A lot of snow fell the week of March 22-27 in Keystone, Colorado, which was accompanied by a flurry of updates from researchers who gathered for the joint Keystone Symposia on “HIV Immunobiology: From Infection to Immune Control” and “Prevention of HIV/AIDS.”

This year’s meeting marked the 25th anniversary of Keystone Symposia’s first HIV/AIDS meeting, which was held in 1984, three years after the first HIV infections were described. The speakers at the conference’s opening session left no doubt that 28 years later, there is still much to do to address the AIDS pandemic. “We probably got rid of the iceberg, but under the water there is a mass of ice, and that’s the current AIDS epidemic,” said Didier Trono, of the Ecole Polytechnique Fédérale de Lausanne, in his introductory address. Nobel laureate Françoise Barré-Sinoussi from the Institut Pasteur said recent developments in the AIDS vaccine field illustrate the need for new directions in research. “We have to come back to basic science,” she said.

If the plethora of findings presented at this year’s conference is any indication, researchers are already heeding her call. A broad collection of updates, ranging from studies of vaccine candidates in animal models to ongoing analysis of clinical trial results, should all serve to inform the development of future vaccine candidates.

STEP by step

Susan Buchbinder, the principal investigator of the STEP trial, provided another update on this now notorious Phase IIb test-of-concept trial of Merck’s adenovirus serotype 5 (Ad5)-based vaccine candidate, MRKAd5. Receipt of MRKAd5 was associated with enhanced susceptibility to HIV infection among some individuals, specifically uncircumcised men who have sex with men (MSM) who had pre-existing immunity to the Ad5 virus used to deliver fragments of HIV to the immune system. In its naturally circulating form, Ad5 is a cause of the common cold, but MRKAd5 cannot cause HIV or Ad5 infections.

At Keystone, Buchbinder described efforts to address some of the possible theories for the apparent increased risk of HIV infection among this group of vaccinated volunteers.

One finding of interest was that volunteers in the STEP trial who received an inactive placebo instead of MRKAd5, and who had the highest levels of pre-existing immunity to the Ad5 vector, actually had the lowest risk of HIV infection of all the volunteers in the trial. This observation led to the proposal that perhaps some unknown factor renders individuals with high Ad5 immunity less susceptible to HIV infection. But based on several analyses, Buchbinder said this association did not seem to be true.

Another factor under consideration was whether volunteers who received MRKAd5 were at an increased risk of HIV infection because they were infected with herpes simplex virus (HSV)-2, another sexually transmitted virus. Infection with HSV-2 was associated with a roughly two-fold increased risk of HIV infection among all STEP participants, but it did not explain the enhanced risk of infection among only vaccine recipients.
Buchbinder then unveiled new data from the extended follow-up of STEP participants, from October 2007 to January 2009, the period after the volunteers were informed whether they had received MRKAd5 or placebo (a process known as unblinding). Researchers were initially concerned that once the study was unblinded, volunteers would alter their behaviors and therefore the data collected would no longer be reliable. Buchbinder said that while there was a slight drop in high-risk sexual activity soon after the trial was unblinded, it quickly returned to the level that was previously observed during the trial.

The rate of HIV infection among MSM remained high, with 48 new infections occurring during this period—26 among those who received the vaccine candidate and 22 among placebo recipients. Buchbinder showed that the increased risk of HIV infection among vaccine recipients seems to be disappearing over time. However, Buchbinder emphasized that while this finding may offer some reassurance that the effect is time-limited, the results must be interpreted cautiously because of the small numbers of volunteers in these groups. Buchbinder also reported that 12 additional infections have occurred among women volunteers (only one had occurred when the first trial results were announced) and these were divided evenly between MRKAd5 and placebo recipients.

New antibody targets

Dennis Burton, a professor at Scripps Research Institute, presented results of an effort by IAVI and the neutralizing antibody consortium (NAC), which he leads, to identify new broadly neutralizing antibodies (see VAX February 2007 Primer on Understanding Neutralizing Antibodies). As part of its research study, known as protocol G, IAVI is collecting samples from individuals who have been HIV infected for at least three years. Researchers then screen the samples in the laboratory against an assortment of viruses and isolate antibodies from them. They then screen the antibodies to see if they can neutralize a broad variety of HIV variants in the lab.

So far, two antibodies have neutralized HIV particularly well, even compared to the four previously identified broadly neutralizing antibodies. “There is great interest in these antibodies,” Burton said. Further analysis will show precisely how these antibodies successfully neutralize HIV and may provide additional targets for vaccine candidates.

DNA prime doesn’t pay

Dan Barouch, an associate professor of medicine at Beth Israel Deaconess Medical Center, reported results from a study in rhesus macaques testing a combination of a DNA and an adenovirus vector-based vaccine candidate.

