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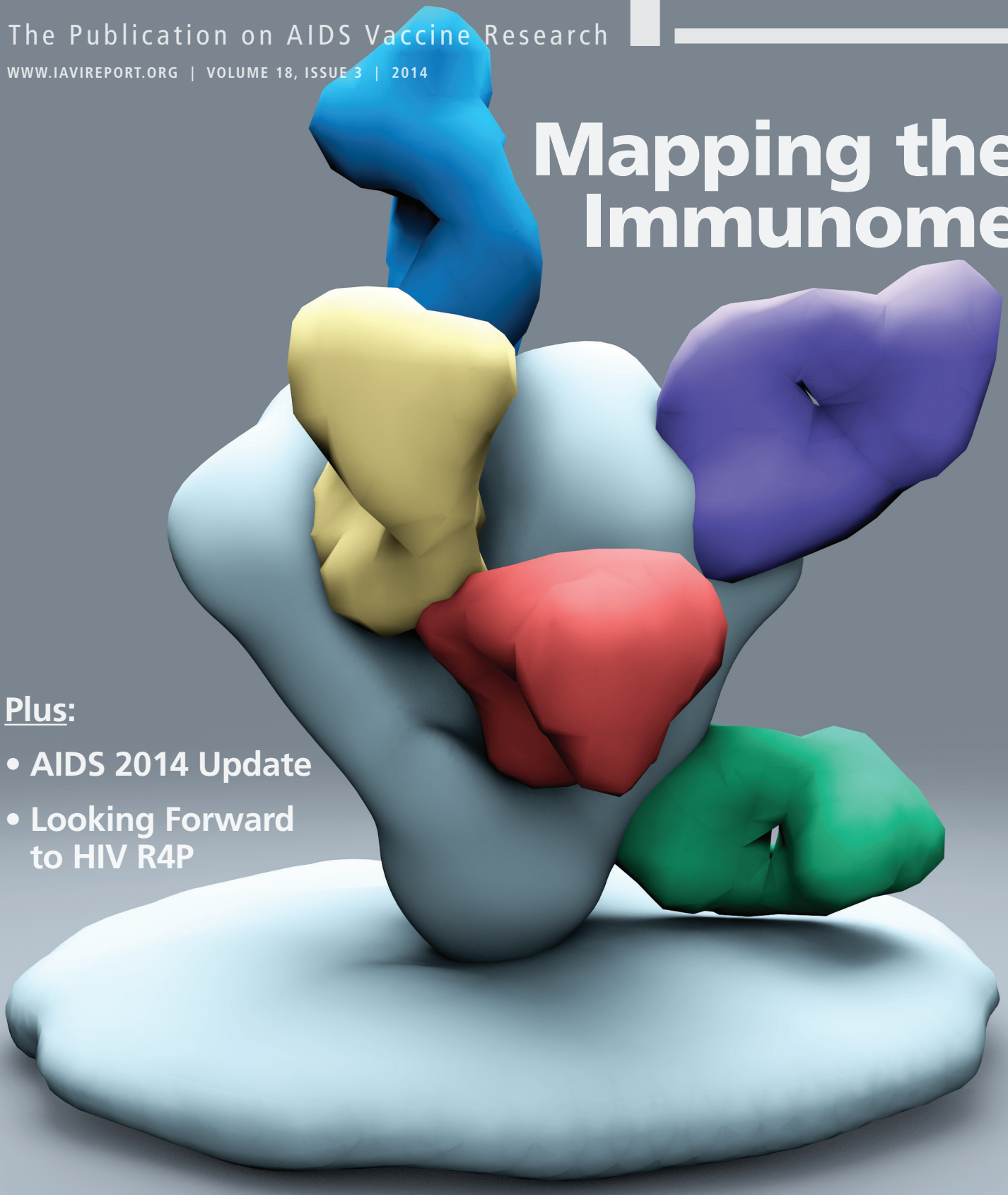
Mapping the Immunome



Plus:

- AIDS 2014 Update
- Looking Forward to HIV R4P

EDITOR'S LETTER

As the last issue of *IAVI Report* closed, thousands of researchers and advocates were preparing to attend the annual conference hosted by the International AIDS Society (IAS), AIDS 2014, which took place this year in Melbourne, Australia. As everyone undoubtedly knows by now, tragedy struck on July 17 with the downing of Malaysian Airlines flight 17 over eastern Ukraine, taking the lives of several heroes in the HIV fight who were en route to the conference. In this issue, we pay tribute to those whose lives were cut short, including former IAS president and noted researcher Joep Lange (see page 12), his longtime partner Jacqueline van Tongeren, and several others (see page 18), and highlight some of their many contributions.

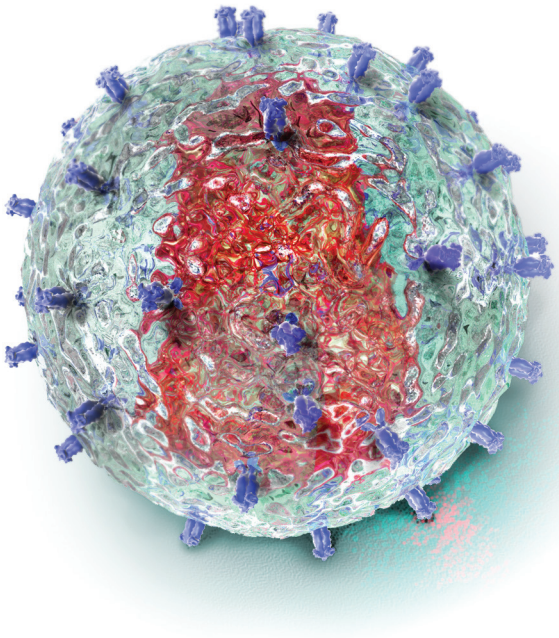
We also report extensively on the research findings presented at AIDS 2014 and the *Towards an HIV Cure* symposium that preceded the conference, which provided a detailed review of the recent advances in cure research, as well as the setbacks, which suggest achieving an HIV cure will still be an onerous task (see page 4). But no matter how difficult, interest in and funding for pursuing an HIV cure is on the rise, according to the latest report by the HIV vaccines and microbicides resource tracking working group released this summer (see page 18).

With one big conference behind us, there is another on the horizon. This year, in lieu of separate conferences focused on HIV vaccine and microbicide research, there will be the first global conference featuring research on all biomedical HIV prevention strategies, including vaccines, microbicides, pre-exposure prophylaxis, and treatment as prevention, among others. The inaugural conference, known as HIV R4P (research for prevention), will be held in Cape Town, South Africa, from October 28-31. Robin Shattock, a renowned researcher and one of the co-chairs of HIV R4P, authored a perspective article for this issue, explaining the rationale for the joint conference and previewing some of the key data that can be expected there (see page 9).

And, of course, you can turn to the next issue for a full report on the research updates presented at HIV R4P, along with context and perspective for this data that you won't find anywhere else.

– KRISTEN JILL KRESGE

IN THIS ISSUE



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SENIOR PRODUCTION MANAGER
Nicole Sender

CONTRIBUTING EDITOR
Kristen Jill Kresge

CONTRIBUTING WRITERS
Michael Dumiak
Neil McKellar-Stewart
Mary Rushton
Robin Shattock

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[ON THE COVER]

Electron microscopic reconstruction depicting antibodies attaching to the HIV-1 envelope glycoprotein trimer at five sites of vulnerability shown in different colors. The newly discovered site, PGT151, is shown in red, MPER in green, V3/V4-glycan in purple, CD4 binding site in yellow, and trimer apex glycan in blue.

Image courtesy of Andrew Ward and Christina Corbaci at The Scripps Research Institute. Image description courtesy of Andrew Ward.

Much Accomplished, *MUCH MORE TO ACHIEVE*

Despite tremendous gains in the realms of HIV treatment and prevention, the focus at AIDS 2014 was on what still needs to be done.

By Neil McKellar-Stewart

The 20th International AIDS Conference (AIDS 2014), held July 20-25 in Melbourne, Australia, commenced on an even sadder and more reflective tone than this biannual meeting typically conjures, as the nearly 14,000 delegates from over 200 countries commemorated the tragic death of their colleagues who died on their way to the conference as passengers aboard the Malaysian airline flight brought down in eastern Ukraine (see pages 12 and 18).

