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Commentary

Accessories to SIV Control: T Cell Vaccination Shows Potential

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Non-human primate (NHP) models utilizing infection with simian immunodeficiency viruses (SIV) remain the most compelling means to inform mechanisms of protection and viremic control as a guide to development of HIV vaccines for prevention and therapy short of human efficacy trials (Hirsch and Lifson, 2000). Occasionally studies executed to evaluate protection from infection yield information relevant to therapeutic vaccines for HIV. Here is such an example as Xu et al. report encouraging results using a vaccine composed exclusively of SIVmac239 regulatory genes expressed as a single Tat-Vif-Rev-Vpr fusion protein coupled to an HLA class II domain (Xu et al., 2017). There are several novel features to this experiment and further exploration of the approach reported here is warranted.

Most vaccines in development express structural proteins for SIV or HIV and the regulatory proteins are not commonly included as they are less frequently recognized targets of the immune system in natural infection. Although the use of heterologous vector prime-boost vaccine strategies is established as a superior approach (Liu et al., 2008), the use of human adenovirus type 5 (hAd5) vector followed by a chimpanzee adenovirus type 63 (chAd63) vector with simultaneous delivery of both by intramuscular and intrarectal inoculation is notable. Four and a half months after the second vaccination the six active and six control animals were challenged intrarectally with a highly pathogenic and genetically distinct SIVmac251. A total of 10 challenges were required to infect all control primates and four of six vaccinated animals became viremic. The two remaining vaccine recipients were infected based on the development of immune responses to Gag which was not a vaccine component. There was a non-significant trend for the vaccinated animals to be protected from infection per challenge (64%, $p = 0.08$). At autopsy, these two aviremic animals had no evidence of SIV RNA or DNA in sampled lymph nodes.

Several features of this experiment are notable. First, the novel immunoadjuvant has been extensively studied in mice, but not humans and only minimally in NHP (Holst et al., 2015; Capone et al., 2014). Since the experimental design did not include the vaccine absent the HLA class II domain we don't know it is important to the outcomes observed here, though previous studies suggest it augments T cell responses. This control will be important in subsequent pre-clinical efficacy studies. The simultaneous administration of vaccine by parenteral and rectal routes is intended to insure responses at the mucosal site of challenge. Similarly, the value of this complex approach needs to be further evaluated with appropriate controls. Most intriguing, is the observed blunting of acute viremia in three of the four viremic vaccinated macaques and the absence of plasma viremia in two infected macaques that appear to have controlled or cleared infection.

Although modestly improved compared to controls, the observed decline in CD4+ T cells occurs despite reduction in T cell activation, T cell exhaustion and relative preservation of the GALT. The two aviremic infected vaccinated animals bear some advantageous HLA alleles which the authors note may contribute to the observed outcome. However, these alleles are usually associated with viremic control after acute infection and early set-point (Muhl et al., 2002; Loffredo et al., 2007), and in this case no evidence of viremia was observed. Further, the absence of SIV DNA in lymph nodes at 1 year after challenge supports clearance of infection similar to that reported using cytomegalovirus (CMV) vectored SIV Gag-Pol-Env vaccines (Hansen et al., 2013; Hansen et al., 2011). The mechanism of protection in the case of CMV vaccination relies on the generation of atypical, class II restricted CD8+ T cell responses and reliably eliminates infection in approximately 50% of vaccinated animals with no beneficial effect among animals that fail to control early viremia. The CMV vector vaccine strategy should be entering human trials in the next year.

There is no question that a vaccine yielding 50% efficacy if durable would be valuable as another component of the strategy to control the HIV epidemic. If the vaccine reported here on subsequent testing also shows a similar rate of protection it could represent an important advance to the field. This is particularly true if the contrasting approaches using adenovirus vectors versus CMV provide new insights to the correlates of the observed protection/eradication in both systems. Certainly the use of the adenovirus vectors reported here has already been examined for safety and immunogenicity. A potential challenge is the general aversion to use of a hAd5 due to results observed in the Step study in 2007. Although there was no increase in activated CD4+ T cells in this NHP experiment there may be reason to consider other vectors in combination with the chAd63 given the uncertainty raised by the Step and Phambili studies which evaluated hAd5 vectored Gag vaccines and seem to be associated with an increased risk of HIV acquisition (Huang et al., 2015).

As a potential tool to further evaluate preventative vaccines the small NHP study reported here is useful and bears further evaluation. A larger study with sufficient follow-up to establish the persistence of observed viremic control is required. Also, administration of monoclonal antibody to eliminate CD8+ T cells would be a very informative

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adjunct to defining correlates. Finally, an exhaustive evaluation of immune correlates in the mucosa and extensive evaluation for SIV nucleic acid in all potential target tissue will help refine and extend these observations to the benefit of the vaccine development field.

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