THE QUEST FOR AN AIDS VACCINE: MYTHS AND REALITY

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The only appropriate animal for the study of prototype HIV-1 vaccines is the chimpanzee. Chimpanzees do not develop AIDS but remain persistently infected, therefore allowing studies concerning protection from infection, but not protection from disease. We have shown that immunization of chimpanzees with a variety of HIV-1 antigens, including purified recombinant gp160 and a synthetic peptide with the sequence of the principal neutralization determinant of the virus, the V3 loop, could protect the animals from experimental HIV-1 infection with either a cell-free or a cell associated T cell line adapted (TCLA) virus inoculum. Protection was also obtained by immunization with ALVAC-HIV-1 vCP250 (a recombinant canarypox virus expressing gp160 and gag). Remarkably, the common surrogate marker found in all protected animals was a high V3-targeted, strain specific neutralizing antibody titer at the time of challenge. However, these antibodies were devoid of neutralizing activity when tested on primary HIV-1 isolates, and there was no protection in the chimpanzees when challenge was with a virulent primary virus isolate, whether from the same clade (HIV-1 DH12) or from a different clade (HIV-1 E402). Protection from homologous challenge by the genital route was also obtained in female chimpanzees using immunization with ALVAC-HIV-1 vCP250. In this case, however, no correlation was found between protection and the titer of virus neutralizing antibodies. An increased secretion of beta-chemokines by PBMC could be observed at the time of challenge in the protected animals. Neutralizing antibodies thus seem to be needed for protection from systemic infection with TCLA virus strains in chimpanzees but other mechanisms must be operating in mucosal protection.

Another relevant animal model for the study of AIDS vaccines is the rhesus macaque, which develops an AIDS disease upon infection with SIV. The most potent vaccine protection against SIV observed so far was that provided by live attenuated virus strains such as the Δnef mutants of SIV. The immune correlates of protection are unclear. It might be high avidity neutralizing antibodies or cellular immune responses, including CTL and the secretion of chemokines, or, perhaps, other non-immunological mechanisms. However, a live attenuated HIV vaccine in humans would suffer from major potential safety pitfalls, that appear to be insurmountable and forbid that approach.

Recently, SIV/HIV hybrids (SHIV) that contain the *env* gene of HIV-1 in a SIV genome have been developed, allowing one to study the impact of HIV envelope diversity on gp160 and SIV Gag, respectively, or a prime boost immunization regime combining the 2 vaccines. The animals were challenged with SHIBV-Sbg, a non pathogenic SHIV with the HIV-1 IIIB (LAI) envelope. The correlates of protection from the SHIV challenge will be discussed.

There is recent evidence that a small percentage of humans can remain uninfected in spite of repeated exposure to HIV. Some of these individuals bear an homozygous defect in the gene encoding CCR-5, the co-receptor for macrophage tropic HIV-1 strains. CCR-5 is the natural receptor of B- chemokines RANTES, MIP-1α and MIP-1β, which competitively inhibit HIV-1 penetration into target cells. Another category of highly exposed persons who remain uninfected and seronegative have developed HIV-1 specific cytotoxic T-lymphocytes (CTL). A cellular immune response in the absence of an antibody response, therefore, seems to be responsible for their protection. The CTL response to HIV-1 primary infection is known to occur in most infected individuals prior to the antibody response and is thought to control the outcome of the primary virus infection. A vigorous CTL response can even bring the virus load down to the limits of detection and help maintain the seropositive individual as a long term non-progressor. These observations have led to the concept that high priority should be given to HIV-1 vaccines able to induce CTL. In that respect, a synergistic effect between a live recombinant poxvirus vaccine used for priming and a soluble recombinant subunit vaccine used for boosting has been observed in human volunteers. The volunteers who received such a prime-boost vaccine regime developed both a humoral (neutralizing antibodies) and a cellular (CTL) immune response. This promising result will pave the way to eventual efficacy trials in human populations at risk. A major effort is being done toward this goal at the present time.