in the classic sense. We'd rather call it a versatile expression platform, useful for expression of all kinds of biomolecules, including antigens," Khan says. "Vaccines based on mRNA could be fantastically versatile, but correct delivery is an ongoing challenge. Technology that allows for efficient, effective, and safe delivery of the mRNA is what will really open up the field and bring it closer to the clinic."

Better techniques for creating RNA sequences, which make mRNA more translatable and stable, are helping. Purifying mRNA using techniques like liquid chromatography, which filters out detrimental mRNA strands, can yield a mix significantly more potent for producing protein in dendritic cells. Modifying the molecules that make up the mRNA code inhibits the induction of antiviral inflammatory immune responses, which could cause potential side effects and raise safety concerns.

The most advanced clinical studies involve an mRNA-based vaccine candidate for rabies being developed by CureVac, a biotech based in Tübingen, Germany. But there are many other companies, big and small, also actively pursuing mRNA-based therapies or vaccines. Another German company, Mainz-based BioNTech, is involved in mRNA platform research. Karikó is now a vice president at BioNTech, leading the company's mRNA-based protein replacement program. BioNTech recently engaged Weissman's lab to run a preclinical research program for mRNA vaccine candidates against infectious diseases. There are also a handful of others now in the field: Tiba, Translate Bio, eTheRNA, and Moderna Therapeutics.

Moderna is running Phase I safety trials of mRNA-based vaccine candidates against cytomegalovirus, chikungunya virus, Zika, and metapneumovirus. Influenza virus is also drawing interest: the most recent flu season killed 80,000 people in the U.S. alone, the highest death toll in more than 10 years, and researchers are in pursuit of new formulations for a more universal flu vaccine (see *A Mean Flu Season Swings a Spotlight on Vaccines, IAVI Report*, Vol 22, No. 1, 2018). “I’m very optimistic for flu vaccine. I think it’s doable,” Pardi says. Weissman and Pardi are testing a nucleoside-modified mRNA vaccine candidate targeting the hemagglutinin stalk of influenza, a less variable target on the virus. So far they’ve been able to induce immune responses in mice, rabbits, and ferrets (*Nat. Comms.* 9, 3361, 2018). CureVac and Moderna are both pursuing mRNA-based flu candidates, as is BioNTech.

Larger pharmaceutical companies are also becoming involved in mRNA research, mostly through deals with biotechs. Earlier this year, BioNTech announced a licensing and equity deal potentially worth up to \$425 million with Pfizer to partner on the company’s flu vaccine development efforts. Eli Lilly is collaborating with CureVac on its cancer vaccine candidates targeting tumor neoantigens, which are fragments of protein found on cancer cells. The Bill & Melinda Gates Foundation is investing \$52 million into CureVac to support construction of a vaccine manufacturing facility and will separately fund the firm’s development efforts for vaccines against infectious diseases.

This enthusiasm, as well as the money and brainpower being invested in this approach stem from mRNA’s attractive qualities. “Since RNA is injected into the host and the host makes the protein, you can be more certain that these proteins will be functional and properly folded,” Pardi says. “That is a really important thing.”

Another quality that makes mRNA advantageous is its persistence. Weissman and Pardi worked on a Zika mRNA candidate, giving a single dose in an experiment with macaque monkeys, and found that the neutralizing antibody levels induced by the candidate remained steady after a year. Other candidates required two or three shots to gain the same level of neutralizing antibodies required to

protect against Zika virus, Weissman says. The team first gave mice single-dose intradermal injections of an mRNA-based vaccine candidate encapsulated in lipid nanoparticles. The mRNA carried the code for pre-membrane and envelope glycoproteins from a Zika strain isolated in the 2013 outbreak. The vaccine elicited Zika-specific CD4<sup>+</sup> T-helper cells and neutralizing antibody responses. The team followed this experiment in mice with a monkey study using the same candidate (*Nature* 543, 248, 2017).

The mRNA platforms appear to also offer advantages in terms of safety and speed of production, and these are significant, Weissman and Pardi say. “It’s two reactions to make and purify the RNA and you are done,” Weissman says.

The mRNA platforms also promise rapid optimization and on-demand production, making them well suited for rapid responses to emerging pathogens. “If you are in an epidemic and need to get a vaccine to people rapidly, I think mRNA has a lot of advantages. The fewer steps you have to get to an immune response the better,” says Wayne Koff, who heads the Human Vaccines Project and was formerly chief science officer at IAVI. Moderna is now a partner of the Human Vaccines Project.

**Efforts to develop** mRNA-based vaccine candidates are further ahead for pathogens such as flu, rabies, and Zika viruses than for HIV, which poses unique challenges. Researchers cite, as they often do, its rapid mutability as one obstacle. Weissman says another is designing an effective and mature antigen. Antibodies that are broadly effective against HIV are often themselves highly mutated in order to bind to and neutralize an ever-mutating, sugar-covered virus. Coding mRNA to replicate this is a complex challenge.

But while it may be challenging, several research groups are pursuing it. The ongoing work ranges from designing potential vaccine candidates to so-called passive injection strategies to experimental cure research.

Xun Sun, formerly at University of Pennsylvania and now a researcher at Sichuan University’s Key Laboratory of Drug Targeting and Drug Delivery Systems, led a team employing cationic micelles—

ionized molecular particles formed in a liquid—to complex and deliver mRNA to dendritic cells in mice. Results showed a detectable immune response specific to HIV’s Gag protein (*Drug Deliv.* 23(7), 2596, 2016). Pardi, Weissman, and colleagues, including Karikó when she was still at University of Pennsylvania, injected mice with naked mRNA that had been engineered in the lab and encoded for the HIV Envelope (Env) protein gp160, along with an adjuvant solution. The team used this as a prime, administered in two doses, and then boosted with an intramuscular injection of Env protein. Even given the potential drawbacks posed by using naked mRNA, the team was able to detect an immune response in antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the mice (*AIDS Research and Human Retroviruses* 30, A249, 2014).

Weissman is currently working with stabilized HIV cell surface trimers for use as immunogens in combination with an mRNA-in-nanoparticle solution. His team also works closely with Bart Haynes’ group at the Duke Global Health Institute to develop novel immunogens for testing as experimental HIV vaccines. And within the Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID), Weissman’s team works with an adjuvant development discovery team at Beth Israel Deaconess Medical Center to optimize the immunogenicity of its vaccine candidates. Weissman and Pardi did their one-shot Zika experiments in collaboration with CHAVI-ID, and Haynes says there are more possibilities for collaboration.

“Our general experience is that the mRNAs are doing quite well,” Haynes says, with immunogen designs including Env trimers, gp160 Env proteins, Env proteins that might induce non-neutralizing antibodies—similar to what researchers discovered during the RV144 trial—and others. “We’re working hard to learn how best to use mRNA to express [HIV] Envelope,” he says. “We’re moving rapidly to be able to make mRNA in lipid nanoparticles at our facility here.” Haynes wants to be able to quickly assess immunogenicity of the mRNA constructs in Phase I clinical trials.

