MILESTONE 19

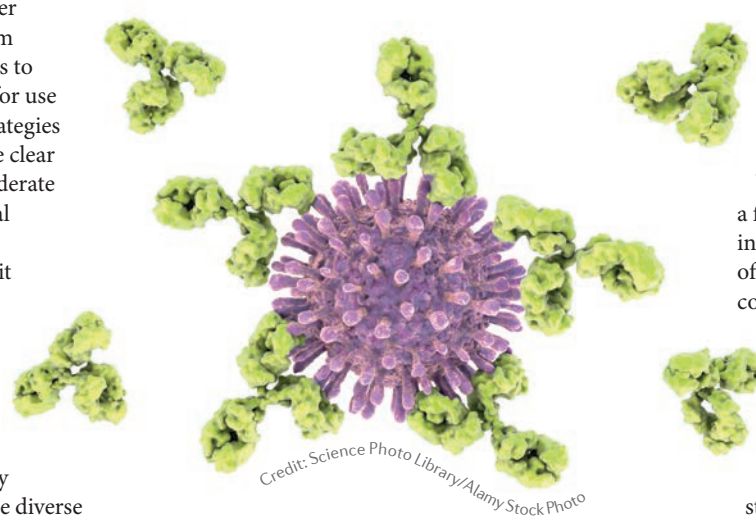
Needles in a haystack: the quest for bnAbs

HIV induces antibody responses in infected individuals, but only a few of these individuals manage to produce antibodies that are capable of viral neutralization—and even fewer produce antibodies that can neutralize different strains of HIV. First attempts to find such broadly neutralizing antibodies (bnAbs) date back to the early 1990s, when phage libraries were used to identify, isolate and amplify antibodies from asymptomatic individuals with HIV-1 infection. Further antibodies were isolated from hybridomas. However, hopes to translate these early bnAbs for use in passive immunization strategies were dashed when it became clear that they displayed only moderate breadth and potency for viral neutralization.

Breakthroughs had to wait for almost 20 years and were eventually facilitated by the development of single-cell antibody cloning, advances in screening methods and a better understanding of structurally conserved epitopes across the diverse circulating strains of HIV-1.

In 2009, Dennis Burton and co-workers used a systematic approach to search for bnAbs in the sera of 1,800 HIV-1-infected individuals. This was followed by a high-throughput neutralization screen of activated memory B cells from one individual. The effort proved worth it—they identified two bnAbs (PG9 and PG16) with remarkable potency and breadth, neutralizing 73% and 79% of viruses tested, respectively. Interestingly, the two antibodies targeted a previously undescribed epitope of the HIV-1 envelope (Env) protein, which is located within conserved regions of the variable loops of the gp120 subunit of Env.

The discovery of these antibodies was followed in 2010 by a report by Gary Nabel, John Mascola and co-workers that described the rational design of probes for the targeted identification of bnAbs. At this time, a conserved site on gp120, which facilitates binding of the virus to the host receptor CD4, had been identified as a common target for naturally occurring bnAbs. With new insights into Env structure and using computer-assisted protein design, antigenically resurfaced glycoproteins were designed that specifically bound to neutralizing antibodies. These were used to screen sera for the presence of bnAbs, and then to screen for probe-specific memory B cells. These efforts led to the identification of two antibodies, VRC01 and VRC02, that neutralize over 90% of all major circulating HIV-1 strains.



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An accompanying paper showed that VRC01 had undergone extensive affinity maturation, resulting in an antibody that partially mimics the interaction of CD4 with gp120. A slight shift in binding allows it to overcome the glycan and conformational masking that diminish the neutralization capacity of other antibodies.

> “combinations of bnAbs provide durable control…”

Since then, many more bnAbs have been identified and the first clinical studies have been initiated. VRC01 and 3BNC117, a bnAb that targets a similar site, first entered the clinic in 2015–2016. They suppressed viral titers in HIV-infected individuals for 6–10 weeks, before viral rebound due to escape mutants. Much longer viral suppression was achieved in recent combination trials. In patients undergoing treatment interruption from antiretroviral therapy (ART), three doses of 3BNC117 and 10-1074, a bnAb that targets a different site in Env, achieved a median of 21 weeks of complete viral suppression before viral rebound. Encouragingly, no viral escape mutants were detected. This indicates that combinations of bnAbs provide durable control in the absence of ART and therefore provide an alternative, less toxic treatment.

Preferable to passive treatment would be a vaccine that elicits bnAbs. This could allow for a functional cure of infected individuals and protect those at risk of infection. Given the rarity and complexity of bnAbs (they typically contain 40–100 somatic mutations and unusual structural features), making such a vaccine is exceptionally challenging. However, insights into their development, structure and function, as well as the immunological mechanisms that make their generation such a rare event, have led to the design of promising vaccination strategies in animal models.

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FURTHER READING Sok, D. & Burton, D. R. Recent progress in broadly neutralizing antibodies to HIV. *Nat. Immunol.* **19**, 1179–1188 (2018)