

# on Vaccine Research

## ABSTRACTS OF SUBMITTED POSTER PRESENTATIONS

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**Epidermal Powder Immunization with HIV gp120 Induces both Humoral and Cellular Immune Responses**

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An effective vaccine against the human immunodeficiency virus (HIV) must be able to elicit both strong cellular immune responses and broadly neutralizing antibodies. The HIV envelope gp120 plays a critical role in the pathogenesis of HIV and has been evaluated as a vaccine candidate for nearly two decades with disappointing results. Intramuscular (IM) administration, via needle and syringe, of envelope proteins fails to elicit strong cellular immune responses or neutralizing antibody against many wild-type isolates of HIV-1. In this study, recombinant gp120 was coated onto 1.5-2.5 $\mu$ m gold particles for intracellular epidermal powder immunization (EPI) or embedded in sugar particles (20-38 $\mu$ m) for extracellular EPI. The particulate formulations were administered to the abdominal skin of mice using a helium-powered PowderJect<sup>®</sup> particle device. In a series of studies, we demonstrated that EPI of both the gold and sugar formulations consistently elicited high levels of antibody titers against the gp120 when measured using an ELISA. EPI with a dose as low as 0.2 $\mu$ g gp120 formulated with the sugar excipient elicited a mean titer that was 20-fold higher than that elicited by IM injection of 5.0  $\mu$ g gp120. Furthermore, most EPI mice (n=8) had detectable antibody titers after a single dose and all mice seroconverted after a boost. In contrast, fewer than half of the IM control mice seroconverted only after receiving both a prime and a boost. The IgG subclass titers and cellular immune responses were dependent on the type of carriers used in the EPI. The gold formulation elicited elevated IgG2a and IgG2b antibodies in addition to IgG1 antibodies whereas the sugar formulation elicited predominantly IgG1 antibodies. The gold formulation elicited higher INF- $\gamma$  production in the splenocytes of mice than the sugar formulation. In addition, the gold formulation induced a more robust cytotoxic T cell response, similar to immunization using a DNA vaccine encoding the gp120. The ability to elicit both cellular and humoral immune responses to HIV gp120 indicates that EPI may have important implications for immunoprophylaxis and immunotherapy. We believe that the high efficiency of EPI is related to targeting antigens to the antigen presenting cells (i.e., Langerhans cells) in the epidermis.

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**Evolution of envelope-specific antibody responses associated with the development of enduring broadly protective immunity in monkeys inoculated with attenuated SIV.**

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The identification of reliable immune correlates of AIDS vaccine protection in the SIV/monkey vaccine model has proven elusive, as standard assays of cellular and humoral immunity have failed to distinguish protective and nonprotective vaccine immunity. Using qualitative assays of antibody conformational dependence and avidity, we have previously described a complex evolution of envelope-specific antibody responses that is associated with the development of protective immunity in monkeys inoculated with attenuated strains of SIV. Further studies have demonstrated a significant correlation of these antibody maturation parameters with protective efficacy of other experimental vaccines in the SIV/monkey model. The current studies were designed to examine in more detail the nature of the antibody maturation to attenuated SIV vaccines and to evaluate potential immune correlates of vaccine protection based on analysis of antibody responses to specific envelope domains, designated "domain-specific serology". To achieve the analyses of predominantly conformationally-dependent antibody responses to the SIV envelope protein, we have produced a novel panel of recombinant HIV/SIV chimeric envelope antigens in which specific domains of the SIV envelope have been substituted into the HIV-1 envelope background and expressed in the baculovirus/insect cell system. These HIV/SIV chimeric envelope antigens are being used in serological assays to monitor the quantitative and qualitative progression of antibody responses associated with the immune maturation and development of protective immunity in monkeys inoculated with an attenuated SIV vaccine. The results of these domain-specific serological assays reveal new aspects of the antibody maturation to attenuated SIV vaccines that better characterize the nature of antibody responses associated with mature, protective immunity and that provide novel parameters that can be evaluated further as potential immune correlates of vaccine protection.

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**WITHDRAWN**

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**A Conjugated Papillomavirus-Like Particle Based Vaccine Generates High Titer Autoantibodies to TNF- $\alpha$  and Protects Against Arthritis Induction in a Mouse Model**

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Autoantibody inducing vaccines may be practical alternatives to monoclonal antibody (mAb) based therapies, which have produced encouraging results in clinical trials for a number of diseases. Because microbial antigens with highly repetitive structures induce strong B cell responses, we hypothesized that autoantibodies could be effectively generated by presenting a target self-peptide in the context of the regular array of assembled capsomeres comprising naked icosahedral Papillomavirus-like particles (VLPs). We took advantage of the strong inter-action between biotin and streptavidin (SA) to develop a flexible system to decorate the VLP surface with self-peptides. A SA-mouse TNF- $\alpha$  fusion protein was generated and conjugated at high occupancy to the surface of biotinylated VLPs. High titer and avidity autoantibodies to native TNF- $\alpha$  were generated after parenteral vaccination of mice with low doses of conjugated particles without adjuvant. Co-administration of Freund's adjuvant enhanced titers 50-fold. Relative to animals inoculated with SA-TNF- $\alpha$  alone, presentation on VLPs increased autoantibody titers 1000-fold, but antibody levels against the foreign component of the fusion protein (SA) were similarly high with or without VLP conjugation. This suggests that presentation in a virion-like context abrogated the ability of the humoral immune system to distinguish between self and foreign. Autoantibody levels declined over time in immunized animals (20-fold over a year) but could be boosted, indicating that autoreactive B cells were not preferentially anergized. TNF- $\alpha$  plays a key role in the pathogenesis of chronic inflammatory diseases, such as rheumatoid arthritis. To assess the protective potential of the induced TNF- $\alpha$  autoantibodies, we examined the effects of vaccination on the development of collagen induced arthritis in mice. The vaccine reduced the incidence of arthritis from 80% in the control group to 53% in the vaccinated animals (N=15,  $p < 0.05$ ), similar to protection reported using an anti-TNF- $\alpha$  mAb. Importantly, disease severity was markedly reduced in vaccinated animals that did develop arthritis. Protection correlated with antibody titer, as strong protection was observed in animals with the highest (>3000) anti-TNF- $\alpha$  antibody titers (arthritis in 2/9 animals,  $p < 0.0001$ ). These results suggest a potentially flexible strategy to efficiently generate long-lasting autoantibodies against specific self-proteins that mediate arthritis and other diseases.