Weissman also thinks research results point the way for mRNA as a potential platform for so-called “passive” transfer of HIV-specific broadly neutral-

izing antibodies (bNAbs) as a way to prevent HIV infection. Weissman, Pardi, and the University of Pennsylvania team worked with Acuitas Therapeutics of Vancouver in deploying a lipid nanoparticle solution carrying modified mRNA encoding for VRC01, one of the first bNAbs of many isolated in recent years that are giving researchers high hopes for developing new vaccine candidates or antibody-based prevention products.

Weissman and his group showed that weekly injections of the VRC01-encoded mRNA caused humanized mice to produce levels of antibody maintained at 40 micrograms per milliliter of blood, and that the translated antibody from a single injection can protect the mice from HIV challenge (*Nat. Comms.* 8, 14630, 2017).

mRNA also has the attention of researchers pursuing an HIV cure. The Belgian eTheRNA is part of a European Commission-funded group, including the AIDS Research Group at the August Pi Sunyer Biomedical Research Institute (IDIBAPS) in Barcelona and the Free University of Brussels, that over the last five years developed and conducted tests of an mRNA-based therapeutic vaccine. Twenty-one HIV-infected volunteers were enrolled in a Phase I safety trial, which indicated the group’s formula was safe and well tolerated (*AIDS* 32(17), 2533, 2018). The group went on to launch a Phase IIa immunogenicity trial with 34 volunteers, the results of which are now under analysis and should be available soon, says IDIBAPS infectious diseases service team leader and project coordinator Felipe García.

**In reviewing the field,** Pardi injects a good dose of caution. “When I talk to company people, they are usually very, very optimistic that mRNA is the best and it’s going to work everywhere. I’m much more cautious because it has turned out so many times—DNA vaccines are probably a good example—that they work very well in mice and then they didn’t work well in people,” he says. “I always emphasize that I’m very cautiously optimistic and really want to start as many clinical trials as possible. Then we will judge if mRNA is really so good or needs to be improved. The next few years will answer this question.” ■

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

## INTERVIEW

# An industry leader in HIV research

Paul Stoffels of Johnson & Johnson talks about the company's broad HIV portfolio and the role of industry in advancing vaccine research.

BY KRISTEN JILL KRESGE

“At a certain point you have to jump and hope that it works,” says Paul Stoffels, vice chair of the Executive Committee and chief scientific officer at Johnson & Johnson (J&J), describing the informed risk the company is taking, with its partners, to test a novel HIV vaccine candidate in an ongoing efficacy trial. Given Stoffels’ successful career, this strategy must be working.

After pursuing medical training in his home country of Belgium, Stoffels began his career as a young physician working in Africa. This is where he was first introduced to HIV/AIDS and its devastating consequences. He then went to work with a fellow Belgian doctor, Paul Janssen, who was the namesake of Janssen Pharmaceutica. Working together, Janssen and Stoffels began researching HIV medicines. Stoffels then became chief executive officer of Virco and chairman of Tibotec, two companies he co-founded with his business partner Rudi Pauwels. While at these companies, Stoffels and colleagues developed several antiretroviral drugs that are widely used today to treat HIV infection.

In 2002, J&J acquired Tibotec and Virco, and Stoffels joined J&J. Today, he oversees the company’s research and development pipeline and also steers their global public health strategy, which aims to make the medicines and technologies developed by the company available to the world’s poorest and most vulnerable populations. He is also credited with spurring innovation within the company by focusing on strategic partnerships, in-licensing, and acquisitions.

“Paul’s dedication to global health innovation is truly admirable, heartfelt, and deep,” says Mark Feinberg, president and CEO of IAVI. “He is a great example of how visionary and committed phar-

maceutical industry leaders can make major contributions to developing biomedical innovations and new partnership models to address major public health challenges such as HIV and tuberculosis that disproportionately impact people living in low-income countries.”

The Janssen Pharmaceutical Companies of Johnson & Johnson are heavily invested in infectious disease research, including programs for HIV/AIDS, tuberculosis (TB), Ebola, polio, and respiratory syncytial virus (RSV). Their HIV portfolio includes three licensed antiretroviral drugs; a long-acting injectable antiretroviral that is being developed in partnership with GSK/ViiV Healthcare, which recently showed promise in a Phase III clinical trial; and an experimental vaccine regimen developed in collaboration with academic and U.S. government researchers that is now being tested for efficacy in a Phase IIb trial in Southern Africa (see *The Imbokodo Phase IIb HIV vaccine trial*, p. 13).

Dan Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center, who helped develop and test this HIV vaccine regimen in collaboration with Janssen scientists, recognizes Stoffels’ critical role in this work. “Paul is an incredible leader of a fantastic group at Janssen. He is brilliant, passionate, insightful, and extremely effective. The HIV vaccine program would not have advanced to where it is today without Paul’s strong support,” says Barouch.

J&J also developed the first drug licensed to treat multidrug-resistant strains of TB, known as bedaquiline. I spoke with Stoffels recently, just after he returned from attending the United Nations General Assembly high-level meeting on TB, about his career, the role of partnerships in advancing infectious disease research, J&J’s HIV and TB programs, and the hope for eventually defeating this deadly duo.



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I have been doing drug and vaccine development for 25 years and I believe that industry has the platforms, resources, and capabilities needed to translate innovative ideas and basic science into solutions for people in need.

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**How did you first become involved with HIV/AIDS?**

I became involved in HIV in the early days, first as a medical student and then as a physician when I spent several years in Africa. My first time in Africa was in 1983, and then I was at a hospital in Kinshasa and I saw a lot of patients diagnosed with HIV. They were the very first patients who were diagnosed and you saw then, already, that it was a catastrophic situation. Then I lived and worked for three years in Congo and one year in Kigali, Rwanda, between 1987 and 1990. That was in the middle of the big outbreak of HIV on the African continent and where I first actually met patients with HIV and saw the challenges they faced.

**Fast forward to today. How would you describe both your personal commitment and Johnson & Johnson’s commitment to tackling HIV?**

Well, my personal commitment really began in my early days as a physician and that first exposure to HIV in Africa. Since then I’ve worked with HIV pretty constantly throughout my career. I worked with Dr. Janssen first in the early 1990s on new molecular drug designs for HIV and then I left the company to start my own companies, Tibotec and Virco, with Rudi Pauwels, my business partner. These two companies discovered

and developed a few HIV medicines and then they were acquired by Johnson & Johnson, at which time I joined J&J, leading their HIV program.

J&J and Janssen have three main HIV drugs: Prezista, which is a protease inhibitor also known as darunavir; the non-nucleoside reverse transcriptase inhibitor [NNRTI] Intelence, also known as etravirine; and the second-generation NNRTI Edurant, which is also called rilpivirine. All three medicines were developed initially at Tibotec and are now used in first-line, second-line, and third-line treatment regimens in combination with other drugs. So we still have a very active business and are also active in HIV research, including a vaccine candidate that is now being tested in an efficacy trial in Africa.

