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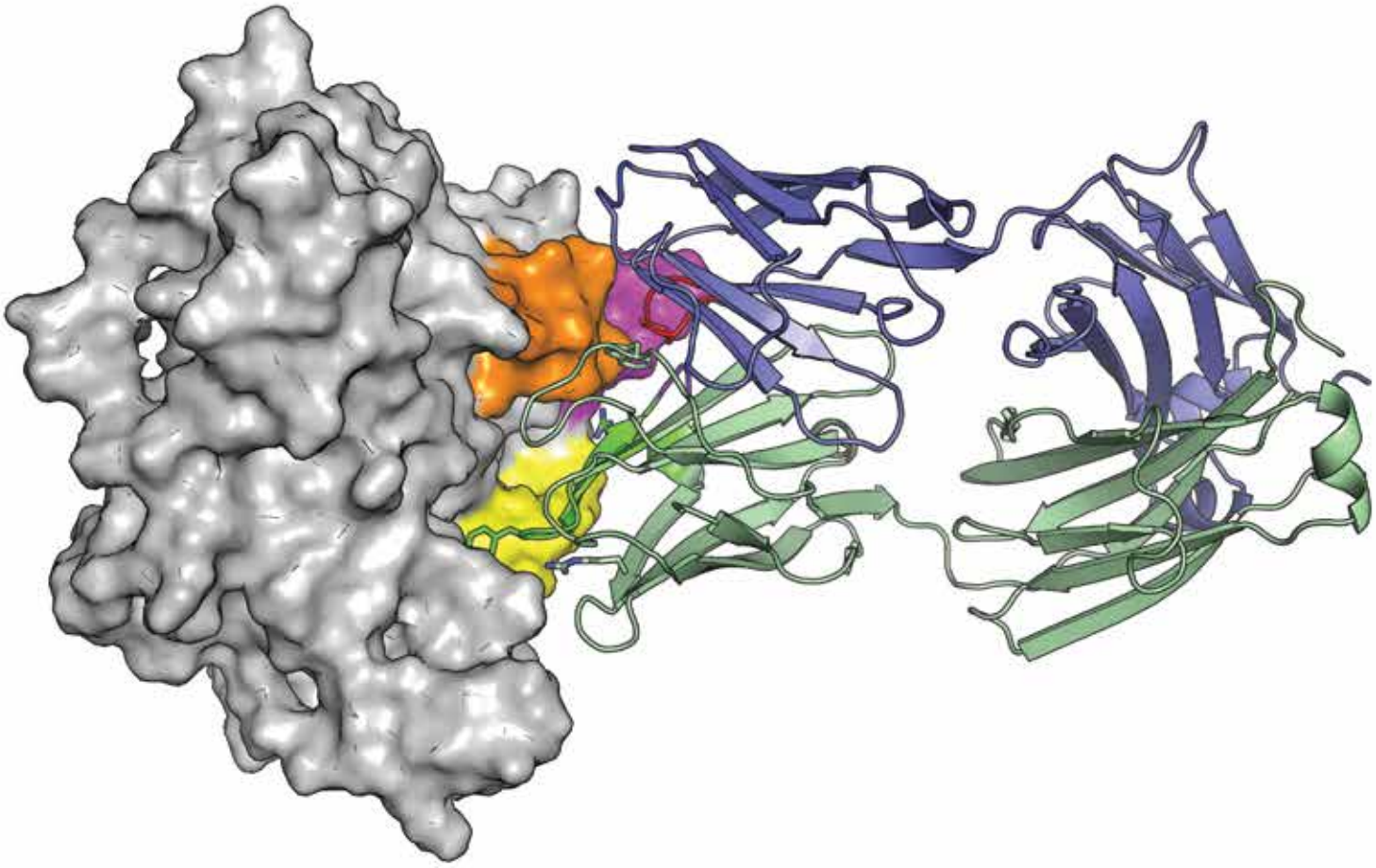
New HIV Antibody: Best in Class



Plus: Scientific Update from CROI and a Look Into The Newly Launched Coalition for Epidemic Preparedness Innovations

EDITOR'S LETTER

This issue of *IAVI Report* marks an important milestone—it ushers the publication into its third decade.

Much has changed in HIV research during the last 20 years. Life-saving antiretroviral therapy works remarkably well, new prevention approaches such as pre-exposure prophylaxis have been proven highly effective, and vaccine research is progressing both clinically, with a recently launched efficacy trial, and pre-clinically, with several candidates being designed to elicit broadly neutralizing antibodies.

The style of *IAVI Report* has changed quite dramatically too. The content is broader, with coverage of more diverse vaccine-related issues and HIV prevention efforts at large. There are also many new features that were introduced over the years, among them the beautiful scientific images that grace the cover.

It is a testament to the science, which is so dynamic and captivating that even as we enter our third decade in covering HIV vaccine research there is always more to report on and write about. Some of that scientific work is highlighted here. In this issue, we report on the latest advances from the Conference on Retroviruses and Opportunistic Infections, held this February in Seattle (see page 13). We also spoke with Mark Connors of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases about the most recent broadly neutralizing antibody his lab isolated from an HIV-infected volunteer and what the advances in antibody discovery mean for HIV prevention (see page 17).

We also describe in depth the Coalition for Epidemic Preparedness Innovations (CEPI), an organization that sprung up in the aftermath of the latest and largest Ebola outbreak and aims to fill the gaps in vaccine development for emerging pathogens that are considered among the top infectious disease threats with pandemic potential (see page 4). CEPI recently appointed its inaugural chief executive officer, Richard Hatchett, whom we spoke with about his plans for the newly formed coalition (see page 10).

Writing about the continuous innovation that is transforming vaccine development is part of what makes all of our jobs at *IAVI Report* a pleasure.

– 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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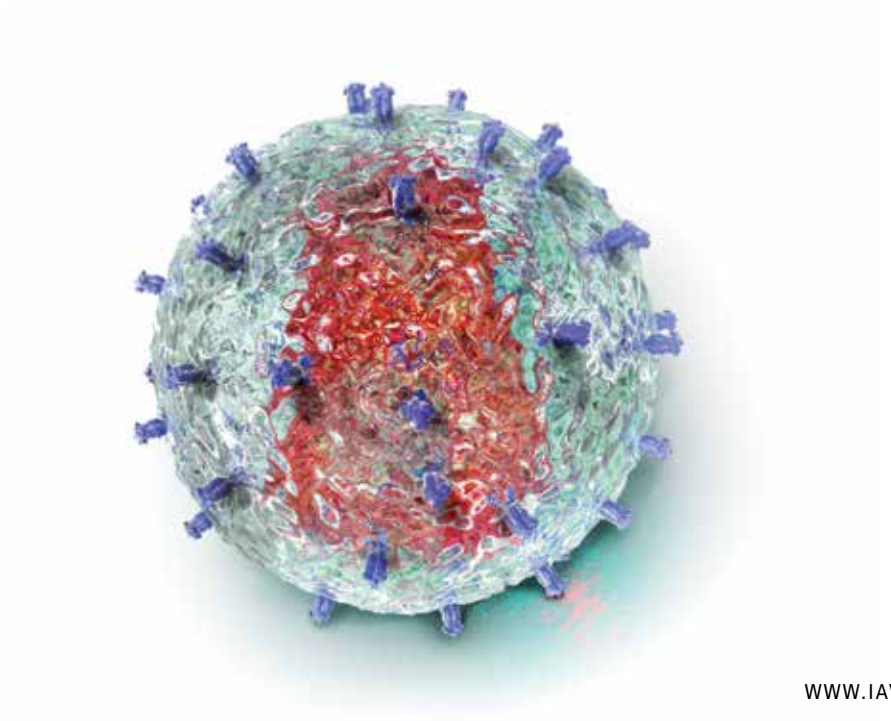

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[ON THE COVER]

HIV-1 gp120 is shown in grey, with the CD4-binding loop, loop D, and V5 loop in yellow, orange, and magenta respectively. N6 is shown in cartoon representation with heavy and light chains colored light green and light blue, respectively. CDR H2 and CDR L3 are highlighted in bright green and red. Key residues for N6 recognition of HIV-1 gp120 are represented by sticks.

Image courtesy of Tongqing Zhou of the Structural Biology Section at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases/US National Institutes of Health.

A Crisis Gives *You Wings*

The latest and largest Ebola outbreak showed the importance of anticipating epidemics. The new Coalition for Epidemic Preparedness Innovations is doing just that by developing vaccine candidates against top pathogens with pandemic potential.

By Michael Dumiak

The hot equatorial spring in Guinea in 2015 was still a shell-shocked place to be, with the western African nation and its immediate neighbors dazed from the Ebola outbreak that began a year earlier and put the entire world on edge. John-Arne Røttingen, Gunnstein Norheim, and Byorg Nilssen recall it well, as it was at that time they helped launch an efficacy trial of an Ebola vaccine candidate.

Two years later, these three Norwegian public health workers are in a vanguard looking to develop vaccines against other emerging pathogens with epidemic potential. They are just part of an international team that debuted the Oslo-based CEPI organization, the Coalition for Epidemic Preparedness Innovations, at the World Economic Forum this past January with US$540 million in funding and a mandate to bring new vaccines to bear against priority pathogens.

