Single dose polyanhydride nanoparticle-based vaccine safely induces both cellular and humoral immunity


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Statement of Purpose: Polyanhydride nanoparticles have been successfully used as vaccine adjuvants and delivery systems and elicit a balanced immune response, characterized by both humoral and cellular components [1-3]. In addition, polyanhydride nanoparticle-based vaccine formulations have demonstrated single dose efficacy and dose sparing capabilities [3]. Here, we investigate the mechanisms by which polyanhydride nanoparticles modulate the immune response to subunit vaccines with respect to antibody-mediated humoral immunity, T cell mediated immunity, and safety. Specifically, we adjuvant F1-V from Yersinia pestis, the causative agent of plague, with either a polyanhydride formulation, monophosphoryl lipid A (MPLA) or MF59, in order to make direct comparisons among adjuvants. F1-V encapsulated into nanoparticles of a 50:50 molar ratio of 1,6-bis-(p-carboxyphenoxy)hexane (CPH) and 1,8-bis-(p-carboxyphenoxy)-3,6-dioxaoctane (CPTEG) and a 50:50 molar ratio of CPH and sebacic acid (SA) demonstrated sustained antibody titers and avidity comparable to traditional adjuvants. While a robust humoral response is critical for protection against Y. pestis, recent studies indicate that CD4+ T cells may also contribute to immunity against plague [4].

Methods: C57BL/6 mice were immunized intranasally with 50 µg of F1-V protein adjuvanted with 50:50 CPTEG:CPH nanoparticles, 50:50 CPH:SA nanoparticles, PLGA nanoparticles, MPLA, or MF59. Animals were bled every 3 weeks until week 34. Mice were “antigenically” challenged with 5 µg of F1-V at week 34 and necropsied at week 35. Serum, lungs, spleens and draining lymph nodes (DLN) were collected for further analysis. Serum was used to measure anti-F1-V antibody titer and avidity. Lungs were formalin-fixed for histopathological analysis. DLN and spleens were harvested to characterize the lymphocyte populations.

Results: All vaccine regimens including those employing polyanhydride nanoparticles demonstrated sustained antibody titers over 24 weeks (Fig. 1). The titers elicited by the vaccine formulations have been previously demonstrated to be protective against lethal challenge with Y. pestis [1].

Following antigenic challenge at week 34, a significant increase in the percentages of antigen experienced CD4+ and CD8+ T cells was observed in the spleens of mice receiving the polyanhydride nanoparticle-based vaccine as compared to mice immunized with MF59 or MPLA.

Conclusions: Immunization with F1-V containing polyanhydride nanoparticles induced both humoral and cellular immune responses, with a safety profile that outperformed that of the oil-in-water emulsion adjuvant MF59. The high titer, high avidity antibody response generated in mice immunized with polyanhydride nanoparticles was comparable with that induced by MPLA and MF59. These nanoparticle formulations have been previously demonstrated to provide protection against lethal challenge with Y. pestis [1]. Moreover, polyanhydride nanoparticle formulations also enhanced the cellular immune response, as demonstrated by increased percentages of antigen experienced CD4+ and CD8+ T cells in the spleen. Histopathological analyses demonstrated the excellent safety profile of polyanhydride nanoparticles. In contrast, lungs from mice immunized with MF59 exhibited tissue damage 35 weeks after a single administration. Together, these data demonstrate that polyanhydride nanoparticles provide a safe and efficacious vaccine platform capable of generating long-lived, humoral and cellular immune responses.

References:
1. Ulery et al. Plos ONE. 2011
3. Kipper et al. JBMR. 2006