Long-term control of HIV

Modern antiretroviral therapy (ART) is highly effective at suppressing human immunodeficiency virus (HIV) to undetectable levels, but suppression relies upon life-long adherence to medications. Issues with adherence, drug side effects and the evolution of ART resistance have prompted the development of alternative therapies aimed at suppressing HIV. Broadly neutralizing monoclonal antibodies (bNabs) that target the HIV envelope glycoprotein (Env) offer a new approach for virological suppression. Regular infusions of two bNabs (3BNC117 and 10-1074) can suppress viremia, but the long-term feasibility of this approach is not well explored.

Chun and colleagues report the findings of a two-component clinical trial using 3BNC117 and 10-1074 and provide evidence that infusion of these bNabs provides sustained virological suppression for up to 43 weeks after analytical treatment interruption (ATT). The first component was a randomized, double-blind, placebo-controlled trial that enrolled 14 individuals who started ART during the acute/early phase of infection and who then underwent ATT 3 days after receiving the first infusion of bNabs or placebo. The second component was an open-label study involving five individuals who had controlled viremia but had not received ART.

Whereas individuals in group 1 who received placebo experienced plasma viral rebound within 8 weeks of ATT, individuals who received bNabs suppressed viremia for up to 43 weeks. Two out of the five individuals in group 2 who had baseline sensitivity to both antibodies suppressed viremia for an average of 41.7 weeks. Importantly, individuals in both groups who were infected with viruses that are resistant to either 3BNC117 or 10-1074 did not achieve virological suppression. The study demonstrates that combination therapy with 3BNC117 and 10-1074 can suppress viraemia in the absence of ART for extended periods, as long as antibody-resistant virus is not present.

In a separate study, Barzel and colleagues performed in vivo engineering of B cells in mice to address some of the challenges that are associated with bNab-based therapies for HIV. For instance, bNabs have a half-life of a few weeks, necessitating regular infusions, and improper glycosylation or maturation can arise when bNabs are not produced in B cells. In their proof-of-concept study, the authors engineered B cells in vivo to secrete 3BNC117.

After intravenously injecting two adeno-associated viral (AAV) vectors (one encoding Staphylococcus aureus Cas9 (saCas9) and the other encoding 3BNC117) into mice, the authors observed editing of B cells. In their proof-of-concept study, the authors engineered B cells in vivo to secrete 3BNC117.

After intravenously injecting two adeno-associated viral (AAV) vectors (one encoding Staphylococcus aureus Cas9 (saCas9) and the other encoding 3BNC117) into mice, the authors observed editing of B cells. The engineered B cells underwent antigen-induced activation, leading to memory retention, clonal selection and differentiation into plasma cells that secrete neutralizing titres of 3BNC117. Further studies are needed to confirm antiviral efficacy in vivo, but this proof-of-concept study suggests the possibility of in vivo B cell engineering for the long-term control of HIV in the absence of ART.

Ashley York

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