COMBATTING EMERGING BIOLOGICAL THREATS – PREPARING FOR THE FUTURE TODAY

Enhanced In Vitro Activity Of Sodium Fusidate Against Bacterial Biothreat Panels At Low Ph

J. Matthew Meinig USAMRIID **Carl Kraus** Aceragen **Stephanie Halasohoris** USAMRIID **Sanae Lembirik** USAMRIID **Ashley Babyak** USAMRIID **M. Kelly Hourihan** USAMRIID

Sodium fusidate (SF) is an orally bioavailable antibiotic that has been extensively used outside the United States for over 50 years. SF demonstrates a wide spectrum of activity and is of particular importance clinically against methicillin-resistant Staphylococcus aureus (MRSA). Given the rise of antimicrobial resistance across bacterial pathogens, reinvestigation and development of potent antibiotics with unique targets is vital. This is especially true for bacterial pathogens of biodefense interest, as engineered resistance remains an ever-present threat. To these ends, ACG-701 is a proprietary oral formulation of SF developed by Aceragen for cystic fibrosis and melioidosis. Given that SF demonstrates pH-dependent changes in antimicrobial activity, the role of reduced pH on SF in vitro susceptibility for bacterial biothreat agents was investigated. Following CLSI guidelines for minimal inhibitory concentration (MIC), SF was tested against a 30-strain panel of Burkholderia pseudomallei (BP) and 10 strain panels each of Bacillus anthracis (BA), Yersinia pestis (YP), Francisella tularensis (FT), and Burkholderia mallei (BM) at both normal and reduced pH. SF demonstrated a 16-fold decrease in MIC90 in BP between pH 7.2 (64 µg/mL) and pH 5 (4 µg/mL). A 32-fold decrease in the MIC90 for BA was observed between pH 7.2 (2 µg/mL) and pH 5 (0.06 µg/mL). Similar decreases in MIC90 for the other biothreat agents tested (YP, BM, FT) were also noted. In contrast, lower pH resulted reduced in vitro potency for all tested standard-of-care comparator antibiotics. The enhancement of activity at lower pH is of particular interest for combating biothreat agents as the environment of the pulmonary tract (as the primary site of infection during inhalation) and the intracellular lifecycle of some agents necessitates the pathogen may reside in more acidic environments. These results support further development of SF as a useful agent in the biodefense space.