Building on the lessons of the 2014/15 Ebola epidemic, the coalition is the latest try at putting in place a mechanism to prevent epidemics or pandemics before they start and to respond to them more effectively when they do. CEPI looks to join other organizations in filling the gaps in vaccine development produced by an unbalanced system of global capitalism, in which there isn't economic incentive to develop costly vaccines without developed country markets to support them. Global health experts want a store of vaccine candidates with potential for rapid development, much like what the Ebola crisis produced albeit in an ad-hoc manner.

CEPI plans to fund new vaccine candidates from development, through preclinical research, to proof of principle in humans. At that point the candidate will wait, much like a fire extinguisher behind a glass pane, to be broken out at the right time. When an outbreak occurs, an existing vaccine candidate could be rushed into efficacy testing and at a greatly accelerated pace toward manufacture and deployment.

Ebola showed even a small outbreak has global consequences. CEPI aims to be a kind of insurance system against other emerging pathogens so that the somewhat chaotic but ultimately successful response to Ebola isn't repeated. So far, the Coalition has had a remarkable run. In a little over 12 months it set a list of priority pathogens, raised $540 million in funding, is now reviewing 30 grant applications, and just hired a full-time chief executive, Richard Hatchett, the former chief medical officer and deputy director of Biomedical Advanced Research and Development Authority (BARDA; see Q&A page 10).

Ebola: lessons learned

John-Arne Røttingen is in a cab moving slowly through Washington, DC, horns blaring around him. That morning, he had discussions with Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), and then with officials at BARDA. That evening included an event with members of Congress and likely members of US President Trump's cabinet.

These are just a few of the long list of conversations with government donors and potential collaborators Røttingen has had over the last six months in his post as interim head of CEPI—in April he will lead the Research Council of Norway. Meetings with government officials in Oslo, Berlin, and Tokyo helped secure commitments of $340 million, while the UK's Wellcome Trust and the Bill & Melinda Gates Foundation each added $100 million. The European Commission has also pledged around $250 million, which would make CEPI's total funding $790 million. Norway's National Health Institute and the Indian Department of Biotechnology in New Delhi are also contributing infrastructure and support. But they haven't crossed the finish line yet. The funding goal for CEPI is a billion dollars, and Røttingen remains confident they will get there.

Røttingen was deeply involved in the Ebola response, along with his Norwegian Institute of Public Health (NIPH) colleagues: virologist/vaccinologist Gunnstein Norheim and project manager Bjørg Dystvold Nilsson. Nilsson helped coordinate the large efficacy trial of the leading Ebola vaccine candidate, while Røttingen and Norheim helped to implement it. On the ground in tented clinics in Guinea, from the World Health Organization (WHO) in Geneva, and within the pharmaceutical multinational Merck, dozens of people helped to initiate the 12,000-person ring trial of the rVSV-ZEBOV vaccine candidate (see *IAVI Report*, Vol. 19, No. 4, 2015, p. 14). Late last year the recombinant viral-vector vaccine, which uses an altered vesicular stomatitis virus to express a protein from the Zaire strain of Ebola virus, showed 100 percent efficacy. The candidate was manufactured and advanced into clinical trials by Merck after being developed by the Public Health Agency of Canada and the biotech company NewLink Genetics. It is currently under expedited review by the US Food and Drug Administration.

Even as Ebola wound down, the impact of this outbreak lingered. In addition to killing 11,300 people out of 28,600 cases in six countries, Ebola raised a lot of questions for public health officials worldwide. The WHO held an Ebola Special Session of the Executive Board in Geneva in January 2015 to try to understand what exactly had gone on during the outbreak. The Ebola response also topped the agenda at the WHO annual meeting in May that year, which commissioned an Ebola Interim Assessment Panel. This panel issued its final report in July (http://www.who.int/entity/csr/resources/publications/ebola/report-by-panel.pdf?ua=1), to which the WHO Secretariat responded a month later (http://www.who.int/entity/csr/resources/publications/ebola/who-response-to-ebola-report.pdf?ua=1).

Depending on your frame of reference, the response to the Ebola epidemic of 2014/15 was either a great success or startlingly slow and ineffective. Critics said the outbreak should have been foreseen. Dire estimates circulated as the epidemic raged with some predicting the dead would soon number in the thousands, perhaps as many as 10,000 a week by the end of 2014. But the thousands of dead per week never did materialize. Effective quarantining, local heroism, government interventions, a huge volunteer response, and public health practices such as publicizing effective hygiene, building sufficient clinics, and providing quality training for health care workers proved enough—eventually—to bring the epidemic under control.

As the outbreak raged, pharmaceutical companies Merck, GlaxoSmithKline (GSK), and Janssen brought viable vaccine candidates and an experimental antibody therapy against Ebola into the field at an incredibly rapid pace. It took less than a year from when a few American and Liberian health workers received the only existing doses of an experimental antibody treatment in 2014 to the start of the efficacy trial of the rVSV-ZEBOV vaccine candidate that involved thousands of people. Decisive actions made this happen. Public and private institutions partnered in unprecedented ways to develop and manufacture these Ebola vaccine candidates. This was in large part possible because the pharmaceutical companies weren't starting from scratch. The vaccine candidates were in stasis, waiting for the need to emerge and organizations with better resources to carry them forward.

But what should be done about the next pandemic: one for which no ready-to-be-tested vaccine candidates exist? "One future option would be developing vaccines and antivirals for emerging pathogens to the point of preclinical development or perhaps Phase I safety testing," Vincent Racaniello, a Columbia University immunologist, blogger, and host of the *This Week in Virology* podcast told *IAVI Report* in the immediate aftermath of the Ebola pandemic. "Then they'll be stored until an outbreak happens."

This was the topic discussed in Geneva at the WHO headquarters in October 2015, a few months after the Ebola panel report was released and three months after an op-ed in the *New England Journal of Medicine* from Stanley Plotkin, Adel Mahmoud, and Jeremy Farrar called for a global vaccine development fund. These WHO discussions led to the concept of CEPI.

By last summer, John-Arne Røttingen accepted a call from the WHO and began putting together a business plan for this new coalition. CEPI's scientific advisory team was ready by August (see sidebar, this page).

With a business plan in hand and the science board in place, Røttingen could knock on doors at health ministries and large philanthropic organizations, this time with a purpose: raising a billion dollars.

Meanwhile the scientific advisory team began selecting CEPI's first targets. They did so by winnowing down a list of pathogens most prone to generate epidemics that was already established by the WHO as part of its R&D Blueprint. Last spring, the WHO's Product Development for Vaccines Advisory Committee produced thorough pipeline analyses for 25 of these pathogens (*Vaccine* **34**, 2863, 2016). CEPI's science team then zeroed in on what the WHO describe as the top 11 pathogens in the world needing urgent R&D attention (see sidebar, page 7).

"Our objective was to designate two or three pathogens," says Norheim, the Norwegian vaccinologist who coordinated CEPI's scientific discussions as it came into being. "The real question from the start is how do you limit the scope? Which diseases? How many products? What is the consensus?" The factors the science board considered were: feasibility, innovation and application potential, time to completion, experience and track record, expected cost and available funding, and capacity building and potential. "There is no perfect decision," Norheim says. "We just have to make a choice, do our best, and start with some of them."

The scientific advisory board conducted a kind of quantitative gap analysis, weighing different factors such as how important it would be to demonstrate that the new venture could deliver among the pathogens they would select. Jim Robinson, a former Merck senior vaccine development executive, pointed out that novel platforms can slow down regulatory review. In some cases it might be better to trade novelty for speed. Also, CEPI did not want too much overlap, or at least where vaccine development efforts are underway, there should be some unique or clearly helpful role that the Coalition could play. CEPI's scientific team eventually landed on prioritizing MERS (Middle East Respiratory Syndrome), Nipah, and Lassa fever (see sidebar, page 7), with the goal of developing two viable candidates for each of these pathogens. In choosing these three pathogens, the Coalition is aiming to cover infectious agents endemic to a broad and vulnerable swath of the developing world including the Middle East, western Africa, and subcontinental Asia.

