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Commentary

The last decade has led to a significant advance in our knowledge of HIV-1 latency and immunity. However, we are still not close to finding a cure for HIV-1. Although combination antiretroviral therapy (cART) has led to increased survival, almost close to that of the general population, it is still not curative. In the current issue of the *JCI*, Wu et al. studied the prophylactic and therapeutic potential of an engineered tandem bispecific broadly neutralizing antibody (bs-bnAb), BiIA-SG. This bnAb's breadth and potency were highly effective in protection and treatment settings, as measured by complete viremia control following direct infusion, as well as elimination of infected cells and delay in viral rebound when delivered with a recombinant vector. These observations underscore the need for the clinical development of BiIA-SG for the prevention of HIV-1.

Tandem bispecific broadly neutralizing antibody – a novel approach to HIV-1 treatment

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Difficulties in exploring curative strategies for HIV-1

Human immunodeficiency virus 1 (HIV-1) is a major global health issue. Each year there are 40,000 new cases of HIV infection among Americans and as many as 2 million new cases worldwide. Strategies toward finding a cure for HIV-1 are hampered by the fact that HIV-1 is extraordinarily variable. This diversity poses a major obstacle to the development of an AIDS vaccine. The genetic diversity of HIV-1 isolates can reach up to 20% for envelope polyprotein (Env) sequences (1). Although the influenza vaccine is promoted as a model system for HIV, the diversity of HIV is greater than that seen in influenza (2), and the variability issues in the design of an influenza vaccine are fundamentally distinct from those for an HIV vaccine. Design of an HIV vaccine constitutes a significant hurdle that must be overcome. A vaccine can induce or leverage, respectively, humoral and cellular immune responses capable of recognizing the different circulating HIV subtypes.

Combination antiretroviral therapy (cART) has been very effective in controlling HIV-1 replication and suppression of HIV-1 to undetectable levels in the peripheral blood of patients for long periods of time. However, the infectious virus still persists in reservoirs and results in the replication competence of integrated HIV-1 genomes in small subsets of latently infected memory $CD4^+$ T cell populations, called viral sanctuaries. This leads to a viral rebound within a few weeks of cessation of cART. Targeting the reservoirs has not been successful. Curative strategies targeted toward the activation of dormant virus that would lead to its destruction via host immune or viral cytopathic effects have had limited success.

It has recently been demonstrated that virus diversity in infected individuals arises because of the pressure exerted by the immune system and the ability of HIV-1 to mutate, leading in turn to the ability of the immune response to develop broadly neutralizing antibodies (bnAbs) (3–5). It is now well known that bnAbs target the glycosylated structure of the HIV-1 envelope present on the viral membrane, referred to as the closed trimeric structure of the gp120/gp41 complex. This closed state is the most infectious among the different conformational states of the envelope present on HIV-1 virions (6, 7). Similar structures can also be exposed on the membrane of the infected cells at the time of virus budding (8).

Broadly neutralizing Abs offer hope

Over the years, several studies have exploited the ability of bnAbs to confer protection from infection, to control virus replication, and to reduce the size of the latently infected cells' reservoir (review in ref. 9). The original passive protection studies in animal models indicated that monoclonal Ab (mAb) combinations are usually more effective in preventing simian human immunodeficiency virus (SHIV) infection in nonhuman primates (10–13). More recently, bnAb combinations have also been tested for their potential activity in reducing viremia, viral rebound in animal models, and in exploratory clinical trials. In the humanized mouse model, a combination of the CD4 binding site 3BNC117 (14), V3 glycan 10-1074 (15), and V1V2 glycan PG16 (16) bnAbs induced decreased viremia in approximately 50% of the mice, and substantially delayed virus rebound compared with animals treated with cART (17). Moreover, a decline in the level of cellular-associated DNA occurred only in the aviremic mice treated with the 3-mAb cocktail. Therefore, bnAbs can significantly impact both plasma viremia and the pool of latently infected cells through recognition of HIV-1 Env on the host cell membrane (17). Similar observations have been reported in the nonhuman primate model in which bnAbs successfully reduced the level of plasma viremia during chronic (18–20) and acute (21) SHIV infection. Additionally, bnAb combinations have been shown to reduce the size of the pool of latently infected cells (19, 21).

