Research BRIEFS

Prime-Boost Regimen with Ad26 Offers Renewed Hope for T-cell Vaccines

Rhesus macaques that received a heterologous prime-boost vaccine regimen comprised of an adenovirus serotype 26 (Ad26) vector expressing simian immunodeficiency virus (SIV)mac239 Gag, followed by an adenovirus serotype 5 (Ad5) vector expressing the same Gag, showed reduced viral loads and remained healthy for 500 days following intravenous SIVmac251 challenge (*Nature* doi:10.1038/nature07469). This heterologous prime-boost regimen reduced peak viral load in vaccinated monkeys by 1.4 logs and setpoint viral load by 2.4 logs, compared to unvaccinated control animals, and is the first to show this level of control in such a stringent challenge model, says Dan Barouch, an associate professor of medicine at Harvard Medical School, who led the study.

> The overall message of the paper is that we are not at the end of the road when it comes to T-cell vaccines. – *Dan Barouch*

The challenge model used in this study was stringent in that it used a lethal dose of SIVmac251 in animals lacking the MHC class I alleles Mamu-A*01 and B*17, which are associated with more efficient control of viral load. Three of the 22 macaques in the study had a protective allele called B*08, but when an analysis was done excluding these animals, the statistical significance of the results still held, Barouch says.

In contrast, a homologous Ad5/Ad5 prime-boost regimen also evaluated in this study did not have any effect on setpoint viral load or protect macaques from dying following challenge. In previous studies, a homologous prime-boost Ad5/Ad5 regimen and a heterologous DNA/Ad5 prime-boost regimen also failed to provide any level of protection against a similar challenge, adds Barouch. "I am really delighted that they are able to improve on the protection studies of the past," says Gary Nabel, director of the Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases, adding that the control of viral load for 500 days is encouraging compared with previous studies. "In many of the other studies the control of viral load is lost after a certain period of time," Nabel says.

In this study the magnitude and breadth of Gag-specific T-cell responses correlated with control of setpoint viral load, according to Barouch. Only *gag* was used as an insert, suggesting that primarily T-cell responses and not antibody responses were responsible for protection, he adds. "[This] shows very clearly that the Gag-specific T cells were doing the job."

T cell-based approaches were called into question after the results of the STEP trial, which showed that Merck's Ad5 candidate vaccine regimen failed to protect vaccinees from HIV infection, and that pre-existing immunity to this relatively common adenovirus serotype appeared to be associated with an increased risk among vaccinees of acquiring HIV. To avoid concerns about pre-existing immunity, Barouch chose to develop a vector based on Ad26, a much rarer serotype. He says this study suggests that there is still hope for T-cell vaccine candidates that control viral load after infection by stimulating T-cell responses. "The overall message of the paper is that we are not at the end of the road when it comes to T-cell vaccines."

In addition, optimizing the breadth of Gag-specific T-cell responses may be a desirable feature for next generation vaccines. This study "begins to define the correlates that we need in terms of magnitude and breadth of responses," says Bruce Walker, director of the Partners AIDS Research Center at Massachusetts General Hospital.

Barouch says the Ad26/Ad5 regimen won't be tested as a candidate vaccine in humans because it contains Ad5, to which many people may have pre-existing immunity. "We think it's important to avoid Ad5 altogether," he says. However, Barouch is currently testing an Ad26 vector containing an Env clade A insert in a Phase I safety trial. This vector is a prototype to test safety and immunogenicity of this approach, Barouch says. He is also currently evaluating a variety of heterologous prime-boost regimens that use two rare serotype Ad vectors, which will be tested in nonhuman primates and then possibly in clinical trials.

The study is not the only finding that suggests that T-cell vaccines are still promising. Recently, Nancy Wilson, an associate scientist in the lab of David Watkins at the University of Wisconsin-Madison, reported that a DNA/Ad5 regimen encoding all SIVmac239 genes except *env* can control viral load in macaques following five low-dose mucosal challenges with the heterologous swarm virus SIVsmE660 (see *AIDS vaccine researchers STEP up to the challenge*, *IAVI Report*, Sep.-Oct. 2008). —*Andreas von Bubnoff*

[ON THE IAVI REPORT CALENDAR]

26TH ANNUAL SYMPOSIUM FOR NON-HUMAN PRIMATE MODELS FOR AIDS:
December 9-12, 2008, San Juan, Puerto Rico

16TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS:
February 8-11, 2009, Montreal, Canada