Although this terrible loss cast a shadow over the entirety of the conference, delegates turned their focus to recent progress in the realms of HIV treatment and prevention research, and the implementation of recently proven effective HIV prevention methods, including voluntary medical male circumcision (VMMC) and pre-exposure prophylaxis (PrEP; the use of antiretrovirals to prevent HIV infection). Salim Abdool Karim, director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA), spoke convincingly of the possibility of controlling the HIV pandemic, even in the absence of an effective vaccine or cure, by implementing existing treatment and prevention approaches. He referenced modeling studies that suggest VMMC, earlier initiation of antiretroviral therapy (ART), and PrEP, if implemented in combination and at ambitious coverage levels, could produce a six-fold decline in global HIV incidence by 2025. However, Karim acknowledged that this would not stop HIV transmission completely.

Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID), concluded that a world without AIDS would require both a vaccine and a cure. Although there was little new data on vaccine research to speak of in Melbourne, cure research once again received top billing as the conference was preceded by the *Towards an HIV Cure* symposium, the fourth such pre-conference meeting on the topic.

One step forward, two steps back?

At the main conference, Jintanat Ananworanich, associate director for therapeutics research at the US Military HIV Research Program, high-

lighted a multitude of recent cure-related studies (see box, page 5), including the recent cases in which transient but encouraging remission from HIV infection was achieved: the two Boston patients who received allogeneic stem cell transplantation, and the Mississippi infant who remained HIV free for several years following early initiation of ART (see *A Toddler Stole the Show*, *IAVI Report*, Spring 2013). In early July, the National Institutes of Health announced that the Mississippi infant had relapsed with recrudescence of viremia and the re-emergence of HIV antibodies. The child has subsequently re-initiated ART.

These and other studies indicate that the pace of HIV cure research has picked up in the last two years, a trend confirmed by the latest report from the HIV Vaccines and Microbicides Resource Tracking Working Group (see page 18). They estimate that global funding for cure research increased by 16% from 2012 to 2013, to a total of US$102.7 million. This may underestimate the contribution by industry, as companies with known programs in cure research did not provide data to the working group. Most of the new funding has come from the public sector, with less than $5 million from philanthropies such as Aides Fonds, amfAR, the Campbell Foundation, and Sidaction.

Ananworanich went on to discuss some of the social and ethical considerations around an HIV cure and suggested that society and individuals living with HIV expected that eradication would mean being free of disease, with no long-term adverse consequences of HIV and diminution of stigma and discrimination. She referred to the Australian research that sought to identify the outcome priorities of participants in a small clinical study of the histone deacetylase inhibitor (HDACi), vorinostat (also known as suberanilohydroxamic acid or SAHA). This study found that the four highest rated priorities for participants were: Not passing HIV onto others (47%); being considered uninfected (32%); not getting HIV a second time (32%); and stopping ART (25%). These priorities were congruent with those from a larger European community survey presented at AIDS 2012.

Fauci covered similar terrain in a review of the critical challenges in HIV cure and vaccine research. He noted that a cure generally denotes permanent remission from disease following cessation of therapy, which in the case of infectious diseases typically involves eradication of the microbe, and in cancer means an absence of relapse for life or for a pre-defined period of time determined as a surrogate for cure. After surveying what is known about the HIV reservoir, Fauci discussed what he thinks will be required for sustained virological remission (SVR) from HIV. He suggested that SVR might be most achievable in individuals who receive early ART, are stimulated to induce natural HIV-specific immunity, and receive passive transfer of HIV-specific antibodies and therapeutic vaccination.

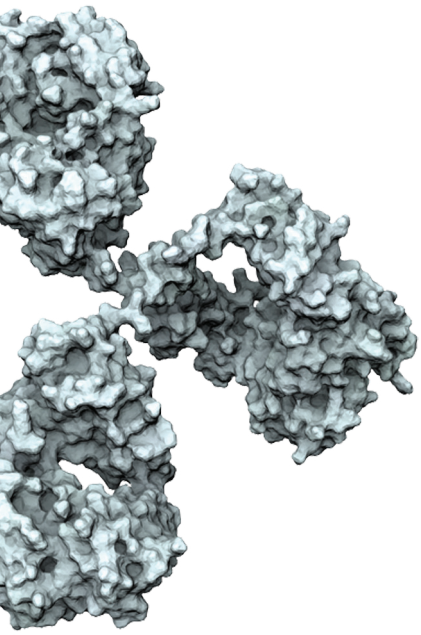
Highlights from the *Towards an HIV Cure* symposium

Like Fauci, Jeff Lifson, director of the AIDS and Cancer Virus Program at the Frederick National Laboratory for Cancer Research and the keynote speaker at this year's *Towards an*

Highlights of Recent HIV Cure Studies

An uptick in the number of cure-related studies has generated a plethora of data that is helping researchers better characterize the viral reservoir and decipher what strategies may help combat it. Below is a list of some recently published studies and their main findings.

- Sizeable reservoirs of replication-competent HIV provirus, which although non-inducible *in vitro*, may nevertheless contribute to ongoing viral re-activation (*Cell* **155**, 540, 2013).
- The majority of HIV proviruses are not activated using HDAC inhibitors (*Proc. Natl. Acad. Sci. USA* **111**, 7078, 2014).
- A therapeutic rhesus cytomegalovirus (RhCMV)/simian immunodeficiency virus (SIV) vector-based candidate in monkeys demonstrated durable control of infection following challenge with the highly pathogenic SIVmac239 virus (*Nature* **502**, 100, 2013).
- A cohort of patients in the VISCONTI study who initiated ART very early were subsequently able to control HIV replication in the absence of ongoing therapy, and are now termed "post-treatment controllers" (*PLoS Pathog.* **9**, e1003211, 2013).
- A dramatically reduced integrated HIV DNA reservoir in central memory CD4$^+$ T cells was achievable by initiating ART in very early infection (*CROI Abst* **47**, 2013).
- Three perinatally HIV-infected infants who received ART from infancy achieved significantly reduced circulating levels of proviral and replication-competent HIV and sustained ongoing decay of their viral reservoirs (*J. Infect. Dis.* online May 21, 2014 doi: 10.1093/infdis/jiu297).
- Macaques infected with the hybrid simian/human virus SHIV-SF162P3 that were administered a single broadly neutralizing antibody (PGT121) had a rapid and precipitous decline in plasma HIV RNA to undetectable levels. PGT121 administration resulted in reduced proviral DNA in peripheral blood, gastrointestinal mucosa, and lymph nodes without the development of viral resistance. Of the 18 antibody-treated macaques, three sustained undetectable viremia through necropsy at 100 days (*Nature* **503**, 224, 2013).
- A study of 12 chronically infected but virologically suppressed volunteers in a gene therapy study suggests infusion of autologous CD4-enriched T cells modified to remove expression of CCR5 by a zinc-finger nuclease is safe (*N. Engl. J. Med.* **370**, 901, 2014). —*NMS*



HIV Cure symposium, classified a functional cure as sustained off-treatment remission, involving reduction of the viral reservoir to levels low enough that with sufficient host control, HIV pathologies and the risk of transmission are reduced or eliminated. Achieving a functional cure is a much different goal than eliminating the virus entirely. And it remains to be seen what lessons can be learned from the recrudescence of virus in the Mississippi child, or whether a functional cure will indeed be possible if a viral reservoir, regardless how small, still exists, according to Lifson.

He reviewed the spectrum of current approaches to curing HIV, including: transcriptional activators to 'shock' HIV out of latency; epigenetic modulators (agents which are able to induce changes in the genes controlling behavior of HIV provirus); immune modulators, including interventions targeting immune checkpoint molecules such as PD-1 and its ligands; immune targeting, including broadly neutralizing monoclonal antibodies; and therapeutic vaccination. Lifson then focused on this final intervention and how non-human primate (NHP) models offer considerable advantages in evaluating therapeutic vaccines. However, NHP models, while accurately recapitulating many essential features of HIV infection, are limited in that HIV is not the same as SIV or the hybrid simian/human virus known as SHIV.

