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Development of Pneumococcal surface protein Antigen (PspA) based Pneumococcal vaccine showing enhanced protective immunity when conjugated to Vi capsular polysaccharide from Salmonella typhi

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Background and Aim: Data from Phase I clinical trials showed that protein based pneumococcal vaccines induced poor immune responses. To address this problem the protein needs to be presented in a way that will induce a stronger antibody response that is more likely to protect humans. Our aim was to develop a more immunogenic vaccine by conjugating α-helical region of PspA family 1 and 2, a protein common to all Streptococcus pneumoniae to Vi capsular polysaccharide from Salmonella typhi. The candidate vaccine provides better protection against lethal intravenous challenge with broad range of S.pneumoniae strains.

Method: A high yielding, scalable method for fermentation and purification of Vi polysaccharide and of PspA family 1 and family 2 proteins have been optimized. Conjugation processes developed have more than 60-80% recoveries of both PspA and Vi polysaccharide and amongst a series of conjugates the most immunogenic conjugate was selected for protection studies against a range of S. pneumoniae strains. We tested the feasibility of formulating a bivalent vaccine containing Vi-PspA conjugates with PspA from both families 1 and 2 and tested its ability to induce cross-protection against strains with different PspAs. Spleen cell culture of immunized mice was checked for induction of both Th1/Th2 cytokines.

Results: A series of Vi-PspA conjugates are prepared and tested in mice. Both Anti-Vi and Anti-PspA family 1&family 2 responses are significantly boosted upon conjugation ($P<0.05$). A high level of protection of vaccinated mice was observed when challenged with a pneumococcal strain expressing a clade that was present in the vaccine (monovalent or bivalent vaccine). Induction of a combination of Th1/Th2 cytokines was observed upon conjugation of protein with Vi polysaccharide.

Conclusion: The bivalent conjugate vaccine consisting of PspA from families 1 and 2 bound to Vi polysaccharide has the potential to protect against typhoid fever and infection caused by a broad range of S. pneumoniae stains. The vaccine has the added advantage that an adjuvant is not required to mount a robust protective response. It is anticipated that this vaccine can be produced at low cost and thus be made available to the world's poorest communities at an affordable price.

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Adjuvant-guidance of T cell mediate immune responses

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Adjuvants are important enhancers of the immune response. The choice of adjuvant is especially crucial in the context of subunit vaccine approaches. In the past, adjuvants have been used with little knowledge of the mechanism by which they exert their effects. Studies on the role of adjuvants on CD4+ T cell responses have shown that different types of adjuvants can polarize the cytokine response while inducing the same proliferative capacity, specificity and avidity of CD4+ T cells. Such responses were shown to be independent of the antigen used and genetic background of the host. Would this also be the case for CD8+ T cells? What is the contribution or importance of providing CD4+ T cell help or toll-like receptor (TLR) ligation in the generation of these CD8+ T cell responses? Studies have shown that CD8+ T cells are guided differently than CD4+ T cells. In addition, it was found that the use of different adjuvants can induce the generation of different CTL populations: cells which kill but do not produce IFN-gamma, cells which do not kill but produce IFN-gamma and cells which both kill and produce IFN-gamma. By understanding the extent to which one can guide the T cell responses through the use of adjuvants and appropriate $CD4^+$ T cell help or TLR agonists, one can improve both vaccine efficacy and safety. These have broad implications not only for vaccine development, but also in the fields of autoimmunity, transplantation and tumor biology.

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