# Tiny steps towards an HIV vaccine

Recent successes are reinvigorating research into a vaccine for HIV, reports **Cassandra Willyard**.

Last September, after more than 20 years of disheartening research, HIV vaccine researchers had their first, albeit small, taste of success.

In a clinical trial of about 16,000 people in Thailand, the candidate vaccine RV144 lowered the rate of HIV infection by about 30%.

RV144 remains far from market, but the trial gave the field a badly needed boost. After Merck's much-hyped V520 failed in 2007, many researchers questioned whether a successful vaccine could be developed.

"We showed for the first time that it's possible," says Jerome Kim, deputy director of science at the US Military HIV Research Program and a lead investigator on the RV144 trial.

No one yet knows why RV144 worked or how to improve on it; however, this glimmer of success, together with recent clues to other ways to boost the immune response to HIV, has researchers feeling optimistic. "This really is a renaissance," says Wayne Koff, chief scientific officer of the International AIDS Vaccine Initiative (IAVI) in New York.

## Thai mystery

Vaccines generally rely on two tactics: tricking the immune system into producing antibodies that can bind to key parts of a virus and prevent it from infecting cells; and activating the immune system's cellular response, which targets and destroys infected cells.

The trouble is that HIV varies widely — even within an infected individual. HIV infection tends to elicit antibodies and immune cells that are specific to one particular strain, and no help against others.

This variability defeated vaccine efforts until RV144. In this combination formula, ALVAC (developed by Sanofi Pasteur) is designed to elicit a cellular immune response, whereas AIDSVAX (made by Global Solutions for Infectious Diseases) is designed to induce production of antibodies[1].

The odds were against this combination from the beginning: ALVAC's efficacy had never been tested alone, and AIDSVAX had flopped in two previous trials. One group of leading researchers was so sure of failure they called on the government to scrap the study. So why did the combination succeed?

Barton Haynes, head of the National Institutes of Health (NIH)-funded Center for HIV/AIDS Vaccine Immunology, is probing this mystery by analysing blood samples from trial participants. "We need to study this trial to try and understand everything we possibly can about what happened and why," Haynes says.

## Genetic diversity

Meanwhile researchers are hunting for 'broadly neutralizing antibodies,' which can bind to numerous HIV strains and block them from infecting cells. A vaccine that could trick the body into producing these antibodies might prevent infection.

In 2009, researchers from IAVI and The Scripps Research Institute in La Jolla, California, isolated two broadly neutralizing antibodies from the blood of an HIV-positive individual in Africa[2]. Last October, at a conference in Paris, NIH researchers announced three more antibodies that bind to a new target on the virus. "We've clearly broken through a wall," says Gary Nabel, head of the NIH's Vaccine Research Center.

Isolating the antibodies is only half the challenge. How can the vaccine prompt the body to produce them? "That's the $64,000 question," says Dennis Burton, director of IAVI's Neutralizing Antibody Consortium, and professor of immunology and microbial science at Scripps.

Burton and others are trying 'reverse engineering' techniques — working backwards from the antibody structure — to build molecules that stimulate the body to produce them.

In March, at a meeting in Banff, Canada, Merck researchers announced that they have designed a molecule that elicits a neutralizing antibody in guinea pigs and rabbits. It is the first time that "this kind of reverse engineering process has been validated on the biologic side," says Koff, "so it's a real advance."

Some groups are exploring strategies that bypass the immune system. For example, a team at the Children's Hospital of Philadelphia has devised a way to insert the genes for these antibodies into cells using an engineered virus. These recombinant vectors produce enough antibodies to protect monkeys from infection with an HIV-like virus[3]. The team plans to test the concept in people.

**"We're doing everything we can to surprise ourselves."**

A good vaccine would also boost the cellular immune response. To overcome HIV's diversity, researchers are testing artificial genetic sequences that mimic parts of its genome but cover the widest possible array of strains. "These sequences are not [ones] that are found in their entirety in any naturally occurring virus," says Dan Barouch, chief of vaccine research at Beth Israel Deaconess Medical Center in Boston, Massachusetts.

Injected into rhesus monkeys, these 'mosaic' sequences incite an immune response broader and deeper than with the natural virus[4,5]. A clinical safety trial is planned, Haynes says.

Although these studies seem promising, continuing obstacles make HIV researchers loath to predict when a vaccine might be ready.

"What you can say is that it would be a major miracle if we had one in less than ten years," Nabel says. "On the other hand, we're doing everything we can to surprise ourselves." ■

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**Although no one yet knows why, a candidate vaccine called RV144 seems to prevent HIV infections.**