Prospects for the Development of an AIDS Vaccine: Lessons from Macaques

R. Paul Johnson

(New England Primate Research Center, Harvard Medical School)

Multiple lines of evidence suggest that induction of sterile protection against HIV/SIV infection by conventional vaccine approaches is likely to be a difficult and possibly unachievable goal. A more readily achievable benchmark for an AIDS vaccine would be to reduce viral loads in infected individuals and thereby delay disease progression and reduce the risk of transmission. In the SIV/macaque model, most vaccine approaches have had only limited success in inducing sustained decreased in viral loads of pathogenic SIVmac strains. Although natural transmission of HIV predominantly occurs through mucosal surfaces at low efficiency, few SIV vaccine studies have examined protective immunity using experimental conditions designed to model these circumstances. We investigated the efficacy of a multigenic DNA/MVA prime/boost vaccination regimen to protect against a repeated low-dose vaginal pathogenic SIV challenge. Female rhesus macaques were immunized intramuscularly with DNA vaccine vectors expressing multiple SIV proteins (Gag, Pol, Env, Nef, Tat and Vif) and then boosted with a recombinant poxvirus (modified vaccinia Ankara, MVA) expressing a similar complement of SIV proteins. Starting at week 8 after the MVA boost, animals were vaginally challenged with repeated doses of SIVmac251 over a course of up to 17 weeks.

DNA/MVA immunization induced vigorous IFN-γ ELISPOT responses to Gag, Env and Nef, with Gag-specific spot forming cells (SFC) that exceeded 3500 SFCs/10⁶ PBMC 2 weeks after the MVA boost. SIV Gag tetramer-binding cells in DNA/MVA vaccinees were detected in vaginal and rectal biopsies at similar frequencies to those observed in peripheral blood 2 weeks after the MVA boost. Following repeated low-dose vaginal challenges, 8/8 controls, and 7/8 of DNA/MVA-vaccinated macaques were infected. The DNA/MVA prime boost regimen resulted in a 33-fold reduction in peak viremia at week 2, a 380-fold reduction in viremia at week 6, and a 340-fold reduction in viremia 15 to 17 weeks after infection compared to controls. DNA/MVA vaccinated animals also had better preservation of CD4+ T lymphocyte counts and improved survival as compared with naïve controls. Our results demonstrate that a multigenic DNA/MVA prime/boost vaccine can mediate protection against disease progression following repeated low dose vaginal challenge in macaques.

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