In February, CEPI held a meeting in Paris to introduce the "CEPI Partners Forum," advertising its first call for candidates against these pathogens. The coalition is also filling its vital

The Scientific Advisory Committee

The Coalition for Epidemic Preparedness Innovations (CEPI) is guided on science themes by a panel of nearly 30 top experts in vaccines and public health. The Scientific Advisory Committee, chaired by Mark Feinberg, chief executive officer of the International AIDS Vaccine Initiative, advises CEPI on scientific matters related to research and development, ruling on technical content for proposal requests, and designing the criteria by which applicants are granted funding. Along with Feinberg, the current team includes the following individuals as well as five non-voting members:

Heinz Feldmann, US National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases

Kathleen Nuezil, University of Maryland

Peter Smith, London School of Hygiene and Tropical Medicine

Alan Barrett, University of Texas Medical Branch

George Fu Gao, Chinese Center for Disease Control and Prevention

Gunnstein Norheim, Norwegian Institute of Public Health

Stanley Plotkin, VaxConsult

Maharaj Kishan Bhan, Jawaharlal Institute of Postgraduate Medical Education and Research

Jesse Goodman, Georgetown University

Helen Rees, Wits Reproductive Health and HIV Institute in South Africa

Daniel Brasseur, consultant

Penny Heaton, Bill & Melinda Gates Foundation

James Robinson, James Robinson Biologics Consulting

Jean-Francois Delfraissy, L'Agence nationale de recherches sur le sida et les hépatites virales (ANRS)/French National Institute of Health and Medical Research

Gagandeep Kang, India Department of Biotechnology

Amadou Sall, Institute Pasteur Dakar

Gary Disbrow, Biomedical Advanced Research and Development Authority

Subhash Kapre, Inventprise

Connie Schmaljohn, US Army Medical Research Institute of Infectious Diseases

Bernard Fanget, Abivax/Neovacs

David Kaslow, PATH

Michael Kurilla, NIH

Kenji Shibuya, Department of Global Health Policy, University of Tokyo

Non-voting members: **Bernadette Murgue**, World Health Organization; **Ali Alloueche**, Takeda; **Kathrin Jansen**, Pfizer; **Jean Lang**, Sanofi Pasteur; **Johan Van Hoof**, Johnson & Johnson

experts database: the high-level experts who will review the grant proposals as they come in.

All three of these pathogens are the cause of recently reported outbreaks: MERS, first reported in Saudi Arabia in 2012, with nearly 2,000 cases confirmed across the Arabian Peninsula and a low-grade outbreak coming in January in the Saudi town of Buraydah; Lassa, first pinpointed in Nigeria with the death of two missionary nuns in 1969 with the most recent outbreak occurring in Togo and Liberia last year; Nipah, a recently emerged paramyxovirus with high fatality rates, has emerged on a near-annual basis in Bangladesh with 300 confirmed cases from 2001 through 2015.

The potential for devastating epidemics from just this deadly trio is alarming. These zoonotic pathogens are easily transmissible among humans. Nipah is endemic to a hugely densely populated part of the world, with two billion people living where the virus is already known to exist or where the *Pteropus* fruit bats that serve as the animal reservoir of the virus are found. The last real outbreak killed 100 people in 1999, but more than a million pigs were slaughtered before the virus was stopped. Lassa and MERS are in places that are only remotely accessible and in difficult straits politically. While for Nipah the US Centers for Disease Control and Prevention (CDC) says that a vaccine making use of Hendra G protein to produce cross-protective antibodies against both Hendra and Nipah has been used in Australia to protect horses (and may show promise in protecting against henipavirus in humans), its main advice to the two billion people living in the Nipah zone is to avoid exposure to sick pigs and bats and not to drink raw date palm sap.

CEPI's first goal is to move new vaccines against these three pathogens through development from preclinical to proof of principle in humans. Its second focus is on "the development of platforms that can be used for rapid vaccine development against unknown pathogens." Research and data produced for Nipah, for example, might have applications in developing vaccines against other paramyxoviruses.

Collaboration across sectors

Mark Feinberg, president and chief executive officer of the International AIDS Vaccine Initiative (IAVI), leads CEPI's scientific committee. Feinberg brings his deep experience dealing with Ebola vaccine development to play in this role. During the last Ebola epidemic he worked for Merck, leading the coordination of the company's collaborative devel-

Pressing pathogens

These 11 pathogens require urgent consideration, according to the World Health Organization (WHO). From this list, CEPI chose its first three targets: Nipah, Lassa fever, and MERS (shown in bold). Descriptions for these pathogens were compiled from information provided by the WHO and the US Centers for Disease Control and Prevention.

Crimean-Congo hemorrhagic fever: an infection caused by the tick-born *Nairovirus* and spread by contact with infected blood or the insects themselves. Symptoms include fever; back, joint, and stomach pain; severe bruising; and uncontrolled bleeding. Case fatality rate is from 10 to 40 percent.

Ebola virus disease (formerly Ebola hemorrhagic fever): infection caused by one of four strains of *Ebolavirus* species found in several African countries and transmitted by direct contact with blood, bodily fluids, contaminated objects, infected monkeys or bats or, possibly, with semen from a man who's recovered from the infection. Symptoms include fever, diarrhea, vomiting, and unexplained hemorrhaging. Case fatality rate averages 50 percent; in past outbreaks fatality rates ranged from 25 to 90 percent.

Marburg hemorrhagic fever: caused by a virus hosted in the African fruit bat *Rousettus aegypticus*, it is not known how the virus is transferred to humans. Causes fever, chills, headache, myalgia progressing to jaundice, delirium, weight loss, massive bleeding, and organ failure. Spreads from human to human by contact with bodily fluids or contaminated objects. Case fatality rate ranges from 24 to 88 percent.

Lassa fever: viral illness caused by a single-stranded RNA member of the family *Arenaviridae*. Transmitted by ingestion or inhalation of virus shed in droppings and urine of *Mastomys natalensis*, the multimammate rat found in west, central, and east Africa. Symptoms include malaise and headache progressing to shock, respiratory distress, and hemorrhaging in gums, eyes, nose, or mucous membranes. Overall fatality rate is about one percent, but during outbreaks the fatality rate can reach 50 percent.

MERS/*SARS*: MERS (Middle East Respiratory Syndrome) is caused by the single-stranded RNA virus of the genus *Betacoronavirus*. Related to SARS (Severe Acute Respiratory Syndrome), another coronavirus-caused disease on the WHO list of 11. Both prompt fever, cough, shortness of breath, and are not always, but often fatal. Researchers think MERS may have originated in bats, but that the true reservoir of the virus is camels. Like SARS, MERS is believed to spread by close contact with ill people, moving via respiratory secretions. Fatality rate is about 30 percent, though this data may be underreported.

Nipah: this virus is part of the *Paramyxoviridae*, distributed through southern Asia, India, and Australia, and is transmitted from bats, pigs, and other Nipah-infected people. Transmission also happens when people have direct exposure to infected bats, for example by drinking raw date palm sap contaminated with bat secretions. Symptoms include fever and headache, followed by drowsiness and disorientation. Nipah is associated with encephalitis. Fatality rate is 74.5 percent.

Rift Valley fever: viral disease caused by a member of the genus *Phlebovirus*. Carried in livestock through eastern and southern Africa and thought to spread by contact with blood, tissue, or bodily fluid of infected animals and by mosquitoes. Symptoms are most often mild, but in some cases (8 to 10 percent) can cause encephalitis, blurred or loss of vision, and hemorrhagic fever. Fatality rate is one percent.

Chikungunya: a viral fever transmitted among humans from bites by the *Aedes aegypti* and *Aedes albopictus* mosquitoes, the same mosquitoes that transmit dengue virus. It is seldom fatal, but can cause severe muscle and joint pain along with fever.

Severe fever with thrombocytopenia syndrome: a newly emerging infectious disease caused by a *phlebovirus* carried by ticks. Symptoms include fever and thrombocytopenia (low blood platelet count). Up to 30 percent of cases in outbreaks studied so far were fatal.

Zika: a virus spread among people by the *Aedes aegypti* and *Aedes albopictus* mosquitoes. Symptoms include muscle pain and headache, but are most often mild and it is not associated with any fatalities. Zika can, however, be transmitted from a pregnant mother to her fetus, and is a cause of microcephaly and other severe fetal brain defects. *–MD*

opment of rVSV-ZEBOV. Now with IAVI, and having spent time earlier in his career in academia and with the NIH, Feinberg hopes that CEPI will show the benefits of cooperation between private and public sectors to a wider community, elaborating on what happened with Ebola.

Merck's vaccine wasn't the only one to emerge from the Ebola crisis. It just happened to be the one furthest along in trials as the epidemic subsided. GSK also has a promising candidate, and the fearsome power of Ebola also drew the first tobacco-grown antibody treatment into field use. "It was an amazing and complicated experience. The speed with which it all progressed and the urgency with which people were motivated were unprecedented," Feinberg says. "It was unusual to involve so many in a collaborative way between the private and public sectors to go after a global health threat. It was an important disease to target, but also one which was not a commercial opportunity and involved a lot of risks and opportunity costs for companies."

This is where CEPI comes in. The coalition might be able to spur conversations among not-for-profit entities, government health and research bodies, and private-sector companies about the development of vaccines for which there is no commercial market. For Feinberg these conversations can't come soon enough. "I've seen the same issues from different perspectives. I've seen opportunities for people working together more effectively across sectors. The Ebola experience, tragic as it was, served as a tipping point in thinking about how the private and public sectors need to work together to go after emerging infectious disease threats," Feinberg says. "Ebola was just one of what is going to be a continuing experience. Before Ebola was even finished, Zika was on the rise. And there will be something to follow Zika. You can't mobilize new teams and move from one crisis to another. We should be able to craft a way to have a robust, proactive, collaborative effort that gets the job done. I don't see how we will be successful unless we figure that out."

