

vaccines that trigger cellular immunity: what can we hope for?

RICHARD JEFFERYS

THE SEARCH FOR an effective HIV vaccine relies heavily on the scientific lessons learned from other vaccines—for example, those that prevent polio and hepatitis B. Until recently, the conventional wisdom was that most vaccines work by triggering the body to produce *antibodies* against the infection. Antibodies are tiny Y-shaped molecules made by immune system cells called *B-cells*. Their main task is to search out invaders, or *pathogens* (like *viruses* or bacteria) floating free in the bloodstream, and then to stick onto them. Once a pathogen is coated with antibodies, it can't infect new cells and is quickly destroyed.

But antibodies are at a big disadvantage when it comes to HIV, because the virus has developed very effective strategies for evading them. The result is that scientists haven't yet found a way of triggering the immune system to make antibodies that block HIV infection (see chapter 7 on the different approaches to designing HIV vaccines). Overcoming this problem is a top priority for the field, but in the meantime, researchers have come to recognize that another arm of the immune system—called *cellular immunity*—is also important in vaccine protection.

HIV vaccines targeting cellular *immune responses* also turn out to be easier to make, and as a result, nearly all the candidates now in *clinical trials* fall into this category. And with a few dozen such candidates in development, it's crucial for the field to figure out whether this approach can induce even partial protection—which, in turn, will tell us whether or not we're on the right track. Here we'll describe what's known about the role of cellular immunity in protection, and discuss how these vaccines might work and how they're being tested.

beyond antibodies: the role of cellular immunity

Cellular responses come mostly from two types of immune cells. First are the “*killer*” *T-cells*, also called by the more technical names of *cytotoxic T-lymphocytes (CTLs)* or *CD8+ T-cells*; their role is to seek out and destroy cells in the body that have already become infected. Second are “*helper*” *T-cells*, or *CD4+ T-cells*, which help both CD8+ T-cells and B-cells do their jobs by acting as overall coordinators of the immune response.

“Killer” T-cells, or CD8+ T-cells, seek out and destroy cells in the body that have already become infected. “Helper” T-cells, or CD4+ T-cells, do their jobs by acting as overall coordinators of the immune response.

There haven't yet been many studies directly proving the role of T-cells in protection by the common vaccines. But antibody expert Dennis Burton (of the Scripps Institute in San Diego, California) says that most vaccines don't induce high enough levels of antibodies to completely block infection, and that cellular immunity must therefore also be playing a role.

In a way it's surprising that this should be discovered only now, since most of the common vaccines have been around for decades. The main reason is a practical one: antibody responses are far easier to measure, and tests to do this have been in use for many years. But until a few years ago, methods for looking at cellular responses were much cruder (and more labor-intensive). Fortunately, new, improved methods are now allowing researchers to tackle the question of what role cellular immune responses play in preventing HIV infection or delaying the long progression to AIDS once a person becomes infected.

So far, research findings suggest that cellular immune responses can play an important role in fighting HIV. Much of this research focuses on two unusual groups of people.

First, there are individuals who remain HIV-negative even though they're repeatedly exposed to the virus. These people are called "*exposed seronegatives*" or ESNs. Researchers have studied different types of ESNs, including uninfected partners of HIV-infected individuals, commercial sex workers and infants who are exposed to HIV via breastfeeding. Many of these studies have found that ESNs show cellular immune responses targeting HIV (that is, HIV-specific CD4+ T-cells and CTLs), but no antibody responses. For example, one study in infants exposed to HIV via breastfeeding found that the presence of HIV-specific CTLs at birth strongly increased the baby's chances of staying uninfected.

Second is the group of rare individuals known as *long-term non-progressors* (LTNPs). LTNPs are HIV-positive people who show no signs of *immune deficiency* although they've been infected for long enough that this is very unusual. (Some have been monitored by researchers for more than 20 years and still show no evidence of disease progression.) They also have very low levels of virus in the blood (*viral load*). At the same time, LTNPs have strong cellular immune responses specific for HIV.

Studies in rhesus monkeys add to the evidence that cellular immunity plays a role in controlling virus *replication*. These animals can be infected with a virus called SIV (*simian immunodeficiency virus*), which is closely related to HIV. Researchers have found that removing CD8+ T-cells from SIV-infected macaques leads to a dramatic increase in viral load, which then gradually declines as the body replenishes its lost CD8+ T-cells. More detailed studies with several vaccine candidates have also shown that the level of vaccine-induced SIV-specific T-cell responses determines how well the animals control SIV replication after infection.

So far, research findings suggest that cellular immune responses can play an important role in fighting HIV. Much of this research focuses on two unusual groups of people.

