Retrovirology

Oral presentation

Rational Design of AIDS Vaccines

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Development of an effective vaccine against HIV has posed significant challenges to the scientific community. Lack of knowledge about the molecular pathogenesis of this disease, and the absence of naturally occurring, protective immune responses, which is attributed in large part to the diversity of the viral envelope and multiple escape mechanisms, have made it difficult to design successful candidates. Recent studies of the envelope have suggested that it is possible to enhance immunogenicity of the envelope by improving the breadth of the neutralizing antibody response and by stimulating cell-mediated immunity. This relies on an understanding of the structure of HIV Env and the use of site-specific mutation to create novel immunogens. Based on structural and functional data, our lab has developed DNA and adenoviral vectors which express envelope proteins containing alterations to regions in the variable loop to better control tropism and improve immunogenicity. These modified HIV genetic vaccine candidates have been tested in combination with Gag, Pol, and Nef immunogens, and shown to improve the potency of cellular and humoral immune responses in primates. An initial Phase I trial (VRC 004) dose escalation study to test a DNA vaccine composed of a 4-plasmid combination of clade B gag/pol/nef with clades A, B, and C envelope was recently completed in 50 healthy adults in the U.S. CD4+ and CD8+ T cell responses were detected in the majority of vaccinees using IFN-(ELISpot) and flow cytometric detection of intracellular IL-2 or IFN-γ. HIV-specific antibody response was detected in about one third of vaccinees. Combination modality regimens using a DNA vaccine prime followed by a viral vector boost have shown promise in non-human primate models of HIV infection. Phase I clinical trials to test the safety and immunogenicity of an adenoviral vaccine expressing proteins similar to the DNA, and a DNA prime, adenoviral boost regimen are in progress. The initial adenoviral vector vaccine uses an Ad5 serotype vector. However, pre-existing immunity can mitigate the efficacy, so alternate serotypes and modifications to the adenoviral fiber regions are being explored.