**Inspired by Nature: Engineering Natural Products and Antibodies to Treat Bacterial Infections**

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The practice of modern medicine is made possible by our ability to effectively treat infections. One of the most ominous issue on the horizon for healthcare is the rise of antimicrobials resistance. Resistance has rendered many antimicrobials ineffective. Thus, failure to effectively treat pathogens, such as multidrug resistant (MDR) Gram-negative bacteria, can have ramifications beyond infectious diseases. Novel chemical matter and/or therapeutic modalities that overcome pre-existing resistance or physiological states of the microbes that render conventional antibiotic therapy ineffective are desperately needed.

Many successful antibiotics are derivatives of natural products. I will present data from a team of scientists at Genentech who exploited insights from natural resistance and structural elucidations to chemically optimize a novel class of antibiotic with potent, broad-spectrum Gram-negative activity from the arylomycin class of natural products that had weak activity and limited spectrum. These molecules are bactericidal against contemporary MDR Gram-negative clinical isolates in vitro and in multiple in vivo infection models and are poised to be translated into a novel therapy to address the growing threat of MDR Gram-negative infections

Next we present a novel therapeutic modality in the form of an antibody-antibotic conjugate (AAC). An AAC has three components: an antibiotic payload to kill bacteria, an antibody to target delivery of the payload to bacteria, and a linker attaching the payload to the antibody. An AAC combines the pharmacological attributes of both antibody and antibiotics into a single molecule, with the potential to revive antimicrobials that otherwise could not be developed due to poor pharmacokinetic properties and/or undesired host toxicity. We provide an example of one such molecule and its in vivo efficacy.