The potential role of therapeutic vaccination received a boost last year with the publication of results of the DCV2/MANON07-ORVACS study (*Sci. Transl. Med.* **5**, 166ra2, 2013). In this study, participants received a therapeutic vaccine utilizing autologous monocyte-derived dendritic cells (MD-DCs) pulsed with autologous, heat-inactivated, whole HIV. The vaccine was administered in three doses before cessation of ART. Participants who received the vaccine pulsed with inactivated HIV had a significantly greater reduction in plasma viral load from baseline levels, with a maximum decrease in viral load at 12 weeks that persisted through 48 weeks.

The use of cytomegalovirus (CMV)-vectored vaccines has also shown promise in animal models. In a previous study, a majority of macaques vaccinated with a rhesus CMV/SIV vaccine established immune control within 12 weeks of established SIV infection following intra-rectal, intra-vaginal, or intravenous challenge, and this viral control persisted until necropsy (*Nature* **502**, 100, 2013). Notably, disseminated infection was controlled, not just infection at the portal of entry. SIV viral load decreased over time at all sites, including plasma, gastrointestinal tract mucosa, lymph nodes, spleen, bone marrow, and tonsils. These results suggest a sustained virological remission occurred in these animals. Additionally, the vaccinated animals appeared to be incapable of infecting other animals. Lifson suggested this apparent viral clearance has many implications for the development of CMV-based therapeutic vaccines.

To further evaluate therapeutic vaccine candidates in NHPs, Lifson and colleagues developed an SIVmac239 clone with molecular tags to track individual infection events. They have also observed, in unpublished research, that the timing of ART initiation can profoundly influence the size and timing of reservoir establishment, as well as the variability in virological control. Animals treated from seven days post-infection all achieved undetectable plasma SIV RNA, and had SIV DNA levels that were 45% less than those who initiated ART weeks later (at day 42).

Additionally, in early treated animals, cell-associated viral DNA was 2.5 logs lower in lymph nodes, 1.5 logs lower in peripheral blood mononuclear cells (PBMCs), and 1.8 logs lower in bone marrow. Lifson suggested that viral persistence in T follicular helper (Tfh) cells might be an obstacle to complete viral clearance, but overall, these finding are encouraging and will be tested further in NHPs.

Eradicating HIV from lymph nodes

It has been known for almost a decade that the germinal center in lymphoid follicles is an anatomical site where HIV replication is active and where substantial reservoirs of inducible HIV are located. It was encouraging therefore to hear the results of research from Richard Koup, deputy director of the Vaccine Research Center at NIAID, on a novel bi-specific antibody (BibNAb), VRC07(fab)-anti-hCD3 that induces lysis of HIV-infected cells in lymph nodes.

This antibody is termed 'bi-specific' because it is active against the CD4 binding site of the HIV envelope and also induces redirected lysis of HIV-expressing $CD4^+$ T cells by $CD8^+$ T-cells. Koup's team was able to demonstrate that administration of VRC07(fab)-anti-hCD3 led to

35-40% lysis of HIV-infected cells in lymph nodes. This antibody-mediated killing of HIV-infected cells was mediated by caspases (intracellular cysteine proteases) associated with increased secretion of granzyme B and perforin, which are the effectors of cell apoptosis.

Rama Amara, associate professor at the Yerkes National Primate Research Center at Emory University, also presented research involving lymph nodes. Amara's work is focused specifically on the fate of PD-1^{+} CD4^{+} T cells in blood, lymph nodes, and rectal tissue in the presence of vaccine-mediated control of SIV-infection in a rhesus macaque model. Memory CD4^{+} cells expressing high levels of PD-1 (PD-1^{hi}), accumulate preferentially in lymph nodes, where they are found at three-fold higher levels compared to plasma, and at 18-fold higher levels than in rectal tissues. Additionally, they are phenotypically Tfh cells, defined as such by high levels of the chemokine receptor CXCR5.

Amara and colleagues observed that when vaccinated macaques were challenged with SIV, they had much lower SIV viral load set points than unvaccinated animals (generally 3-4 logs lower). These SIV-controllers also had significant lower proportions of PD-1^{hi} CD4^{+} T cells (levels similar to SIV-uninfected animals) in all three anatomical sites. This lower frequency of PD-1^{hi} CD4^{+} T cells was strongly associated with plasma viral load. PD-1^{hi} CD4^{+} T cells supported both SIV replication and production in lymph nodes in non-controllers during chronic infection.

Amara proposed several possible explanations of this reduced expansion of PD-1^{hi} CD4^{+} T cells. First, higher frequencies of SIV-specific CD8^{+} T cells are found in lymph nodes of controllers, and there was a strong inverse correlation between SIV-specific CD8^{+} T cells (especially those expressing granzyme B) and PD-1^{hi} CD4^{+} T cells. Secondly, there was a higher frequency of functional follicular CD8^{+} T cells in controllers. There was also an increased co-location of CD8^{+} T cells with PD-1^{hi} cells within the lymph nodes of controllers. Amara's team developed an *in vitro* CD8^{+} T-cell killing assay that was able to demonstrate that it was indeed SIV-specific CD8^{+} T cells located in the lymph node that were able to limit the proliferation of PD-1^{hi} Tfh cells.

These data suggest that it may be possible to develop vaccine-based therapies to reduce or eliminate virus-infected CD4^{+} T cells located in the B-cell zone of lymphoid follicles by stimulating higher frequencies of cytotoxic T lymphocytes (CTLs). Such vaccine-based therapies might be augmented by other interventions to down-regulate PD-1 and its ligands.

Targeting HIV-infected cells as they come out of latency

David Margolis, director of the Program in Translational Clinical Research at the University of North Carolina, presented additional research on HIV reservoirs and how HIV-infected cells might be targeted as they come out of latency. His team is developing model systems to assess viral clearance from reservoirs, focusing in particular on how CTLs and natural killer (NK) cells might to be used to target reactivated cells.

CTLs have been well characterized through the work of oncologists who used expanded autologous CTLs *ex vivo* to treat viral infections, such as herpes viruses, in cancer patients. Margolis's team has produced a suite of such

Can bNAbs Block HIV Dissemination in Dendritic Cells?

At the *Towards an HIV Cure* symposium, which took place in advance of the AIDS 2014 conference in Melbourne in July, Bin Su from the Université de Strasbourg presented data illustrating the ability of broadly neutralizing antibodies (bNAbs) to inhibit HIV transmission from primary plasmacytoid dendritic cells (pDCs) to CD4^{+} T cells. pDCs are particularly rich in the submucosal epithelium, where they very effectively transfer HIV to CD4^{+} T cells. HIV replicates poorly in pDCs because of their expression of the host restriction factor SAMHD1, which blocks HIV replication in DCs, monocytes, and macrophages. Therefore, if bNAbs are able to block both cell-free transfer of HIV and pDC-facilitated transfer to CD4^{+} T cells, the presence of bNAbs could stop HIV in the submucosal epithelium before it has the opportunity to disseminate further.

To study this interaction, Su and his colleagues developed an HIV transfer assay to mimic early mucosal transmission of HIV infection. In this model in which pDCs and CD4^{+}T cells were co-cultured, pDCs quite freely exhibited increased HIV replication in the presence of autologous CD4^{+} T cells, as the function of SAMHD1 was overridden. However, in the presence of VCR01 and PGT121, two recently identified bNAbs, transfer of HIV was inhibited in this model. When a 20µg/ml VCR01 solution was added to co-cultured cells two hours post-infection, 80% of HIV transmission from pDCs to CD4^{+} T cells was blocked, and the same amount of CD4^{+} T-cell free infection was inhibited. PGT121 even more effectively blocked HIV transfer from pDCs to CD4^{+} T cells, and also effectively neutralized cell-free infection.

Su observed that both bNAbs also induced pDC maturation and increased interferon-alpha (IFN-α) expression by infected pDCs in the presence of co-cultured CD4^{+} T cells. He suggested this increased immune surveillance and pDC maturation during pDC/T cell cross talk might promote effective innate immune responses and contribute to viral control. He suggested that a future role for vaccination might be to induce bNAbs directly at mucosal sites to prevent early dissemination of HIV after sexual exposure. —*NMS*

expanded CTLs (styled HXTCs), which consist mainly of CD8+ T effector memory cells that elicit responses to *gag*, *pol*, and *nef* cognate peptides. Such HXTCs in a superinfection assay are demonstrated to blunt active viral replication and potently inhibit autologous reservoir virus. Additionally, they have been demonstrated to clear infected cells that have been stimulated from latency by both the global mitogen phytohemagglutinin (PHA), and also the more selective reactivation agent, vorinostat. Margolis's team has demonstrated that vorinostat does not impair CD8+ or HXTC antiviral activity at physiologically relevant exposures.