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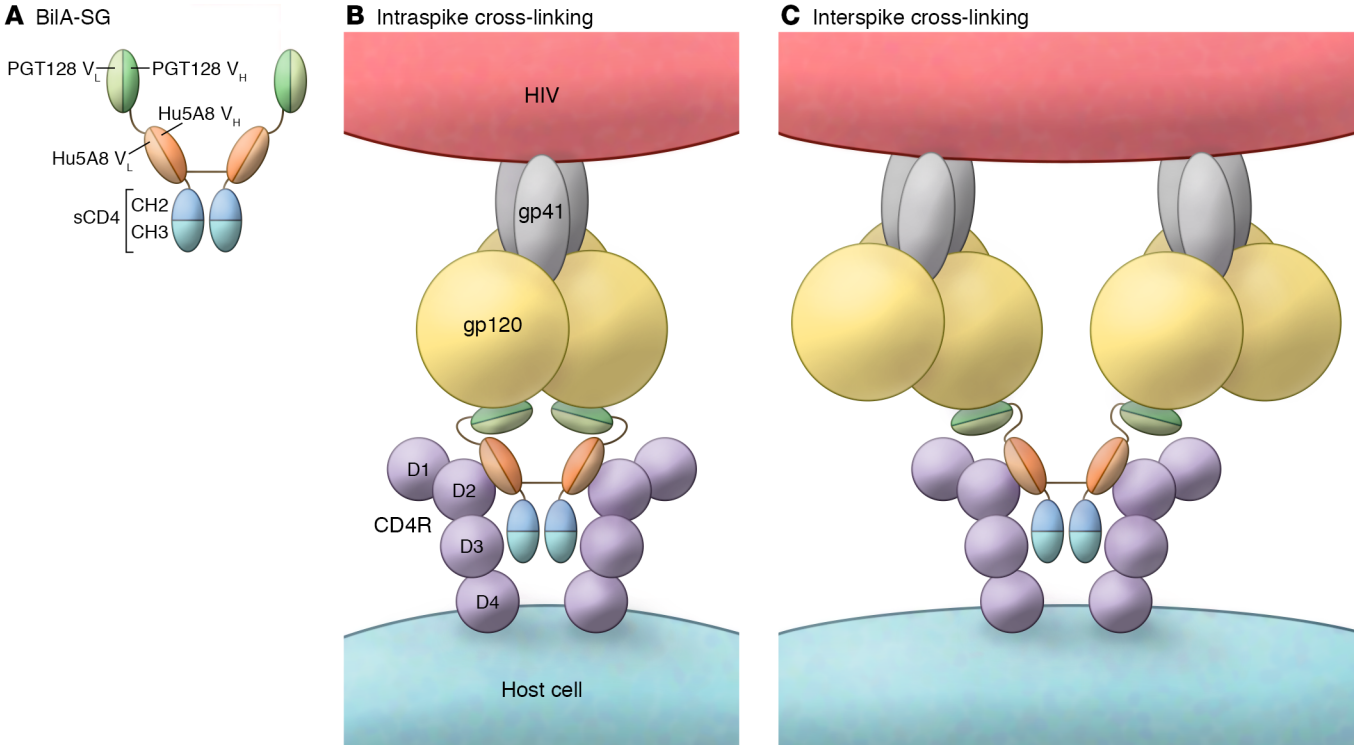

Figure 1. Schematic diagram showing binding of the BiIA-SG antibody. (**A**) Engineered tandem bispecific bnAb BiIA-SG antibody with scFv domain(s) for binding to HIV-1 gp160 trimer (green VH/VL chain of PGT128) and to soluble CD4 (orange VH/VL chain of Hu5A8) via 20-mer linkers. Two possible interactions are predicted for the molecule: intraspike cross-linking (**B**) and interspike cross-linking (**C**). scFv, single-chain variable fragment; VH, heavy-chain variable region; VL, light-chain variable region.

