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Medical Countermeasures to Address Intracellular Bacterial Pathogens

Innate Defense Regulators – Supercharging Antibiotic Treatment for Resistant or Unknown Infectious Disease

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Innate Defense Regulators (IDRs) are a novel class of synthetic peptides that enhance the control of microbial infections while attenuating tissue damage and suppressing inflammation. IDRs target host innate immunity rather than the bacterium itself, evading antibiotic resistance mechanisms. The lead IDR, SGX94, has been demonstrated to be safe in a Phase 1 clinical study and efficacious in a variety of Gram-positive and Gram-negative infections at various sites of infections and in immune-competent and immunocompromised animals. A recent Phase 2 trial in a non-infectious disease indication nonetheless indicated that there was a reduced infection rate in the SGX94 treated groups. The Phase 2 trial has demonstrated that all preclinical findings translated to the human clinical setting.

Preclinical studies with SGX94 have demonstrated it does not interfere with and is complementary to antibiotic mechanisms of action. Moreover, IDRs, both alone and / or in combination with antibiotics have been demonstrated to increase bacterial clearance and enhance survival in preclinical infection models of methicillin-resistant *S. aureus* (MRSA), *K. pneumoniae*, *P. aeruginosa* and *E. coli*. In addition, SGX94 has been shown to be effective in infection models with *B. pseudomallei* infection, the causative agent in melioidosis and a top 5 biodefense threat because of its robustness in the environment, capacity for aerosol delivery and high mortality. The advantages of IDRs include 1) the ability to use IDRs preventively without fear of engendering resistance, 2) the ability to use IDRs before the causative infectious agent is fully identified and 3) the ability to use IDRs irrespective of the antibiotic resistance status of the organisms. The broad spectrum efficacy of IDRs against both Gram-negative and Gram-positive bacteria whether antibiotic resistant or not and whether intracellular or extracellular, and their ability to work in tandem with current standard of care antibiotics, clearly demonstrates the advantages of further developing innate immune modulators for the treatment of resistant infections, particularly in a biodefense context where the bacteria may be bioengineered for resistance to known antibiotics and/or may be of unknown origin at the time of treatment.

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