There may also be some lessons from CEPI's launch for the HIV vaccine field. "When you go after the kind of issues CEPI is taking on, you're creating something where something didn't exist. People bring innovative thinking and frank discussion to the table," says Feinberg. "When I reflect on where the HIV vaccine field is, it's clear we can learn a lot from CEPI's fresh approach. Progress towards an HIV vaccine would derive enormous benefit from the kinds of discussions that have taken place to create CEPI."

CEPI's launch

Months of preparation went into CEPI's launch in Davos, but there was at least one influential person there who did not need to be convinced of the importance of what CEPI is trying to accomplish: Bill Gates. "The world is tragically unprepared to detect local outbreaks and respond quickly enough to prevent them from becoming global pandemics," the Microsoft founder and co-chair of the Bill & Melinda Gates Foundation, said from Davos. "Without investments in research and development, we will remain unequipped when we face the next threat."

Wellcome Trust Director Jeremy Farrar, representing another big CEPI funder, made the case for using vaccines to ward off these threats. "Epidemics are among the significant threats we face to life, health, and prosperity," he said from Davos. "Vaccines can protect us, but we've done too little to develop them as an insurance policy. CEPI is our chance to learn the lessons of recent tragedies, and outsmart epidemics with new vaccine defenses." Japan, through its health minister Yasuhisa Shiozaki, views CEPI as part of its vision of universal health coverage; Berlin's Minister of Education and Research, Johanna Wanka, as part of the United Nations' sustainable development agenda. "The Ebola crisis made us painfully aware of the gaps in the international health system," Wanka said. "Prevention is the best means to ensuring healthy lives for all."

Representatives of big pharma organizations leading the industry vaccine response were also on hand at CEPI's launch in Davos, with GSK sending its outgoing chief executive, Andrew Witty. He described anticipating and preparing for future health threats as one of the greatest challenges of our time. GSK is spearheading a project called Biopreparedness Organization (BPO) in response. The plan is to build a Rockville, Maryland-based unit with a $40 million to $50 million annual budget on a 'no profit, no loss' footing, joining its new vaccines plant there. Luc Debruyne, GSK's vaccine president, describes the future BPO as a permanent and dedicated facility to avail the company's scientific expertise against emerging infectious diseases. Debruyne, penning a post about the BPO on LinkedIn, specifically pointed out his hope for it as a proving ground for faster vaccine development. GSK spokeswoman Catherine Hartley says the firm would welcome the creation of a network of approaches and projects—coordinated through a governing body such as CEPI—working on different threats simultaneously.

Neither GSK nor Merck has ongoing programs for MERS, Nipah, or Lassa fever, however, neither is ruling out their involvement. Merck spokeswoman Pamela Eisele says the company is actively engaged in discussions about how it can best contribute, and GSK is evaluating the CEPI requests for candidate proposals to see if the BPO can help contribute. Merck says it is also taking a broader approach. "Our responsibility does not end with the availability of a new vaccine," Eisele says. "We collectively rely on sustainable health systems to make sure these vaccines reach the people they are intended for. As we have seen with the Ebola vaccine trials and with routine immunization programs, trust and confidence in vaccines, in delivery systems, and in the institutions and people that make decisions about vaccines is critical to success. Sharing knowledge, best practices, our own experiences, and working with stakeholders is another way we seek to support sustainable, resilient public health and health care systems and to prevent the next calamity."

There might also be potential for CEPI to engage more with Indian vaccine developers and manufacturers. Gagandeep Kang, executive director of the Translational Health Science and Technology Institute in Faridabad, points out that India is building a large and growing domestic vaccine production industry. Pursuing Nipah, MERS, and Lassa via CEPI, Kang says, is an opportunity for India, and researchers in developing countries more broadly.

Filling gaps

CEPI is not the first public health initiative to come out of Davos. Myron "Mike" Levine, associate dean at the University of Maryland, recalls the debut of Gavi, the Vaccine Alliance, at Davos and his role as co-chair of a task force on R&D. Gavi serves as a funding and distribution agency for vaccines in the developing world. But Levine thinks CEPI could fill a vital gap left by Gavi. "Sometime in the future when the constellations align, there will emerge a pathogen with the severity of swine influenza from 1918 and 1919, with the ability to spread. It will be so infectious it will shut down cities and affect industrialized countries, as we saw with SARS [Severe Acute Respiratory Syndrome] and Ebola," he says. "We saw what SARS did. Such a lesson. That's why MERS is important. That kind of thing—the translation of the lessons of Ebola, Zika in its own right—is not what Gavi does."

Gavi Chief Executive Seth Berkley was at Davos this year, extending a hand to CEPI. Preparing for epidemics ahead of time is in the global interest, Berkley says. "Gavi will work closely with CEPI to be sure vaccines that are relevant for developing countries have a market and are stockpiled, ensuring vaccines are available when the next epidemic strikes."

These are major considerations, according to Laurie Garrett, global health fellow at the Council on Foreign Relations in New York City, where Røttingen recently spoke about CEPI. Garrett is no stranger to thinking about future pandemics as author of, among others, *The Coming Plague: Newly Emerging Diseases in a World Out of Balance*. Along with Richard Preston's *The Hot Zone*, these two books set off alarm bells about coming pandemics that have been ringing for more than 20 years.

Garrett says there are a lot of questions that are reasonable to ask about the CEPI approach, even while by and large supporting it. "In my 30 years of being involved in epidemics, I've never seen one where we knew in advance that this was a likely target so we would be ready with a vaccine, except with Ebola. And that situation with Ebola was goosed by a set of bioterrorism concerns in the United States."

This is part of the reason that CEPI is drawing on outside expertise and building partnerships. Fauci says staffers from NIAID and the US Department of Health and Human Services are already in touch with the group and participating in scientific advisory conversations. NIAID's existing vaccine platforms can support development of candidates for the CEPI pathogen targets. NIAID has a years-old development program for Lassa fever, for example. "We'd certainly share our expertise and our knowledge," Fauci says. "We're doing work on paramyxoviruses, such as respiratory syncytial virus, and we've developed novel vaccine platforms using structural biology to develop immunogens." Since Nipah is also a paramyxovirus, Fauci says, NIAID will lend CEPI some technology and advances, and the same thing holds true for MERS. "We can be an implementation and supplementation of the research component of what they do," he says. "There's always a little overlap. If they're going to develop platforms for different vaccines, we have a major investment in platform technology. But I think it's much more complementary than it is overlapping." ■

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

An Interview with *Richard Hatchett*

The recently launched Coalition for Epidemic Preparedness Innovations appointed its inaugural chief executive officer, Richard Hatchett. He talks here with *IAVI Report* about his plans for leading the new multilateral organization in its quest to fill gaps in the global response to infectious disease outbreaks.

By Michael Dumiak

Richard Hatchett

By public health standards, the Coalition for Epidemic Preparedness Innovations (CEPI) is moving quickly. The idea for the coalition sprung from the largest and most recent Ebola outbreak in 2014-2015. Since then it has raised hundreds of millions of dollars in funding and issued its first call for proposals to develop vaccine candidates against three top pathogens with pandemic potential (see page 4). Starting in mid-April, CEPI will forge ahead under the leadership of new chief executive Richard Hatchett.

From his time as head of the main triage facility near ground zero of the September 11, 2001, attacks on New York City, the former emergency room physician and oncologist has been thinking about how best to organize medical resources to meet public health emergencies. In the wake of the 9/11 attacks, Hatchett and a small group of fellow physicians proposed the idea of organizing a trained group of medical volunteers to respond to emergencies. This idea was expanded and eventually became the US Medical Reserve Corps, a community-based public health network with 200,000 volunteers located throughout the US.

From 2011, Hatchett worked at the Biomedical Advanced Research and Development Authority (BARDA), an effort established during US President George W. Bush's administration to develop and deploy medical countermeasures such as vaccines, personnel, or infrastructure to man-made and natural threats. Hatchett started there as chief medical officer and then became deputy director. While with BARDA, he directed the team that designed and staffed the US government's Monrovia Medical Unit during the 2014-15 Ebola outbreak.

As the concept for CEPI arose, Hatchett followed its development closely, dispatching representatives from BARDA to the developing organization and inviting it to participate in the annual BARDA portfolio review of its investments and strategy. The 48-year-old father of three will kick off his tenure with CEPI at the coalition's current headquarters in Oslo, where he will first conceive and create a vaccine development team. Hatchett then plans to move to London, splitting his time between the three branches (London, Oslo, and New Delhi) of what will be a networked secretariat. He is driven by what he says is the unique opportunity CEPI offers the world to be better prepared for dangerous epidemics.

What are some of your strategies for CEPI, and do you feel a need to quickly show to the public or to donors that the concept works?

Quick successes are great if you can achieve them, and we'll have a better idea of whether that is going to be feasible once we see the vaccine candidates that come in for the first call for proposals. We're just getting our first look.

The only real metrics of success for CEPI are whether it can develop the vaccines we need and whether CEPI can ensure that they're going to be available to the individuals and populations that need them.

