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Advanced Development Of Vaccines Against Francisella Tularensis (ft), A Category “a” Select Agent

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Background: Currently, the only vaccine used to treat tularemia caused by F. tularensis is the Live Vaccine Strain (LVS) of F. tularensis, an attenuated type B (subsp. Holarctica) strain that does not appear to cause disease in humans.

Purpose/Objective: LVS has questionable genetic stability and safety which makes it unlikely that the FDA will license this vaccine in the U.S. Therefore, there is an urgent need for an approved prophylactic that reduces the threat tularemia poses to the Warfighter. Southwest Research Institute (SwRI) and the University of Texas at San Antonio (UTSA) are collaborating to produce a formulated vaccine against F. tularensis, allowing intradermal delivery while providing high protective immunity and enhanced storage stability.
Rationale: The Klose Lab at UTSA has developed a candidate that demonstrated protective immunity in Fischer 344 rats and non-human primates previously. This vaccine is based on the Francisella novicida. This BSL-2 organism offers a safe alternative to F. tularensis-based vaccines. Klose’s group has modified the novicida vaccine strain (Fn-iglD OAgFtt, strain KKF768) in order to reduce its virulence yet enhance protection gained by incorporating the O-antigen from the tularensis species. SwRI used its formulation experience in an effort to produce a storage-stable form of this live vaccine.

Progress: Growth of the organism was transferred to SwRI for formulation development. SwRI explored emulsion-based strategies of encapsulation (alginate- and PLGA-base approaches) as well as drying strategies of both the vaccine culture itself as well as formulations to enhance storage stability of the product. UTSA researchers evaluated protective efficacy of the intra-dermally administered vaccine and formulations against aerosol challenge of LVS in mice (BAlb/c).
Formulations made by SwRI were down selected based on survival for subsequent studies in the Fischer 344 rat model challenged with SchuS4. Fluorescence Assisted Cell Sorting (FACS) was used to analyze immune correlates of protection in the mouse model. While no encapsulated formulations resulted in acceptable viability of the organism, SwRI performed initial stability studies on lyophilized samples and determined the most stable formulation contained the stabilizer mix of 10% Trehalose, 5% Mannitol, and 0.2% Cysteine. Samples with an initial 1E9.6 cfu’s/vial were stored for up to six months at various conditions. Storage at -20 °C for six months resulted in minimal loss of viability (1E9.4 cfu/vial) and storage at 4 °C resulted in 1.5 log CFU loss at three months (1E8.1cfu/vial). UTSA verified that this formulation maximized survivability of the rat model. UTSA evaluated a boost regime to further optimize the efficacy of the formulation finding that one boost in beneficial.

The next phase involves protective efficacy of the formulation in NHP’s. As the efficacy of the vaccine strain itself administered intra-dermally has already been shown, and based on the enhanced stability and protection of the formulation in the mouse and rat model, we expect a high level of protection in the primate model as well.
The results of these studies will be a stable formulation of a live attenuated vaccine against tularemia that will be of great benefit to Warfighter.

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