Margolis also reviewed the role of NK cells, which are able to access HIV-infected cells that are protected from antiviral activity of T cells. NK cells are crucial innate immune effectors that do not recognize specific antigens or require prior antigen sensitization, and kill cells by insertion of granzyme and perforin, resulting in apoptosis. Their action may be augmented by clinically applicable cytokines such as interleukin (IL)-2 and IL-15. His team used NK cells stimulated with either of these cytokines to inhibit autologous HIV by over 90%. In a latency clearance assay they were able to demonstrate that cytokine-stimulated NK cells were able to clear almost all virus coming out of latency. Margolis said plans are to test this approach clinically within the next six to eight months.

Advances in HIV prevention

Discussion of PrEP is hardly new at international AIDS conferences, but as evidence of its effectiveness in at-risk populations mounts, recommendations for its use are also being strengthened. In the 2012 guidelines issued by the World Health Organization (WHO), PrEP was recommended upon review of evolving evidence, however, the recently updated guidelines now strongly recommend PrEP use based on high quality evidence.

At a media briefing, Chris Beyrer, incoming president of the International AIDS Society, emphasized that the guidelines recommend PrEP as "an additional prevention option for men who want it," as part of a comprehensive set of interventions. He explained that an individual's preferred HIV prevention method, like contraceptive options for women, may change over an individual's lifetime, and PrEP is now another possible option.

Bob Grant, Director of Gladstone Institute of Virology and Immunology at the University of California, San Francisco, presented late-breaking findings from the iPrEx OLE trial, an opt-in, open-label extension Phase of the original iPrEx trial that showed the fixed dose combination antiretroviral Truvada (tenofovir disoproxil fumarate and emtricitabine, or FTC) was an effective PrEP strategy in men who have sex with men and transgender women. These findings were published simultaneously (*Lancet Infect. Dis*. online Jul 22, 2014 doi: 10.1016/S1473-3099(14)70847-3).

Among study participants who elected to take PrEP, regardless of the frequency and regularity with which they did so, the annual HIV incidence rate was 1.8%, compared to 2.6% for those who opted out of taking the drug. Overall effectiveness of PrEP during this study was about 50%. Among participants who took at least four doses of drug weekly, there were no new HIV infections.

However, as in the original study, poor adherence was strongly associated with incident infections. Only about one-third of OLE participants took drug regularly, with younger people being less likely to have measurable drug levels in blood. However, adherence was better among people who reported more high-risk sex or more sexual partners, indicating that they may have adopted PrEP as a perceived risk-reduction strategy.

Intermittent PrEP

Given the overall poor adherence to PrEP in clinical trials, the Agence nationale de recherches sur le sida et les hépatites virales' (ANRS) IPERGAY study is evaluating the efficacy of intermittent or "on demand" PrEP in an ongoing, randomized, double-blind, placebo-controlled trial. The trial began enrolling gay and bisexual men in France and Canada in early 2012. Participants are randomly assigned to take two Truvada or placebo pills 24 hours before they expect to have sex, and one pill at both 24 and 48 hours afterwards.

As the trial is still enrolling, data on effectiveness are not yet available, however, Jean-Michel Molina, from Saint-Louis Hospital reported early findings on adherence in Melbourne. The interim analysis included 129 men with an average age of 35 who reported having a median of two instances of sexual intercourse per week (range: 0-31), and a median of 10

Continued on page 17

Shaping the Science OF PREVENTION

Next month, researchers from around the globe will gather in Cape Town, South Africa, for the first conference focused on all HIV prevention strategies.

By Robin Shattock

Robin Shattock

Many people have been asking how the HIV R4P (Research for Prevention) conference to be held in Cape Town in October will differ from other HIV conferences. HIV R4P will be the first conference to focus exclusively on prevention science. This marks an important turning point in HIV biomedical prevention research that in many ways reflects the maturity of the field. Having brought different prevention approaches to a certain scientific standard and level, it now makes sense to draw the different branches together. This conference provides a critical opportunity to build in a coordinated way on the significant gains made in recent years across a variety of prevention modalities.

As with any change, some will be nostalgic for separate meetings of the past where vaccines, microbicides, and pre-exposure prophylaxis (PrEP) were seen as distinct areas of focus. But having the meeting in South Africa provides a natural backdrop for this move. South Africa has already hosted an HIV vaccine and a microbicide meeting, and so it was logical to build on that experience. More importantly, sub-Saharan Africa is also the focus of a major part of the epidemic, where prevention is not seen as the domain of any individual scientific discipline, but as an urgent unmet need, where communities and individuals are eager for things that work and are applicable to their daily lives. Holding the inaugural HIV R4P conference in Africa will help to bring together scientists working across the discovery end of prevention research with those working on the ground who understand the practical challenges of carrying out prevention trials and engaging communities and stakeholders.

Advances in prevention

There have been some really promising developments in the area of PrEP, following the licensure by the US Food and Drug Administration of the HIV drug Truvada for use as a once-a-day prevention option for HIV-uninfected men and women. It's clear that adherence to daily PrEP dosing is likely to be difficult for many people, especially for young people, who are often those most in need of new HIV prevention options. Researchers are looking at a range of new options that may be less dependent on strict adherence to a daily pill and therefore may be easier and more desirable for people to use.

Many groups are investigating intermittent

use of PrEP that might reduce the compliance burden. Two groups in the US (the Aaron Diamond AIDS Research Center and the US Centers for Disease Control and Prevention) have also been evaluating long-acting, injectable antiretrovirals. These groups report that injection of long-acting HIV drugs can completely prevent infection in monkeys (see *CROI: Progress on Prevention and Cure*, *IAVI Report*, Vol. 18, Issue 1, 2014). This is significant because, if it works in humans, it might be possible to get a shot every three months to protect against HIV. It would also be useful if it could be administered along with injectable forms of long-acting contraception to prevent pregnancy. This may be more acceptable in resource-limited settings, specifically sub-Saharan Africa, where the trajectory for daily oral PrEP implementation is much less clear.

It's also possible that the same technology could be used to treat those already infected with the virus. Drug resistance happens mostly when patients miss taking their drugs. Long-acting, injectable antiretrovirals will get around this problem as patients won't need to remember to take tablets everyday, or be left without drugs should there be a disruption to access. This might be very beneficial in hard to reach communities, highly mobile groups, or those in areas of instability where maintaining a supply of oral drugs might be problematic.

Long-acting injectable antiretrovirals may also have a role to play in implementation of treatment as prevention (TasP), particularly where targeted toward the most at-risk populations. This will raise other questions for prevention researchers. As TasP approaches drive down the incidence of HIV, this in turn will increase the intrinsic research value of higher-incidence cohorts, raising ethical issues over how and when to introduce different biomedical interventions as they become available. It's likely we will see more promising developments in this area at the R4P meeting and active discussion over changing and appropriate standards of care.

Microbicide development, too, is at a critical stage with pivotal trials currently ongoing. Should the FACTS 001 Phase III efficacy trial confirm earlier observations of CAPRISA 004, which first established the protective efficacy of a tenofovir gel-based microbicide, we may see the first licensed microbicide become widely available to at-risk populations. This has important implications, as this vaginal microbicide may become the baseline intervention for future AIDS vaccine trials if it gains licensure. Its licensure will also fuel efforts to accelerate the development and clinical assessment of rectal microbicides.

Two other microbicide trials are currently assessing the efficacy of the drug Dapivirine administered via a vaginal ring (the Microbicide Trials Network ASPIRE trial and the International Partnership for Microbicides Ring Study). It's hoped that the ring will ease the burden of compliance, releasing the antiretroviral over a month, and therefore avoid the need to plan for dosing around sex. It's too early to anticipate data from these efficacy trials at the R4P meeting. However, there is an explosion in developing novel delivery strategies not only for microbicides, but also for co-delivery with contraceptive options and other multi-purpose technologies designed to be active not only in preventing pregnancy and protecting against HIV infection, but also protecting against other sexually transmitted infections.

