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HIV

Sequential vaccine elicits broadly neutralizing antibodies

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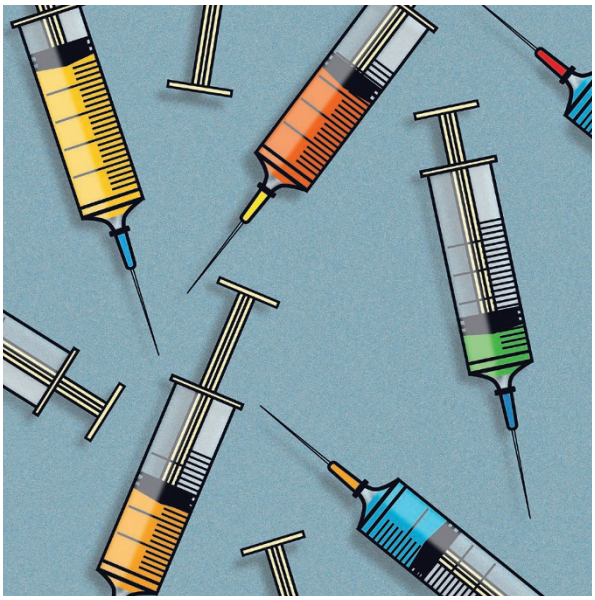
Some (rare) HIV-infected individuals develop antibodies with broad and potent neutralizing activity (bnAbs). A vaccine that elicits such bnAbs is likely to be protective; however, the development of such a vaccine has proved to be exceptionally challenging. Now, two reports by Nussenzweig, Schief and colleagues present a sequential vaccination strategy that elicits anti-HIV bnAbs in immunoglobulin knock-in mice.

Anti-HIV bnAbs generally have very unusual features, such as a long complementary determining region 3 (CDR3) and a high rate of somatic hypermutations. Moreover, the inferred germline precursors of such antibodies do not appear to have any measurable affinity for the antigen that is targeted by the mature bnAb. In order to advance vaccination approaches that may allow for the development of such antibodies, a germline-targeting strategy has been proposed. This strategy uses a series of antigens to initiate and direct the affinity maturation of specific germline precursor B cells.



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One of the most potent and well-characterized classes of anti-HIV bnAbs is the PGT-121 class, which targets a highly glycosylated site of the HIV envelope (Env) trimer. Reporting in *Immunity*, the authors now present a lentivirus-based mammalian cell surface display method that allows for the directed evolution of glycan-bearing modified Env molecules. A collection of six germline-reverted PGT-121 antibodies was used to identify mutated Env molecules that may activate PGT-121 germline precursor B cells. The mutational information from the Env molecules was then used to produce HIV Env trimers with different affinities for germline-inferred and mature PGT-121 bnAbs. Structural analysis revealed that such trimers adopt native-like conformations and *in vitro* B cell activation experiments demonstrated that Env trimers can indeed activate B cells that produce inferred germline precursors of PGT-121. Ensuing experiments, using knock-in mice that produce PGT-121 family precursor B cells, showed that the mutated Env trimers can also activate these cells *in vivo*.

An accompanying paper in *Cell* investigated the vaccination strategy further. Here, the authors present a step-by-step process to elicit bnAb responses in B cells: after priming animals with the germline-targeting epitope-modified immunogen, responses are boosted by an ELISA-guided sequence of native-like Env trimers with decreasing epitope modification, followed by incubation with a cocktail of Env variants to expand breadth. Antibody cloning confirmed that the resulting bnAbs contained high levels of somatic mutations and resembled authentic human bnAbs.

These results provide proof of principle that bnAbs can be elicited by sequential prime-boosting strategies, and the methods presented are likely to be applicable to the design of immunogens for other epitopes and pathogens. However, the authors caution that their experiments are currently limited to knock-in mice. As humans have a diverse immune system, in which the germline precursor B cells frequency is limited, vaccination strategies are likely to require additional immunogens to activate the rare bnAb precursor cells found in the normal B cell repertoire.

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ORIGINAL ARTICLES Steichen, J.M. *et al.* HIV vaccine design to target germline precursors of glycan-dependent broadly neutralizing antibodies. *Immunity* **45**, 483–496 (2016) | Escolano, A. *et al.* Sequential immunization elicits broadly neutralizing anti-HIV-1 antibodies in Ig knockin mice. *Cell* **166**, 1445–1458.e12 (2016)