

Broadly neutralizing antibodies to prevent HIV-1

Studies show the potential of synthetic and combinations of broadly neutralizing antibodies

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Advances in technology—especially single-cell antibody cloning techniques—have led to the isolation and characterization of antibodies from people with HIV infection that can neutralize many variants (1). These are referred to as broadly neutralizing antibodies (bnAbs). Such antibodies can be detected in about 25% of persons with untreated HIV-1 infection (2), reflecting a host immune response to unremitting viral replication, generation of large numbers of viral variants, and shifting antigen exposure (3). Although bnAbs may exert some selective pressure as they develop, they generally do not reduce viral burden, improve health, or slow the progression of disease (4). However, they offer considerable opportunities for treatment and prevention of HIV-1 infection in others. At this time, hundreds of bnAbs have been identified; those that have attracted the most attention are bnAbs with the greatest breadth, neutralizing the largest number of HIV-1 strains, including those traditionally most neutralization resistant (1, 5); or bnAbs that have the greatest potency, requiring the smallest concentration to neutralize resistant strains of HIV-1 (5–7). A study by Xu *et al.* (5) on page 85 of this issue and by Julg *et al.* (7) in *Science Translational Medicine* illustrate advances in the potential use of bnAbs to prevent HIV-1 infection.

The key purpose of the initial search to detect and understand HIV-1 bnAbs was to identify HIV-1 envelope proteins that might be targeted by an effective HIV-1 vaccine (8), because induction of antibodies to levels associated with protection from an infectious agent has been the most effective approach for vaccine development (4). However, can-

didate HIV-1 vaccines designed to generate bnAbs have been confounded by the difficulty of inducing human germline cells that produce such antibodies, the high degree of somatic mutation required for the evolution of most bnAbs, and the potential for autoimmunity—and hence elimination—of such antibodies early in the ontogeny of B cell and antibody development (9).

As an alternative, HIV-1 bnAbs can be manufactured and administered through intermittent blood infusions, providing both circulating and mucosal concentrations of antibodies at levels that might be able to block HIV-1 acquisition (genitourinary and rectal mucosal epithelia are the sites of HIV-1 acquisition) (4). The bnAbs isolated so far target proteins expressed on the HIV-1 envelope (8): the critical CD4 binding

site (which HIV-1 uses, via its glycoprotein gp120, to enter cells); glycan-coated viral loops, including the V1-V2 glycan and V3 glycan; and a conserved viral membrane-proximal external region (MPER) (see the figure). bnAbs directed at these targets reduce simian

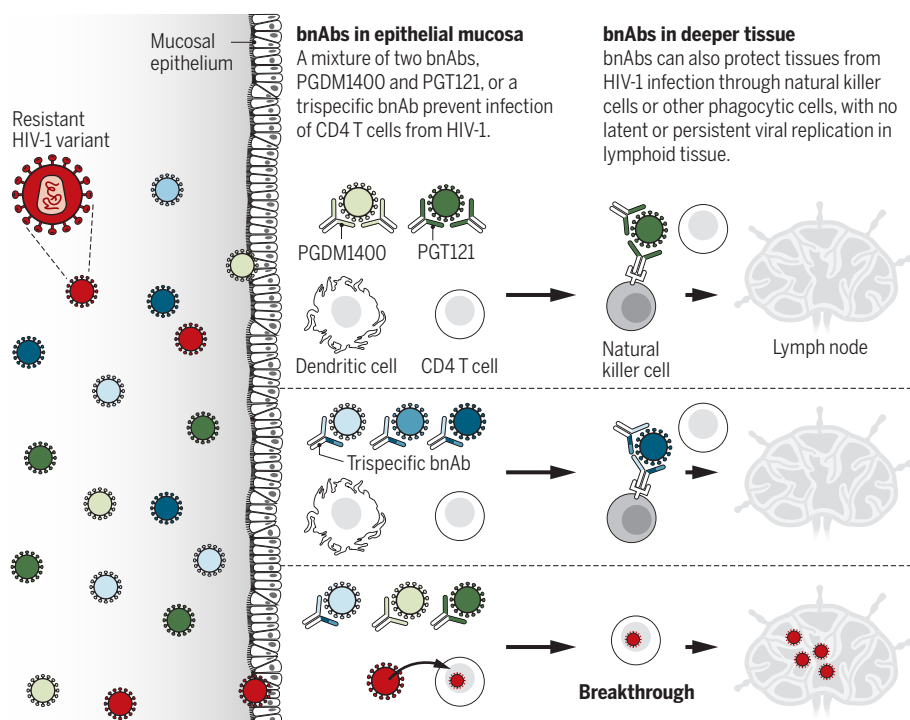
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HIV (SHIV) replication in nonhuman primates (NHPs) (7) and HIV-1 in humans (10), and can prevent SHIV in NHPs (5, 7). However, after treatment of an infected NHP or person with a single bnAb, rebound viremia from outgrowth of low-frequency resistant strains has been observed (7, 10), providing a potential barrier to the use of bnAbs for long-term therapy of people with HIV-1 infection. Outgrowth of resistant strains occurs less frequently when a bnAb is administered prior to experimental challenge for prevention from infection, rather than for treatment of existing infection. In the latter experimental situation, passive administration of bnAbs can produce complete mucosal protection even at low serum concentrations (4, 5, 7). However, a weakness of the NHP models is the homogeneity of the SHIV inoculum used, because humans are generally exposed to a large and diverse HIV-1 viral “swarm” (i.e., a mixture of viral variants) (4).