**Part of your role at J&J is steering the global public health strategy. What does that strategy entail and how do you view this component of your work?**

If you want to implement programs to treat diseases like HIV and TB, you have to have people on the ground to help with training and implementation. These things don’t happen automatically with new drugs, especially if you have complicated medicines, like second-line therapies for HIV. So we set up our global public health team to be fully dedicated to developing and ultimately supporting access to medicines and devices that have an important impact in

the developing world. Right now we have about a hundred people on our global public health team—including colleagues in Africa and Asia, who work with the local companies we have in the countries.

There are four key global public health priorities we are tackling at the moment. One is in the availability of our HIV drugs, which we deploy in Africa through generic companies, or directly ourselves. We also have a big program in TB, through which we are bringing bedaquiline to treat multidrug-resistant TB in all countries that have a high need, and the vast majority of those are in the developing world. Then we have a mental health program to evaluate whether new long-acting antipsychotics can be helpful in treating patients on the African continent. Finally, we are working to lessen the burden of intestinal worms in children through our mebendazole donation program.

We also have a collaboration between our global public health and vaccine programs to conduct clinical trials. As we speak, we have 11 clinical trials running around the world, some of which are in Africa. We have an HIV vaccine that is being tested in Southern Africa, and we also have clinical trials ongoing for new vaccines against Ebola,

Zika, polio, respiratory syncytial virus (RSV), and drug-resistant forms of the bacteria *E. coli*.

**You mentioned the ongoing Phase IIb HIV vaccine trial. J&J is also involved in development of the vaginal ring containing the antiretroviral dapivirine. What role do you think pharmaceutical companies should have in HIV prevention research, particularly in vaccine research and development?**

I have been doing drug and vaccine development for 25 years and I believe that industry has the platforms, resources, and capabilities needed to translate innovative ideas and basic science into solutions for people in need. However, at the same time, research and development can be a slow, long process, and you may never get to an approved product. So there have to be collaborations and partnerships between the public sector, not-for-profits, and industry to keep the momentum going.

At J&J we have about 10,000 people in R&D, so we have all kinds of capabilities to deploy, whether it's statistics, clinical trials, pharmacology, vaccine platforms, antibody knowhow, or developing long-acting formulations. All these technologies and platforms can be used for both treatment and prevention.

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## The Imbokodo Phase IIb HIV vaccine trial

The Janssen Pharmaceutical Companies of Johnson & Johnson is sponsoring a Phase IIb efficacy trial called Imbokodo (HVTN 705/HPX2008) that is testing an experimental HIV vaccine regimen in 2,600 women in Southern Africa.

The trial is co-funded primarily by Janssen, the Bill & Melinda Gates Foundation, and the NIH's National Institute of Allergy and Infectious Diseases. Other partners include the U.S. Military HIV Research Program, the Ragon Institute, the HIV Vaccine Trials Network, and the South African Medical Research Council.

The vaccine regimen consists of an adenovirus serotype 26 (Ad26) viral vector-based

candidate that carries a tetravalent mosaic antigen as the prime, and the same vaccine along with a clade C HIV gp140 protein boost. Mosaic antigens are computationally derived to provide optimal protection against the diverse strains of HIV that are in circulation globally. The Ad26 mosaic candidates were developed by Dan Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center, and his team, in collaboration with colleagues at Janssen. The mosaic immunogens incorporated in the vaccine were designed by scientists at the Los Alamos National Laboratory.

In preclinical studies, mosaic antigen-based vaccine candidates were able to

protect against a virus equivalent to HIV in monkeys. Several earlier stage clinical trials were also conducted with different versions and regimens of the Ad26 mosaic candidate and protein boosts. One study, known as APPROACH, showed that the same regimen that protected animals in preclinical studies induced the strongest antibody and cellular immune responses in human volunteers. Results from another Phase I/IIa study known as TRAVERSE, showed that the tetravalent mosaic vaccine candidate, the same version that is being tested in the HVTN 705 efficacy trial, induced enhanced immune responses as compared to the trivalent version that was tested in APPROACH.

For HIV, we had to first understand the science and then develop new medicines. The vaginal ring is an application in development to deliver one of these medicines. Our long-acting technologies were originally developed for schizophrenia and now we are working to apply those learnings and make a long-acting injectable for HIV treatment containing two antiretrovirals, one of which is rilpivirine. We now have two Phase III studies together with GSK that showed very good results and I think it's going to get to market as a monthly injection for HIV treatment.

And for all of this, we have collaborated with others. The development of our TB drug bedaquiline was done in collaboration with the TB Alliance, the vaginal ring with the International Partnership for Microbicides [IPM], and our HIV vaccine clinical trials have been conducted in collaboration with several partners, including the Bill & Melinda Gates Foundation; the National Institute of Allergy and Infectious Diseases [NIAID], part of the U.S. National Institutes of Health [NIH]; the U.S. Military HIV Research Program at the Walter Reed Army Institute of Research; Beth Israel Deaconess Medical Center; the Ragon Institute; the NIAID-funded HIV Vaccine Trials Network; the South African Medical Research Council; and the International AIDS Vaccine Initiative. So it's all the result of different types of collaborations.

**Even the development of the mosaic HIV vaccine candidate seems to have been a uniquely collaborative process between Janssen and Dan Barouch. Was it?**

I don't know whether it is a unique collaboration, but I don't know many others like it. In this case, we were able to bring together our biological capabilities with Dan Barouch's scientific work with animal models and laboratory work in non-human primates, which was done in collaboration with researchers at the U.S. Military HIV Research Program. The mosaic immunogens incorporated in the vaccine were designed by the Los Alamos National Laboratory. It was a very integrated partnership, built first on the scientific and medical capabilities of the different groups, with a long-term commitment to get to a solution and in the end develop a product. All the time we worked on scaling up and validating the product, making the different vaccine constructs, and are now testing them for efficacy in people with support from the Bill & Melinda Gates Foundation and the NIH.

**And are you optimistic about the prospects for the candidate given the preclinical data?**

Yes. We wouldn't be in the clinic if we weren't. And it's not just us—our partners are also optimistic, which is why we have joined forces to evaluate this vaccine candidate in a large-scale clinical trial. Based on the animal models and the experience with the RV144 trial, which was the first trial to show some kind of efficacy, I think we should see something. Something significant. You never know with an HIV vaccine, but you have to test it before you can even predict what it's going to do. It could completely fail, but at a certain point you have to jump and hope that it works.

**Something else that the HIV field seems to be grappling with these days, particularly with respect to oral pre-exposure prophylaxis [PrEP], is the need to think about access and implementation earlier on in the development process so that once a product is developed there isn't as much of a lag time between product licensure and introduction in developing countries. How do you think about these issues at J&J with regard to the eventual access and affordability of the HIV prevention products you are developing?**

We have a very strong mission in that regard. You don't start this type of work without knowing that you have to make this available to people in countries where health care spending amounts to a few dollars per person per year. We commit to access, jointly with our partners, meaning any HIV prevention product has to be accessible on a large scale. So we carefully consider a pricing strategy that takes the economic status of different countries into account. For TB products, which only have a developing world market, it is very difficult to offset your investment in innovation and it can be a challenging business model for companies.