Meanwhile, vaccine development has been energized by the increasing number of broadly neutralizing antibodies (bNAbs) isolated from a small number of HIV-infected subjects. The field now has a very clear picture of the evolutionary pathways leading to the induction of bNAbs in infected subjects, matched by rapid advances in structural insight into bNAb docking strategies and the envelope architectures underlying these surfaces. It's anticipated that these discoveries will drive the development of immunogens and strategies needed to induce bNAb responses in those at risk of infection. Recent understanding that this may be critically dependent on effective engagement of the human germline encoded B-cell receptors are driving efforts to screen immunogens in human experimental medicine trials. These trials focus on screening immunogens in small numbers of volunteers with an emphasis on immunogen discovery rather than traditional product development.

Alongside this fast paced effort to improve immunogen design are the international efforts to build on the potential promise of the RV144 vaccine trial conducted in Thailand—the first AIDS vaccine trial to show any protective effective effect. This involves plans to test the same strategy in a sub-Saharan setting. This required changing the component immunogens of the vaccine to those relevant to a clade C setting, reflective of circulating strains in sub-Saharan Africa. Early immunogenicity data for these new con-

structs is eagerly awaited and will likely be featured at the R4P meeting.

Bringing it all together

Given these advances across the different prevention fields, and the many crosscutting issues in prevention research that need to be addressed, a combined biomedical HIV prevention conference makes sense.

All prevention strategies are impacted by the mechanisms of HIV transmission—the nature of the virus transmitted, the virology behind that transmission, and the factors influencing susceptibility to infection. One challenge is to understand exactly where and when the first target cells become infected. In terms of antiretroviral-based prevention, the answer to this question determines where the drugs have to be and at what concentration. This is also relevant to vaccine development, in terms of ensuring that protective antibodies or effector cells reach the same sites at sufficient levels to provide immunity that prevents infection.

Another key crosscutting area concerns animal models of infection. Having animal models that can represent transmission to humans as closely as possible will be vital to all biomedical prevention strategies and their pre-clinical modeling.

Yet another issue that cuts across disciplines is the increased use of adaptive trial design that takes account of what we hope will be continuing decreases in HIV incidence as we implement a growing array of different biomedical prevention strategies. Having all of these issues covered by a single conference will ensure the very best science in this area is shared across prevention fields.

As HIV prevention research progresses, the advantages of collaborating—and the disadvantages of working in silos—increase. Ultimately, all investigators want to have the greatest possible impact on reducing HIV transmission. Understanding the overlapping issues that impact prevention research and implementation are essential to getting the best out of prevention.

As different approaches mature along different timescales, they will start to coalesce in various ways. It is clear that we need to understand how all of these prevention options will interact in the field, and potentially within individuals. Indeed, it is highly likely that many prevention trials will be conducted in the context of an increasing background of licensed biomedical options. This is already the case with respect to PrEP. And it is highly likely that both the tenofovir gel and the two Dapivirine ring studies will be completed before the start of trials to evaluate a vaccine regimen similar to that tested in RV144 in sites across sub-Saharan Africa. Should either or both of these microbicide approaches be licensed, they may become the default background to all further vaccine trials. Therefore, understanding the interaction of these different technologies could be critical. There is a range of potential synergies between different prevention approaches and studying them together could help us understand the potential benefits of combining different strategies that on their own might be partially effective in reducing HIV acquisition.

Another potential benefit of a combined prevention meeting is the impact on advocacy. HIV R4P will provide a focus for maintaining progress and funding for HIV prevention as scientific progress increases and competition for resources becomes greater.

To make the most of these emerging approaches and their potential combinations there is a need to accelerate the testing of these different concepts in randomized clinical trials. Ideally, this will involve adaptive trial designs. We have to be sure that any approach is safe, effective, affordable, accessible, and wanted by those most at risk of infection. There is no point in developing something that nobody can afford or will want to use. This can only be accomplished by involving broad groups of individuals from the development sector and affected communities, and these partnerships will be a focus of the HIV R4P conference.

The theme of the conference, *Shaping the Science of Prevention,* seems particularly timely. Through scientific investigation we can develop a growing toolbox of new biomedical prevention options and understand how to use those to bring down incidence most effectively. To me, shaping the science of prevention means learning how to get the best out of different prevention approaches. The sooner we can do that and the smarter we are at employing those different approaches, the more effective we can be at protecting at-risk individuals. It's hard to argue against that. ■

Robin Shattock is one of the co-chairs of the HIV R4P conference and is Professor of Mucosal Infection and Immunity at the Department of Medicine, Imperial College London.

Joep Lange's *LONG REACH*

Along with his partner Jacqueline van Tongeren, the globe-trotting researcher built an impressive body of work. They leave it far too soon.

By Michael Dumiak

Geert Haverkamp sits looking at a screen at his third-floor desk in a nondescript concrete building on a corner off the harbor in Dar es Salaam. Maps of Tanzania in various detail stand pinned to a cluttered corkboard behind him. They plot 100 or so police, military, and prison clinics that form the foundation of HIV/AIDS treatment in the southern African nation. Haverkamp first toured clinics like these years ago with his friend and longtime collaborator Joep Lange.

No more. As the global health, and now much of the broader world knows, Lange, 59, father of five daughters and a leading HIV researcher and former president of the International AIDS Society (IAS), died this summer aboard Malaysia Airlines flight 17 (MH17) while traveling to Australia to attend the annual IAS conference.

"Joep sent me here in 1995 to work on a trial," says Havercamp, who never left Tanzania. He's now a program director for PharmAccess, a non-profit founded by Lange aimed at speeding the availability of antiretrovirals in Africa. He recalls what it was like in Tanzania then. "It was quite shocking to come to the big academic centers in Tanzania or Uganda and see … patients lying everywhere. You hear in the corner a few women crying and you know someone has died again. To see that this is completely not necessary, completely unacceptable."

Lange set out to do something about it. And that he did. Some 500,000 Tanzanians are now on HIV treatment. The trial Lange sent Havercamp to Tanzania for was the Petra Study, part of the landmark research showing that HIV drugs could reduce the risk of breastfeeding mothers transmitting the virus to their babies.

Lange planted many seeds which continue to

flourish. He was responsible for nurturing more than 40 doctoral candidates; founding the Amsterdam Institute of Global Health and Development (AIGHD) in the same medical center where he began as a young clinician at the start of the AIDS crisis years; exploring nascent health insurance schemes in sub-Saharan Africa; starting the INTEREST workshops to give young African researchers a place to start presenting their work; and pressing industry and pharmaceutical companies for access to HIV treatment.

David Ho, director of the Aaron Diamond AIDS Research Center in New York City, recalls Lange sticking by him in the first experimental days of what would become antiretroviral combination therapy. "The more controversial part at the time was whether that strategy could ultimately be the cornerstone of a cure," Ho says. "We were barely beginning to treat in those days, so whenever you mentioned cure, there was a lot of hostility directed toward him and me. People who talk about cancer don't get criticized like that. We may be as far from a cure today as we were in 1996, but now the mindset is totally different. Joep was brave."

Catherine Hankins, former chief scientific adviser at the Joint United Nations Programme on HIV/AIDS, got to know Joep in the early 1990s after speaking about women living with HIV at the Montreal international AIDS conference in 1989. Hankins knows what it's like to be on the other side of Lange in an argument. The two clashed publicly over the design of the initial Petra trial, and later at length over his run-ins with activists trying to disrupt trials on pre-exposure prophylaxis. "He was a kind and gentle guy, but he did not suffer differences of opinion quietly," she says. "He sent me a harsh e-mail. I probably didn't talk to him for a few years. It's a hoot that he pushed really hard for me to come here." Here is the AIGHD, where Hankins is now deputy science director.

Hankins shared an office with Jacqueline van Tongeren, the AIGHD's communications director, former research nurse, and Lange's longtime partner, who also died aboard MH 17. "She was my neighbor and best friend in Amsterdam," says Hankins. "She helped me find my apartment. I still find myself asking her for advice." Van Tongeren had a deep interest in art, while Lange had eclectic tastes in music and was always handing out books. Friends recall that there was hardly a place to sit down in his Beethovenstraat apartment. He recommended the American writer Paul Auster to Hankins; the last opera they attended together was La Bohème.