Barouch’s adenovirus vaccine candidate, referred to as Ad5HV48R, is almost entirely composed of Ad5, except one of its proteins was replaced with the corresponding protein from another strain of adenovirus (Ad48), which is much less prevalent worldwide than Ad5.

The study involved 30 rhesus macaques, evenly divided into five groups, each receiving a different vaccination regimen. All animals were then injected with a high dose of simian immunodeficiency virus (SIV), the monkey equivalent of HIV. Immediately after being exposed to SIV, T-cell responses were much higher in the animals that received the DNA prime/Ad5HV48 boost compared to those that received only Ad5HV48. But Barouch was surprised to find that the final outcome was actually different. The animals that received only Ad5HV48, had on average much lower levels of virus circulating in their blood than those that received the combination regimen.

After 500 days, four of 12 animals in the DNA/Ad5HV48 groups were alive, compared to 10 of 12 in the Ad5HV48-only groups and one of six monkeys that received a placebo injection.

The combination regimen tested by Barouch is similar to the DNA/Ad5 vaccine candidates developed at the Vaccine Research Center (VRC) that are slated to undergo testing in a 1,200-person Phase II trial called HVTN 505. This trial, a smaller version of the originally proposed Phase Ib test-of-concept trial known as PAVE 100, is currently under review by the US Food and Drug Administration. Scott Hammer, the principle investigator of the trial, stressed that these results could not be directly extrapolated to the VRC’s DNA/Ad5 prime-boost regimen. There are several differences between the vaccine candidates, and other monkey studies with the VRC’s prime-boost regimen have provided different results than this study by Barouch and colleagues.

This article was adapted from an article written by Andreas von Bubnoff and Richard Jefferys in the March-April 2009 issue of IAVI Report.
CAVD Reports Progress Toward AIDS Vaccine Development

Work by the Collaboration for AIDS Vaccine Discovery (CAVD), an international research network created in 2006 by the Bill & Melinda Gates Foundation to accelerate development of an AIDS vaccine, has been highlighted in a first-ever cumulative review. The report, available at www.cavd.org, provides an overview of the scientific and operational (legal and business) progress made by the CAVD network, which now comprises 400 investigators in 21 countries, over the past two and a half years. Total funding for the CAVD now exceeds US$327 million, representing the majority of the Foundation’s support for AIDS vaccine research and development.

The CAVD supports the goals of the Global HIV Vaccine Enterprise, as described in its Scientific Strategic Plan, which was first proposed in 2003 by a number of HIV researchers and policymakers as a way to promote multidisciplinary and collaborative approaches to generating and testing vaccine candidates. When it was created, the CAVD model included 16 funded institutions but it has since grown to include 19 primary grantees that all work with a number of other collaborating institutions around the world. Additionally, two grantees funded through the Gates Foundation’s Grand Challenges in Global Health program are also collaborating with the CAVD.

Researchers Catch HIV on Film

Using high-speed three-dimensional imaging equipment and a version of HIV embedded with a green fluorescent protein, a team of virologists and physicists were recently able to track and film in real-time the process by which an HIV-infected cell passes the virus to other cells. The movie tracked one of HIV’s proteins, known as Gag, as HIV was transmitted from an already infected CD4+ T cell to another CD4+ T cell that it was targeting (http://www.youtube.com/GreenVSLab).

In Day-Glo colors, these movies illustrate what happens when HIV-infected cells collide with uninfected cells and convey how rapidly the Gag proteins—with the help of adhesive contacts called virological synapses that are formed at the junction of CD4+ T cells—pass from infected cell to uninfected cell.

Together, virologists at Mount Sinai School of Medicine in New York City, who created the fluorescent version of HIV, and physicists at the University of California-Davis, who supplied the expertise in high-speed imaging, produced 12 movies detailing this process. Some depict just a few seconds in the life cycle of the virus, while others—with the help of time-lapsed photography—span several days. Although these short films may not compete with Hollywood blockbusters, after a week on YouTube, one of the short films had more than 150,000 hits.

Benjamin Chen, the Mount Sinai virologist who created the glowing HIV, says a fast video microscope capable of taking three-dimensional images of infected cells every second or so, showed that HIV Gag quickly congregates at the virological synapse, forming a button shape. The footage then shows the viral proteins being ushered into a target cell’s endosome, a membrane-bound compartment that many other viruses use to gain entry into cells but which HIV was not thought to favor much.

Chen says the footage depicting cell-to-cell transfer of HIV could provide valuable insights into new strategies for AIDS vaccine and drug development.

A Living History of AIDS Vaccine Research

IAVI Report is launching a special series this month on the history of AIDS vaccine research and development as told by some of the most integral scientists and policymakers in the field. Each chapter in the Living History of AIDS Vaccine Research will feature a video podcast, which can be viewed or downloaded at www.iavireport.org, as well as articles in the print and online versions of IAVI Report.

