anti-inflammatory efferent vagus nerve signals. In all likelihood, Henry Dale would be pleased to learn about the specificity of these neural circuits as uniquely defined by their physiology and function.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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One shot forward for HIV prevention

Lawrence Corey & M Juliana McElrath

The expression of antibodies to protect against an infectious disease can be achieved by the injection into the host of vectors carrying the gene to the relevant antibodies. Here the authors demonstrate the applicability of this technique to protection from HIV in a humanized mouse model, showing this to be a valid route to pursue in vaccine development for humans (pages 296–300).

Persistent levels of functional antibodies have been the mainstay for preventing the acquisition of viral infections. This is most economically achieved by administration of an immunogen that induces neutralizing antibodies (active vaccination); however, direct infusion of antibodies themselves (passive immunoprophylaxis) has also proven to be effective, especially for rapid protection from a defined exposure to an infectious agent such as hepatitis A or B or respiratory syncytial virus infection in infants. Technological advances over the last five years have markedly increased the identification and characterization of epitope specificities of naturally occurring, broadly neutralizing antibodies to HIV-1 (ref. 1). Molecular procedures to insert the genes of neutralizing antibodies into a persistent viral vector such as recombinant adeno-associated virus (AAV) have been developed[2,3]. Upon injection into the muscle of animals, the vectors transduce cells to continuously secrete the expressed antibodies into serum (vectored immunoprophylaxis). The ability of the AAV vector to persist episomally in muscle cells provides the potential for prolonged secretion of antibodies.

One important question for the HIV-1 vaccine field is whether the expressed neutralizing antibodies will diffuse to relevant mucosal epithelial surfaces in concentrations that are sufficiently high and durable enough to prevent against sexual acquisition of HIV to mediate protection from infection. The article by Balazs *et al.*[4] in this issue illustrates the potential of this approach in protecting against mucosal HIV-1 infection. Although these findings provide a critical step forward, they also raise concerns that even vectored immunoprophylaxis may, by itself, be an imperfect modality for HIV prevention.

The investigators used a humanized bone-liver-thymus mouse model of female immunodeficient NOD/SCID/γc mice implanted with human liver and thymus tissue and transplanted with autologous human fetal liver CD34$^+$ stem cells (BLT mice). These were each administered a single dose of an AAV vector expressing one of a wide variety of currently available broadly targeted neutralizing antibodies with known epitope specificities[4]. The majority of antibodies protected against intravenous HIV-1 challenge in the humanized mouse model at concentrations as low as 350 ng/ml. More importantly, given that HIV is sexually transmitted, one potent, broadly neutralizing antibody to the CD4 binding region, called VRC-07, was consistently detected in the vaginal fluid of the mice at a thousand-fold lower concentration than in serum. To see whether this concentration of antibody was high enough to protect against infection, a repeated low-dose intravaginal viral challenge designed to mimic HIV-1 exposure and acquisition in humans was given to the mice (**Fig. 1**). The VRC-07 anti–HIV-1 neutralizing IgG in the mucosa was high enough to reduce experimental HIV-1 challenge rates among vector-immunized animals completely; other less potent antibodies protected less completely.

One of the vagaries of this mouse model is that despite homogeneity in genetics of the animals and the HIV-1 inoculation source, there was great variability in the number of HIV-1 inoculations required to infect the control animals. Whether variations in the extent and persistence of engraftment of the BLT-humanized mice contribute to the variability in exposures needed for infection is unclear. More sobering data showed that even among mice from whom protection from challenge was achieved, as measured by serial measurements of plasma HIV, localized replication in the genital tract post challenge was detected, suggesting that sterilizing immunity was not universally achieved. In addition, escape HIV-1 envelope variants were detected soon after infection, despite challenge with a more homogeneous virus inoculum than likely to occur in humans susceptible to mucosal exposures.

For nearly two decades, great interest has developed in the use of AAV vectors for gene therapy and more recently for immunoprophylaxis against infectious diseases[5]. The appeal of these vectors is their ability to transduce cells, both dividing and non-dividing, and their apparent lack of pathogenicity in humans[6]. However, pre-existing immunity from natural AAV infections with various AAV serotypes is prevalent, and the resulting extent of AAV antibody cross-reactivity may have an impact on the efficacy of HIV-1 antibody delivery and distribution following AAV-vectored immunoprophylaxis in humans, particularly in developing countries. Moreover, the high AAV vector particle doses administered (10^9–10^{11} genome copies) in the mice reported in Balazs *et al.*[4] to achieve *in vivo* protection against HIV-1 may be challenging in humans if even higher doses are needed to achieve protective antibody levels. In time, these barriers may be overcome with use of less common AAV serotypes and improvements in transduction efficiencies.

