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A Cross-protective, Multivalent Mrna Vaccine Against Burkholderia

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Background
The Burkholderia genus includes over 80 species, including at least four recognized human pathogens. Within this genus are tier 1 Select Agents (SA) B. mallei and B. pseudomallei, the causative agents of the zoonotic disease glanders and melioidosis, respectively. There are currently no vaccines against either glanders or melioidosis so the development of effective vaccines is a priority for public health and as well as for military personnel who may be deployed to areas of conflict where Burkholderia related illnesses are endemic.

Purpose
To develop a vaccine that provides cross-protection against the phylogenetically related pathogens B. malleiand B. pseudomallei.

Objective
Identification of antigens involved in eliciting cross-protection against B. mallei and B. pseudomallei to be used in a multivalent mRNA vaccine.

Rationale
Recently, nucleic acid vaccines have been shown to elicit robust, broadly protective antibody and T cell responses against a variety of emerging infectious disease. Furthermore, DNA/mRNA vaccines obviate some of the technical and manufacturing limitations associated with purifying protective antigens for subunit vaccines. Our lab has previously shown that antigens delivered in a multimeric particle are able to co-stimulate APCs and enhance both B cell maturation and memory T cell responses. We believe a similar approach using multimericity in an mRNA format with lipid nanoparticles could be a favorable approach to designing a cross-protective vaccine against B. mallei and B. pseudomallei.

Methods
We used convalescent serum from patients recovering from either melioidosis or glanders and probed a library of >2000 antigens on a Burkholderia Immuno-Proteome Array (BIPA) to identify a panel of immunodominant antigens. Next, we screened antibody responses from non-human primates (NHPs) immunized with a B. pseudomallei vaccine derived from outer membrane vesicles (OMV) that were subsequently protected from a pulmonary melioidosis challenge.

Preliminary results
Among the antigens identified were those specific to melioidosis and glanders infection, as well as a cluster of shared antigens present in both patient sets. BIPA analysis of vaccine derived serum from NHPs immunized with OMVs was confirmatory for several well-characterized outer membrane proteins as well as some additional hypothetical and lipoprotein antigens with immunogenic potential that had not previously been considered as vaccine targets. We have selected 5 antigens from these two screens that we believe play an important role in host directed protection from Burkholderia infection.

Preliminary conclusions
Serologic analysis of convalescent serum from patients and NHPs immunized with a protective OMV vaccine identified a cluster of antigens conserved between B. mallei and B. pseudomallei. We believe these present as favorable targets to be incorporated into a multivalent mRNA vaccine format to elicit cross-protection in humans. In doing so, a successful vaccine would reduce the number of immunizations warfighters have to receive and increase the mission effectiveness of military personnel by releasing for deployment sooner.