MILESTONE 9

HIV vaccines: gp120 and beyond

Identification of the cell receptors that serve as a gateway for HIV, first reported in the 1980s, opened the door to the development of immunization protocols based on the viral envelope proteins with which they interact. In a breakthrough study reported in 1990 by Philip Berman and colleagues, a vaccine based on the HIV glycoprotein gp120, which binds CD4 and chemokine receptors on target cells, protected chimpanzees from HIV-1 infection. The study showed that vaccination with a single recombinant viral protein (in the context of an aluminum hydroxide adjuvant) was sufficient to elicit a protective immune response to HIV in a nonhuman primate, without requiring attenuated viral particles or complexes of multiple viral proteins.

Berman and colleagues tested two vaccine formulations containing distinct HIV-1 proteins: two chimpanzees were immunized against recombinant gp120 and two were immunized with a formulation containing recombinant gp160. The animals received three immunizations and were then challenged with the IIIb isolate of HIV-1.

Whereas chimpanzees immunized with the gp160 vaccine as well as a control animal showed evidence of HIV infection, the researchers found no signs of infection in the animals inoculated with the recombinant gp120 formulation. Infection in the control and gp160-immunized animals was further confirmed by PCR, and viable HIV-1 could only be recovered from these chimpanzees, and not from the two animals immunized against gp120. Levels of virus-neutralizing antibodies on the day of challenge were higher in the protected animals than in the unprotected ones, suggesting a possible key role for them in preventing infection.

The study provided the first evidence of protection against HIV infection by vaccination in an animal model and highlighted the potential of the HIV-1 envelope protein as a candidate vaccine target. The work would eventually lead to tests of recombinant-gp120-based vaccines in humans.

But whether a single-target strategy for vaccination could be successfully translated to humans and elicit a persistent protective response against heterologous viruses remained unclear at the time, particularly when taking into consideration the broad diversity of HIV-1 variants infecting human populations and the speed and efficacy of viral immune escape. A further consideration is that, unlike humans, HIV-infected chimpanzees do not develop AIDS, so protection against disease development induced by vaccination with gp120 could not be assessed by the Berman study. Nevertheless, the strategy was taken further in multiple efforts in nonhuman primates and was eventually tested in large clinical trials (e.g., the ALVAC-HIV and AIDSVAX B/E formulations). The human studies showed that gp120- or gp160-based vaccines could elicit HIV-specific cellular and humoral responses in vaccinated individuals, but the protection rates reported were low.

> “first evidence of protection against HIV infection by vaccination in an animal model”

More detailed understanding of the molecular structures of HIV envelope proteins and host factors such as CD4 and CCR5, as well as the viral epitopes recognized by broadly neutralizing antibodies, is now enabling the design of targeted vaccine strategies using defined immunogens and the testing of passive immunization in humans using monoclonal antibodies that bind gp120 and neutralize the virus. Novel adjuvants, viral vectors and delivery methods, as well as approaches that aim to elicit responses to conserved regions of viral proteins or to diverse HIV-1 subtypes, are also in development and will generate important clinical insights in the near future.

Given that HIV can integrate into the host genome during its replication cycle, it can persist as a long-lived reservoir of latent virus that may be invisible to the immune system (MILESTONE 16). Therapeutic vaccines that aim to eradicate existing infection have been tested, but without success, and new strategies—such as gene and genome editing, checkpoint blockade and latency modulation—will be needed in conjunction with novel vaccine modalities to both prevent and eliminate infection.

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ORIGINAL ARTICLE Berman, P. W. et al. Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp120 but not gp160. *Nature* **345**, 622–625 (1990)
FURTHER READING Escolano, A., Dosenovic, P. & Nussenzweig, M. C. Progress toward active or passive HIV-1 vaccination. *J. Exp. Med.* **214**, 3–16 (2017) | Barouch, D. H. & Picker, L. J. Novel vaccine vectors for HIV-1. *Nat. Rev. Microbiol.* **12**, 765–771 (2014)