Although the development of a vaccine regimen that induces immune responses including potent, broadly reactive neutralizing antibodies is likely to be a more economical and preferable approach to HIV-1 prevention[7], vectored

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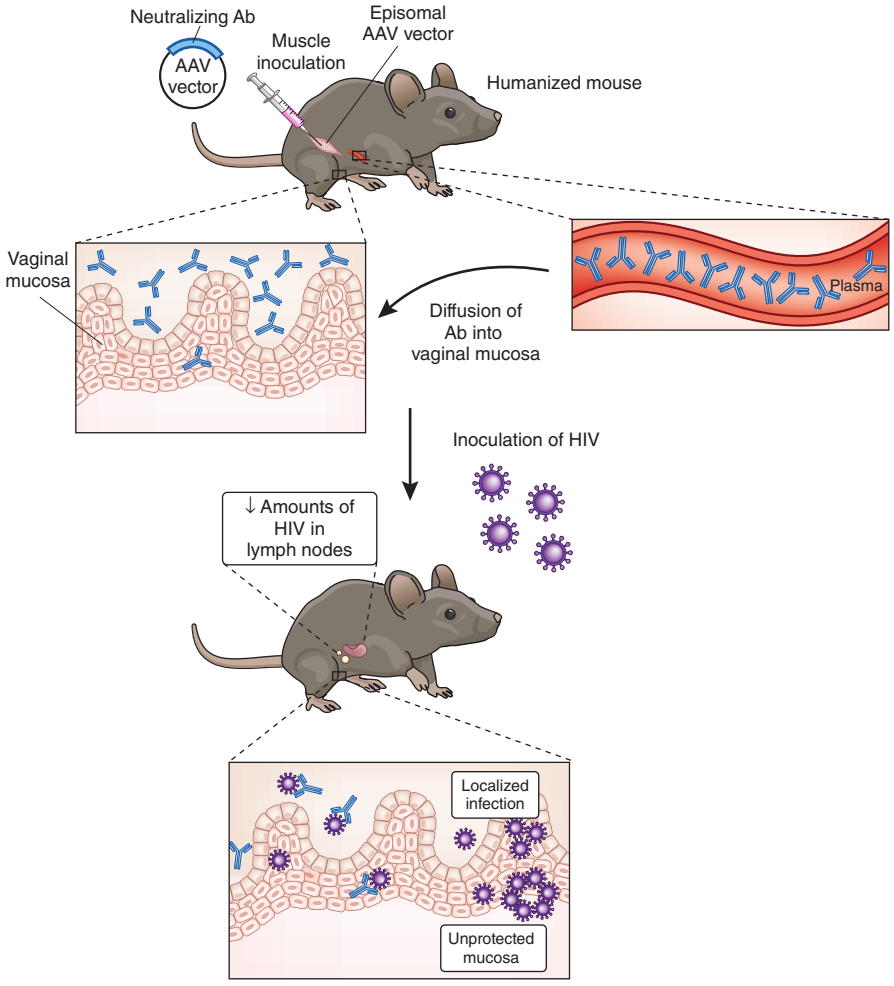

Marina Corral Spence

Figure 1 Proof of principle of protection from HIV-1. Balazs *et al.*[4] show that muscle inoculation of the humanized mouse with AAV vector including the anti-HIV-1 antibody cassette results in the production of neutralizing antibodies (Abs) to HIV. These are found at higher levels in the blood plasma than at the vaginal mucosa. Infection with HIV resulted in protection against infection of the vaginal mucosa compared with controls. However, localized infection of the vaginal mucosa did occur. HIV levels were lower in the spleen and lymph nodes when compared with control animals.

immunoprophylaxis offers an important strategy to be considered, especially for populations or countries with high HIV-1 incidence rates. Reducing HIV-1 infection on a population basis requires an approach that is durable and can be administered reliably for extended time periods to persons at risk for their sexual lifetime[8]. The daily use of antiretrovirals as prophylaxis has been amply shown to have limited long-term protection from HIV-1 infection, particularly owing to lack of adherence[9,10]. The use of injectable agents, whether antivirals or monoclonal antibodies delivered systemically or mucosally, offers an advantage when adherence is a concern. Yet these approaches will still require frequent administration and will most likely be costly. By contrast, administration of vectors such as AAV to deliver continuous antibody expression after a single dose offers an attractive alternative. Thus, continued advances in vectored immunoprophylaxis to achieve high concentrations of highly potent HIV-1 antibodies used alone or as an adjunct to other modalities of HIV-1 prevention deserve serious consideration.

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Corrigendum: One shot forward for HIV prevention

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In the version of this article initially published, there are two incorrect sentences in the text due to incorrect interpretation of the publication highlighted in this News and Views article. The sentence "The VRC-07 anti–HIV-1 neutralizing IgG in the mucosa seemed high enough to reduce experimental HIV-1 challenge rates among vector-immunized animals by 62.5%" should read "The VRC-07 anti–HIV-1 neutralizing IgG in the mucosa was high enough to reduce experimental HIV-1 challenge rates among vector-immunized animals completely; other less potent antibodies protected less completely." Also, the sentence "Furthermore, there was detectable depletion of $CD4^+$ T cells in the spleen and gut, indicating that systematic spread of HIV-1 still occurred in animals, despite the presence of neutralizing antibodies in the mucosa at the time of challenge" should not have been included. In addition, the word "spleen" should not have been included in Figure 1. The label "episomally replicating AAV" in the figure should have been "Episomal AAV vector." The errors have been corrected in the HTML and PDF versions of the article.