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

CZ-02188 Is A New Class Of Antibacterial Agent, With A New Mechanism-of-action To Mitigate Multidrug-resistant Pathogens, Including Tier 1 Select Agents, With Efficacy In Mouse Models Of Infection And Safety In Multiple Animal Species

Chad Testa Curza, Inc **Henry Heine** Univerity of Florida **George Drusano** University of Florida **Bret Purcell** University of Florida **Arnold Louie** University of Florida **Paul Sebahar** Curza, Inc **Ken Bartizal** Curza, Inc

CZ-02188 is a member of a new class of antibacterial agent (AIIPS) that selectively target the P-site of the bacterial ribosome. AIIPS are being developed for treatment of multi-drug resistant (MDR) bacterial infections in multiple indications, including those for biodefense. The bacterial P-site is a clinically un-drugged binding site representing a new mechanism-of-action against a validated antibacterial target (the ribosome) that does not show cross-resistance to other antibiotics, including protein synthesis inhibitors.

New antibiotics to circumvent drug-resistance are urgently needed. Widespread use of antibiotics has selected for resistance in both pathogenic and non-pathogenic bacteria. Notably, a recently discovered 4 amino acid insertion into PBP3 conveys resistance to most beta-lactam/beta-lactamase inhibitor combinations which is increasing in prevalence amongst E. coli already resistant to frontline carbapenems. Bacterial Tier 1 Select Agents, B. anthracis, B. mallei, B. pseudomallei, Y. pestis and F. tularensis, are naturally resistant to many antibiotics and are known to have been engineered resistant to those that are used clinically. Intentional release of any of these biologicals will lead to substantial morbidity and mortality before it becomes clear that a drug-resistant isolate has been utilized. Therefore, new therapeutics that are able to salvage patients, even after initiation of ineffective therapy, are warranted. Knowing that drug-resistant bioweapons have been engineered, AIIPS present a compelling treatment option.

Curza, Inc's AIIPS (Amicetin-Inspired Inhibitors of the P-Site) are being developed for multiple therapeutic indications in a partnership with the University of Florida. These represent a class of bacterial ribosomal antibiotics for treatment of MDR bacterial infections, including those caused by agents of biowarfare/terrorism. Their unique antimicrobial class acts on a clinically un-drugged binding site of the most validated intracellular antibacterial target (the ribosome) that does not show cross-resistance to other protein synthesis inhibitors in a bactericidal manner, all while sparing eukaryotic ribosomes and mitochondria.

In relation to other ribosomal antibiotics, AIIPS span the activity spectrum of macrolides (better Gram–) and aminoglycosides (better Gram+) with no cross-resistance. This combined with the fact that AIIPS are active against MDR pathogens is especially important with respect to Biothreat pathogens as many of these agents have been engineered to be resistant to currently available antibiotics, suggesting that AIIPS will likely maintain activity even against an engineered Biothreat.

AIIPS demonstrate high-level potency against Gram-negative and Gram-positive pathogens, including Y. pestis, F. tularensis and B. mallei with sub-µg/mL MICs. Newer AIIPS have excellent potency against those pathogens as well as B. pseudomallei. ADME profiling demonstrates good metabolic stability, low volume of distribution, excellent bioavailability with very low protein binding. AIIPS are rapidly distributed from plasma to organs with promising toxicology supporting their use in pneumonia indications. AIIPS have shown efficacy in multiple in vivo models of infection validating the class as a potential new therapeutic option in the antibacterial armamentarium as a single agent or in combination with other approaches to protect our warfighters.

Research reported in this publication was supported in-part by DTRA-funded OTA-project MCDC 18-06-16-010. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response.