One of my critical early missions and goals coming in is going to be building a strong vaccine development team. We're beginning our recruitment process for a vaccine development lead and for the various areas where we're going to need expertise internally. We are talking with a lot of people about different approaches to structuring the vaccine development team: who needs to be in-house, what kind of expertise can be contracted, and what kinds of expertise obviously can reside within our private-sector partners.

What type of vaccine development team do you envision CEPI needing?

I think there are a number of different models for how you can pull together the expertise that you need. I know how we approached this at BARDA, and I've had lots of conversations with the [Bill & Melinda] Gates Foundation to understand how they do it. I've also talked with some partners from inside industry and I'm continuing to talk to others.

It's a very important issue for CEPI. A lot of people have used the expression "lean and mean," in that it lets you be agile and fast. I want to make sure that we're lean and mean, not emaciated.

My experience is that an organization's needs evolve over the course of working with its partners. Many of BARDA's partners on many of the projects ended up being small- to mid-sized biotechs, not big pharmaceutical companies. And the small- to mid-sized biotechs have certain advantages, but they also lack certain capabilities, and so we needed to build an internal capability as well.

CEPI has the great advantage of having very large vaccine partners. I'm sure that we're going to have a number of small- to mid-sized biotechs come in, and what we're going to need internally is going to depend to a certain extent, even to a large extent, on who our partners are. So this is a work in progress.

How might you approach building partnerships to accomplish the coalition's goals?

We have signed a memo with WHO [World Health Organization], and have set up a partnership forum and a joint coordination group to engage with various stakeholders. CEPI's mission requires close working relationships with industry partners and coordination with upstream funders. Coordination has to happen with agencies and organizations that may take responsibility for stockpiling and deploying eventual vaccines during an emergency response. The partnership model I am most familiar with is the US government's Public Health Emergency Medical Countermeasure Enterprise, which enables coordination of medical product development across the entire spectrum of the product life cycle, from basic discovery to delivery. This is one I hope CEPI and its partners can emulate.

How will you see that CEPI avoids duplication of ongoing research efforts?

We are very focused on not duplicating ongoing research efforts, but on using CEPI's investments catalytically, including through co-funding and creating synergies by supporting cooperation between existing efforts. The marvelous thing about CEPI's creation is the commitment of the various partners to bring their own unique capabilities to the table to achieve a common objective of epidemic preparedness. We all have the same goal and will accomplish much more if we build on the capabilities that already exist.

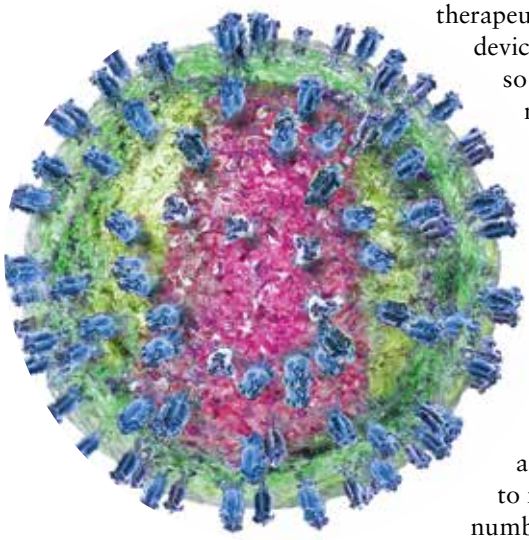
Are multi-use vaccine platforms an explicit goal for CEPI?

Yes, supporting the development of rapid-response platforms is an explicit goal and we are planning a specific call for such platforms. Nucleic acid technologies have been around for a while, but [they] are beginning to be really exciting and lend themselves to a plug-and-play approach. You have a new pathogen, you identify a target that can produce an immune response, and if you have a well-developed platform where you plug in the information from the new pathogen that you need, then you can proceed, hopefully quite rapidly, with vaccine development.

How will you approach your new role? How will it differ from your role at BARDA?

I'm still in listening mode. I'll start in Oslo for several months and then move over to London.

And then I'll be splitting my time. CEPI's secretariat is divided between three main nodes right now: Oslo, London, and New Delhi. I will be looking at that organizational structure and trying to think about the allocation of functions across that structure that makes the greatest sense. Resource mobilization is a critically important role. CEPI is only about halfway to its billion-dollar goal for the first five years, so working to close that gap will be a major focus.



BARDA has a pretty broad mission to develop vaccines, biological therapeutics, small molecule therapeutics, diagnostics, and other medical devices against threats a terrorist can use: so chemical, biological, radiological nuclear weapons, pandemic influenza, and emerging infectious diseases. And more recently, that mission has been expanded to include the threat of antimicrobial resistance.

CEPI's mission right now is more narrowly defined. It aims to develop vaccines against emerging infectious diseases with epidemic or pandemic potential. In a very smart move, CEPI has elected to focus its initial efforts on a limited number of pathogens. I would say that one of the keys to BARDA's success over the years—and it's become a pretty considerable success cumulatively over time—has been to define the mission and then stick to the mission very closely. CEPI has tremendous resources at its disposal, but in the context of vaccine development programs there are significant budget restraints. I think the choice to narrow the focus down to just a couple of high-priority pathogens is going to serve CEPI really well.

What I can bring to CEPI from BARDA is really a deep understanding of what has and hasn't worked, how a successful medical countermeasures program should be organized and administered, and what it takes to succeed. I want CEPI to make its own mistakes, not repeat old mistakes.

Do you have any examples?

One of the signature US programs was an attempt to develop a recombinant protective antigen anthrax vaccine—a next-generation vaccine. One of the first programs that was funded when the program just got started was a vaccine program by a company called Vaxgen. The US government made close to a US$900 million investment in Vaxgen, which was a very small company that didn't have deep vaccine development experience. That program did not succeed. The government was able to recuperate almost all of that $900 million, so it wasn't that we lost a lot of money. But they weren't cautious in how they represented the program. There was a lot of ballyhoo about it. When the failure came, it was damaging in a way that it, perhaps, shouldn't have been.

We learned our mission. The US government was very successful in advancing flu vaccine manufacturing technology. At the time when the US flu program started or really got running in 2005 or so, there were no cell-based vaccines that had been approved, and certainly no recombinant influenza vaccines approved. Both of those technologies offered advantages in terms of scalability and potentially in terms of speed. That's particularly true with the recombinant vaccine over the existing egg-based technology. We had large partners working with us. Even that comparatively incremental advance was fraught with a lot of risk, and so it took investing in six programs to end up with one that succeeded.

You have to take a risk-based approach, you have to invest in multiple programs, and you have to be tolerant of failure and keep your eye on the end objective and make sure that you make enough investments to ensure that you succeed. ■

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

Rallying CROI

The 24th Conference on Retroviruses and Opportunistic Infections, which took place from February 13-16, is the preeminent US-based scientific meeting on HIV research.

By Richard Jefferys and Michael Dumiak

The annual Conference on Retroviruses and Opportunistic Infections (CROI) oscillates back and forth between the east and west coasts of the US from year to year. In 2017 it was Seattle that played host. Much of the science presented there represents subtle advances toward treating, preventing, and curing HIV infection, rather than the showstoppers that were a mainstay in some years. The HIV field seems poised to benefit from slow and steady progress, whether it be in the use of broadly neutralizing antibodies (bNAbs) to design vaccine immunogens or prevent infection through passive administration, or the use of the therapeutic vaccination in cure research.

The challenges and promise of bNAbs

Preventive HIV vaccine research occupied a relatively small plot on this year's conference agenda. But what discussion there was on vaccines centered primarily around bNAbs. William Schief, professor in the Department of Immunology and Microbiology at The Scripps Research Institute (TSRI) and director of Vaccine Design for IAVI's Neutralizing Antibody Center at TSRI, addressed efforts to create vaccine immunogens capable of eliciting these highly desirable antibodies, and did not sugarcoat the magnitude of the challenge. The task involves tracing the long and tortuous maturation pathway that B cells follow in order to produce bNAbs in some rare HIV-infected individuals, and then attempting to figure out if immunization regimens might be able to guide B cells down that pathway in the broad swath of the human population that needs an effective HIV vaccine. "This is something nobody has ever had to worry about for a vaccine before," Schief emphasized.

He then reviewed the preliminary progress that has been made toward this goal with a class of bNAbs that target the CD4 binding site, so-called VRC-01 class antibodies (see page 17). An initial assessment of the likely frequency of the naïve B-cell precursors that can give rise to these antibodies suggest they are present at a reasonable frequency in the human population (*Science* **351**, 1458, 2016). "Basically everybody in this room, in your resting lymph nodes, you have about 90 VRC01-class B-cell precursors," Schief explained.

Schief and colleagues have designed an immunogen that contains 60 copies of an engineered CD4 binding site on a nanoparticle, dubbed eOD-GT8 60mer, capable of activating VRC01-class B-cell precursors, and shown that it appears to accomplish this task in mouse models (*Science* **353**, 1557, 2016). A Phase I clinical trial of this vaccine immunogen in humans is scheduled to begin in the first quarter of 2018. It will be tested along with GlaxoSmithKline's ASO1B adjuvant, which has been tested with other vaccine candidates, including those for malaria and herpes zoster.