The first segment in this series features Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health. As one of the early pioneers of AIDS research, and a critical player in vaccine development since the discovery of HIV, Fauci provides a unique perspective on pivotal moments in history that have steered AIDS vaccine research, as well as reflections on where the field is headed. Online and print versions of this inaugural installment in the series are available in the March-April issue of IAVI Report. Additional chapters will focus on specific areas of vaccine research, and will be introduced over the coming months.

“We are living through one of the most devastating pandemics ever to confront human civilization” – Anthony Fauci
Understanding the Transmitted Virus

What are researchers learning about the enemy that a preventive AIDS vaccine would need to block—the virus that is transmitted and establishes infection?  

By Regina McEnery

While many factors have hindered the development of an AIDS vaccine, HIV’s astonishing degree of diversity remains one of the biggest obstacles. To put HIV’s diversity in perspective, consider this: The global diversity of influenza A, the virus that causes the flu, each year is roughly equivalent to the diversity of HIV in a single individual after six years of being infected. With 33 million people around the world currently infected with HIV, it makes for a mind-boggling degree of diversity.

Designing and developing an AIDS vaccine to tackle that degree of viral diversity can seem an overwhelming prospect, so researchers have turned their attention to studying the enemy that a preventive AIDS vaccine would need to block—the virus that is transmitted and establishes infection.

Early detection

But nailing down the earliest events of HIV infection is a tricky proposition. For one, HIV is most often a sexually transmitted infection, making it impossible for scientists to study the actual infectious event. Also, since most individuals do not recognize or learn of their HIV infection immediately, it is difficult for researchers to obtain samples from individuals very soon after they become infected.

To overcome this hurdle, scientists have been collecting samples with greater frequency from cohorts of uninfected individuals who are at risk of acquiring HIV. Discordant couples, in which one partner is HIV infected and the other is not, are one group that is particularly useful to study. Discordant couples are uniquely valuable because they allow scientists to study both the virus that establishes infection in the newly infected partner, as well as the virus population that is circulating in the transmitting partner.

Large cohorts of discordant couples have been established in Rwanda and Zambia and frequent sampling—every month instead of every three months—of uninfected partners in these cohorts has helped researchers identify new HIV infections much closer to the point of transmission. The more frequent testing and sampling also helps reinforce risk-reduction counseling messages and promotes condom use among couples.

As a better picture emerges of the virus that is transmitted from person to person, there is some welcome news for vaccine researchers.

Technical insights are also helping researchers collect information about HIV transmission. Researchers are now able to analyze historical blood samples that were collected from a single individual and work back in time, using models that predict virus evolution, to determine with a high degree of certainty the genetic characteristics of the virus that initially established infection.

The transmitted virus

As a better picture emerges of the virus that is transmitted from person to person, there is some welcome news for vaccine researchers. Evidence now suggests that the virus that is transmitted and establishes a new infection is not nearly as diverse as HIV in an individual that has been infected for some time.

When researchers analyzed samples from just under 200 individuals who were newly infected with HIV, they found that in the majority (81%) of these individuals, a single virus led to infection. This observation was later confirmed in a group of discordant couples—in 20 discordant couples studied, 90% of infections were initiated by a single virus, despite the fact that the transmitting partner had multiple HIV variants circulating in their bodies.

This has led researchers to propose that there is a bottleneck in HIV transmission—even though many variants of HIV are in an infected individual, only certain ones are capable of getting through and establishing an infection. This transmission bottleneck effectively limits the number of HIV variants in a newly infected individual.

These observations may have important implications for AIDS vaccine design since it could indicate that a preventive vaccine would only have to contend with a very small number of viral variants to block an infection from ever occurring. However, since the virus that establishes an infection quickly mutates and varies, there is still a very short period of time in which a preventive vaccine would have to act before diversity of the virus becomes a problem.

Some exceptions

Despite the bottleneck that appears to ensue during sexual transmission, researchers believe that a quarter of the time, two or more viruses succeed in establishing infection in a newly infected individual. In studying these cases, researchers have found an association between the presence of genital infections and the number of transmitted viruses that establish infection in a single individual, suggesting that other sexually transmitted infections may alter the transmission bottleneck.

New data also suggest that the number of viral variants that are transmitted and establish infection may vary greatly depending on the mode of transmission. For example, in cohorts of injection-drug users or men who have sex with men, researchers have observed that on average, a much higher number of viral variants are responsible for establishing infection than are seen in heterosexual transmission.

Researchers are now genetically analyzing the properties of the virus that gets transmitted and establishes infection to look for additional clues that may inform vaccine design.