21st Century Vax

Vaccine advances into unexplored territory, a place where prevention and treatment may meet.

October 1, 1999 By Richard Jefferys

“AIDS Endgame.” With this bravura January headline, *Lesbian and Gay New York* publisher Troy Masters trumpeted his enrollment in VaxGen’s AIDSvax trial, the first-ever large phase III HIV vaccine study. Magazines and newspapers across the country began to feature sexy recruitment ads, cheerleading “Make a Difference.” By May, *OUT* magazine had billed the study, launched a year earlier, as a new frontier in AIDS activism.

Public and private powerbrokers have jumped in to make a difference, too. Microsoft guru Bill Gates pledged $25 million for research to the International AIDS Vaccine Initiative (IAVI), while President Clinton recently dedicated a new vaccine research center at the National Institutes of Health (NIH) to his impeachment savior, former Arkansas senator Dale Bumpers (D). In Congress, longtime friend of the AIDS community Rep. Nancy Pelosi (D-CA) introduced H.R. 1274, the Lifesaving Vaccine Technology Act of 1999, to spur corporate vaccine development for AIDS, malaria and tuberculosis (TB) by means of substantial tax credits.

Just as the number of new HIV vaccines entering federally funded trials hit an all-time low, this flurry of activity seems to have restored public faith in an HIV vaccine. And with 5.8 million infected annually around the globe, advocates say the need is more urgent than ever. Meanwhile, the fate of the 33 million already infected and without access to treatment remains obvious, if unspoken. For Americans living with HIV, this outbreak of vaccine fever, with its emphasis on prevention, not treatment, may have an all-too-familiar, fatalistic ring. The question is: Would a preventive vaccine offer as little to those already infected as a free condom?

“In the last 15 years, the field of immunology has exploded, giving HIV research in general, and vaccine research in particular, a boost,” says Sam Avrett, executive director of the AIDS Vaccine Advocacy Coalition. This accelerating science may be about to play a wild card. Scattered examples of people whose immune systems control HIV without drugs have provoked a startling hope: The desirable immune responses -- for HIV prevention *and* HIV therapy -- may be exactly the same.

At the Second Annual Vaccine Research Conference last March, Nobel Prize-winning immunologist Peter Doherty, PhD, captured the sense of scientific surprise: “I now find myself talking about post-exposure vaccines, which I never thought I would.” Visionary polio pioneer Jonas Salk had predicted this possibility years ago, but “back then,” Doherty joked, “I thought maybe he had gone

around the bend."

One-Armed Bandit

Unfortunately, AIDSvax, now enrolling 5,000 volunteers across the United States and 2,500 more in Thailand, does not represent the vaccine vanguard. To understand why, it's critical to know that scientists divide immune responses into two general types, or "arms." One arm is called humoral, and refers to antibody responses. And this is exactly what AIDSvax is about, stimulating antibodies against gp120, one of the protein spikes on HIV's outer coat, or envelope (see diagram, page 70). Antibodies are themselves made by a type of lymphocyte (white blood cell) called a B cell, with direction from certain CD4 cells.

For years, many common vaccines have been thought to succeed by producing antibody responses, but so far these approaches appear ineffective in preventing chronic viral infections such as HIV (one exception may turn out to be "fusion-competent" antibodies; see box, page 73). Also, AIDSvax bombed as an HIV treatment, as did similar vaccines based on another envelope protein, gp160.

It seems personalities, not science, pushed AIDSvax farther than any vaccine before.

The Vax Files

Only five years ago, on June 17, 1994, AIDSvax was at a turning point. A contentious group of scientists and community reps had gathered in Bethesda, Maryland, to debate the merits of the gp120 and gp160 vaccine candidates. At this point, two of these envelope vaccines -- one the precursor to AIDSvax -- had stumbled into phase II of human testing. Now it was up to this NIH-sponsored committee to decide whether large phase III studies were warranted. But attendees' enthusiasm was cooling. Several early trial participants who received the gp120 product, made by Genentech, had become HIV infected while in the study. Although the numbers were low, they certainly didn't bode well.

In its favor, Genentech could offer up the leader of its vaccine research effort, Don Francis, MD, the scientific star of Randy Shilts' *And the Band Played On*. A typically passionate Francis stood up at the meeting to declare that his bright hopes for the gp120 product were undimmed: "We think we have developed a vaccine that will protect humans from HIV."

Longtime community activist David Scondras countered from the floor: "You are asking me to tell my friends to participate in a trial that may not get the answers you are looking for, of a product that you are not too sure is going to work that well, that would preclude them from participating later in a trial of a product that might be better."

