Optimization and immunogenicity testing of multi-gene HIV-1 (CRF02_AG) DNA vaccine constructs

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We developed an AIDS vaccine for West Africa based on a DNA plasmid vector expressing CRF02_AG gag, pol, tat, rev, vpu, and env genes. To optimize the vaccine and improve the production of HIV-like particles (VLP), we generated four potential vaccine constructs: the parental with associated deletions and safety mutations and three modifications containing mutations within the HIV protease. While the parental construct expressed predominantly protein aggregates when transfected in vitro, inactivation of the protease at the catalytic site (position 25) resulted in the production of immature particles. The remaining two constructs employed naturally occurring drug resistance mutations in protease; a G48V mutant and a M90L mutant. Importantly, these attenuated protease constructs produced mature HIV-like particles in addition to immature VLPs and protein aggregates.

To determine improved immunogenicity from mature VLPs that potentially could fuse and enter target cells analogous to authentic HIV, immunization trials were recently initiated. Young adult rhesus macaques were immunized with either the non-mature VLP expressing construct (protease mutation at position 25) or the mature VLP expressing construct (protease mutation at position 48); 0.6 mg of DNA intramuscularly (IM) at 0 and 8 weeks. This DNA priming will be followed by a MVA IM boost expressing Gag, Pol and Env CRF02_AG proteins. Serologic responses and peak cellular responses, with peptide pools made from the vaccine construct CRF02_AG sequence, will be measured for all animals. We are also evaluating the extent of immunologic cross-recognition for diverse HIV-1 subtypes by using peptide pools from Kenyan A, U.S. B, and Thai A/E sequences. While both DNA vaccine constructs are anticipated to prime significant cellular responses reminiscent of DNA vaccines, production of mature VLPs in vivo may hold additional immunologic advantages.