In Kampala, Uganda, not far from where he started the first African AIDS clinic in 1987 seeing 350 patients a day, Elly Katabira also remembers Lange and his books. "He said he'd bring something back for me. I figured no way he'd remember," says Katabira, also a former IAS president and medical professor at Makerere University. "But he did. Very influential. About why you should never underrate the poor."

If you have a vision for something, you take advantage of every venue you have. And he did.

– Catherine Hankins

Katabira hosted Lange during his first trip to Africa. Together they helped debunk a fake AIDS remedy, which Lange recalls in a moving essay called *Africa on the Rise*. What he would have seen there at the time is also captured in a piece by Kathleen Hunt in the *New York Times Magazine* called *Scenes from a Nightmare*.

When current Duke Global Health Institute director Michael Merson was at the World Health Organization in the early 1990s, he recruited Lange to run drug development for the Global AIDS Program. From there Lange would soon meet Katabira, and then go on to get PharmAccess up and running in Dar es Salaam and sub-Saharan Africa. Now Merson is once again linked to Lange—the Duke director recently spent a week with Hankins planning a new joint health and technology institute in development with the city of Amsterdam. One of Hankins' next tasks, meanwhile, is to start arranging the next INTEREST workshop, planned for next spring in Harare. Lange's long reach is lengthening. "If you have a vision for something, you take advantage of every venue you have," Hankins says. "And he did." ■

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

Prepping for the *IMMUNOME*

Could a group of experts lead the way to ambitious new vaccine trials that aim to map the human immune response and speed vaccine development?

By Michael Dumiak

In New York City this summer, Marie-Paule Kieny, assistant director-general for health systems and innovation at the World Health Organization, and Ted Bianco, innovations director at the Wellcome Trust, convened a small group of researchers, public health experts, and medical industry insiders pursuing an audacious idea: mapping the human immune system.

What is starting with small steps could develop into big science. The July gathering is the second in a set of workshops underwritten by the Robert Wood Johnson Foundation (RWJF) aimed at developing a scientific and, equally vital, business plan for what the International AIDS Vaccine Initiative's chief science officer Wayne Koff, University of Melbourne microbiologist Ian Gust, leading University of Pennsylvania vaccine authority Stanley Plotkin, and others are dubbing the Human Vaccines Project. Analogous in scope, if not method, to the Human Genome Project of the 1990s, the group outlined the initiative's objective last May in the journal *Science* and this June in *Nature Immunology* as a comprehensive assessment of human immune responses to licensed and experimental vaccines in rapid, focused, and iterative clinical research trials.

It would be a vast undertaking: a small number of volunteers, a huge number of experiments, and testing untold hundreds of thousands of antigens and the immune responses they induced at a level of detail and scale that is only now becoming possible due to technological and methodological advances in antigen discovery, genomics, and immunological monitoring. Koff describes it as an effort focused on the major problems impeding vaccine development. "One is how to elicit a specific, broad, potent, and durable immune response in people," he says. "Another is how can we optimize the efficacy of licensed vaccines and improve the potential for the next generation of vaccines for specific populations: like in the developing world, in newborns, or in the elderly."

Overall, the goal is to speed development of new and improved vaccines for major global diseases such as HIV, influenza, cancers, dengue, and other infectious illnesses. The Human Vaccines Project aims to do this by creating a reproducible platform for screening related vaccine

The Brains Behind the Human Vaccines Project

Wayne Koff
Chief Science Officer, IAVI

Ian Gust
Microbiologist,
University of Melbourne

Stanley Plotkin
Emeritus Professor,
University of Pennsylvania

immunogens in humans to determine which are able to elicit the broadest, most potent, and durable immune responses. The immune responses to these immunogens could be tracked and analyzed using the new molecular tools and technologies coming online over the last decade. By cataloguing the comprehensive responses from these small human trials, Koff and the others behind the Human Vaccines Project hope to create a map of the immunome—much like the map of the human genome—which details all of the genes and proteins associated with the human immune response to vaccine antigens and as much as can be learned about their modes of action.

"You don't want to just immunize one or two people here and there and make a few anecdotal findings. You want to do this on a big scale and in a systematic way so it's absolutely clear what the conclusions are," says Dennis Burton, an immunologist and HIV vaccine researcher at the Scripps Research Institute in La Jolla, California. "The strategy is to look at the response of different individuals and find those magic antibodies, the ones that are extraordinarily effective, and garner information allowing you to design a more effective vaccine." One example would be using this information to develop a universal influenza vaccine. Now, vaccination against flu requires an annual shot that is manufactured based on what strains of the virus are predicted to be in circulation in a given year. But if researchers could identify an immunogen that could induce antibodies that would protect against many different types of flu, it might be possible to develop a vaccine that would provide life-long protection against several strains of the virus.

Inner workings

In some ways, the easy vaccines have been made. Current vaccines have been so successful, saving tens of millions of lives, but most existing vaccines were developed without a deep understanding of how they work, Burton says. Over time there's been a progression: in the 1950s, the strategy for developing vaccines was to isolate a pathogen, kill it or weaken it, and inject this modified form into a person. This strategy worked well for polio and smallpox. But this strategy isn't practical for viruses like HIV: it's not safe. Many of the pathogens researchers are now trying to create vaccines against are also more challenging foes. "A lot of the diseases we and others are looking at now are either complex pathogens, persistent pathogens, immunovasive pathogens, or hypervariable pathogens," Koff says. "Or cancers."

Koff, Gust, and Plotkin outline a landscape of problems facing contemporary vaccine research in their *Nature Immunology* article. Genetic variation impedes development of vaccines against HIV, blood-stage malaria, and influenza; population-specific characteristics, such as the immaturity of the immune system in newborns and its deterioration in the elderly, limit the efficacy of some already-licensed vaccines and pose hurdles for creating new ones; and identifying potential antigens that can induce the necessary protection is still difficult. Animal models for vaccine research are another limiting factor—as Burton says, ultimately researchers want to gain

information in humans because that's who the vaccines are for.

Several vaccines tested in the last decade targeting these more complex pathogens have either completely failed in efficacy trials or only provided a modest level of protection: vaccines to prevent HIV, malaria, herpes simplex, staphylococcus aureus, melanoma, and pancreatic cancers all make this grim list. "When you look at all the time and expense, you're looking at decades of work and billions of dollars," Koff says. Meanwhile, the Human Genome Project cost about $3.5 billion, including public and private efforts. A Human Vaccines Project might be equally thrifty—comparatively speaking—if it could eliminate some of the hurdles in vaccine development and get new products to market more quickly. But this doesn't mean funding a project like the one Koff and colleagues are proposing is easy.

The strategy is to look at the response of different individuals and find those magic antibodies, the ones that are extraordinarily effective, and garner information allowing you to design a more effective vaccine.

– Dennis Burton

"I think one of the key points is that any study in humans costs a lot of money. We need a lot of funding for this," says Burton. "You'd need stakeholders with very deep pockets. But the rewards could be massive," he adds, referring to the ability to design vaccines with much greater certainty and reliability. Venture capitalists and industry representatives came to the table for the last workshop and will no doubt play a vital part, given limited prospects for government funding of big initiatives.

The group behind the Human Vaccines Project is putting polishing touches on its business and scientific draft plans and expects to publish an update in the first part of next year, in advance of a third workshop funded by the RWJF grant. At that point they hope to reach agreement on the infrastructure and resources—the "enabling environment"—necessary to create something that resembles the Human Genome Project. The group's already met with senior leadership of the US Food and Drug Administration to discuss a key element of their plans: how to ensure that products for a large number of clinical trials involving a relatively small number of individuals can be delivered safely.

The Human Vaccine Project will also need a home. The question is should this effort be independent, part of a research institute or university, a for-profit or a non-profit endeavor? "In that sense it is similar to the Human Genome Project. It would require collaboration among many different groups with different expertise in order to develop the answers we want," Burton says. There are also other questions regarding intellectual property and leadership that need to be addressed.