Unsurprisingly, the committee decided not to support NIH funding for large phase III trials. But, unstoppable as always, Francis undertook a Herculean effort to raise private funds for AIDSvax, taking leadership of VaxGen, a Genentech spinoff, to do so. By mid-1998, the Food and Drug Administration gave him the green light to enroll phase III volunteers.

At press time, about half of VaxGen's slots had been filled. And the study will undoubtedly answer some questions about the usefulness of antibody responses. Though most researchers expect the ultimate value of that information to be slight, the energy and hope generated by the efforts of Francis and the thousands of volunteers serve as a forceful reminder of the feasibility of large-scale vaccine trials. "We're not asking the antibody to be omnipotent," says John Curd, MD, VaxGen's vice president of medical research. "The current rate of exposure to infection is one in 100. Even if AIDSvax reduces that to one in 200, it's worthwhile." As Patricia Kahn, associate editor of *IAVI Report*, says, "You do the best that you can as quickly as you can -- and improve upon it."

Beyond Antibodies

The old-school AIDSvax is far from the sole vaccine candidate in the works. Over the past few years, a slew of new vaccine approaches has emerged, all aimed at stimulating the more mysterious second arm of immune response: cellular immunity. Jonas Salk's own "whole-killed" vaccine, Remune, is the best known. But among the most promising are "naked DNA" vaccines, which send pieces of genetic code into the body to make cells produce fake HIV proteins. These, in turn, trigger a cellular immune response.

Cellular immunity does not prevent viruses from entering the body -- *but it can prevent them from causing illness*. Many researchers are now convinced -- as, in fact, Salk always was -- that the key to controlling HIV is nestled in this arm of the immune system. Several different avenues of research suddenly seem to be heading in the same direction.

We've know for years that the lead players in the cellular immune response belong to a group of lymphocytes called CD8 cells. Especially important are the CD8s called cytotoxic T-lymphocytes (CTLs), which hunt down and destroy infected cells in the body. CD8 cells -- particularly CTLs -- have long been a subject of intense study.

A recent lightning bolt on this front came from immunologist Rafi Ahmed's research group at Emory University in Atlanta. Studying mice infected with a virus called LCMV, they found that CD8 cells needed assistance from a particular group of CD4s -- called type 1, or Th1, helper cells -- to control the infection.

The first person to fully grasp the implications of this new research was Bruce Walker, MD, a young immunologist affiliated with Harvard University. Walker published a research article in November 1997 that focused attention on responses to HIV by these specific Th1 helper cells. While reams of prior research had focused on CD8 CTL cells, the vital supportive role of HIV-specific Th1 helpers had never been fully acknowledged before Walker's report. Since then, he's become a proselytizer, waxing optimistic about these cells on PBS's February *Nova* program "Surviving AIDS" and before a packed audience at last year's World AIDS Conference in Geneva, where he bravely stated, "Eradication is not necessary. The immune system can control HIV."

Walker's bold conclusions derive primarily from two groups of people: HIV-infected folks who don't show signs of disease progression, called "long-term nonprogressors," and people who are

repeatedly exposed to HIV but remain antibody negative. What do these people have in common? *In virtually every case, they have a potent cellular immune response against HIV*. And they don't have just HIV-specific CTLs, but evidence of Th1 CD4 helpers targeting HIV as well. Importantly, these cells take aim at core proteins from HIV -- the inner parts of the virus that are only revealed once it enters a T-cell. These core proteins don't mutate as much as the ones on HIV's envelope -- the type of protein used in AIDSvax.

A recent University of Washington study suggests that long-term nonprogressors and those who are exposed but negative have another thing in common -- they both harbor HIV. In other words, people who are exposed but antibody negative may be the ultimate long-term nonprogressors. Walker speculates that their cellular immune response may have controlled HIV so well that they haven't even produced antibodies.

HIV and Immune Control

So why don't most people who are positive control HIV? The difference appears to involve how T-cells -- both CD4s and CD8s -- mature in the face of HIV replication. Normally, when a virus first gets into the body, it's the job of previously unemployed, or naïve, T-cells to respond. These T-cells divide rapidly, creating a swarm of daughter cells to fight the virus. Most of these newly minted T-cells die within a matter of days. A few, however, mature into memory T-cells and can respond rapidly to the virus, patrolling the body and preventing further viral replication. With most viral infections this process works well and viruses are controlled.

But HIV is different. While there's evidence that memory CD8 cells, including CTLs, develop in people with HIV infection, Walker found that functional Th1 CD4s are absent in all but nonprogressors. And Ahmed's mouse studies showed that without these Th1 CD4s to trigger them, CD8 memory cells don't work properly.

