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INFECTIOUS DISEASES

Two-pronged attack on HIV

Broadly neutralizing antibodies (bNAbs) against HIV, isolated from individuals who have evidence of controlled infection, have provided a starting point for passive immunization strategies, but overcoming viral escape mechanisms remains a challenge. Now, two studies published in *Cell* report the development of two bispecific antibodies that retain favourable drug-like properties and show broad and potent neutralization of HIV in mouse models.

In one study, Huang *et al.* used a platform called CrossMAb to generate a panel of 20 bispecific antibodies around the minimally immunogenic IgG backbone. One arm of the antibody targeted either the human CD4 receptor or the human CCR5 co-receptor, which the viral envelope glycoprotein (Env) binds to during HIV entry into T cells. The other arm was derived from a bNAb and targeted one of five gp120 epitopes on Env.

The bispecific antibodies were tested *in vitro* against a panel of 118 diverse HIV pseudotyped viruses. Two antibody candidates showed particularly high potency and breadth of neutralization, comparable to a mixture of five bNAbs, as well as synergistic activity relative to the parent monoclonal antibodies. The authors subsequently performed antibody engineering to address physicochemical heterogeneity and to increase manufacturing potential.

The most promising bispecific antibody, termed $10E8_{V2.0}$/iMab, was advanced into proof-of-concept studies in a humanized mouse model of HIV infection. Weekly intraperitoneal injections of $10E8_{V2.0}$/iMab at least 4 weeks after establishment of HIV infection was associated with significantly greater reduction of viral load than was placebo or injection with a 1:1 mixture of the parent antibodies. However, HIV began to rebound after 2 weeks as viral mutations conferred resistance, suggesting the need for combination therapy in this setting.

$10E8_{V2.0}$/iMab showed greater promise for pre-exposure prophylaxis. Daily injections of the antibody for 7 days before HIV infection, followed by weekly treatments for another 8 weeks plus two further exposures to HIV, completely protected 7 of 7 mice from viraemia during the 18-week experiment. By contrast, only 3 of 19 vehicle-treated mice showed no signs of viral infection 2 weeks after a single HIV exposure.

In the other study, Bournazos *et al.* took a different approach and generated a bispecific antibody in which both arms targeted epitopes on HIV Env. They hoped to create a single therapeutic agent capable of overcoming viral escape from singly targeted bNAbs.

Previous attempts to generate bispecific antibodies against HIV Env have displayed reduced neutralizing activity, possibly due to the trimeric structure of Env, which precludes bivalent interactions of the two antibody binding domains. In the current study, Bournazos *et al.* made use of an engineered version of the IgG3 hinge domain, which increases flexibility of the antibody binding domains while retaining the physiological properties of human IgG.

The authors used the CrossMAb platform to develop a panel of bispecific antibodies that target various distinct Env epitopes. One candidate in particular, termed 3BNC117/PGT135, showed substantial synergistic activity compared with the parent antibodies, and was able to neutralize more than 93% of a panel of 120 virus strains *in vitro*.

In humanized mouse models of HIV infection, treatment with the bispecific antibody after establishment of infection significantly reduced viraemia over a period of 40 days compared with treatment with a mixture of the parent antibodies.

Together, the two studies provide novel lead candidates for further development and a useful framework for optimization of additional bispecific antibodies against HIV.

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ORIGINAL ARTICLES Huang, Y. *et al.* Engineered bispecific antibodies with exquisite HIV-1-neutralizing activity. *Cell* **165**, 1621–1631 (2016) | Bournazos, S. *et al.* Bispecific anti-HIV-1 antibodies with enhanced breadth and potency. *Cell* **165**, 1609–1620 (2016)

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