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bnAbs prevent HIV-1

Combinations of bnAbs and a trispecific antibody can bind to virions and prevent HIV-1 mucosal infection and elicit antiviral responses in deeper tissue. It is hoped this multitarget approach will prevent resistant breakthrough.



Xu *et al.* and Julg *et al.* extend the potential use of bnAbs for HIV-1 prevention. Julg *et al.* demonstrated complete protection of rhesus macaques from a swarm of SHIV variants by a bnAb “cocktail” of PGT121 (targets the V3 glycan) and PGDM1400 (targets the V1-V2 glycan). PGT121 or PGDM1400 alone failed to protect rhesus macaques from the SHIV swarm employed.

Xu *et al.* used structural information derived from years of intensive study of bnAbs to construct synthetic trispecific bnAbs directed concomitantly to the CD4 binding site, MPER, and the V1-V2 glycan. The trispecific antibody prototype selected for further development demonstrated considerably greater potency and breadth than any known single human bnAb. The trispecific antibody protected NHPs from a mixture of SHIVs that “overwhelmed” several other bnAbs. Should the trispecific antibody prove safe and effective in clinical trials, it would herald a new class of synthetic drug.

One of the concerns seen with long-term infusion of human monoclonal antibodies is antidrug antibodies that may reduce activity and/or lead to allergy-type reactions over time (11). The construction of a trispecific bnAb introduces more synthetic components, thus increasing the potential for these reactions. Only clinical testing of such a drug can evaluate this concern.

The first human clinical trials of a bnAb to prevent HIV-1 acquisition are under way [“antibody-mediated prevention” (AMP) trials, NCT02716675 and NCT02568215]. These trials provide intravenous infusions of the bnAb VRC01 (which blocks the HIV-1 CD4 binding site) every 8 weeks to 4500 high-risk HIV-1–negative subjects at 47 sites in 11 countries. The VRC01 bnAb neutralizes about 90% of HIV-1 variants at concentrations that will be achieved in the blood of trial participants (4). The AMP trials are designed to determine if VRC01 can prevent HIV-1 acquisition, to establish the concentrations of bnAbs required for protection, and to define the relationship between any “breakthrough infections” and in vitro sensitivity to VRC01. If VRC01 works as anticipated, breakthrough variants should be resistant to this bnAb, whereas sensitive variants should be eliminated at the mucosa or at sites distant to the mucosa (12).

The feasibility of infusion of bnAbs in the clinic is challenged by the requirement for frequent treatments. An important advance in antibody engineering has been the introduction of selective mutations in the Fc portion of the antibody. These mutations improve binding to the neonatal Fc receptor that protects against antibody degradation, thereby increasing the concentration of antibody in serum for longer periods of time.

In addition, Fc receptor mutations appear to enhance mucosal localization of VRC01 in the genital tract of NHPs (13). Both Fab and Fc effector functions have been shown to be important, providing different mechanisms to prevent viral acquisition in antibody-mediated protection (13).

The rapid growth of bnAb use in HIV-1 prevention is a great example of how important clinical observations led to new technologies and a concerted basic science program to identify targets for HIV-1 vaccine design, and now new products for the treatment and prevention of HIV-1 (4, 8–10). These are early days in bnAb development with a focus on proof-of-concept studies, such as the AMP trials. Improved delivery methods to allow long-term generation of bnAbs may prove revolutionary. For example, bnAbs can be delivered as an alternative to a vaccine for constitutive production in people through adeno-associated virus gene transfer. This method was used to produce the CD4 binding site bnAb VRC07 (a broader-specificity antibody than VRC01) in vivo, which offered protection from SHIV infection in NHPs (14). More recently, studies of the evolution of bnAbs have led to the identification of candidate gp120 antigens that, through sequential exposures, led to the formation of bnAbs CH103 and CH235, which block the CD4 binding site (3, 15). A clinical trial (HVTN 115, NCT03220724) is underway in which sequential injections of immunogens are administered to mimic the B cell mutations observed during the ontogeny of CD4 binding site bnAb generation (3, 15). The history, scope, and depth of bnAb research emphasize the hope that use of such antibodies will affect the trajectory of the HIV-1 pandemic. ■

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