There are two leading theories as to why Th1 CD4s seem to be absent in most people with HIV. Walker has suggested that the cells might be somehow "deleted" early in infection. Other investigators have posited that these cells develop, but HIV replication makes them dysfunctional. Whichever it is (new evidence seems to support the latter), the upshot is that HIV remains unfinished business. Naïve T-cells continue to get triggered by the virus over the course of infection, slowly depleting the pool of cells vital for responding to infectious challenges.

Here prevention and treatment converge. Getting some HIV-specific memory T-cells working -- both Th1s and CD8s -- may prepare a person's immune system so that HIV can be controlled like other viruses. And in people who are already infected, generating such cells could be the key to drug-free immune control. "The goal of immune-mediated containment of HIV is realistic," Walker says. "It needs to be pursued with vigor."

Vaccines: The Next Generation

While envelope-based strategies may be running aground just as AIDSvax brings them national attention, vaccines that induce Th1 helper and CTL memory responses are steaming ahead. Unlike AIDSvax, these vaccines use many more HIV proteins than just those found on the outside of the

virus. Typically, these include a few of the virus' core components, such as gag, pol and nef genes (see diagram, page 70).

Jonas Salk's Remune, once known as the Salk Immunogen, is almost an entire dead HIV, missing only -- but perhaps critically -- the gp120 and gp160 envelope proteins. After more than a decade of inconclusive treatment studies in people with HIV, Remune is making a comeback. The ability of HAART therapy to dampen HIV replication seems to allow Remune to spur the development of functional memory T-cells, according to studies like those by New York University's immunology specialist, Fred Valentine, MD. Widely respected doctor Mike Saag, MD, of the University of Alabama at Birmingham, is now testing Remune's ability to establish HIV-controlling immunity in people who stop HAART. And last year, turning vaccine development on its head, Remune also entered animal studies as a preventive vaccine.

Salk's approach focuses on the Th1 CD4 cells critical in coordinating the cellular immune response. But naked DNA vaccines may be more effective because they can trigger both Th1 CD4s and CD8s -- the two key elements of the cellular system. An Australian research team, led by Stephen Kent, MD, has recently published encouraging results with an experimental DNA product called Co-X-Gene. The vaccine is based on DNA injections followed by a booster made from a harmless bird virus that has been tinkered with so it makes dummy HIV proteins. The booster seems to further rev up the memory T-cell response, making the combo even more potent.

When given to macaque monkeys, the Co-X-Gene vaccine protected against active infection by HIV. Although it didn't prevent HIV from getting into the body, vaccinated monkeys mounted an immune response similar to that seen in HIV-exposed but antibody-negative humans. HIV replication was soundly squelched, and it was tough to find virus in the monkeys' blood cells. Co-X-Gene is now entering human trials in Australia. According to Ian Ramshaw, PhD, a member of the research team, "The advantage of our system is that it is only a few cents per shot and can be administered without expensive equipment or training. And it does not require refrigeration, which can be a major difficulty in tropical countries." If the new studies show promise, the researchers intend to expand trials into the developing world within two years. IAVI's Kahn lauds DNA vaccines as "stupendous, [potentially] the cheapest and most effective medicine that could be available globally." But she also calls it a "technology of the future."

Equally exciting results have been reported by an American researcher, Harriet Robinson, MD, of the Yerkes Primate Research Center in Atlanta. In Robinson's study, a DNA vaccine with a bird virus booster elicited controlling immunity in a group of monkeys. After vaccination, the monkeys were repeatedly "challenged" -- infected with -- live virus. Each challenge had the salutary effect of further boosting the strength of the memory T-cell response, suggesting that such a vaccine may be able to protect against repeated exposures. In fact, with this vaccine, repeat exposures could even help preserve the strength of the immune response.

Both the Australian and Atlanta-based research teams have high hopes for the therapeutic potential of their vaccines. As this article went to press, pharmaceutical giant Merck & Co. announced human studies of its own naked DNA and booster vaccine. While the number of vaccine

trials in humans is still tiny, Merck’s arrival on the scene is another signal that things are changing for the better. “It’s an exciting time in vaccine research,” says *IAVI Report* editor David Gold.

After two decades of talk, harnessing the power of the cellular immune system finally seems to be more than just a fantasy. During the weeks that this article was in preparation, two other cellular-based vaccines hit the news -- one against TB, the other against human papilloma virus (HPV), a leading cause of anal and cervical cancer. Study results on this kind of HIV vaccine are likely to pour in over the next year or two, and Bruce Walker’s early findings are already the hot topic in the halls of scientific conferences. Jonas Salk passed away in 1995, before the scientific seeds he’d sown had fully blossomed, but his vision becomes clearer every day.

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