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HIV immunity goes direct

The commencement of human trials of a gene therapy delivering HIV-neutralizing antibodies is a welcome addition to efforts to develop conventional vaccines against this scourge.

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At the start of the year, the International AIDS Vaccine Initiative, in collaboration with The Children's Hospital of Philadelphia and the US National Institute of Allergy and Infectious Diseases, initiated a phase 1 clinical trial at the University of Surrey, UK's Surrey Clinical Research Centre to analyze the safety of an experimental HIV 'vaccine'. The trial is a landmark because the agent is not a conventional B-cell vaccine but a gene transfer that generates passive immunity via intramuscular injection with adeno-associated virus serotype 1 (AAV1) encoding the HIV broadly neutralizing antibody PG9. The approach, called vector-mediated gene transfer or vectored immunoprophylaxis, represents an intriguing alternative to efforts to create a conventional vaccine to HIV. Vectored immunoprophylaxis not only sidesteps some major drawbacks of traditional B-cell vaccines against HIV, but also could be a useful adjunct, particularly in some populations. No one should be in any doubt, however, that it still faces some stiff challenges to achieve successful translation.

The field of conventional HIV vaccines also remains a work in progress. The most successful vaccine trial to date—after more than three decades of effort—was of RV144, a recombinant canarypox vector vaccine plus two booster injections of a recombinant glycoprotein 120 subunit vaccine (*N. Engl. J. Med.* **361**, 2209–2220, 2009). That vaccine, administered to 16,402 healthy men and women between the ages of 18 and 30 years in Thailand, was, at most, 31% effective.

The modest success of conventional HIV vaccines can be explained in part by numerous confounding challenges in vaccination trials, including variation in volunteer immune status, the co-occurrence of other sexually transmitted pathogenic agents and differences in the frequencies at which volunteers are exposed to virus. But the key limitation of RV144 and other conventional B-cell vaccines to date has been their inability to reliably elicit production of a broad spectrum of virus-neutralizing antibodies. Although new technologies for antibody repertoire sequencing have spurred progress in isolating broadly neutralizing antibodies from HIV-infected individuals and longitudinally tracking the natural B-cell response to HIV (a key prerequisite for development of an effective vaccine), we're not nearly there yet.

One reason is that HIV-neutralizing antibodies contain an unusually high number of somatic hypermutations and therefore diverge markedly from the unmutated ancestor germline antibodies expressed by naive B lymphocytes. The rare, unmutated ancestor antibody of HIV-neutralizing antibodies was recently identified in one individual, but whether humans of different genetic backgrounds and living in different geographical regions harbor similar, rare, unmutated ancestors is unclear. In other words, one vaccine may not cover everyone. In addition, it's likely that multiple rounds of immunization with precisely engineered immunogens will be needed to guide unmutated ancestor B cells down a relatively convoluted path of somatic hypermutation toward broadly neutralizing progeny.

Even if the scientific hurdles to conventional vaccination are surmounted, practical ones will remain. For example, vaccine regimens requiring several precisely designed boosters may prove an impractical if not impossible option for those in areas constrained by geography and/or clinical resources. And, obviously, because vaccines, by definition, require a functional immune response, they may not be effective in individuals with compromised or altered immune function.

Which brings us back to the idea of directly delivering the neutralizing antibody itself, rather than coaxing the immune system to produce it. Because the vectored immunoprophylaxis strategy bypasses the requirement for an immune response, it could in theory protect individuals regardless of their immune status. And if the vector pumps out enough antibody for a long enough time, it could feasibly protect people for whom regular doctor visits for vaccine boosters are impossible.

The trial commencing at Surrey Clinical Research Centre will determine whether participants receiving AAV1 encoding PG9 achieve serum antibody levels sufficient to neutralize HIV in cell culture. Durability of antibody expression will also be examined. But, as with a conventional vaccine, many other questions relating to efficacy and safety will need to be addressed for vectored immunoprophylaxis to become reality.

In terms of efficacy, will vector-mediated gene transfer drive expression of enough antibodies to neutralize virus entering through the blood and mucosal surfaces in humans? If so, how long will antibody expression last? Results in humanized mice and nonhuman primates have been encouraging with regard to the level and duration of antibody expression, but these highly hypermutated antibodies may still prove immunogenic in humans. Another safety concern is potential antibody cross-reactivity with healthy human tissue, which could lead to autoimmunity. Especially as some HIV-neutralizing antibodies are polyreactive, methods enabling the inducible suppression of AAV-driven expression of the antibody would likely be very useful.

Finally, might selective pressure exerted by constant expression of a single antibody promote HIV escape and resistance? This seems less likely in a prophylactic setting (in the absence of virus) than in a therapeutic scenario where the antibody would be introduced into a patient infected with a mix of HIV quasispecies. Related to this, it may be possible to simultaneously or sequentially administer AAVs encoding antibodies that target distinct regions of the HIV envelope.

As the answers to these questions may be species-specific, human studies are essential to move the HIV prophylactic field forward. What is certain is that the success of vectored immunoprophylaxis is not guaranteed. Funders and researchers should continue to pursue a diverse set of options for prophylactics against HIV, given that a variety of approaches will be needed to counter the virus in all populations. There will be no one-size-fits-all solution for this viral scourge.

Corrected after print 5 June 2014

Erratum: HIV immunity goes direct

Editorial
***Nat. Biotechnol.* 32, 397 (2014); doi:10.1038/nbt.2907; published online 8 May 2014; corrected after print 5 June 2014**

In the version of this article initially published, AAV1 was incorrectly identified as AAV9. It was not noted that the Surrey Clinical Research Centre is at the University of Surrey. The phase 1 clinical trial is for a gene transfer, not a gene therapy, and will test whether levels of AAV1 encoding, not expressing, PG9 will neutralize HIV in cell culture. Finally in the third from last paragraph, the question posed is "will vector-mediated gene transfer drive expresssion" not "will AAV9 drive expression." These errors have been corrected in the HTML and PDF versions of the article.

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