CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Mapping the Journey to an HIV Vaccine

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"Universal" vaccines that elicit cross-reactive and broadly neutralizing antibodies (bNAbs) are the ultimate goal of efforts to provide protective immunity against both the influenza virus and the human immunodeficiency virus (HIV). Infection with either virus leads to the induction of abundant strain-specific antibodies that are easily evaded by subsequent viral variants. However, the circulating diversity of HIV is greater than that of influenza by orders of magnitude, posing a tremendous challenge to the achievement of vaccine-mediated protection.

New hope for a universal sterilizing HIV vaccine arose several years ago with the evidence that bNAbs emerge in 10 to 30% of infected persons.[1] Because these bNAb responses typically appear after 2 to 3 years of infection, they fail to control established infection: the kinetics of the evolving B-cell response lag behind the rapidly diversifying virus, and they cannot "catch up" to control established infection. However, these bNAbs have provided protection from infection at remarkably low doses in animals, suggesting that vaccine-induced bNAbs could provide sterilizing immunity if they were present before infection. Translating our current knowledge of bNAbs into a vaccine remains a daunting challenge, since the mechanism by which such antibodies are induced remains enigmatic.

As compared with other antibodies, bNAbs have unusual characteristics, including odd physical structures (e.g., elongated antigen-binding loops) and remarkably high levels of mutation that affect antibody–antigen binding and structural domains.[2] These changes accumulate over years of infection as exposure to diverse viral variants drives antibody evolution, resulting in the generation of a set of antibodies that bears little similarity to their original antigen-naive B-cell ancestors (i.e., germline sequences).

Liao et al.[3] have recently described the path along which bNAbs develop. They tracked the evolution of a single bNAb and the counter-evolution of an HIV virus (Fig. 1), starting in the first weeks of infection. Their findings offer a roadmap for the induction of bNAbs through vaccination (Fig. 2).

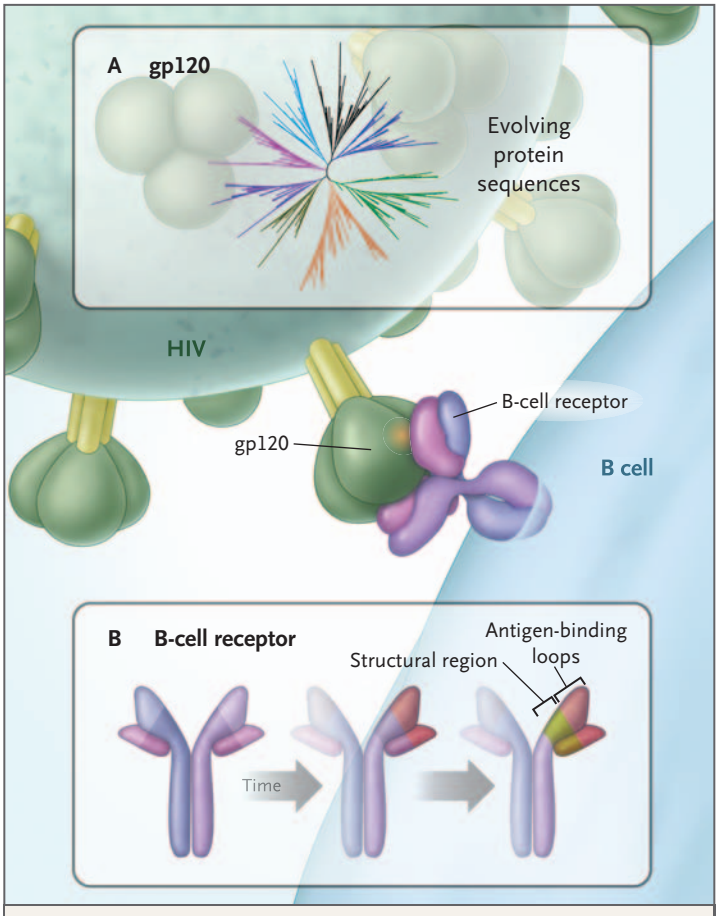

Figure 1. The Coevolution of Virus and Antibody.

