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Advancing Cz-02s (aiips) As A New Class Of Medical Countermeasure, With A New Mechanism-of-action Against Drug-resistant Bacterial Infections, Including Those Caused By Multi-drug Resistant Tier 1 Select Agents

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New antibiotics to circumvent drug-resistance are urgently needed. Widespread use of antibiotics has selected for horizontally transferred resistance in both pathogenic and non-pathogenic bacteria. 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. Should any of these biological agents be employed in an intentional release, there will be substantial morbidity and mortality engendered before it becomes clear that a drug-resistant isolate has been utilized. Consequently, it is important to identify new therapeutic interventions that are able to salvage patients even after initiation of therapy with an antimicrobial that is less effective. With the knowledge that drug-resistant bioweapons have been engineered, agents with new mechanisms of action that are not susceptible to cross-resistance would present a compelling treatment option.

Curza Global, together with the University of Florida, is developing the AIIPS (Amicetin-Inspired Inhibitors of the P-Site) class of bacterial ribosomal antibiotics for treatment of multi-drug resistant (MDR) bacterial infections, including those caused by agents of biowarfare/terrorism. AIIPS represent a new class of bactericidal antibiotics that are active against a validated antibiotic target (bacterial ribosome) with a new mechanism of action (P-site inhibitors). This unique antimicrobial class acts on a clinically un-drugged binding site of the most validated intracellular antibacterial target (the ribosome) and does not show cross-resistance to other protein synthesis inhibitors.
AIIPS are potent, selective inhibitors of bacterial protein synthesis while sparing eukaryotic ribosomes, including mitochondrial. AIIPS show activity against Gram-negative and Gram-positive clinical isolates that are resistant to other antibiotics targeting the bacterial ribosome and are not affected by resistance mechanisms that render front-line therapies for biodefense pathogens ineffective. In relation to other ribosomal antibiotics, AIIPS span the antibacterial spectrum activity of macrolides (better Gram−) and aminoglycosides (better Gram+) with no cross-resistance. This observation 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 are being advanced as medical countermeasures against Tier 1 select agents, showing high-level potency against 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. Bioanalysis of tissue samples from healthy and infected mice shows that AIIPS are rapidly distributed from plasma to organs, including lung, kidney, thigh, liver and urine, and epithelial lining fluid (ELF) along 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.

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