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

Evaluation Of Immunogenicity And Efficacy Of A Novel, Live Attenuated Anthrax Spore Vaccine, 'LAV-BASTA-48', For Postexposure Prophylaxis (PEP)

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The spore-forming bacterium Bacillus anthracis is the etiological agent of anthrax, a rare disease that can affect animals and humans and potentially result from weaponization of the bacteria as an agent of bioterror. Inhalational anthrax, the most severe manifestation of anthrax, is caused by inhalation of B. anthracis spores, which germinate in the lung into rapidly dividing vegetative cells that secrete a variety of toxins and virulence factors. Due to its potential to be easily weaponized and released as an aerosolized agent, the US government (USG) has led an extensive campaign to develop and stockpile effective anthrax vaccines to be used in individuals at risk of exposure (i.e., warfighters) or in the case of a large-scale attack. Such efforts supported the licensure of the first anthrax vaccine BioThrax® (Anthrax Vaccine Adsorbed) (AVA, Emergent BioSolutions), a recombinant vaccine based on the protective qualities of Protective Antigen (PA), which mediates the intracellular translocation of the lethal subunits of the anthrax toxin complex into the host cell. These aspects contribute to significant challenges with vaccine adherence and inflate the cost obligation to the USG, which in turn compromises its ability to develop and procure medical countermeasures for other biodefense indications. For this reason, the USG has long prioritized the development of a next-generation, safe, single-dose anthrax vaccine to replace AVA, but to-date no such vaccine has been approved for use in humans. To address this gap, Elusys Therapeutics, Inc. (Elusys) and the Israel Institute for Biological Research (IIBR) are collaborating on developing a novel, live attenuated anthrax spore vaccine based on disruption of the htrA (High Temperature Requirement A) gene and mutations in the lef and cya genes, encoding for the toxin components lethal factor (LF) and edema factor (EF), in the B. anthracis Sterne veterinary vaccine strain (ΔhtrA;lefMUT;Δcya derivative strain designated LAV-BASTA [Bacillus anthracis Sterne Triple Attenuated]-48; "BASTA"). This vaccine, which was originally funded by the US Department of Defense (DoD), includes the stepwise addition of several mutations that resulted in a progressive increase in attenuation of the vaccine strain and most importantly, did not affect its ability to elicit protective immunity. Immunization of guinea pigs and rabbits with a single or double doses of the BASTA vaccine strain induces a robust immune response and provides complete protection against a subsequent respiratory lethal challenge. In rhesus macaques, a single dose of BASTA protects animals from a lethal challenge with the highly virulent Vollum strain. Acute non-GLP safety measures were reported for treated monkeys revealing no changes in body temperature, weight gain, clinical signs, blood chemistry, or cytology. A mild increase in plasma C-reactive protein (CRP), consistent with a vaccination, was observed. Immunological read-outs included anti-PA, anti-core, and anti-toxin neutralizing antibody (TNA) assays, which correlated with challenge survival and clinical symptoms. Based on these compelling data, Elusys and the IIBR seek to examine BASTA vaccine potential for near-term/post-exposure protection (PEP), perform final IND-enabling efficacy studies, and complete process development and manufacture of GMP drug product for toxicology/Phase 1 evaluations.

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Chitlaru T, Israeli M, Rotem S, Elia U, Bar-Haim E, Ehrlich S, Cohen O, Shafferman A. A novel live attenuated anthrax spore vaccine based on an acapsular Bacillus anthracis Sterne strain with mutations in the htrA, lef and cya genes. Vaccine. 2017 Oct 20;35(44):6030-6040.

Chitlaru T, Israeli M, Bar-Haim E, Elia U, Rotem S, Ehrlich S, Cohen O, Shafferman A. Next-Generation Bacillus anthracis Live Attenuated Spore Vaccine Based on the htrA(-) (High Temperature Requirement A) Sterne Strain. Sci Rep. 2016 Jan 6;6:18908.