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

ATI-1701: Ongoing Development Of A Live Attenuated Tularemia Vaccine Based On A SCHU S4 Δclpb Mutant

Carl Gelhaus Appili Therapeutics USA Inc **Wayne Conlan** National Research Council Canada **Joseph Barbercheck** MRIGlobal **Vikalp Vishwakarma** MRIGlobal **Joel Bozue** USAMRIID **Kevin Mlynek** USAMRIID **Sara Ruiz** USAMRIID **Arthur Baran** Appili Therapeutics USA Inc **Gary Nabors** Appili Therapeutics USA Inc

Tularemia is caused by Francisella tularensis, a gram-negative bacteria which is naturally found throughout the environment but has been previously developed as a biological weapon. The current military actions in Ukraine have led to public health conditions that mimic conditions associated with historic wartime periods where there were significant outbreaks of tularemia. There is no FDA-approved tularemia vaccine. The legacy F. tularensis Live Vaccine Strain (LVS) has not been approved, partially due to its unknown mechanism of attenuation. In an effort to develop a safe, effective and licensable vaccine, we developed a defined ΔclpB mutant of F. tularensis strain SCHU S4, termed ATI-1701. As part of a broad public-private partnership, we are advancing ATI-1701 into clinical trials. ATI-1701 was grown at 3L and 25L scale and the lyophilized final drug product was prepared at a 2000 vial scale. Rats vaccinated with 105 CFU ATI -1701 and subsequently exposed to aerosolized fully virulent F. tularensis SCHU S4 survived a lethal challenge at day 42 post-vaccination with 5.83 x 104 cfu (5,600 LD50) deposited dose. Spleens from unvaccinated control rats contained ~107 cfu/g spleen whereas vaccinated rats had <3 x100 cfu/g of spleen, and were often sterile. The breadth of protection of ATI-1701 was tested against three different strains of F. tularensis in USAMRIID's culture collection and found that 87.5-100 % of rats were protected in all experiments. A limited examination of the tissue distribution of ATI-1701 after vaccination showed that regardless of immunizing dose (103 to 109 cfu), rat spleens contained from 103 to 105 cfu of bacteria 14 days post-vaccination. SCHU S4 ΔclpB was cleared from the spleen between 28- and 42-days post-vaccination. A series of vaccination and challenge studies in Indonesian-origin cynomolgus macaques demonstrated that ATI-1701 was effective at promoting survival in 9 of 11 macaques challenged via aerosol 28 days after vaccination with a presented dose up to 4.25 x 105 cfu (157,000 LD50) of virulent SCHU S4 bacteria. These tests were repeated in mixed origin cynomolgus macaques at USAMRIID, where 7 of 8 macaques survived challenge. ATI-1701 was also 100% effective at promoting survival in macaques exposed to aerosolized F. tularensis SCHU S4 90 days after vaccination. Efficacy in macaques at one year post-vaccination was reduced, with 2 of 7 (29%) macaques surviving. However, there was a statistically significant prolongation in time to succumbing to infection in the animals .We are continuing to develop ATI-1701 through IND submission and a first in human dose escalation trial is being planned.

The USAMRIID research studies described herein was sponsored by the DTRA JSTO-CBD (project # CB11415 & CB10201). Other studies were funded by DTRA # HDTRA1-16-C-0028 and USAFA cooperative agreement FA7000-23-2-00007.

Animal research at The United States Army of Medical Research Institute of Infectious Diseases (USAMRIID) was conducted and approved under an Institutional Animal Care and Use Committee (USAMRIID IACUC) in compliance with the Animal Welfare Act, Public Health Service Policy, and other Federal statutes and regulations relating to animals and experiments involving animals. The facility where this research was conducted is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 2011.

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army. This study does not constitute an endorsement by the US Government of this or any other industry partner.