Given that the B-cell receptor is simply a membrane-bound antibody, Liao et al.[3] hypothesized that the parallel sequencing of B-cell receptors and viral diversity could elucidate the interplay of host and pathogen, evasion and adaptation, that resulted in a broadly neutralizing antibody. Specifically, as the virus evolves (Panel A), so does the B-cell receptor (Panel B), resulting in point mutations initially in the antigen-binding domain but eventually in the structural domain, as shown by Klein et al.,[4] allowing for enhanced antibody neutralizing activity.

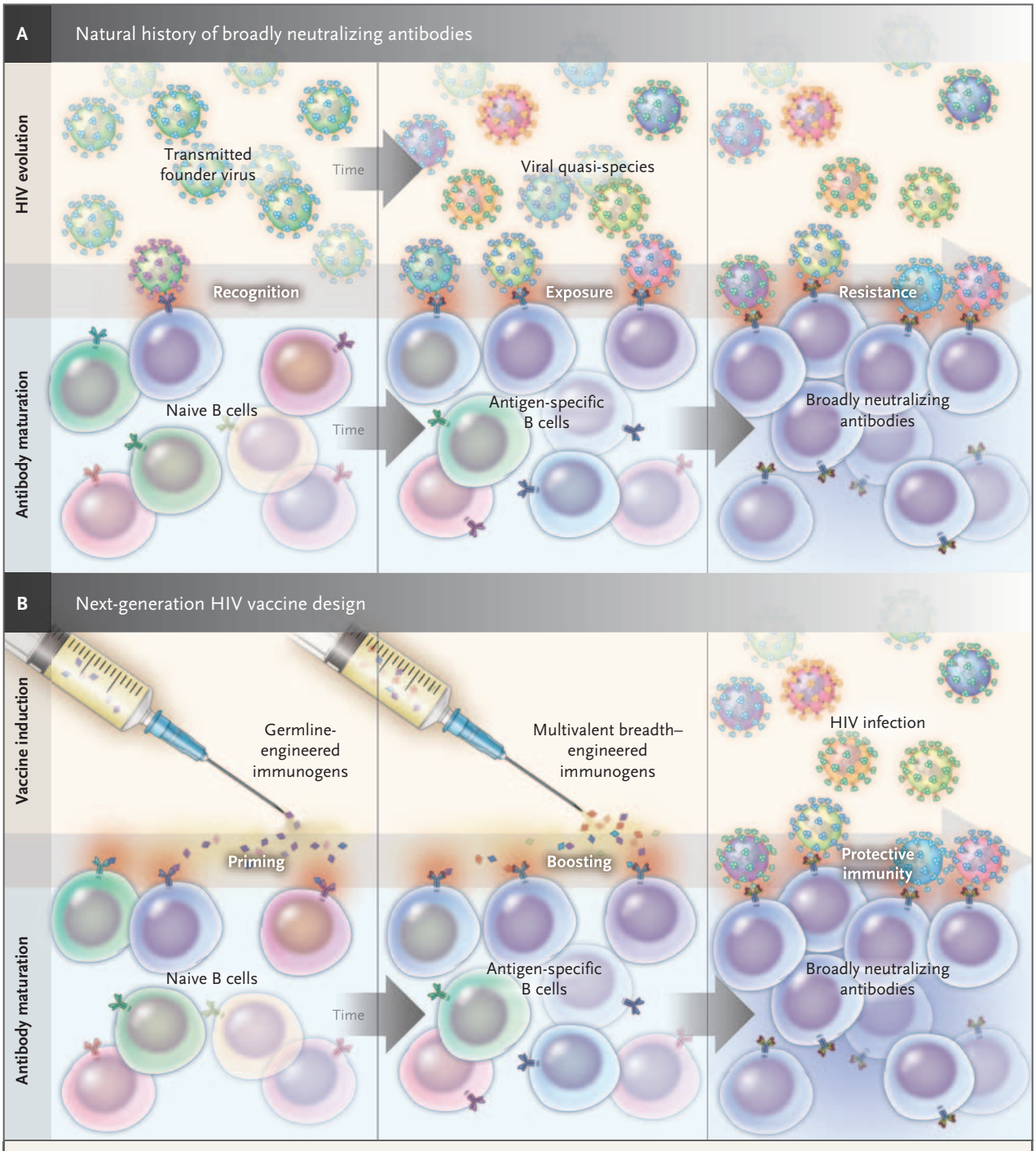

Figure 2. Leading Antibodies Down the Path to Neutralization.

