COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Evaluating mRNA-based Vaccines Against Burkholderia Pseudomallei Infection

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Burkholderia pseudomallei, the etiologic agent of melioidosis, is an emerging pathogen present in soil and water in tropical regions around the world. Infection can occur through skin abrasions, inhalation of bacteria in aerosolized dust or water, or ingestion of contaminated water. B. pseudomallei is considered a potential biological weapon and presents a risk to the warfighter, especially if disseminated as an infectious aerosol. Two key protective antigens have been identified for conjugate subunit vaccines: capsular polysaccharide (CPS) and the protein antigen Hcp1. Conjugate subunit vaccines, consisting of a CPS-CRM197 conjugate and Hcp1 adjuvanted with CpG 2006 and alum, have proven to successfully ameliorate disease in rodent models of pneumonic melioidosis. In this study, we evaluated the ability of mRNA-based vaccines to elicit immunological responses in C57BL/6 mice. While mRNA vaccines have proven highly effective against a number of viral pathogens, their efficacy against bacterial pathogens is less established. Two different mRNA-based constructs encoding Hcp1 were studied: conventional mRNA and self-amplifying mRNA (based on alphavirus backbone). mRNAs were encapsulated in lipid nanoparticles (LNPs) prepared with the SM-102 ionizable lipid used successfully in Moderna's Spikevax COVID-19 vaccine. Animals were vaccinated at day 0 and 28 with either Hcp1-mRNA:LNP alone or in combination with the CPS conjugate adjuvanted with CpG 2006 and Alhydrogel. Immunological responses were compared to animals vaccinated with the conjugate subunit vaccine and negative controls. Humoral and cell-mediated immune responses were assessed at 7-days post-boost. Our data demonstrate that mRNA-based constructs elicit minimal immunological responses against Hcp1 compared to the conjugate subunit vaccine, both in terms of antibody titer and T-cell responses, although immunological responses were higher against the self-amplifying mRNA vaccine. Hcp1 responses were enhanced in animals that received both mRNA and adjuvanted conjugate vaccines, compared to mRNA alone, suggesting that adjuvant may have an important role in enhancing the immunogenicity of mRNA-based vaccines. These data suggest that mRNA-based vaccines against B. pseudomallei are feasible, but additional optimization in mRNA design and in vivo expression are likely needed to achieve efficacy of current subunit-based vaccine formulations. Overall, this work represents an effort to strengthen our capacity to safeguard the nation and warfighters against B. pseudomallei infection and other related pathogens.

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