Novel antibiotics against new targets in multi-drug resistant microorganisms

Technology Description

Developing antibiotics with new targets will be essential in combatting multiple drug resistant pathogens. In 2016 both our collaborators and subsequently Nobel prize winning crystalographer Ada Yonath revealed the surprising discovery that a class of natural product antibiotics known as orthosomycins act on a novel site in the bacterial ribosome, distinct from all antibiotics in the clinic today. Everninomicins have highly potent broad-spectrum activity against Gram positive strains, including methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococci, and Clostridium difficile. Notably, a compound in this class (Ziracin) was developed into advanced stage III clinical trials by Schering Plough in 2000, but discontinued, due in part to business strategic reasons, and in part reportedly due to unoptimized pharmacological properties of this complex natural product. Indeed, the potential of this class was so significant that a total chemical synthesis was developed. However clocking in at >140 steps, this was not efficient enough to generate analogs to bring to the clinic. Vanderbilt researchers have developed a synthetic biology solution to this problem, decrypted the biosynthetic gene cluster of everninomicins, and identified a method of efficiently editing the genome of everninomicin producing-organisms (Micromonospora). Using targeted mutagenesis we have isolated several new bioactive everninomicin antibiotics including a structurally surprising and potent bifunctional antibiotic natural product targeting two different and distant ribosomal sites. Developing resistance to this bidentate antibiotic should be very difficult for pathogenic microorganisms.

Commercial Applications

- New compositions of matter in the everninomicin family have been generated for the first time in decades, revitalizing an antibiotic class with significant proven potential in treating drug resistant bacterial infections.

Problems Addressed

- This platform supports discovery and development of novel oligosaccharide antibiotics, addressing the ever-growing need for antibiotics to treat multi-drug resistant infections.
- Hundreds of variants of everninomicins accessible via a synthetic biology approach.
- Key biosynthetic enzymes have been identified, allowing modification at specific sites within the molecule.

Unique Features

- A bifunctional everninomicin analog has been identified with activity against gram positive and gram negative bacteria.

Intellectual Property Status

- A PCT patent application has been filed.