**And what about issues of acceptability by the ultimate recipients of these products, particularly for a product like the dapivirine vaginal ring that requires regular use to be effective? Is this something you and your colleagues are thinking about?**

With the ring, yes. I think IPM's decision to go from a vaginal gel to a once-monthly ring was extensively tested and evaluated for feasibility and it was found to be the best possible option.

For an HIV vaccine, our approach is to just get to maximum possible efficacy, which right now requires four injections over the course of a 12-month period. And that is where, for me, acceptability is not the first question. The first question is: Can we get it done? Can we protect people from HIV? Then, the second question is: Is it feasible to have four injections in a year?

But I think you have to say that if there is more than a 50 percent chance that this vaccine will protect you from HIV, to be very conservative, then I don't think four injections is such a burden. Acceptability comes in as a second phase. It all has to do with the level of efficacy. If this is highly efficacious, people will use it.

**What is the one message you think is important in the conversation about HIV today?**

The world should stop saying that HIV is over. It's not over. It is still a huge challenge and we shouldn't get too optimistic. The HIV epidemic is only at the beginning. It is fantastic how many people are on therapy, but it is also a huge challenge to keep them on therapy for the next several decades. People who are infected will need to be on therapy for 40 years to live a normal life and that comes at a huge cost.

Also, we are not going to stop the spread of HIV in the near future without a vaccine or other good prevention tools. This could be a combination of

PrEP, a vaginal ring, long-acting injectables, but the bottom line is we need many prevention tools, as well as better therapies to address the need for long-term use.

**You just returned from the U.N. high-level meeting on TB. Was there renewed optimism for TB vaccines there following the recently reported clinical data?**

Yes. The meeting was highly attended by many ministers of health from all over the world and some heads of state, so it was quite impressive, and the vaccine data is great because we will never end the epidemic without a vaccine. But it will take some time before we're there.

**Is J&J currently involved in TB vaccine research?**

No, not at the moment. We had some TB vaccine activity that didn't work out, but we are working on developing TB drugs. We have the first new TB drug in over 40 years, bedaquiline, which we developed over 15 years and is now being implemented with fantastic success for patients. So that's a good first step. We also have four new targets that we discovered and are working on to get to new drug combinations, so we are still very active in TB research with our partners. We have collaborations with the Institute of Microbial Technology in India, and with many partners around the world to develop new TB drugs. ■

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## Renewed promise for tuberculosis vaccines

Two recent studies are injecting promise into the decades-long quest to develop newer and better vaccines against tuberculosis (TB), the world's deadliest infectious disease and the top killer of people who are living with HIV.

In July, a Phase II trial showed that revaccinating South African adolescents with the only licensed TB vaccine, known as BCG (bacille Calmette-Guérin), that they received as infants was 45 percent effective in preventing sustained TB infection (*N. Engl. J. Med.* 2018; 379:138-149). The BCG vaccine was developed nearly 100 years ago and is admin-

istered routinely to infants in high-incidence settings to protect against the development of TB disease; however, its efficacy is variable and the precise duration of the protection it affords is unknown. Revaccination might be a viable way to extend the protection of the BCG vaccine into adolescence.

Then in September, results from a Phase IIb study involving more than 3,500 adult volunteers from Kenya, South Africa, and Zambia showed that GSK's investigational TB vaccine candidate known as M72, administered along with the company's AS01<sub>E</sub> adju-

vant, was 54 percent effective at preventing active pulmonary TB disease from developing in adults with latent TB infection (DOI: 10.1056/NEJMoa1803484).

These scientific advances come at a time when TB is also receiving increased political attention. Researchers are now hopeful that political will, funding, and scientific progress will come together to help reduce the global TB disease burden, which remains staggeringly high. In 2017, there were 10 million new cases of TB disease reported according to the World Health Organization.

# Overflowing with antibodies and optimism

There is more optimism than ever that researchers are on the path to developing vaccines and antibodies that can help stem HIV's persistent spread.

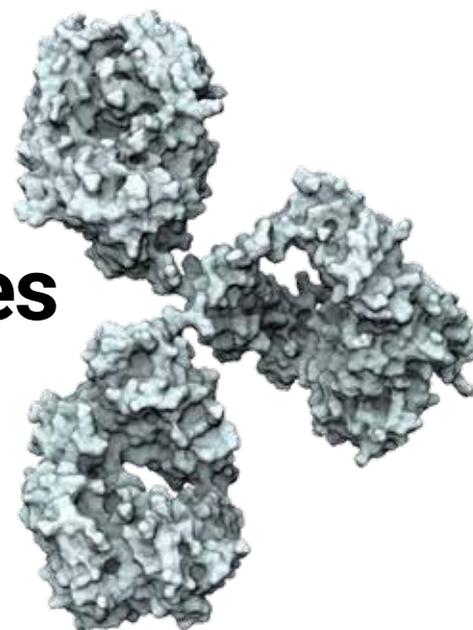
BY KRISTEN JILL KRESGE

"A new era. An exciting time. More optimism than ever before." These are just some of the ways researchers are describing the current state of play in HIV vaccine and antibody research.

"There is very exciting new research that gives us great hope that we are making substantial progress with vaccines and antibodies," says John Mascola, director of the Vaccine Research Center (VRC) at the U.S. National Institute of Allergy and Infectious Diseases. "We have better vaccine antigens in the last few years than we've ever had, and also better vaccine platforms. An effective vaccine is likely, and we're on that path."

This overarching sense of optimism was palpable when thousands of researchers gathered in Madrid, Spain, this October for the biennial HIV Research for Prevention (HIVR4P) conference. With two vaccine candidates in ongoing efficacy trials, numerous other candidates entering clinical testing, and a flurry of activity in developing antibodies for prophylaxis, the field seems undeniably enthusiastic about the prospects for developing new HIV prevention strategies.

**Since 2009, when the first** of what now amounts to hundreds of potent antibodies with the ability to broadly neutralize HIV were isolated from HIV-infected volunteers, researchers have gained a remarkable understanding of just how these antibodies form in response to natural HIV infection.



HIV is coated with bulky sugar molecules that themselves are not immunogenic and largely deflect immune responses mounted against the virus. "Antibodies prefer to see proteins," says Mascola. "It's very hard for an antibody to navigate that glycan shield, find a protein, and neutralize." Yet some HIV-infected individuals can and do make the types of broad and potent antibodies known as broadly neutralizing antibodies (bNAbs) a vaccine would ideally induce. What researchers have found is that despite its glycan shield, HIV's outer protein known as Envelope (Env) actually has many sites of vulnerability. "Virtually the entire Env can be targeted [by antibodies]," says Andrew Ward, a professor at Scripps Research in La Jolla, CA, and a principal investigator of IAVI's Neutralizing Antibody Center (NAC).

