

In the 2 decades since researchers identified HIV as the cause of AIDS, more money has been spent on the search for a vaccine against the virus than on any vaccine effort in history. The U.S. National Institutes of Health alone invests nearly \$500 million each year, and more than 50 different preparations have entered clinical trials. Yet an effective AIDS vaccine, which potentially could thwart millions of new HIV infections each year, remains a distant dream.

Although AIDS researchers have turned the virus inside-out and carefully detailed how it destroys the immune system, they have yet to unravel which immune responses can fend off an infection. That means, as one AIDS vaccine researcher famously put it more than a decade ago, the field is “flying without a compass.”

Some skeptics contend that no vaccine will ever stop HIV. They argue that the virus replicates so quickly and makes so many mistakes during the process that vaccines can't possibly fend off all the types of HIV that exist. HIV also has developed sophisticated mechanisms to dodge immune attack, shrouding its surface protein in sugars to hide vulnerable sites from antibodies and producing proteins that thwart production of other immune warriors. And the skeptics point out that vaccine developers have had little success against pathogens like HIV that routinely outwit the immune system—the malaria parasite, hepatitis C virus, and the tuberculosis bacillus are prime examples.

Yet AIDS vaccine researchers have solid reasons to believe they can succeed. Monkey experiments have shown that vaccines can protect animals from SIV, a simian relative of HIV. Several studies have identified people who repeatedly expose themselves to HIV but remain uninfected, suggesting that something is stopping the virus. A small percentage of people who do become infected never seem to suffer any harm, and others hold the virus at bay for a decade or more before showing damage to their immune systems. Scientists also have found that some rare antibodies do work powerfully against the virus in test tube experiments.

At the start, researchers pinned their hopes on vaccines designed to trigger production of antibodies against HIV's surface protein. The approach seemed promising because HIV uses the surface protein to latch onto white



cytokines, and so-called natural killer cells—that have received scant attention.

The hunt for an antibody-based vaccine also is going through something of a renaissance, although it's requiring researchers to think backward. Vaccine researchers typically start with antigens—in this case, pieces of HIV—and then evaluate the antibodies they elicit. But now researchers have isolated more than a dozen antibodies from infected people that have blocked HIV infection in test tube experiments. The trick will be to figure out which specific antigens triggered their production.

It could well be that a successful AIDS vaccine will need to stimulate both the production of antibodies and cellular immunity, a strategy many are attempting to exploit. Perhaps the key will be stimulating immunity at mucosal surfaces, where HIV typically enters. It's even possible that researchers will discover an immune response that no one knows about today. Or perhaps the

Is an Effective HIV Vaccine Feasible



blood cells and establish an infection. But vaccines that only contained HIV's surface protein looked lackluster in animal and test tube studies, and then proved worthless in large-scale clinical trials.

Now, researchers are intensely investigating other approaches. When HIV manages to thwart antibodies and establish an infection, a second line of defense, cellular immunity, specifically targets and eliminates HIV-infected cells. Several vaccines which are now being tested aim to stimulate production of killer cells, the storm troopers of the cellular immune system. But cellular immunity involves other players—such as macrophages, the network of chemical messengers called

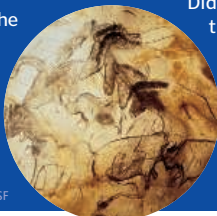
answer lies in the interplay between the immune system and human genetic variability: Studies have highlighted genes that strongly influence who is most susceptible—and who is most resistant—to HIV infection and disease.

Wherever the answer lies, the insights could help in the development of vaccines against other diseases that, like HIV, don't easily succumb to immune attack and that kill millions of people. Vaccine developers for these diseases will probably also have to look in unusual places for answers. The maps created by AIDS vaccine researchers currently exploring uncharted immunologic terrain could prove invaluable. —JON COHEN

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