These findings don't prove that cellular immune responses protect against HIV infection or prevent disease progression. But they provide a good scientific justification for developing vaccines targeting HIV-specific cellular immunity.

the importance of memory

One issue which has plagued the pursuit of this approach is that scientists haven't been able to define just what particular CD4+ and CD8+ T-cells are needed for protection—these cells exist in many varieties, each with different levels and types of biological activity. So when researchers test vaccines in either animal models or people, they don't know precisely which responses best identify the most promising candidates.

Immunological memory is key to our ability to fight off pathogens we've been exposed to before.

But as they hone in on this problem, researchers are starting to pay more attention to the *memory* CD4+ and CD8+ T-cells.

Immunological memory is the key to our ability to fight off infection by a pathogen we've been exposed to before, either from an earlier infection or from a vaccine. But until recently, scientists didn't know much about how immune memory is formed. Fortunately, that's now starting to change, opening up new opportunities for making vaccines that do a better job at inducing memory—for example, by smarter dosing of the vaccine and more optimal frequency and spacing of *immunizations*. And this, in turn, could give the immune system a crucial “head start” against HIV.

Another new finding is that CD4+ T-cells are needed to make fully functional memory CTL; without them, memory CTLs don't kill infected cells as effectively. This gives HIV vaccine makers the crucial piece of information that their vaccines must induce CD4+ responses along with the CD8+'s, information that is now getting incorporated into vaccine design and testing.

potential problems with cellular immunity

On the down side, there are some reasons to worry that vaccines that target *only* cellular immunity may have serious limitations.

One big concern is the potential for “*immune escape*.” HIV has a breathtaking ability to mutate (change its genetic material)—which it does continuously, as it copies itself thousands of times in each infected cell. Some of these *mutations*, in turn, change the structure of the viral *proteins*, or more specifically, of the small regions within them (called *epitopes*) recognized by T-cells. Even if a vaccine suppresses HIV multiplication almost completely, over time it's still possible that mutation will generate *strains* which are no longer recognized by the vaccine-induced T-cells—effectively making an end-run around vaccine protection. A somewhat related worry is that an immune system weakened by age, or by a disease unrelated to HIV, could lose its ability to control virus.

This enormous *variation* in HIV proteins (and epitopes) presents another potentially serious challenge for vaccines: will a single vaccine be able to protect against *all* HIV strains, or will it protect only against strains closely related to the one used in making the vaccine? This issue is discussed at length elsewhere in this volume (see chapter 10); at present, the answer is that we just don't know. But the hope is that, even if the match is poor, those T-cells which recognize the *unchanged* (or minimally changed) epitopes might still be enough for protection. And even if they hold a new infection at bay only temporarily, it might give the immune system enough time to generate new memory responses that lead to more lasting protection.

testing cellular immunity-based vaccines

MOST OF THIS DISCUSSION so far is about what these vaccines *might* do, or what something *could* mean. But we need to know for sure: can vaccines that induce cellular immune responses to HIV (in particular, memory CD4+ and CTLs) either protect against HIV infection or control virus replication

in vaccinated people who become infected? Another very important question is whether, if they do hold viral load to low levels, this will also reduce the frequency of HIV transmission.

The usual assumption in the field is that these vaccines won't give much protection against HIV infection, but that they may slow or prevent progression to AIDS. But the fact that ESNs have T-cell responses without any signs of infection argues that the potential for complete protection shouldn't yet be ruled out.

After years of testing candidates in *Phase I* and *II* trials (and finding out that many of them induce at least modest T-cell responses), the first trial to give some real answers is getting underway. The 1,500-person "proof-of-concept" study started at the end of 2004 at several international sites and is testing a vaccine (designed by Merck & Co.) that uses a weakened cold virus (called *adenovirus*) to carry HIV genes into the body. The trial—a so-called *Phase IIb* study (see chapter 11)—should give some indication about whether these vaccine-induced cellular responses are effective at either preventing HIV infection or reducing viral load in vaccinees who become infected. If all goes as planned, results will be available around 2007/2008. However, if it works, this vaccine will need to be modified and re-tested before an application for licensure. That's because a high percentage of people already have *immunity* to the type of adenovirus used to make the vaccine, which means that they don't respond nearly as well as people without this pre-existing immunity. (Such individuals will be excluded from the Phase IIb trial).

More information about the role of T-cell responses could also come from an ongoing vaccine *efficacy* trial in Thailand. This trial is evaluating a combination of two vaccines (one based on a harmless bird virus called *canarypox*; and *AIDSVAX*, the VaxGen product described in chapter 22). The canarypox-based vaccine induces HIV-specific T-cell responses in about 10–20% of vaccinated people.

As these and other crucial trials get underway, work on vaccines that stimulate antibodies is continuing (and intensifying). And many scientists think that, in the end, the best HIV vaccines will need to stimulate both cellular immunity and antibody responses.