

S13 Novel Adjuvants for Hepatitis B Protein and DNA Vaccines

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In a preclinical model, we compared the immunogenicity of a hepatitis B surface (HBs) antigen vaccine with that of a DNA vaccine expressing the corresponding protein. The antibody response to HBs protein (formulated with an aluminum adjuvant) was ~100-fold higher than that to the naked DNA vaccine. However, without an adjuvant, the HBs protein vaccine and the DNA vaccine were similar in potency. In an effort to improve the antibody response to the DNA vaccine, a phosphorothioate oligodeoxynucleotide (ODN) consisting of the sequence 5'GACGTT3' was tested as an adjuvant for the HBs DNA and protein vaccines. The ODN was found to be a potent adjuvant for the protein antigen whereas it had no beneficial effect on the potency of the DNA vaccine. Finally, the CpG-containing ODN was found to alter the isotype profile of the humoral response (to one dominated by IgG2a) as well as to enhance the CTL response to the protein vaccine. These results indicate that a shift from a TH2 to a TH1 response accompanied the induction of a CTL response to the ODN-adjuvanted HBs protein.

S14 Rational Design and Development of Adjuvant-Active Nonionic Block Copolymers

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Nonionic block copolymers are surfactants synthesized using propylene oxide and ethylene oxide, they can be designed so that individual copolymers have unique vaccine adjuvant properties. We have designed and produced nonionic block copolymers based on high molecular weight (MW), 9-15 kDa, cores of polyoxypropylene (POP) coupled with smaller polyoxyethylene (POE) end blocks. Copolymers synthesized with less than 10% (w/w) POE will spontaneously assemble into 300nm-3µm micelles or microparticles in aqueous solutions at physiological pH and when formulated with protein, complex microparticles consisting of both the protein and copolymers are formed. The adjuvant activity of nonionic block copolymers is influenced by both size and POE content. Maximal adjuvant activity is also correlated with low POE content, 5-10%, and a molecular size of 11-12 kDa. The type of immune response produced is also influenced by the POE content. Copolymers with 10% POE significantly augmented Type 2 helper T-lymphocyte responses whereas copolymers with lower POE contents augmented both Type 1 and Type 2 helper T-lymphocyte responses. This property allows for vaccines to be "customized" by using adjuvant-active nonionic block copolymers that will augment the most appropriate types of immune responses.

S15 Introduction to Combination Vaccines

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The wealth of new vaccine products and candidates over the last ten years has focused considerable attention onto ways to alleviate the negative impact of increasing numbers of shots given to young children. For injectible vaccines, combining components is an attractive approach allowing multiple antigens to be given simultaneously. This is not a new concept as witnessed by such long-standing successful vaccines as DTP, MMR and polio. However, developing new combination products is not trivial and the interference between antigens delivered simultaneously is more the rule than the exception. Recent experience with interference between such products as DTaP and Hib conjugates has been particularly troublesome because for two of the components, aP and Hib conjugate, good correlates of immunity have not been established. Differences in immunogenicity must therefore be assessed not only in absolute terms but in terms of clinical significance. It can be argued that any reduction in immunogenicity will decrease efficacy but these decreases may pale in comparison to the advantages of the combined product. It is also not clear why, from a biochemical or immunological perspective, these interferences have occurred with a broad range of different aP and Hib conjugate vaccines. In the future it will be necessary to pay more attention to the character of the antigens and attempt to combine like antigens. Recent studies with pneumococcal conjugate vaccines have shown that combinations of 4, 7 and 9 components have similar immunogenicity suggesting that glycoconjugates are compatible immunogens. Future combinations containing conjugates from other encapsulated pathogens such as *Neisseria meningitidis* and Hib along with the pneumococcal conjugate may be more compatible for childhood immunization.

S16 Clinical Experience with Combination Vaccines

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Combining vaccines into a single injection provides a number of benefits including increased compliance, improved vaccine coverage, fewer immunization visits, decreased pain and improved consumer satisfaction. There may also be negative effects of combination vaccines including delays of licensure, delayed implementation of new products, decreased market competition, and increased cost. Vaccine-associated adverse effects are usually not increased by combining antigens into a single injection compared to separate injections of the same visit; however, immunogenicity may be augmented, diminished or remain unaffected. Although some antigens appear inherently more difficult to include in combinations (such as *Haemophilus influenzae b* conjugate vaccine), the magnitude of the antigen interaction varies widely among formulations with some demonstrating no antigenic interference. Clinical trials over the past 10 years with acellular pertussis vaccine combinations have demonstrated that it is difficult to predict the effect of antigenic combinations. This has serious implications on the design of future studies that add new antigens to the basic combinations. Consistent criteria are needed to assess the equivalency of combination vaccines with their components. Long-range strategies are needed to identify the optimal roster of vaccines that should be routinely administered and the acceptable number of immunization visits and injections per visit.