This doesn't, however, mean that bNAbs form easily. There are a myriad of reasons why bNAbs are unusual and don't develop often or quickly in response to natural infection. "Most B cells do not have the intrinsic capacity to make broadly neutralizing antibodies," says Rogier Sanders, adjunct associate professor of research in microbiology and immunology at Weill Cornell Medicine and a professor of virology at the University of Amsterdam.



We have better vaccine antigens in the last few years than we've ever had, and also better vaccine platforms. An effective vaccine is likely, and we're on that path.



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Another reason is that many protective antibody lineages are disfavored by the immune system and are therefore controlled by immune tolerance mechanisms. In a recent study comparing nearly 50 HIV-infected individuals whose immune systems generate bNAbs with a similar number of individuals who did not, researchers found evidence of natural killer (NK) cell dysfunction in the individuals who made bNAbs (*Cell* 175, 387, 2018). This NK cell dysfunction resulted in higher levels of follicular T-helper (Tfh) cells or dendritic cells that support B-cell responses in those individuals whose immune systems make bNAbs compared to those who don't. This finding suggests that the ability to induce bNAbs through vaccination may be aided by modulating NK cell activity.

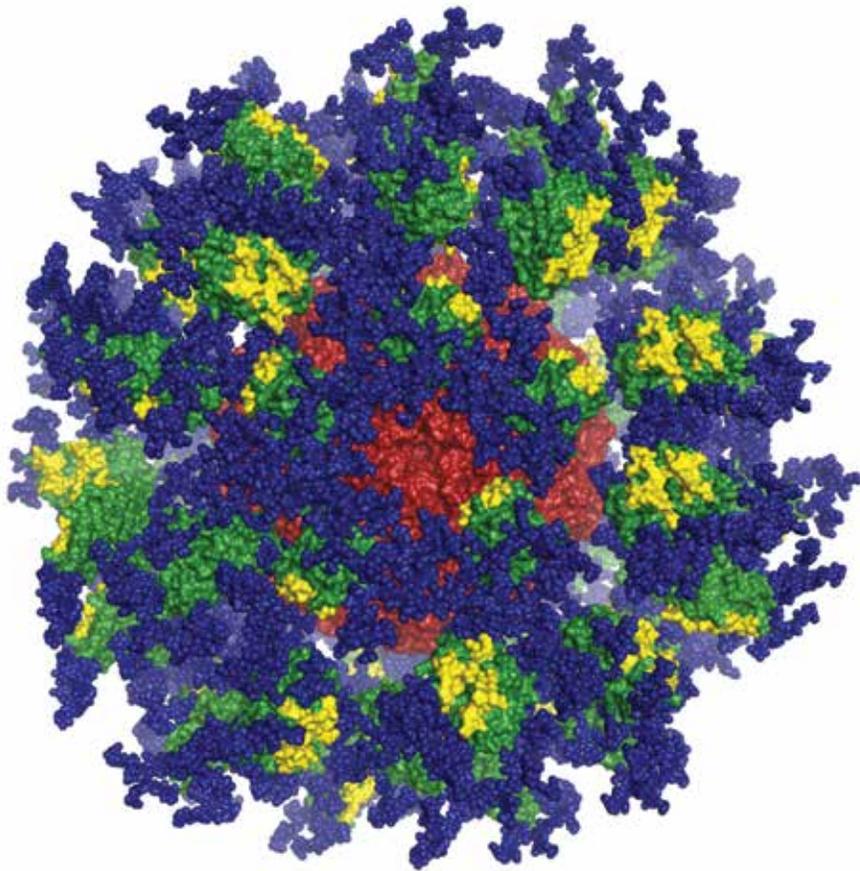
At HIVR4P, assistant professor of medicine Todd Bradley from Duke University, who led this study, reported on his lab's efforts to study how modulating immune tolerance mechanisms might affect the development of neutralizing antibody responses following vaccination. They found that in rhesus macaques, depletion of NK cells by the cytokine interleukin (IL)-15 enhanced formation of germinal centers and Tfh responses following immunization, and that this resulted in higher levels of both binding and neutralizing antibodies in the IL-15 treated animals as compared to controls.

Other studies were designed to see if transient modulation of the immune checkpoint molecules CTLA-4 and PD-1 would in any way alter antibody responses that develop following immunization with HIV Env in macaques. This year's Nobel Prize in Physiology or Medicine was awarded to two scientists for their discovery of

cancer therapies based on inhibition of these immune checkpoint molecules that function as brakes on the immune system. Bradley and colleagues found that while inhibiting CTLA-4 augmented the development of antibody responses to HIV Env with the ability to neutralize the less challenging tier-1 viruses, inhibiting PD-1 actually resulted in lower levels of antibodies that could bind to or neutralize HIV when co-administered with an HIV vaccine.

They also tested whether inhibiting CTLA-4 or the co-stimulatory immune checkpoint molecule OX-40 would have any effect on antibody responses following a prime-boost vaccination with the engineered germline-targeting vaccine immunogen known as eOD-GT8 60mer and the native-like trimeric protein known as BG505 SOSIP in a humanized VRC01 bNAb precursor knock-in mouse model. They found that blocking CTLA-4 and OX-40 agonism increased the antibody titers in the vaccinated mice. The next step is to determine whether depleting NK cells along with inhibiting CTLA-4 and stimulating OX-40 would have a synergistic effect. While still in early stages, efforts to understand how immune system modulation might encourage the formation of bNAbs is an active area of study. This work led William Schief, a professor in the department of immunology and microbiology at Scripps Research and a principal investigator in IAVI's NAC, to conclude that "immune system modulation has legs."

**Another reason that bNAbs are unique** is that they are almost always heavily mutated, or



An image of the eOD-GT8 60mer engineered immunogen. Image courtesy of Scripps Research/IAVI's Neutralizing Antibody Center.

matured, as a result of undergoing repeated rounds of somatic hypermutation in germinal centers in response to an evolving and ever-mutating virus. This is why in most cases it takes between three to five years of chronic stimulation before the human immune system can generate potent and broadly cross-reactive antibodies against HIV.

This presents a challenge for vaccine researchers. While they want to develop a vaccine that can mimic the process of bNAb development in natural HIV infection, “we don’t want to recapitulate the timeframe it takes,” says Kevin Wiehe, assistant professor in medicine at Duke University. “What we’re looking for are shortcuts.”

