Immunomodulatory Polyanhydride Particle Vaccines to Provide Protection Against Plague

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Statement of Purpose: The causative agent of pneumonic plague, Yersinia Pestis, has been labeled by the CDC as a Category A bioterrorism agent due to its ease of transmission and high mortality rate.1 A recombinant fusion protein, F1-V, has shown effectiveness as a vaccine antigen against plague.2 The major drawbacks of this vaccine are that it must be delivered via multiple doses to be effective and induces an overwhelmingly antibody-mediated immune response. Utilizing the long-term delivery, adjuvant and immunomodulatory capabilities of polyanhydride particles, a single dose plague vaccine can be realized.

Methods: Random copolymers of 1,8-bis(p-carboxyphenoxy)-3,6-dioxaoctane and 1,6-bis(p-carboxyphenoxy)hexane (CPTEG:CPH) were tested as adjuvants for a potential plague vaccine. Polymers with molecular weights ~ 10,000 Da were synthesized via melt polycondensation under vacuum and were characterized by 1H nuclear magnetic resonance, gel permeation chromatography and differential scanning calorimetry. An anti-solvent precipitation method was used to fabricate microparticles and nanoparticles. Scanning electron microscopy was employed to evaluate particle morphology and size distribution. Vaccines were delivered intranasally to C57BL/6 mice and were evaluated with an antigenic or pathogenic challenge. Antigenic challenge was assessed by IgG antibody titers, cytokine secretion, 3H-thymidine lymphocyte blastogenesis and carboxyfluorescein succinimidyl ester incorporation. Fourteen day post-challenge survival was considered a success for pathogenic protection.

Results: Spherically shaped, F1-V loaded 50:50 CPTEG:CPH polyanhydride nanoparticles between 50 and 250 nm in diameter and microparticles between 1 and 20 μm in diameter were fabricated. Scanning electron micrographs of the particles are shown below in Figure 1. Pathogenic protection experiments using 25 μg F1-V delivered intranasally twice with multiple doses of an adjuvant, IL-12, were conducted with 62% of mice surviving challenge. Protected mice had an average 35-day total IgG antibody titer of ~ 10,000. In order to determine the adjuvant and immunomodulatory capacity of polyanhydride particles, 500 μg of 2% loaded F1-V particles (10 μg encapsulated F1-V) were co-delivered with 15 μg soluble F1-V were delivered intranasally (40% encapsulated). MPLA, monophospholipid A, was utilized as a control and supplemental adjuvant. 25 μg of F1-V alone induced a 35-day total IgG antibody titer of 350. 25 μg of F1-V delivered with 10 μg MPLA gave a titer of 6700. 50:50 CPTEG:CPH microparticles alone induced a titer of 500 and a titer of 2100 when coupled with MPLA. 50:50 CPTEG:CPH nanoparticles stimulated titers of 1500 and 20,000, alone and with MPLA, respectively. Figure 2 shows the IgG subtype antibody titers.

Conclusions: The data provided reveals the potential for 50:50 CPTEG:CPH particles to be used as adjuvants as well as a delivery systems for a single dose, aerosol plague vaccine. The ability for polyanhydride particles to both enhance and modulate the immune response is a highly desired adjuvant function since subunit vaccines alone often do not induce a robust enough response or correct immunological profile to protect against disease.

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References: