HHS Public Access

Author manuscript

Trends Microbiol. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Trends Microbiol. 2017 December ; 25(12): 954–956. doi:10.1016/j.tim.2017.10.006.

Anti-HIV Passive Immunization: New Weapons in the Arsenal

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Abstract

Anti-HIV passive immunization with human neutralizing monoclonal antibodies (nmAbs) has made exciting gains: (i) identification of the HIV envelope V2 apex as a new *in vivo* protective epitope, (ii) a novel clade C SHIV for challenge studies, and (iii) a highly protective, trispecific nmAb. Potent, broad-spectrum protection by nmAbs holds promise.

Keywords

broadly neutralizing monoclonal antibody; trispecific neutralizing monoclonal antibody; clade C SHIV; nonhuman primate models; passive immunization

As a safe, effective vaccine against HIV/AIDS has remained elusive, passive immunization with human neutralizing monoclonal antibodies (nmAbs) has gained momentum as an alternative strategy, for which the potency and breadth of the nmAbs will be a key factor. Two newer-generation human nmAbs that target the V2 apex of the HIV envelope (Env) glycoprotein, CAP256-VRC26.25-LS and PGDM1400, protected rhesus macaques against the newly constructed R5 tier 2 clade C simian-human immunodeficiency virus (SHIV-C; strain SHIV-325c) at surprisingly low doses when given intravenously 24 hours before high-dose intrarectal challenge [1]. Remarkably, CAP256-VRC26.25-LS was fully protective at 0.08 mg/kg, whereas PGDM1400 completely prevented viremia at 0.4 mg/kg – doses that are orders of magnitude lower than those previously reported. As an example, the first-generation anti-CD4 binding site (CD4bs) nmAb b12 prevented viremia in 89% of SHIV-challenged macaques at 25 mg/kg [2]. The more recently isolated PGT121, which targets the V3 loop and V3-related glycans, was fully protective at 1 mg/kg but not at a lower dose [3]. Clearly, the *in vivo* potency of the two anti-V2 apex nmAbs stands out.

One possibility is that SHIV-325c may be unusually sensitive to neutralization by anti-V2 nmAbs. SHIV-325c encodes *env* from a relatively recently HIV clade C-infected individual, and without prior adaptation to nonhuman primates, induced viremia in all intrarectally

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inoculated rhesus macaques, although some had delayed peak viremia [1]. Several clade B and C SHIVs were tested for their susceptibility to neutralization by the anti-V2 nmAbs; SHIV-325c was easily neutralized with IC_{50} values of 0.003 and 0.037 μg/ml (for CAP2566-VRC26.25 and PGDM1400, respectively). Neither nmAb neutralized any of the other SHIVs tested except SHIV-1157ipd3N4 [4], a tier 2 SHIV-C that was neutralized by PGDM1400 with a ~5x higher IC_{50} than SHIV-325c but was resistant to CAP256-VRC26.25.

Next, Julg *et al.* [1] tested the susceptibility of SHIV-325c and two R5 clade B SHIVs (SHIV-Bs) to a panel of mAbs targeting different HIV Env domains. The striking finding was that SHIV-325c was either resistant or poorly neutralizable by several anti-CD4bs nmAbs that were able to neutralize SHIV-Bs. The converse was true for nmAbs targeting V1V2 or the V2 apex: SHIV-325c could be neutralized by PG9 as well as the two anti-V2 nmAbs, whereas the SHIV-Bs were completely resistant or poorly neutralized by such nmAbs. The Env trimer structure on SHIV-325c appears to have a configuration that hinders access to the CD4bs by most anti-CD4bs nmAbs. It would be interesting to examine with a larger number of viruses whether exquisite sensitivity to neutralization by anti-V2 apex nmAbs carries the price of resistance to anti-CD4bs nmAbs.