Wiehe and colleagues have found that broadly reactive neutralizing antibodies are more likely

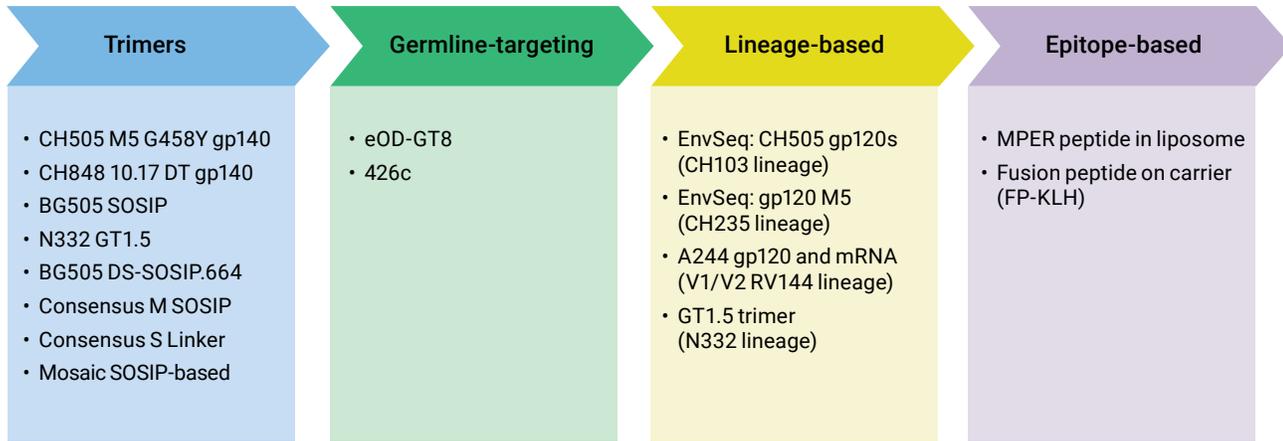
to have what they call improbable genetic mutations, but that not all of these mutations are critical. Wiehe and others are trying to identify the individual or subset of improbable mutations that can have the biggest effect on bNAb development, and then are focusing on ways to induce only these mutations in an effort to speed up the maturation process of antibodies. “These critical and improbable mutations are what we need to go after with vaccine immunogens,” says Wiehe. This mutation-guided approach to vaccine design is just one method researchers are exploring to induce mature bNAbs as quickly as possible through vaccination.

**After decades of largely disappointing results** from clinical trials, the HIV vaccine field has entered a new phase. There are two ongoing vaccine efficacy trials, one of which is testing a reformulated version of the only vaccine regimen to date that offered any protection against HIV infection in the RV144 efficacy trial (HVTN 702; see *Awaiting Results from Efficacy Trials*, *IAVI Report*, Vol. 22, No. 2, 2018). The other is testing a vaccine regimen based on an adenovirus serotype 26 (Ad26) mosaic candidate-based regimen that provided promising results in both pre-clinical animal studies and early phase clinical trials in humans (HVTN 705; see *The Imbokodo Phase IIb HIV vaccine trial*, p. 13).

Now there are even tantalizing clues that suggest these two vaccine candidates may be activating similar genetic pathways. At HIVR4P, Rasmi Thomas, chief of the host genomics section at the U.S. Military HIV Research Program, reported that a vaccine-induced B-cell pathway that was found to be associated with partial protection against HIV in RV144 vaccine recipients was also detected in non-human primates that were protected against simian immunodeficiency virus (SIV) in two preclinical studies of the Ad26 mosaic-based regimen. The enriched genes in this pathway are involved in B-cell development and proliferation, as well as toll-like receptor signaling, and are associated with a higher magnitude of antibody-dependent cellular phagocytosis, according to Thomas. Though she warns that “a lot of this is preliminary.” Previous studies have also shown that this genetic pathway was associated with higher antibody responses to both influenza and yellow fever vaccination.

## Antibody-based immunogens in clinical development

These immunogens designed to induce broadly neutralizing antibodies are either in or about to enter clinical testing.



Information presented at HIVR4P courtesy of Mary Marovich, director of the Vaccine Research Program at the Division of AIDS at the National Institute of Allergy and Infectious Diseases

In addition to these efficacy trials, there are also several new vaccine constructs either in or about to enter Phase I clinical trials. Many of these candidates are based on designer immunogens that aim to induce long sought-after bNAb responses against the virus. Hundreds of bNAbs have been identified and some of them are effective at protecting against an SIV/HIV hybrid in non-human primate studies. “The coupling of these bNAbs and the trimer with structural studies have immensely facilitated structure-guided immunogen design and have made the development of an HIV neutralizing antibody vaccine appear to be an achievable goal,” according to a review article by Raiees Andrabi and colleagues at Scripps Research and IAVI’s NAC (*Curr. Opin. Immunol.* 53, 143, 2018).

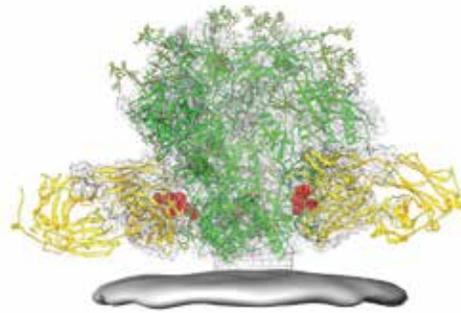
The new crop of vaccine candidates now entering clinical trials hinges primarily on four major approaches to inducing bNAbs, all of which are complementary and in many cases are being studied in combination. The first is referred to as lineage-based vaccine design. This approach is based on detailed study of the co-evolution of HIV and antibodies in infected individuals in real time and attempts to mimic this antibody maturation process with a series of immunogens that

are derived from sequential HIV Env variants.

One of the lineage-based approaches in development by Barton Haynes, director of the Human Vaccine Institute at the Duke University School of Medicine, and colleagues at the Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID) is already in clinical trials (HVTN 115). This trial is testing a series of immunogens based on viruses identified from a single individual, referred to as CH505, who was enrolled in an acute infection study and followed from the time HIV infection occurred through the development of bNAb responses. In the ongoing Phase I HVTN 115 trial, researchers are testing a series of sequential HIV gp120 immunogens administered along with a GLA-SE adjuvant either alone or in combination with a DNA mosaic-based candidate. A trial similar to HVTN 115 is also being proposed in infants, given that the immune systems of infants and children may more readily generate bNAbs. Many other lineage-based approaches are also in development (see table, above).

The second major approach to inducing bNAbs through vaccination is referred to as germline-

## Designing a vaccine candidate based on the HIV fusion peptide



This protein structure diagram illustrates the location of the fusion peptide epitope (red) on the HIV spike (green), which projects out of the viral membrane (grey). The diagram also shows how a broadly neutralizing antibody (yellow) binds to the fusion peptide. Researchers at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and their colleagues designed an experimental vaccine based on this fusion peptide affixed to a carrier protein (FP-KLH). This vaccine candidate, tested along with a trimeric HIV Envelope boost, elicited antibodies in mice, guinea pigs, and monkeys that neutralize dozens of HIV strains from around the world (*Nature Medicine* DOI: 10.1038/s41591-018-0042-6; 2018). One antibody that was identified in monkeys following vaccination was able to neutralize 59 percent of HIV isolates, according to research presented at the recent HIV Research for Prevention conference.

targeted vaccine design. This approach utilizes a priming immunogen—engineered based on a specific epitope on HIV that is targeted by bNAbs—to activate B cells that have the intrinsic capability to make bNAbs. This is followed by boosting with one or more HIV Env immunogens that are increasingly similar to the native structure of HIV Env to shepherd the germline antibodies to accrue the mutations that will make them broadly neutralizing. The germline-targeting candidate eOD-GT8 60mer recently entered a Phase I clinical trial (G001). This candidate was engineered by scientists at Scripps Research and IAVI’s NAC to activate B cells with the capacity to make CD4 binding-site directed antibodies.