Now researchers have turned their focus to investigating the best strategy for boosting the response induced by eOD-GT8 60mer in hopes of taking B cells further down the path toward producing VRC01-like bNAbs (*Cell* **166**, 1459, 2016). The US Food and Drug Administration has indicated that when candidate boosters are ready for human trials they can be tested in individuals who have already received the eOD-GT8 60mer prime, rather than first being required to undergo assessment alone.

Schief also offered a glance at work assessing whether the same strategy can be employed to try and generate antibodies resembling the potent bNAb PGT121. While VRC01 interacts with the CD4 binding site of the HIV Envelope (Env), PGT121 is specific for a region known as the N332-supersite, which has been shown to be a common target in HIV-infected individuals who develop bNAbs (*PLoS Pathog.* **12**, e1005369, 2016). In a

Zimbabwe's example

CROI's opening session put forth someone who knows quite a bit about progress in dealing with HIV. The Sudanese cardiologist and HIV researcher James Hakim, who gave the annual N'Galy-Mann Lecture, described his move to Zimbabwe in the early 90s and how he organized an increasingly robust HIV research network, establishing the University of Zimbabwe's Clinical Research Center, and becoming head of the National Institute of Allergy and Infectious Diseases' (NIAID) AIDS clinical trial unit in Harare.

For a country still torn by political violence and wild economic gyrations, Zimbabwe has made dramatic progress. The country collects a three percent tax on personal and corporate income for a national AIDS Trust Fund (the AIDS Levy). This money, along with help from the US President's Emergency Plan For AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria, helps provide antiretroviral therapy (ART) to over 900,000 people out of a population of 1.2 million living with HIV in the country. This corresponds to 86.8 percent of those in need on treatment, with 86.5 percent virally suppressed, almost reaching the United Nations goal of 90-90-90 (90 percent diagnosed, 90 percent on treatment, and 90 percent of those virally suppressed) set in 2014 as a means toward ending the AIDS epidemic. "Progress towards these targets is testament to the robust global coalition to fight AIDS and the resilience of the Zimbabwean people," Hakim said. —*MD*

pair of papers published last year, Schief and colleagues reported the successful design of stabilized Env trimers that were able to activate the inferred naïve precursors of PGT121-producing B cells (*Immunity* **45**, 483, 2016). When given in an immunization series involving Env trimers with progressively fewer mutations compared to the wild-type or native Env trimer, antibodies capable of neutralizing tier-2 HIV isolates were generated (*Cell* **166**, 1445, 2016). However, Schief stressed that these experiments involved mice genetically manipulated to only possess precursors of PGT121-producing B cells. The frequency of appropriate naïve B-cell precursors in humans is currently being investigated.

Michel Nussenzweig, the Zanvil A. Cohn and Ralph M. Steinman professor at Rockefeller University and Schief's collaborator on the PGT121 studies, discussed clinical studies involving passive administration of bNAbs to either help control or prevent HIV infection. Nussenzweig's group has conducted several trials involving passive administration of the bNAbs 3BCN117, which targets the V3 glycan supersite, and 10-1074, which is a CD4 binding-site targeting antibody. Both demonstrated antiretroviral activity after single infusions in HIV-infected individuals not on antiretroviral therapy (ART; *Nature* **522**, 487, 2015; *Nat. Med.* **23**, 185, 2017). 3BCN117 has also been studied in the context of treatment interruption: administration of four doses was associated with a significant delay in viral load rebound, averaging around 10 weeks (*Nature* **535**, 556, 2016); a longer delay than that documented in similar studies with VRC01 (*N. Engl. J. Med.* **375**, 2037, 2016), Nussenzweig noted. However, the rapid development of resistance is a problem with bNAbs administered singly, so trials are now exploring combinations.

Nussenzweig gave a preview of an unpublished macaque experiment conducted in a partnership with Malcolm Martin at the National Institute of Allergy and Infectious Diseases, in which a combination of 3BCN117 and 10-1074 was given for two weeks (three injections per week) starting three days after infection with the pathogenic hybrid SIV/HIV strain SHIVAD8. Interestingly, many of the animals have maintained low viral loads and preserved $CD4^+$ T cells for many months after the administration of the bNAb combination, suggesting a prolonged beneficial impact on virus-specific immunity. Depletion of $CD8^+$ T cells has been performed in some of the macaques, which caused an increase in viral load. This further supports the idea that the short-term bNAb intervention promoted immunological control of the SHIVAD8 challenge virus. The results were published shortly after the conference (*Nature* **543**, 559, 2017). Nussenzweig pointed to the potential for bNAbs to modulate immunity in various ways, including via antibody-dependent cellular cytotoxity (ADCC) and the formation of immune-stimulating antibody-antigen complexes; these capacities underlie the mounting interest in studying bNAbs in the context of HIV cure research (see page 17).

With regard to prevention, Nussenzweig's lab was involved in macaque studies, again in collaboration with Martin, which demonstrated the rationale for the ongoing trials of passive immunization with VRC01 for the prevention of HIV infection (the Antibody Mediatied Prevention studies, a joint effort of the HIV Prevention Trials Network and the HIV Vaccine Trials Network). In this case macaques received a single infusion of one of four bNAbs—3BCN117, 10-1074, VRC01, or a long-acting version of VRC01 (VRC01LS)—followed by weekly, low-dose intra-rectal challenges with SHIVAD8 until viremia was detected. The median time to infection in control animals was a little over three weeks, whereas significant delays in acquisition were observed in all bNAb recipients, ranging from eight to 14.5 weeks. Importantly for the human trials, protection was achieved at low antibody concentrations (*Nature* **533**, 105, 2016).

In pursuit of a cure

The pursuit of an HIV cure has gained momentum and a higher profile at CROI over the past decade, and the trend continued this year. One of the presentations that drew intense attention highlighted a possible role for therapeutic vaccination as a means to suppress HIV viral load in the absence of ongoing ART. The study was described by Beatriz Mothe, HIV Unit associate investigator at the Institut de Recerca de la Sida (IrsiCaixa) in Barcelona Spain, and involved HIV vaccine candidates designed by Tomas Hanke and colleagues at the University of Oxford that encode antigens designed to focus T-cell immune responses on conserved regions of the virus (primarily from Gag, Pol, Env, and Vif proteins).

In an initial trial, 24 individuals who began ART within three months of becoming HIV infected received immunizations with two vector-based candidates: a prime derived from a chimpanzee adenovirus (ChAdV63), and a booster from a modified Vaccinia Ankara strain (MVA). Both vaccines carried the conserved HIV antigen inserts, dubbed HIV-consv. As reported in a poster at last year's CROI, the vaccine regimen successfully induced T-cell responses to the included antigens—close to half of all detect-

able HIV- specific T cells were targeting those regions of the virus (CROI 2016, Abstract 320). Fifteen of the participants (14 men and one woman) were then enrolled in a follow-up protocol. These participants received three infusions of the anti-cancer drug romidepsin, a histone deacetylase (HDAC) inhibitor that has been shown to induce replication of latent virus in the reservoir, in combination with additional boosters of the MVA HIVconsv vaccine given before and after the drug.

Eight weeks after the final MVA immunization, all participants interrupted ART until their viral load exceeded 2,000 copies/mL. So far, 13 have reached this stage, with eight of them rapidly experiencing viral load rebounds necessitating ART reintroduction. Five individuals, however, have been able to maintain low viral loads, with three below the limit of detection (20 copies/mL). One of these individuals has maintained a suppressed viral load for over six months. Mothe pointed out that while cases of post-treatment control of viral load have been reported in some studies of early ART, the frequency has been around 10 to 15 percent at most, compared to 38 percent of the cohort in this trial.

Additional studies are underway to try and better understand this outcome, but Mothe noted there is some evidence that the vaccine-induced T-cell responses to conserved HIV antigens, which were successfully boosted by the additional MVA immunizations, are contributing. The role of romidepsin will likely be challenging for researchers to tease out because there was no control group. The drug did not have a measureable effect on the size of the HIV reservoir overall, based on pre- and post-administration comparisons of HIV DNA levels. It also caused an array of side effects that are known to be associated with HDAC inhibitors, including one case of sepsis.

Transient low-level increases in HIV viral load during romidepsin infusions suggest it did, however, exert latency-reversing effects. But Mothe also highlighted that 60 percent of participants saw similar blips of viremia after receiving the MVA vaccine candidate, which is consistent with evidence that latent virus can reside in HIV-specific $CD4^+$ T cells and therefore may be stimulated to replicate by HIV antigens (*AIDS Res. Hum. Retroviruses* **28**, 835, 2012). Despite the small sample size and remaining unknowns, the trial represents something of a milestone—it is the first time an evaluation of the strategy known as "kick and kill," which combines a latency-reversing agent with an immune-enhancing approach, has been associated with an increased frequency of viral load suppression after ART interruption.

