

Comparison of Whole Gene and Whole Virus Scrambled Antigen Approaches for DNA Prime and Fowlpox Virus Boost HIV Type 1 Vaccine Regimens in Macaques

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ABSTRACT

T cell immunity plays a critical role in controlling HIV-1 viremia, and encoding a limited set of HIV-1 genes within DNA and poxvirus vectors can, when used sequentially, induce high levels of T cell immunity in primates. However, a limited breadth of T cell immunity exposes the host to potential infection with either genetically diverse HIV-1 strains or T cell escape variants of HIV-1. In an attempt to induce maximally broad immunity, we examined DNA and recombinant fowlpox virus (rFPV) vaccines encoding all HIV-1 genes derived from a global HIV-1 consensus sequence, but expressed as multiple overlapping scrambled 30-amino acid segments (scrambled antigen vaccines, or SAVINEs). Three groups of seven pigtail macaques were immunized with sets of DNA and rFPV expressing Gag/Pol antigens only, the whole genome SAVINE antigens, or no HIV-1 antigens and T cell immunity was monitored by ELISpot and intracellular cytokine staining. High levels of cross-subtype HIV-specific T cell immunity to Gag were consistently induced in the seven macaques primed with DNA and rFPV vaccines expressing Gag/Pol as intact proteins. It was, however, difficult to repeatedly boost immunity with further rFPV immunizations, presumably reflecting high levels of anti-FPV immunity. Unfortunately, this vaccine study did not consistently achieve a broadened level of T cell immunity to multiple HIV genes utilizing the novel whole-virus SAVINE approach, with only one of seven immunized animals generating broad T cell immunity to multiple HIV-1 proteins. Further refinements are planned with alternative vector strategies to evaluate the potential of the SAVINE technology.

INTRODUCTION

HIV IS A FORMIDABLE PATHOGEN and a great challenge to vaccine development. Although tremendous successes have been achieved in the development of antiretroviral drug therapy, the progress of vaccine development has been slow. These difficulties are in part the nature of HIV replication, which can evade host immune responses, both T cell and humoral,¹⁻⁴ as a result of its high replication rate, frequent recombination events, and low fidelity of replication.^{5,6}

Although desirable, preventive vaccines based on the generation of neutralizing antibodies are still in the early stages of

development. The most advanced current HIV vaccine efforts are directed toward the generation of effective CD8⁺ cytotoxic T lymphocyte (CTL) responses that aim to control viral replication and prevent the onset of disease that is associated with progressive CD4⁺ T cell depletion.⁷ The generation of HIV-specific CD4⁺ T cell immunity, often lacking in HIV-infected individuals, is also highly desirable.^{8,9} Recombinant viral carrier vaccine vectors, such as vaccinia, avian poxviruses (e.g., canarypox and fowlpox viruses [rFPV]), and adenoviruses, either alone or in combination with DNA vaccination, have been most effective in inducing T cell immunity.¹⁰⁻¹⁴ Although live, attenuated SIV vaccines are highly effective in macaques,¹⁵ and

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