Another germline-targeting immunogen developed by Haynes and colleagues may enter clinical

trials next year. This immunogen is a stabilized trimeric version of the transmitted founder virus from the CH505 donor.

The third vaccine design approach is referred to as either an epitope-focused strategy or immunofocusing. Two candidates based on this approach will also enter clinical trials next year.

Peter Kwong, a senior investigator in the structural biology section of the VRC, and colleagues first identified an antibody referred to as VRC34 that targets the fusion peptide (FP) region of HIV Env, which plays a critical role in viral entry into cells (see image at left). Kwong and colleagues then developed an immunogen by linking this FP, which consists of eight amino acids, to a carrier protein called KLH. This immunogen was tested extensively in preclinical studies in combination with a trimeric HIV Env boost. One antibody that developed following vaccination of rhesus macaques neutralizes 59 percent of a 208 virus panel of global isolates. Now the team is modifying the immunogen by affixing it to a nanoparticle, which will make the immunogen more closely resemble a virus in size and structure, and is preparing to advance this prime-boost strategy into Phase I clinical trials next year.

Another epitope-based immunogen that is scheduled to enter clinical trials next year is based on the membrane proximal external region (MPER) epitope associated with lipid. These MPER peptide-liposomes are being developed by Haynes and colleagues at Duke.

The fourth approach is testing native-like trimers as immunogens. It is only since 2013 that researchers have been able to make stable proteins that look like the native HIV Env trimer. Doing so allowed scientists to develop a stable crystal structure of the virus for the first time and is, in addition to the isolation of bNAbs from HIV-infected volunteers, the other breakthrough that is fueling today’s vaccine design efforts.

There are now several native-like trimers in development, with the first—the BG505 SOSIP trimer developed by Sanders and John Moore of Weill Cornell Medicine—entering clinical trials imminently. Others, including those that are based on consensus sequences, are slated to enter clinical trials next year, and a modified BG505

trimer that engages germline precursors of bNAbs known as BG505 GT1.1 will also enter clinical trials in 2019.

There is also an effort underway by the European AIDS Vaccine Initiative (EAVI2020) to decipher just what makes a cohort of acutely HIV-infected individuals able to develop bNAbs much earlier in the course of infection. “They are very rare, much rarer than in chronic infection, but there are some individuals who have some level of [antibody] breadth even as soon as two to three months after infection,” says Sanders. If there is something unique about the Envs of the infecting viruses in these individuals that is driving the antibody response to develop much more rapidly, they would make ideal vaccine candidates. This is why researchers are making HIV Env proteins similar to those isolated from these individuals and will test them in clinical trials beginning next year.

“There is a huge explosion of candidates going into clinical trials,” says Haynes. “It’s going to be an exciting time.”

What’s notable, in addition to the number of candidates being investigated, is the pace at which this

research is moving. “This is all three or four years old,” says Mascola. “It is really moving fast.”

At the same time, researchers are still mining for additional antibodies from human volunteers. At HIVR4P, Mohammed Sajadi, associate professor at the University of Maryland School of Medicine, reported on the identification of a single donor whose serum could neutralize 99 to 100 percent of a global panel of HIV isolates. The individual was HIV infected for almost 20 years at the time the serum samples were collected. From this serum, researchers were able to isolate three new monoclonal antibodies, dubbed N49 P6, P7, and P11, which Sajadi referred to as the “most broad and potent *in vitro* antibodies identified to date.”

But even with multiple strategies and budding optimism, it isn’t likely to be easy to induce bNAbs through vaccination. “There are a lot of factors we have to get right all at the same time to get this system to work,” says Haynes. “We’ve only just begun to learn the rules of how to do this.” Scientists will need to optimize the immunogens, adjuvants, and delivery systems, and potentially also explore strategies to overcome host tolerance responses. One thing almost all researchers agree on is that developing vaccines

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## Understanding how bNAbs protect

Several broadly neutralizing antibodies (bNAbs) can protect non-human primates from infection with simian immunodeficiency virus (SIV), or a hybrid SIV/HIV virus known as SHIV. This protection is largely driven by their ability to effectively neutralize the virus.

But this is by no means the only way in which antibodies can block infection. For certain bNAbs in certain model systems, non-neutralizing activity that is mediated by the fragment crystallizable (Fc) region of the antibody seems to play an important role. Dan Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center, presented data at HIVR4P showing that the bNAb PGT121 completely protects rhesus

macaques from SHIV challenge at least in part because of Fc-mediated activities.

In a study involving 25 rhesus macaques, Barouch and colleagues found that on days one and three following SHIV challenge, there was actually more virus in PGT121 antibody-treated macaques than in control animals. But by day seven, virus levels in control animals increased, while virus levels in the antibody-treated monkeys declined dramatically. By 10 days after SHIV challenge, 100 percent of tissues samples in the control animals contained virus and there wasn’t any detectable viral DNA in any distal tissues tested in the PGT121-treated group.

When Barouch and colleagues analyzed the

tissues of the antibody-treated animals before day 10, they found virus that differed from the inoculum. “I wouldn’t say this is definitive, but it suggests that virus in distal tissue may have undergone very limited viral replication,” says Barouch. In fact, when viral RNA from two of three rhesus macaques in the PGT121-treated group was transferred to monkeys not involved in the original study, it was sufficient to establish infection in these new animals. “Sterilizing protection with PGT121 does not appear to involve complete blockade of virus at the mucosal surface,” says Barouch. This finding suggests that Fc-mediated antibody activities may be playing an important role in the protection afforded by PGT121 in non-human primates.

that can induce bNAbs will require iterative cycles of clinical evaluation and optimization.

HIV infection. Rick Koup, a senior investigator at the VRC, says that while researchers are exploring “elaborate strategies to make bNAbs in people, the easier way is to make bNAbs in a bioreactor.”

**In the meantime,** nine bNAbs are in clinical development for antibody-based prophylaxis—the direct administration of antibodies to prevent

So that is exactly what researchers are doing,

## The current clinical pipeline of bNAbs for HIV prevention

bNAb	Non-LS	LS	IP Holder	Phase I Safety, PK
VRC01	X	X	NIAID	completed
VRC07-523		X	NIAID	preclinical
10E8V		X	NIAID	ongoing
N6		X	NIAID	ongoing
CAP256		X	NIAID, CAPRISA	planned 2019
PGT121	X	X	IAVI	preclinical
PGDM1400	X	X	IAVI	preclinical
3BNC117	X	X	Rockefeller	ongoing (LS)
10-1074	X	X	Rockefeller	ongoing (LS)

LS: a mutation that increases the half-life of the bNAb; IP: Intellectual property; NIAID: National Institute of Allergy and Infectious Diseases; CAPRISA: Centre for the AIDS Programme of Research in South Africa

Information presented at HIVR4P by Rick Koup, senior investigator at the Vaccine Research Center at the U.S. National Institute of Allergy and Infectious Diseases.