Jintanat Ananworanich, associate director for Therapeutics Research at the US Military HIV Research Program (MHRP), emphasized the rarity of post-treatment control in a talk about a cohort of extremely early treated individuals (now numbering over 400 individuals) who have been recruited in Bangkok, Thailand. Ananworanich and colleagues have previously reported that study participants at Feibig stage I—estimated to be within 10-17 days of HIV acquisition, and diagnosed by having detectable HIV RNA but negative antibody and p24 antigen tests—have a significantly smaller viral reservoir than individuals diagnosed later (*J. Virus Erad.* **2**, 43, 2016). The logical question that flowed from this observation was whether the initiation of ART at Feibig stage I might be associated with an increased possibility of achieving virological remission when ART is interrupted.

Eight individuals (seven men and one woman) were recruited in a study designed to address this question. A small group was chosen to minimize any negative consequences of treatment interruption with contingency plans to enroll an additional seven volunteers if at least one case of post-treatment control to a viral load of less than 50 copies/mL was documented in the initial group. The median time on ART prior to interruption was 2.8 years. Viral load was monitored every three to seven days and the criteria for restarting ART were two viral load measurements above 1,000 copies/mL. All participants rebounded after a median of 26 days (with a range of 13 to 48 days). There were no significant safety issues, and while the size of the HIV DNA reservoir transiently increased, it declined to levels similar to baseline when treatment was restarted. However, Ananworanich noted that four of six individuals who were initially non-reactive on HIV antibody tests, due to how quickly after infection they had begun ART, seroconverted and subsequently remained HIV positive by traditional antibody tests after the interruption.

Ananworanich also highlighted MHRP's involvement in a clinical trial underway in adults employing therapeutic vaccines based on adenovirus serotype 26 (Ad26) and MVA vectors. The next step will be to combine vaccination with a toll-like receptor (TLR)7 agonist, as this approach has shown promise in the simian immunodeficiency virus (SIV)/macaque model (*Nature* **540**, 284, 2016).

What a difference a day makes

In a symposium dedicated to cure research, Louis Picker, associate director of the Vaccine & Gene Therapy Institute at Oregon & Health Science

University, provided an update on work involving his much-discussed cytomegalovirus (CMV)-based vaccine vector. As has been extensively documented, a version of the vector encoding SIV antigens reliably leads to robust control of pathogenic SIV challenges in half the macaques that receive it (*Nature* **473**, 523, 2011). This control of SIV is associated with the induction of unusually broad CD8+ T-cell responses, some of which are class II-restricted—an antigen presentation pathway typically thought to only be utilized by CD4+ T cells (*Science* **340**, 1237874, 2013). Many of the animals in these studies even appear to eventually clear SIV infection (*Nature* **502**, 100, 2013), and Picker noted there are two possible explanations for this outcome: either the SIV reservoir is progressively eliminated by vaccine-induced SIV-specific immune responses, or these immune responses initially limit the formation of the virus reservoir to such an extent that the size eventually decays to zero over time.

In an attempt to distinguish between these possibilities, Picker and colleagues conducted an experiment in which the CMV-based SIV vaccine was tested as a therapeutic intervention in macaques started on ART at various times after SIV infection. A version of the vaccine encoding tuberculosis antigens was used as a control. The reasoning was that if vaccine-induced T-cell responses were capable of clearing the SIV reservoir, then immunization might lead to a lack of viral load rebound after ART withdrawal. But this was not what the researchers found. Receipt of the CMV-based SIV vaccine was not associated with prevention of SIV rebound, leading Picker to conclude that, in the prevention setting, the approach is working by limiting the formation of the viral reservoir rather than actively clearing it.

The study did produce some interesting observations, however. A feature of the experimental design called for ART to be initiated in the macaques when an inflammatory signature indicating monocyte activation, which was associated with initial establishment of the reservoir in prior studies, was observed. This made it possible for Picker to segregate macaques into different groups depending on how many days after SIV challenge ART was first administered: days 4/5, day 6, day 7, days 8/9, or day 12.

Picker showed that the six animals treated starting on days 4/5 had dramatically lower viral load peaks (which rose by a log in each subsequent group) and significantly smaller SIV reservoirs compared to those treated later. Furthermore, all the macaques in days 4/5 group did not display any rebound of SIV viral load when ART was interrupted after 600 days. Only one of the remaining 35 animals showed a similar lack of rebound, and that was one out of 13 macaques in the day 6 group.

To test whether CD8+ T cells were controlling SIV replication, a depletion experiment was conducted, but no return of SIV viral load was observed. Cells transferred from the non-rebounding macaques to naive animals were also unable to establish an infection. Necropsy studies revealed some evidence of SIV DNA, but no replication-competent virus could be detected. The sole exception was the macaque from the day 6 group, in which a rebound of SIV viral load occurred eight months after ART was stopped, just prior to necropsy. Picker drew a parallel between this animal and the famous human cases of HIV remission that have been described, most notably the Mississippi baby, in whom no sign of HIV could be detected for over two years after an ART interruption before viral load ultimately rebounded (*N. Engl. J. Med.* **372**, 786, 2015).

Picker concluded that the SIV reservoir established within the first five days of infection is likely unstable, perhaps because the virus has not yet entered long-lived cells, and can wane during sustained suppression of viral replication by ART. But just one day appears to make a difference. Data from this study indicates that the reservoir had become more permanently established in the macaque that eventually rebounded. As has been suggested by the example of the Mississippi baby, latently infected cells can clearly persist in an inactive state for extended periods, making it challenging to establish whether a cure has been achieved and, Picker argued, supporting the need for strategies that attempt to expose and deplete the latent reservoir.

In addition to the Mississippi baby, the two other widely publicized cases of HIV remission in humans are known as the Boston patients. These were two HIV-infected individuals who underwent stem cell transplants required for the treatment of concomitant cancers while remaining on ART. Post-transplant, after their immune systems had been successfully reconstituted by the donor stem cells, HIV reservoirs could no longer be detected. Both ultimately underwent an ART interruption with careful monitoring, and no HIV could be detected for three and eight months, respectively, before a sharp and sudden rebound in viral load occurred accompanied by symptoms of acute retroviral syndrome, necessitating the reinstitution of treatment (*Ann. Intern. Med.* **161**, 319, 2014). At CROI, a poster presentation from the research group of Nathan Cummins, assistant professor of medicine at the Mayo Clinic in Rochester, Minnesota, described an additional

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Best in Class

Adding to the now lengthy list of broadly neutralizing antibodies is the recently discovered antibody N6. This one tops the list in terms of neutralization breadth—knocking out 98 percent of HIV isolates—and also packs a potent anti-viral punch.

By Kristen Jill Kresge

Antibody researchers are experiencing a windfall. They continue to isolate HIV-specific antibodies that can neutralize a broad swath of HIV isolates, so-called broadly neutralizing antibodies (bNAbs), at a rapid clip even though they are made by only about 20 percent of HIV-infected individuals. From what was a meager handful of bNAbs just seven years ago, researchers have amassed hundreds of these powerful infection-fighting proteins to guide vaccine design, aid in HIV prevention more broadly, serve as a potential long-acting HIV treatment, or even be part of an eventual cure strategy.

One of the more recent antibodies isolated by researchers at the US National Institute of Allergy and Infectious Diseases (NIAID) is getting top billing for its unprecedented ability to knock out 98 percent of HIV isolates, and to do so at a low dose, meaning it is potent as well (*Immunity* **45**, 1108-1121, 2016). This antibody, dubbed N6, targets the CD4 binding site on the virus—the critical location where HIV attaches to $CD4^+$ T cells, its primary targets (see cover image and caption, page 3). Several other antibodies researchers have isolated recently also target this spot on the virus, the most well studied of them being the antibody VRC01 that was isolated back in 2010 by scientists at the Vaccine Research Center (VRC) at NIAID. But none of them so far can match the breadth or potency of N6, which are just some of the attributes that make this antibody so intriguing to vaccine researchers. Another factor is that N6 is even active against the vast majority of virus isolates that are resistant to other CD4 binding-site antibodies. Taken together, these characteristics make N6 an attractive antibody from which to design vaccine immunogens.

Mark Connors

In addition to helping guide vaccine design, these bNAbs have other applications. In animal studies, passively administered or vector delivered bNAbs can prevent infection (*Curr. HIV/AIDS Rep.* **13**, 31–37, 2016). Clinical trials are now testing whether passive administration of VRC01 (given during regularly scheduled intravenous infusions) can block HIV infection in humans (https://clinicaltrials.gov/ct2/show/NCT02716675). An antibody like N6, which researchers note is five to ten times more potent than VRC01, is an attractive candidate for passive administration because less antibody would need to persist for the protective effect to be sustained. Still, given HIV's unprecedented ability to mutate to avoid immune responses, researchers suspect an ideal recipe for passive administration would be a cocktail of the best bNAbs targeting multiple sites of vulnerability on the virus. N6, the latest and greatest in the class of CD4 binding site antibodies, would definitely be a prime candidate for this.

As Devin Sok of IAVI and Dennis Burton of IAVI's Neutralizing Antibody Center at The Scripps Research Institute in La Jolla, CA, suggest (*Immunity* **45**, 958-960, 2016), "Not only will the continued isolation of bNAbs like N6 contribute to vaccine efforts, but antibodies with such levels of breadth and potency and minimal autoreactivity are also being championed for potential use as prophylactic and therapeutic agents."