Technology leads the way

Efforts to better characterize the human immune response are possible now because new technologies are creating unprecedented potential for analysis and cataloguing. Researchers can now use genetic sequencing to analyze tens or even hundreds of thousands of different antibodies induced by a vaccine. "If we're talking about a large number of clinical research studies with comprehensive immunologic assessments, looking at the whole antibody repertoire, this is a huge amount of data," says Koff. You want to be able to manipulate that data and get as much information out of the study as you possibly can. We now have the data management and informatics tools to be able to do that."

Pharmaceutical companies could also benefit from collecting the types of data Koff is referring to. In recent weeks Sanofi claimed success in a second large clinical trial with its experimental dengue vaccine, into which it has invested $1.7 billion already. But against dengue serotype 2, protection was only 42%. Knowing whether this was because of a population or immunology effect would make it easier to make adjustments to the vaccine to improve the response against this serotype.

Technology is also aiding antigen design. Vanderbilt Vaccine Center director and pediatric infectious disease specialist James Crowe points to the widening collection of three-dimensional antigen structures made with sequences and molecular modeling systems like the one developed at the University of California, San Francisco, known as Chimera. These along with pathogen genome sequencing and the identification, expression, and screening of protein antigens are leading to the increasing viability of opti-

mized structure-based vaccine candidate design or reverse vaccinology. Earlier this year Crowe was part of a large group publishing a proof of principle for epitope-based vaccine design (*Nature* **507**, 201, 2014).

Advances in synthetic biology—namely the ability to synthesize genes at a large scale, to the point of the whole organism genome—are also allowing researchers to study the effect of genetic diversity upon antigens and the immune repertoires. In terms of immunologic monitoring, new techniques for measuring gene expression, such as RNA-Seq, the use of metabolomics, and immune repertoire sequencing bring extremely detailed views of the human immune response into view. As Koff points out, the identification of broadly neutralizing monoclonal antibodies has recently re-energized efforts toward the development of vaccines against HIV and influenza. In part this is thanks to advances in computational and structural biology.

Despite these advances, researchers are still groping somewhat in the dark when it comes to eliciting these antibodies through vaccination. "We don't know how to elicit neutralizing antibodies because we don't really know the rules of immunogenicity around affinity maturation," Koff says, referring to the way in which immune cells mature and mutate in lymph nodes in response to pathogen exposure and are able to produce higher affinity antibodies. For those developing HIV vaccine candidates, knowing how different antigens guide the immune system to make more highly affinity-matured antibodies is a huge challenge. Researchers need a map. Enter the immunome. ■

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

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partners over the previous two months. About 80% of participants reported that they had used PrEP the last time they had sex. Based on pill counts, they took an average of 15 pills per month, meaning they were on PrEP about half the time. At any clinic visit approximately 86% of participants had detectable levels of tenofovir in blood, and 82% had detectable levels of FTC.

Circumcision continues to deliver

Male circumcision as an HIV prevention strategy continues to produce encouraging results. The WHO and the Joint United Nations Programme on HIV/AIDS recommend VMMC as an additional intervention for prevention of heterosexually acquired HIV, particularly in settings with generalized HIV epidemics. And the most recent data from Uganda show that in the five years since the Rakai trial—one of the first to establish the efficacy of VMMC in preventing HIV infection—was completed, high effectiveness has been maintained among the men who were circumcised, with a 73% protective effect against HIV infection.

Other benefits of circumcision were reported by Kévin Jean of the Institut national de la santé et de la recherche médicale (INSERM), who presented data from the ANRS-12126 study in Orange Farm, South Africa. He reported for the first time that male circumcision not only protected men but also was beneficial for their female partners. VMMC protects against some sexually transmitted infections in both men and women, reducing the risk of herpes simplex virus-2 and human papilloma virus acquisition in men and their female partners. It is also associated with a reduction in the risk of genital ulcer disease and genital cancers in both men and women. However, protection against HIV in women was not observed in epidemiological studies until now. The ANRS showed that HIV incidence among women who only had sex with circumcised men was reduced by 17% in those aged 15-49 years, and 20% in women aged 15-29 years, a notable outcome in a context where HIV prevalence in women aged 15-45 years is around 32%.

In a related presentation, Jillian Pintye from the University of Washington reported on new data from the Partners PrEP Study that shows circumcised men are also less likely to acquire syphilis. She reported that syphilis incidence in participants in this study involving heterosexual, mostly married, serodiscordant couples in Africa was a statistically significant 42% lower in circumcised men. When stratified by HIV serostatus, the researchers found a significant risk reduction of 62% among HIV-infected men, and a similar non-significant trend among HIV-uninfected men. In women, there was a statistically significant 59% risk reduction of syphilis associated with having a circumcised male partner. These results extend even further the health benefits associated with VMMC. ■

Neil McKellar-Stewart is HIV Health Promotion Officer at ACON (AIDS Council of New South Wales) and an active member of the National Association of People with HIV Australia Treatment Officers Network. He is a community representative on the Australasian Society of HIV Medicine Sub-Committee for Guidance in HIV Management in Australia.

In BRIEF

HIV/AIDS Community Mourns Loss of its own Aboard MH17

If we can see a future without HIV—if we get to the end of AIDS—it will be more than a vaccine that gets us there, says Gregg Gonsalves, HIV-infected activist, former ACT UP (AIDS Coalition to Unleash Power) member, and co-director of the Global Health Justice Partnership at Yale University Law School.

It will be the people.

Among the many lives tragically lost the day Malaysia Airlines flight 17 came down over eastern Ukraine, the HIV/AIDS community is still hurting from the loss of Lucie van Mens, a former program director with the Dutch STOP AIDS NOW! Group; Bridging the Gaps' Martine de Schutter; lobbyist Pim de Kuijer, and Glenn Thomas, who helped the World Health Organization's outreach in global health, tuberculosis, and HIV/AIDS as a communications officer. Also killed in the crash were Joep Lange, leading HIV researcher and former president of the International AIDS Society, and his longtime partner Jacqueline van Tongeren, who was also communications director of the Amsterdam Institute of Global Health and Development (see page 12).

Alvaro Bermejo, director of AIDS Alliance, knew both Martine de Schutter and Pim de Kuijer and says it is people like them who make a difference. "They were people who dedicated themselves to making the world a better place," Bermejo says. "They were passionate and committed to working for a common good, and that makes it particularly difficult to have lost them."

Working in HIV often means connecting with disenfranchised and marginalized parts of both wealthy and poor societies. Van Mens found her calling there. A former program director with the Dutch STOP AIDS NOW! group, van Mens set up outreach and health care initiatives for sex workers and people in red light districts across Europe before joining the Female Health Company to make female condoms more widely available, especially in African countries.

Like many initiatives in Europe, STOP AIDS NOW! is a partnership. Started by project funder Aids Fonds, STOP AIDS NOW! marshals the collaborative efforts of several groups in fighting AIDS with an eye to development and anti-poverty initiatives.

STOP AIDS NOW! director Louise van Deth brought de Kuijer aboard because of something he said. "I was an activist diplomat. Now I want to be a diplomatic activist," van Deth recalls. "He was just that—he was our lobbyist but good in reaching out to people and building a network, building relationships." De Kuijer was active in Dutch politics and was sent out to be an election monitor in teetering or fledgling democracies—including the Ukraine. He was persuasive and effective, van Deth says, playing a role in defeating a government proposal to reform sex work in Holland—prostitution is legal there—which would have driven people underground again, where they would have little access to public health services.

Van Deth says de Schutter worked with STOP AIDS NOW! for a dozen years before going to Bridging the Gaps. "She was right for the role because she was good at connecting people. It's a complicated program," van Deth says. "It has five partners in the Netherlands, all different, and they work with 100 partner organizations in 13 countries, all supporting sex worker organizations, marginalized groups, men who have sex with men, and drug users."

Both Gonsalves and Bermejo describe the hurt to what is still an HIV community. "The AIDS response loses many of its leaders: to stigma, violence, planes, to AIDS itself," he says. "We often take our colleagues for granted, and when you lose them and reflect on the work that they do, you really appreciate the difference they make."