The findings of Liao et al.[3] suggest that next-generation HIV vaccines could be modeled on the natural history of broadly neutralizing antibodies. Early recognition of the transmitted virus by a naive B cell (in blue) leads to the selection, expansion, and diversification of the antigen-specific population, followed by exposure to a rapidly diversifying viral quasi-species and leading to the rapid mutation and down-selection of the most potent B-cell population (Panel A). Accordingly, immunogens could be designed to interact with specific germline-naive B-cell receptors and coax B cells along specific maturation pathways (Panel B). Immunogens used to prime the B-cell response may be engineered to bind to common germline-naive B-cell receptors. These B cells could then be boosted by designer envelope immunogens engineered to mimic the rapid diversification of the viral population and thereby accelerate the pace of B-cell selection and mutation — all of which would be intended to drive the induction of the most potent neutralizing antibody responses in all vaccinated persons.

Two key events distinguished the interaction of B-cell and virus during the developing natural history of this bNAb. First, whereas in most scenarios the naive B-cell population cannot bind to HIV, the naive B-cell repertoire in this infected person bound to the earliest incoming virus (the transmitted virus), which suggests that early rapid diversification of the B-cell response was initiated very soon after infection. Second, the rapid evolution of mutations affecting antibodies, which is required for potent antibody neutralization, occurs simultaneously with the rapid diversification of the virus in the first few months of infection. This occurrence suggests that the timing of the exposure to diverse viral variants may be crucial to the induction of protective antibody immunity.

Although the early evolution of the antibody response predominantly occurred within the antigen-recognition site, Liao et al. found that later evolutionary changes in the antibody occurred in structural regions, which are thought to have a limited role in antigen recognition. However, in a recent publication by Klein et al.,[4] the authors report that mutations affecting these structural regions can potentiate antibody function. The authors found that among a set of diverse bNAbs, mutations affecting the structural regions are not just incidental to extensive mutation but are actually critical to neutralization, providing breadth and potency through multiple mechanisms — by expanding the antigen-recognition footprint, by subtly altering binding-loop positioning, and perhaps by changing the conformational dynamics of antibody–antigen binding.

Together, these studies highlight key features of the immune system's natural induction of bNAbs. First, effective initiation of the antibody response depends on the early interactions between the virus and the naive B-cell repertoire. Second, an explosion of viral diversity can drive the molecular evolution of a bNAb. Finally, neutralization potency arises in an unanticipated way — by means of mutations affecting structural regions of the antibody.

Although we encode a finite number of B-cell–receptor sequences within our naive antibody repertoire, these sequences can become hugely diversified after initial selection and driven in specific directions by subsequent antigen exposure, in a process called affinity maturation, permitting nearly infinite exploration of antibody-recognition space. This idea raises the following questions: How can this finite set of naive sequences be effectively recruited initially, and how can the evolution of the antibody response be constrained to recognize HIV in a way that leads to neutralization? These studies suggest that the rational design of an effective HIV vaccine will require directed-antigen evolution to generate HIV-envelope immunogens that will robustly bind and trigger the germline-naive B-cell repertoire[5] (Fig. 2).

Despite the 200 years that have elapsed since Edward Jenner's smallpox vaccine, the development of vaccines has remained, for the most part, an empirical process. The studies by Liao et al. and Klein et al. outline the evolution of bNAb activity and may therefore enable the design of a universally protective vaccine against HIV and possibly other viruses.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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