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HIV

On the road to an HIV vaccine?

> “neutralizes a very broad and diverse panel of HIV-1 isolates”

Conventional vaccine approaches have been unsuccessful in protecting against HIV. However, recent efforts to generate a vaccine that neutralizes the virus have gained traction. Reporting in *Nature*, Farzan and colleagues describe a new construct — containing an immunoadhesin (a chimeric, antibody-like molecule) of CD4 fused with a small CC-chemokine receptor 5 (CCR5)-mimetic sulfopeptide — that provides robust protection from multiple simian–human immunodeficiency virus (SHIV) challenges in rhesus macaques.

In recent years, a large panel of HIV broadly neutralizing antibodies has been described and adeno-associated virus (AAV)-expressed broadly neutralizing antibodies can protect humanized mice from an HIV-1 challenge. However, a proportion of HIV-1 isolates remain resistant to even the best broadly neutralizing antibodies. So, broader and more potent inhibitors of HIV are needed.

CD4-Ig is an immunoadhesin of CD4 that is comprised of CD4 domains 1 and 2 fused to the Fc domain of IgG1. This molecule irreversibly inactivates the HIV envelope glycoprotein (Env; which is involved in recognizing the CD4 receptor) and neutralizes most HIV isolates. However, its affinity for Env is lower than those of broadly neutralizing antibodies and it can promote infection. The CCR5-mimetic sulfopeptide CCR5mim1 is derived from the HIV-1 neutralizing antibody E51 and specifically binds the CCR5-binding region of Env.

Here, the authors generated a fusion protein, termed eCD4-Ig, in which CCR5mim1 was inserted at the CD4-Ig carboxyl terminus. Extensive analysis showed that this construct neutralizes a very broad and diverse panel of HIV-1 isolates, including neutralization-resistant tier 2 and 3 viruses, more effectively than CD4-Ig or the best broadly neutralizing antibodies. This greater potency of eCD4-Ig is due, at least in part, to the fact that it binds only conserved regions of CD4 and to its higher affinity than CD4-Ig for Env. Further analysis showed that eCD4-Ig blocked HIV-1 replication in human peripheral blood mononuclear cells, even at low concentrations, and inoculation of humanized mice with eCD4-Ig protected them from HIV-1 infection.

Finally, the authors assessed whether AAV-delivered eCD4-Ig could function like an HIV-1 vaccine in rhesus macaques. The construct was modified to include the Fc domain of rhesus IgG2 rather than IgG1 and an Ile39Asn mutation in the rhesus CD4 domain. This rh-eCD4-Ig construct was cloned into a single-stranded AAV2 vector and injected into four male rhesus macaques. All of the treated monkeys resisted infection following six challenges of increasing doses of SHIV-AD8 over 40 weeks, whereas the monkeys that did not receive rh-eCD4-Ig became infected. Furthermore, rh-eCD4-Ig induced fewer endogenous antibodies than rhesus forms of four well-characterized broadly neutralizing antibodies, indicating that it is less immunogenic.

Thus, the ability of AAV-delivered rh-eCD4-Ig to protect macaques from multiple SHIV infections, along with its potency and unmatched breadth, makes this molecule a candidate that is worthy of further investigation as an effective and near universal HIV-1 vaccine.

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ORIGINAL RESEARCH PAPER
Gardner, M. R. *et al.* AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges. *Nature* **519**, 87–91 (2015)
FURTHER READING Kwong, P. D., Mascola, J. R. and Nabel, G. J. Broadly neutralizing antibodies and the search for an HIV-1 vaccine: the end of the beginning. *Nature Rev. Immunol.* **13**, 693–701 (2013)