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

Human Sirtuin-2 Protein (SIRT2) - A Host-target Providing Broad-spectrum Effectiveness Through Multiple Mechanisms Of Viral Restriction And Immunity

Lillian Chiang Evrys Bio LLC **Stacy Remiszewski** Evrys Bio LLC **Rekha Panchal** USAMRIID **Daniel Streblow** Oregon Health Science University **Alison Beare** Evrys Bio LLC **Jay Wells** USAMRIID **Sean Vantongeren** USAMRIID **Xiaoli Chi** USAMRIID **Kathleen Cashman** USAMRIID

Current antivirals and vaccines target the virus. Virus are diverse in their biology and disease pathogenesis. Infection by a given virus-type requires a distinct, direct-acting therapeutic option. In the case of biodefense, this minimally requires development and stockpiling of one therapy/vaccine for each threat. Given biological diversity, the use cases are potentially infinite. Per session topic, “Host-directed therapies can improve host cellular responses to pathogens/biologicals, target disease-causing virulence factors, and activate innate and adaptive immune responses and immunological memory.” Small-molecule host-directed therapies are additionally rapidly manufactured, can be taken in shelf-stable pill-form, and do not require cold-chain logistics for distribution. Evrys Bio has developed small-molecules targeting the human sirtuin-2 protein (SIRT2) that are simultaneously effective against diverse virus families: alpha-, arena-, and filoviruses.

An accumulating body of literature shows that small molecule modulation of SIRT2 can provide effective anti-infective activity against diverse viral and non-viral pathogens: herpes viruses, HSV-1, cytomegalovirus and Epstein Barr virus1-3; hepatitis A and B virus4,5; Zika, other arboviruses (West Nile, Chikungunya, Rift Valley fever, and La Crosse viruses)6, and intracellular bacteria Listeria7, Salmonella8, and M.tuberculosis9. SIRT2 is a ubiquitously expressed (NAD)+-dependent lysine-deacylase that regulates cellular metabolism, stress response, and epigenetics through post-translational modification of key proteins that regulate cellular processes. Depending on the specific context, the SIRT2-targeted effect results from modulation of infected host-cell metabolism and biosynthetic pathways needed for productive viral infection, epigenetic disruption of pathogen regulation of host-restriction and/or virulence factors, and activation of innate and adaptive immunity.

Given the urgency of biodefense against innumerable pathogens, timely validation and prioritization of host targets as medical countermeasures is crucial. This presentation will discuss the mechanism of SIRT2-targeted antivirals for distinct virus-types. We also will present preclinical in vitro and in vivo pharmacology predicting beneficial clinical effects including reduced morbidity, mortality, and viral dissemination to end organs as exemplified by alphavirus and filovirus challenge studies in mice. Finally, we will present our data supporting combination dosing that may boost effectiveness of existing direct-acting antivirals.

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