To test whether the high susceptibility of SHIV-325c to neutralization by anti-V2 apex nmAbs is the exception rather than the rule, Julg *et al.* [1] assessed the neutralization profiles of SHIV-325c and many pseudoviruses carrying *env* genes from different HIV clades against PGDM1400 and CAP256-VRC26.25. Approximately half of the pseudoviruses were resistant to CAP256-VRC01 and a third to PGDM1400. When assessed with the remainder of the pseudoviruses that were sensitive to the two nmAbs, SHIV-325c neutralization was close to the mean of IC_{50} values. Based on these data, SHIV-325.c is more sensitive to anti-V2 nmAbs than an estimated two-thirds of the viruses tested, although it should not be considered an outlier.

The extended analysis with multiple pseudoviruses carrying primary HIV envelopes also revealed another pattern of mutually exclusive neutralization sensitivity: viruses tended to be susceptible to neutralization by either anti-V2 or anti-V3 nmAbs but not both. However, when anti-V2 and anti-V3 nmAbs were combined, an astounding 98% of viruses became sensitive to neutralization [1].

Using SHIV-325c as challenge virus requires some considerations. Its pathogenicity is uncertain as none of the infected macaques described had $CD4^+$ T-cell losses to levels <500 cells/mm^3 [1]. The initial virus stock was grown in human peripheral blood mononuclear cells (PBMC). For use in vaccine efficacy studies requiring multiple low-dose mucosal virus challenges, SHIV-325c should be grown in rhesus PBMC to avoid xenoresponses to human host-cell components [5], an important consideration for evaluating candidate immunogens prepared in human cell lines. For passive immunization studies, SHIV-325c resistance to all anti-CD4bs nmAbs must be kept in mind. Xu *et al.* [6] found an elegant solution: challenging macaques with a mixture of SHIVs.

This study sought to test the efficacy of a novel trispecific nmAb, VRC01/PGDM1400-10E8v4, engineered to simultaneously target the HIV CD4bs, the conserved gp41 membrane proximal external region (MPER), and the V2 apex [6]. The antibody variable genes to construct the trispecific nmAb were derived from VRC01 (anti-CD4bs), PGDM1400 (anti-V2 apex), and 10E8v4 (anti-MPER). *In vitro*, the trispecific nmAb completely neutralized a 1:1 mixture of R5 SHIVs, the tier 1 SHIV BaLP4 [7] and the tier 2 SHIV-325c, whereas neutralization by the parental VRC01 and PGDM1400 plateaued at 50%. Viremia was prevented in all macaques challenged with the 1:1 SHIV mixture five days after intravenous treatment at 5 mg/kg with the trispecific nmAb, whereas VRC01 and PGDM1400 protected only 25% and 50% of the animals, respectively.

This is an exciting development: immunoprophylaxis with a triple combination of nmAbs targeting different epitopes has coalesced into a single-molecule therapy with significant, dose-sparing efficacy. Triple combinations of individual nmAbs were highly synergistic in PBMC-based neutralization assays [8] as shown by dose-reduction index$_{90}$ values (DRI$_{90}$) ranging between 5 and 20. DRI$_{90}$ values indicate by what factor the dose of each nmAb in a synergistic combination was reduced at 90% neutralization compared with doses of each nmAb alone. A trispecific nmAb will likely be effective at low doses and decrease the risks of selecting neutralization escape viruses. The overall *in vivo* potency of trispecific nmAbs or triple combinations of individual nmAbs can be further maximized by optimizing effector functions, especially antibody-dependent cellular cytotoxicity (ADCC) [9, 10]. If the trispecific nmAb or triple combinations exhibit ADCC activity in addition to broad neutralization coverage, using such agents would be promising not only for pre-exposure prophylaxis, but also for post-exposure prophylaxis (PEP) and passive immunotherapy for established infection, as killing infected target cells via ADCC will decrease viral reservoirs.

To summarize, identifying the V2 apex as a protective epitope through passive immunization against mucosal SHIV-C transmission provided an nmAb partner to synergize with nmAbs targeting the conserved CD4bs and MPER – to defend against almost all HIV strains circulating worldwide.

Acknowledgments

The author wishes to thank Juan Esquivel for assistance with this manuscript. Supported by NIH grants P01 AI048240 and R01 AI100703.

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