The efficacy of individual bnAb infusions was recently tested in human trials and appeared to have a beneficial effect on the control of plasma viremia (22). However, in 2 different regimens, resistant virus isolates were either observed before treatment and hampered the therapeutic effect of the bnAb (23), or appeared following infusion of the bnAbs during analytical treatment interruption (24). Taken together, these studies have thus far indicated that development of mAb-based molecules with several epitope specificities is a desirable goal to circumvent HIV-1 envelope sequence diversity and propensity to escape.

A novel approach toward the broadly neutralizing Abs

Wu and collaborators (25) decided to take a different approach to circumvent the diversity of HIV-1 envelopes. They based their molecule on 1 single gene–encoded tandem bs-bnAb, namely BiIA-SG, where 2 single-chain variable fragment (scFv) binding domains against the V3 glycan epitope recognized by the PGT128 mAb and the CD4 receptor recognized by the Hu5A8 mAb are simultaneously present (Figure 1). This represents a radically different approach compared with a predecessor of this molecule reported by Huang and collaborators (26) that included a single scFv for each anti–HIV-1 envelope broadly neutralizing monoclonal antibody (bnmAb) against the CD4 receptor. The aspects related to the new class of molecules discussed herein do not include obvious considerations on the pharmacokinetic, tissue distribution, and ability to induce anti–drug antibody responses, since these will have to be addressed in further dedicated studies.

As reported by Wu et al. (25), the neutralizing breadth and potency of the new BiIA-SG molecule are definitely higher than those of the original neutralizing PGT128 mAb, or the BiIA-DG with a single scFv domain. The authors suggest that the improved activity of the BiIA-SG may be due to the ability of the anti-CD4 arm to bring the PGT121 arm in proximity to the HIV-1 Env. In addition, this effect may also be due to the presence of 2 binding sites that favor the binding of the molecule to the targeted antigens. In developing a new class of therapeutics, this aspect could be relevant to improve the performance of bispecific molecules such as those based on the potent class of membrane proximal epitope region–specific (MPER-specific) mAbs that do need a simultaneous bivalent binding to the membrane lipid layer and to the HIV-1 envelope (27). It is interesting that a similar molecule was originally designed and characterized to include the MPER 10e8 specificity and was also developed into a trispecific molecule (28). Ultimately, it will be interesting to observe if this newly engineered molecule can address the need for the simultaneous recognition of 2 different regions of the HIV-1 envelope to broaden the breadth and prevent escape. These new molecules could represent the benchmark for comparison with the recently reported trispecific mAb-based molecules that are also aimed at increasing breadth and potency of anti–HIV-1 activity (29).

The authors also demonstrate that the BiIA-SG molecule is able to protect from

infection and control virus rebound in the humanized mouse model for HIV-1 infection. Of note, the molecule, delivered as an adeno-associated virus construct, led to a reduction of $P24^+$ T cells in the blood and spleen.

Concluding remarks

Additional information about the activity of BiIA-SG against the so-called sanctuary for HIV-1 in the latent reservoir will have to be obtained before designing studies to prevent the appearance of escape mutants and to reduce the virus reservoir in tissues such as lymph nodes, the GI tract, and the central nervous system. If the mechanism of action of the BiIA-SG is related to its broadly neutralizing function, it still remains to be determined how this molecule will perform against the circulating HIV-1 isolates, taking into account HIV-1 diversity and the dichotomy already observed between in vitro breadth of individual bnAbs and the presence of escape mutants (23, 24).

In addition to the neutralization activity, bnAbs can significantly impact both plasma viremia and the pool of latently infected cells through recognition of the HIV-1 Env on the host cell membrane (17) and engagement of Fcγ-R–bearing cells (30). Therefore, the possibility of further enhancing the activity of this promising class of immunotherapeutics needs to be explored by designing bnAbs that can engage Fcγ-R–bearing cells and facilitate the killing of latently infected cells.

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