Managing Editor Kristen Jill Kresge spoke recently with Mark Connors, chief of the HIV-specific immunity section at NIAID whose laboratory isolated N6, about this all-star antibody and its unique mechanism of action.

Could you start by explaining how N6 was isolated?

The method of isolation we use is micro-culture of peripheral blood B cells. The strength of that is that it allows you, without any sort of prior knowledge, to ask the question of what in this patient is mediating neutralization. The patient from whom

N6 was isolated had particularly broad and potent serum. That technique has allowed us to isolate novel antibodies that maybe wouldn't have been expected. In this case we had some inkling that at least one of this patient's specificities would have been a CD4 binding site antibody, and that is what we pulled out. The remarkable thing in initial testing was that it has pretty remarkable breadth and potency, but also that it can neutralize the VRC01-resistant isolates quite potently. So we thought that this antibody might have a novel mode of binding and that we could learn some things from this.

Is it unusual among the antibodies isolated to date to show such potency and breadth at the same time?

Yes, it has been so far. Some of the most potent antibodies like PGDM1400 and PGT16 tend to be a bit less broad. And some of the most broad antibodies, such as 10E8, are considerably less potent. N6 combines both of those features into one antibody.

The potency has become more and more of a focus in addition to breadth because it increases the likelihood, from a practical standpoint, that you can use the antibody for passive administration for prophylaxis. Combining some of these antibodies with a long-acting mutation that enhances the half-life potentially could offer the possibility—if the antibody's potent enough—that you could administer it subcutaneously on the order of months apart between doses.

When the idea of passive administration was first introduced it seemed that people described it as a way to show that bNAbs could indeed protect against infection and therefore would be reasonable vaccine targets. Now it's considered an implementable prevention strategy. Was there a switch in how passive administration is viewed?

Well I think that the incorporation of some of these mutations that alter the half-life are really what changed people's minds with regard to that, as well as the increases in potency we see with some of the more recently isolated antibodies. Once we got to the threshold where you could potentially administer a dose subcutaneously and that dose is going to last for months, then that made this prevention approach feasible. In earlier years we had neither of those two things: the antibodies were not especially potent and they had not been combined with some of these binding mutations that would enhance half-life.

Can you describe how N6 uniquely neutralizes HIV?

Well it binds the CD4 binding site similarly to other antibodies, but there's an important twist there, and that is that its flexibility allows it to shift the light chain out of the way. One of the constraints of CD4 binding site antibodies is that they require the short CDRL3 [light chain complementarity-determining region 3] in order to get out of the way of changes in the V5 loop of the virus. Meanwhile, the virus co-evolves to change V5 and put up bulky groups there that potentially can keep VRC01-like antibodies from binding. N6 sort of rotates the light chain out of the way and so it enables it to bind some of these highly resistant isolates that have changes at the V5 loop, and therefore N6 maintains its potency against some of those viruses.

Another thing is that N6's binding seems to be more spread out across the various binding regions of the antibody, so it is better able to tolerate point mutations. Even if HIV makes changes in individual amino acids, N6 is better than other CD4 binding site antibodies at tolerating the loss of some of those contacts.

Those two features together really dramatically improve the breadth of the N6 antibody and its ability to neutralize resistant isolates.

What are the next steps for N6 and optimizing it for testing in animal studies or in humans?

Our lab is more involved in discovery of new antibodies and trying to stimulate specificities similar to N6, but we have collaborators either in large pharma or at universities, as well as at the VRC, who are pursuing many of these avenues of research. The pharmacokinetic studies in macaques have already been done. And Dan Barouch has done some studies of N6 in therapy in macaques… There are quite a few different groups who are pursuing this for either therapy or prophylaxis in macaques, and then ultimately in humans.

What advantages, if any, do CD4 binding site-specific antibodies offer to vaccine researchers?

Well, number one is that this is a highly conserved site. I think that most people now feel that we're going to need to induce neutralizing antibodies to at least a couple of different sites, and so the CD4 binding site, in addition to MPER, and possibly some of the apex-directed antibodies, are a few possible sites that are areas of vulnerability, or so-called vulnerability for HIV. The research that we, Dennis Burton, John Mascola [director of the VRC], Michelle Nussenzweig [Zanvil A. Cohn and Ralph M. Steinman Professor in the laboratory of molecular immunology at the Rockefeller University], and others in the field that have discovered

these antibodies have done has now put us in a position where we could potentially use that information. The answer that we've gotten back is that here are the areas of HIV vulnerability, and I think that probably it's wise to target those areas that are relatively conserved. Clearly the human immune response can mediate broad and potent neutralization through those areas of vulnerability. So, I think the human immune system has now told us what the critical vaccine targets are.

So do you foresee a future passive administration trial involving multiple antibodies?

Yes. It's just getting started now with single antibodies before using multiple antibodies in animal models, but it's just a matter of time. The fraction of isolates that aren't sensitive to N6 are smaller than for other antibodies, and it's possible that combining these antibodies that are increasingly difficult to mutate around together might be the best possible combination to move forward with, but that has not yet been demonstrated in animal experiments.

One important feature that I and others have done a lot of work on is the resistance pattern after passive administration of antibodies. It remains to be determined what the relative advantage that antibodies like N6 have with regard to the selection of resistance, but it's another property in addition to potency and breadth that needs to be considered. ■

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HIV remission case similar to the Boston patients.

This individual underwent a stem cell transplant for the treatment of acute lymphoblastic leukemia and afterward displayed a dramatic reduction in measures of the viral reservoir, which were extremely low or undetectable from day 56 post-transplant. ART was eventually interrupted, and no HIV could be detected for 288 days, at which point the virus reemerged. The rebound was slower and less dramatic than in the Boston patients and symptoms were not observed, but the resumption of ART was nonetheless required. This new case underscores Picker's point that latently infected cells can persist for long periods in a dormant state before a reactivating event occurs. The presenter of the poster, Stacey Rizza, associate professor of medicine at the Mayo Clinic, noted that the individual had been involved in a car accident shortly before the viral load rebound, leading to speculation that while he was not seriously hurt, perhaps stress-related inflammation precipitated the activation of a latently infected cell or cells.

Worlds within worlds

HIV researchers over the last few years are turning more and more attention to microbial environments, particularly the single-celled flora in the intestines. After all, HIV is a disease of the gut. But scientists are now on to other biomes: the biota found in the vagina. Last summer in Durban researchers presented data suggesting that women carrying the uncommon *Prevotella Bivia* bacteria are 19 times more likely to have genital inflammation and 13 times more likely to contract HIV than those without this kind of vaginal bacteria. Variants in the vaginal biome also seem to play a role in the varying effectiveness of a vaginal gel used as pre-exposure prophylaxis (PrEP), but not when PrEP is administered orally.

The vaginal microbiome continues to be an environment attracting great interest. Scott McClelland, an epidemiologist at the University of Washington, cites bacterial vaginosis as a longtime indicator of increased HIV acquisition risk. But McClelland emphasized that while the composition of the vaginal microbiome may boost the chances of acquiring HIV, women with standard microbiota can still become infected. "Women do not have to have a particular microbial profile to acquire HIV," he said, adding that it's possible that treating bacterial vaginosis may alter these odds, but further research is needed.

Women with greater number of partners and more frequent sexual activity are at greater risk of bacterial vaginosis, and, incidentally, of HIV, said Sharon Hillier, director of reproductive infectious disease research at the Magee-Women's Hospital of the University of Pittsburgh School of Medicine. It raises the possibility, Hillier said, that the relationship between a vaginosis-type biota and the reduced effectiveness of topical PrEP may have less to do with the bacteria itself than a coincidental lower adherence to using the gel or unmeasured differences in behavior. ■

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Upcoming HIV-Related Meetings

MARCH 2017

Keystone Symposia: HIV Vaccines
March 26-30; Steamboat Springs, Colorado, USA
More information: www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1440

APRIL 2017

HIV & Hepatitis in the Americas
April 6-8; Rio de Janeiro, Brazil
More information: www.hivhepamericas.org

Keystone Symposia: B Cells and T Follicular Helper Cells – Controlling Long-Lived Immunity
April 23-27; Whistler, British Columbia, Canada
More information: www.keystonesymposia.org/index.cfm?e=Web.Meeting.Program&Meetingid=1462

MAY 2016

Cold Spring Harbor Laboratory: Retroviruses
May 22-27; Cold Spring Harbor, New York
More information: meetings.cshl.edu/meetings.aspx?meet=RETRO&year=17

JUNE 2016

Asia Pacific AIDS & Co-infections Conference 2017
June 1-3; Hong Kong
More information: www.virology-education.com/event/upcoming/apacc2017

12th International Workshop on Co-infection – HIV & Hepatitis
June 21-23; Lisbon, Portugal
More information: www.virology-education.com/event/upcoming/13th-co-infection-workshop-2017

JULY 2017

9th IAS Conference on HIV Science (IAS 2017)
July 23-26; Paris, France
More information: www.ias2017.org

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