T cell-based HIV vaccine candidate demonstrates positive results

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The question of whether or not to continue to pursue the development of T-cell-based HIV-1 vaccines has been a source of controversy following last year's widely publicized failure of the field's most promising candidate, a vaccine developed by Merck known as V520.

Now a study led by investigators at Beth Israel Deaconess Medical Center (BIDMC) provides the proof-of-concept that a T-cell-based strategy remains a viable course to follow.

Described in today's dvance On-line Publication of *Nature*, the study showed that an improved regimen using two distinct adenovirus vectors – rAd26 prime/rAd5 boost – and expressing the simian immunodeficiency virus (SIV) Gag protein, resulted in potent T-cell immune responses leading to long-term immune control of an SIV challenge in monkeys. The findings demonstrate for the first time using this stringent animal model that such a vaccine may be effective in the fight against AIDS.

"This is a controversial field right now," says the study's lead scientist Dan Barouch, MD, PhD, Principal Investigator of the NIH-sponsored Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) program, who is working to develop new HIV-1 vaccine candidates. "Despite the disappointing setbacks in HIV-1 vaccine development this past year, our findings suggest that we're not at the end of the road when it comes to T-cell vaccines. Our data show that T-cell vaccines that elicit greater magnitude, breadth, and quality of immune responses as

compared with the Merck vaccine can result in improved protection in the rhesus monkey model of AIDS."

The induction of the immune system's "killer" T-cells as a means of protecting against HIV-1 is designed to overcome a number of unique obstacles that make the virus impervious to traditional vaccine strategies, which typically work by producing antibodies to eliminate the invading virus. Instead, T-cell generated immunity works by selectively targeting and destroying any cells that have already been infected by the virus.

"Although our vaccine regimen did not prevent acquisition of SIV infection, it substantially reduced the levels of virus in the blood of these animals and prevented the development of AIDS," says Barouch, who is also an Associate Professor of Medicine at Harvard Medical School.

Barouch and his colleagues in the Division of Viral Pathogenesis at BIDMC, in collaboration with the biotechnology company Crucell Holland BV, have spent the past three years developing new rare serotype adenoviral vectors, which deliver HIV antigens and are the basis for one strategy of HIV-1 vaccine development. Viral vector vaccines are made by deleting one or more genes from a harmless or attenuated virus, in this case, adenovirus. Segments of DNA-encoding HIV-1 proteins are inserted in place of the deleted genes and thereby transfer the proteins into human cells to stimulate an immune response to the HIV-1 virus.

Last year's Merck trial used as its vector adenovirus serotype 5 (rAd5) which is a virus responsible for the common cold. "Because Ad5 is encountered frequently in the environment," explains Barouch, "many individuals harbor preexisting immunity to this virus." As a result, following vaccination, this vector often proves ineffective in delivering its "cargo" to induce an immune response to HIV.

In the new study, Barouch's laboratory used an rAd26 viral vector as its means of transport. Ad26 is rarely encountered in the human population and has the ability to induce a potent immune response, providing protective efficacy against SIV.

Also distinct from the Merck study, the authors made use of a heterologous "prime-boost" system to enhance the vaccine's immunogenicity. "In most cases, the immune response induced by a single dose of a vaccine isn't strong enough or sustainable enough to provide effective protection," explains Barouch. By administering a second "boost" the antigen's immune response can be enhanced. In this case, the scientists successively administered the same antigen in two separate vectors: The first rAd26 vector "primed" the animals' immune responses; re-exposure to the same antigen in a second rAd5 vector provided the "boost."

Their results showed that when challenged with a lethal dose of SIV, the vaccinated animals were able to reduce viral replication and to remain healthy for more than 500 days following infection, indicating that the vaccine had sparked a powerful immune response.

"This is an extremely important study because it shows that there is still hope for vaccines currently in the pipeline," says Bruce Walker, MD, Director of the Harvard University Center for AIDS Research (CFAR). "It also gives the first clear indication of the level and type of immunity that will likely be needed for an AIDS vaccine to work."

More than 25 years after the discovery of HIV-1, AIDS remains one of the world's most devastating health problems. An estimated 33.2 million people currently live with HIV/AIDS while 2.5 million new infections were reported in 2007 alone.

Source: Beth Israel Deaconess Medical Center