Targeting Host-cell Metabolism to Address Multiple Intracellular Pathogens

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Current anti-infectives and vaccines target the pathogen, whether bacterial, viral, fungal, or protozoan. Unfortunately, pathogens are diverse in their biology requiring a different therapy/vaccine for each pathogen or closely-related class of pathogens. In the case of biodefense, this ultimately requires the development and stockpiling of a distinct therapy/vaccine for each threat. Given biological diversity, the case scenarios are infinite. Despite improvements in biologic and vaccine technologies, manufacture, and cold chain logistics, the recent Zika virus pandemic is a reminder of the slow response inherent in developing a pathogen-targeted therapy against a newly emergent pathogen. Additionally, human pathogens are clever, particularly intracellular pathogens; they have evolved mechanisms to escape detection by the immune system and to develop resistance.

FORGE Life Science, a company developing anti-infective drugs that can be taken in pill form, is taking a different approach. Intracellular pathogens depend on the host cell's metabolism for energy; metabolic precursors for production of pathogen components and genomic material; as well as the organization of specialized compartments in the host cell for replication, maturation, and dissemination. As such, regulation of the host cell's metabolism is a fundamental component of the host-pathogen interaction. FORGE is pursuing a paradigm-shifting anti-infective mechanism-of-action, the modulation of host-encoded sirtuin-proteins, central regulators of host-cell metabolic-homeostasis. Sirtuins are a family of seven enzymes that regulate cellular metabolism and gene activity (including epigenetics) through chemical modification (de-acylation) of other regulatory proteins of the cell. Koyuncu *et al.* (*mBio* 5:e02249) propose sirtuins are evolutionarily-conserved components of the cell's pathogen-defense system (intrinsic immunity); they showed sirtuins restrict the growth of RNA and DNA viruses in mammalian cells, and lytic and lysogenic bacteriophages in bacterial cells. Direct interactions of pathogens with sirtuins actively reprogram the host-cell's metabolism and/or epigenetics to support the intracellular pathogen's life-cycle (*e.g. Leshmania infantum*, Moreira *PLoS Pathog.* 11:e1004684; *Listeria monocytogenes*, Eskandarian *Science* 341: 1238858). Downstream effects of active disruption of homeostasis by the pathogen can provide a means to circumvent intrinsic immunity mechanisms such as cellular autophagy that normally eliminate the pathogen (*e.g. Salmonella typhimurium*, Ganesan *PLoS Pathog*. 13:31006227).

FORGE has data showing sirtuins can be effectively modulated by drugs that are readily synthesized, can be taken orally, and have chemical properties predicting ambient storage and stability. Sirtuin-based drugs also demonstrate broad-spectrum effectiveness against diverse pathogens in culture, block acquired drug-resistance, and synergize with existing anti-infectives. By optimizing target-organ delivery and broad effectiveness against diverse pathogens, the vision is to develop a panel of sirtuin-based drugs that are field ready in event of future pandemic or biodefense threat. Because each sirtuin-modulator is broad-spectrum, the path to clinical readiness would be through preclinical/clinical studies for a traditional pathogen such as seasonal influenza infection of lung. These studies would validate the dosing regimen required for safe, sufficient drug-exposure in humans to achieve an anti-infective effect against the traditional pathogen. In the future, a newly emerging pathogen would be tested in culture against the panel of clinical-stage sirtuin-based drugs to select the most effective one for rapid roll-out and field trials.

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