With the advent of highly active antiretroviral therapy in 1996, prospects massively improved for millions of HIV-infected people, perhaps leaching some of the urgency that brought together researchers and activists in the early days of AIDS. "Maybe some of that camaraderie and community is gone," Gonsalves says. "But it's still vital to keep it alive if we are ever to conquer this epidemic." —*Michael Dumiak*

HIV Vaccine Funding Declines, While Cure Funds Rise

The latest report on funding for HIV prevention research, released by the HIV Vaccines and Microbicides Resource Tracking Working Group two days before the start of AIDS 2014 in July, notes that investment in HIV prevention research dropped to US$1.26 billion in 2013, a 4% decline, with funding for HIV vaccine research and development declining by 3% from $847 million in 2012 to $818 million last year. This is the largest real decrease in AIDS vaccine investment since 2008, and it follows five years in which funding had either declined or remained stable, from a high of $961 million in 2007 (see figure, next page).

A major factor driving down HIV prevention funding was the across-the-board spending cuts known as sequestration that were mandated by Congress last year to reduce the US federal budget deficit. The legislative action drained $153.7 million in AIDS research spending from the US National Institutes of Health (NIH), resulting in a 7% drop in NIH funds for AIDS

Decline in Prophylactic Vaccine Funding in 2013

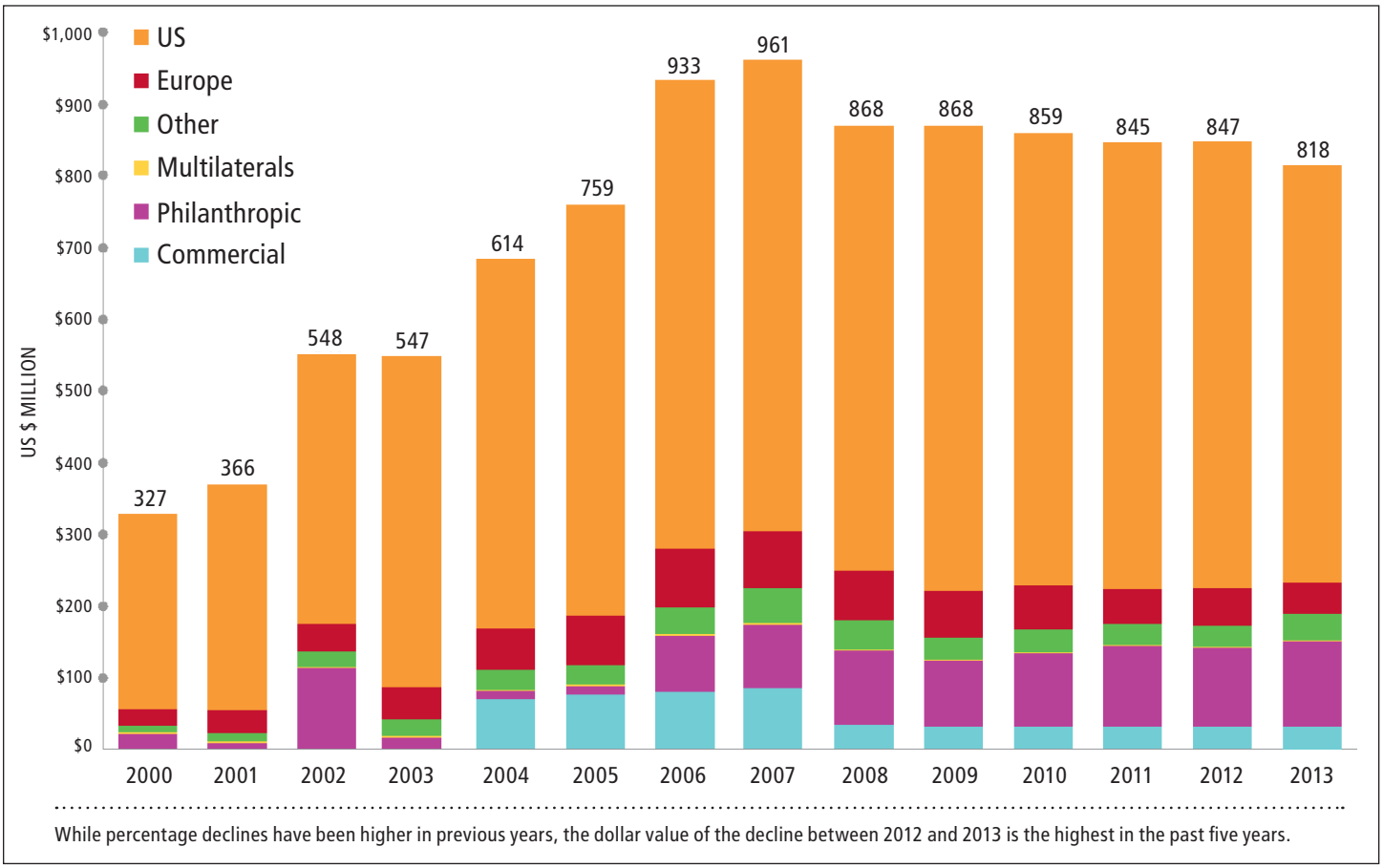

Figure courtesy of AVAC and the HIV Vaccines & Microbicides Resource Tracking Working Group. See the full report at http://hivresourcetracking.org/sites/default/files/RTWG2014.pdf.

vaccine research and a 14% drop in funding for microbicides.

The report notes that European countries also invested 10% less in HIV prevention research and development in 2013 compared to 2012, while philanthropic support fell 5%, a drop that would have been even greater if not for contributions by the Bill & Melinda Gates Foundation, which maintained its significant support for HIV prevention research ($160 million) in 2013, and the UK-based Wellcome Trust that upped its contribution from $10 million to $16 million.

Still, with US public sector investments—primarily from the NIH—financing 70% of HIV prevention research across the globe, the significant decline in US funding had a significant impact on grants and programs. As a result of sequestration, 280 research grants went unfunded, including 31 dedicated to AIDS vaccine research, according to the working group.

Emily de Lacy Donaldson, program coordinator at AVAC, a global HIV prevention group based in New York and a member of the working group that prepared the report, said no one quite anticipated how much cuts by the US government would impact funding levels. The drop in the number of grant proposals being funded and the support for early career investigators was particularly troublesome, she said. "We're hopeful things will turn around in the coming year."

Despite the dip in funding for vaccine research, other prevention strategies, including treatment as prevention and pre-exposure prophylaxis (the use of antiretrovirals to prevent infection), received more funding last year as researchers conducted dozens of demonstration projects on how best to implement the strategies.

There was also an uptick in spending on HIV cure and therapeutic vaccine research, areas in which funding rose from $88.1 million in 2012 to $102.7 million in 2013. US investment in this area is expected to increase even more with US President Barack Obama's announcement that $100 million in NIH funds will be reprioritized to launch a new HIV Cure Initiative. Cure funding could also be higher than captured in the resource tracking report as companies invested in cure research do not directly report their expenditures to the working group.

For more detail, the full report is available at www.hivresourcetracking.org. —*Mary Rushton*

Upcoming HIV-Related Meetings

OCTOBER 2014

16th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV
October 6-8, 2014; Philadelphia, PA
More information: http://www.intmedpress.com/comorbidities

3rd Antivirals Congress
October 12-14, 2014; Amsterdam, The Netherlands
More information: http://www.antivirals.elsevier.com/index.html

5th International Conference on Retroviral Integration
October 23-26, 2014; Pacific Grove, CA
More information: www.cvent.com/events/5th-international-conference-on-retroviral-integration/event-summary-83ab9a3c9cb3456f8fb1b997f201bdb8.aspx

2nd International Conference on HIV/AIDS, STDs, & STIs
October 27-29, 2014; Las Vegas, Nevada
More information: http://omicsgroup.com/hiv-aids-std-conference-2014

HIV Research for Prevention 2014 (HIV R4P)
October 28 - 31, 2014; Cape Town, South Africa
More information: http://medschool.umaryland.edu/ihvmeeting/default.html

NOVEMBER 2014

HIV Drug Therapy Glasgow
November 2-6, 2014; Glasgow, U.K.
More information: http://hivglasgow.org

32nd Annual Symposium on Nonhuman Primate Models for AIDS
November 11-14, 2014 , Portland, Oregon
More information: www.nhp2014.com

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