## Pediatric trials of bNAbs for HIV prevention

Network	Name of Trial	Description	Status
IMPAACT <sup>1</sup>	P1112	VRC01, VRC01-LS, and VRC07-523LS in at-risk infants	ongoing
IMPAACT <sup>1</sup>	P2008	VRC01 in infants with or without antiretroviral therapy (ART)	starting enrollment
IMPAACT <sup>1</sup>	P1115	VRC01 HIV+ or at-risk infants with or without ART	protocol development
Independent <sup>2</sup>	TBD	VRC01-LS & 10-1074 in long-term suppressed HIV-infected children	protocol development
Independent <sup>3</sup>	TBD	VRC01-LS in infants at risk of HIV infection	proposal stage

<sup>1</sup> International Maternal Pediatric Adolescent AIDS Clinical Trials Network

<sup>2</sup> Roger Shapiro (Harvard) in Botswana; sponsored by Division of AIDS at the National Institute of Allergy and Infectious Diseases

<sup>3</sup> Michael Hoelscher (Munich) in Mozambique and Tanzania; funded by the European & Developing Countries Clinical Trials Partnership (EDCTP)

Information presented at HIVR4P by Mary Marovich, director of the Vaccine Research Program at the Division of AIDS at the National Institute of Allergy and Infectious Diseases.

and within a couple of years they will have the first human data on this approach from the Phase IIb proof of concept trials known as the Antibody-Mediated Prophylaxis or AMP studies. These studies (also known as HVTN 703 and HVTN 704) are testing whether administration of the bNAb known as VRC01 can protect against HIV infection in trials involving more than 4,600 women, men who have sex with men, and transgender individuals from multiple countries in North and South America, Europe, and Africa. Enrollment in these studies is now complete.

There is also a trial testing whether VRC01 or the variant VRC01LS, which has the LS mutation that increases the half-life of the antibody from 14 to 71 days, can protect infants born to HIV-infected mothers from contracting the virus during breastfeeding (the IMPAACT or P1112 trial).

But even before the AMP study results are in, researchers are already preparing for the possibility that it will take more than one bNAb for optimal protection against HIV infection, just as it does for therapy. “When it comes to getting a good clinical agent, we’re going to need a combination,” says Bette Korber, a computational biologist at Los Alamos National Laboratory.

Korber gave a somewhat sobering presentation at HIVR4P that suggested it may even take as many as four bNAbs for a prophylactic combination that would be effective globally. This is because the potency and breadth of the different bNAbs in development are variable against different clades of the virus. Even though all of these antibodies neutralize broadly enough to earn the distinction of being bNAbs, many of the individual antibodies are completely ineffective at neutralizing a significant fraction of viruses in laboratory panels. For example, the antibodies VRC01 and 3BNC117 don’t neutralize clade C viruses well, while PGT121 poorly neutralizes viruses from clade A as well as the CRF01 and CRF02 recombinants. Therefore the more antibodies that are combined, the harder it will be for viral escape to occur.

One antibody that seems to neutralize almost all viruses in laboratory panels, including those that others don’t, is 10E8. This antibody targets the gp41 membrane-proximal external region of the

virus, which is highly conserved across clades. Unfortunately, there are now safety concerns with this antibody, calling its utility in prophylaxis into question. Koup reported that investigators observed large patches of erythema or redness at the injection sites in seven of eight individuals who received this antibody. Biopsies showed evidence of panniculitis, a group of diseases that result in the inflammation of fat tissues under the skin, and lymphocytic inflammation. No adverse event or safety concerns have arisen with VRC01 in the AMP studies. “This antibody is acting differently than other antibodies,” says Koup, who went as far as to cross 10E8 off the list of potential antibodies for HIV prophylaxis. “Until we can figure out what’s going on here, 10E8 should be off the table.”

A tri-specific antibody engineered by scientists at Sanofi and the VRC that combines the antigen-binding fragment or Fab of three bNAbs, including 10E8, into one molecule is slated to enter clinical trials. But Koup warns that the safety issues with 10E8 must be addressed before the tri-specific antibody enters clinical trials. However, researchers present at HIVR4P speculated that there may be less concern with 10E8 as part of the tri-specific, given it only contains the binding region and not the entire antibody.

In addition to the tri-specific, many groups are working to optimize bNAbs to be more potent and have longer half-lives, as well as to test combinations of antibodies that would have a greater likelihood of protecting against HIV. The longer-acting antibodies 3BNC117-LS and 10-1074-LS, developed by scientists at Rockefeller University, are already being tested alone and in combination in a Phase I trial involving both HIV-infected and uninfected volunteers. But Korber tempered expectations that just two antibodies will be enough. “We can’t lose heart if two antibodies fail. It doesn’t mean we’re not going to succeed,” she says.

Her words could serve as a metaphor for the HIV vaccine field more broadly. Despite many failed attempts at inducing protective immunity, researchers seem more optimistic than ever that scientific advances will ultimately lead to success. While the path to developing effective vaccines and antibodies against HIV may still be long, it is at least becoming clearer. ■



## Upcoming HIV-related meetings

### JANUARY 2019

#### **Keystone Symposium – Tuberculosis: Mechanisms, Pathogenesis and Treatment**

January 17-21 | Banff, Alberta, Canada

[www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1627](http://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1627)

### MARCH 2019

#### **Conference on Retroviruses and Opportunistic Infections**

March 4-7 | Seattle, Washington

[www.croiconference.org](http://www.croiconference.org)

#### **Keystone Symposium – HIV Vaccines**

March 24-28 | Whistler, British Columbia, Canada

[www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1629](http://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1629)

#### **Keystone Symposium – Functional Cures and the Eradication of HIV**

March 24-28 | Whistler, British Columbia, Canada

[www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1628](http://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1628)

### JULY 2019

#### **STI & HIV 2019 World Congress**

July 14-17 | Vancouver, Canada

[stihiv2019vancouver.com](http://stihiv2019vancouver.com)

### IAS 2019

July 21-24 | Mexico City, Mexico

[www.ias2019.org](http://www.ias2019.org)

### NOVEMBER 2019

#### **17th European AIDS Conference**

November 6-9 | Basel, Switzerland

[eacs-conference2019.com](http://eacs-conference2019.com)

### DECEMBER 2019

#### **9th International Workshop on HIV Persistence during Therapy**

December 10-13 | Miami, Florida

[www.hiv-persistence.com](http://www.hiv-persistence.com)

For a full list of meetings and their descriptions, go to [www.iavireport.org/meetings](http://www.iavireport.org/meetings).