ARNA **Seminar Series**

Tuesday, May 13 at 3 pm (BBS auditorium)

Two birds, one stone: Antibacterials that target the ribosome and DNA gyrase and evade multiple resistance mechanisms

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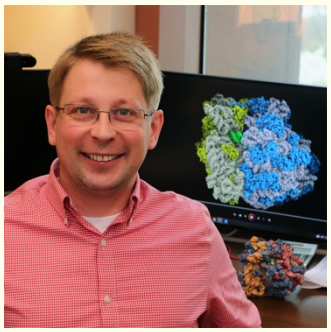

Growing resistance towards ribosome-targeting macrolide antibiotics has limited their clinical utility and urged the search for superior compounds. Macrolones are synthetic macrolide derivatives with a quinolone side chain, structurally similar to DNA topoisomerases-targeting fluoroquinolones. While macrolones show enhanced activity, their modes of action have remained unknown. Here, we present the first structures of ribosome-bound macrolones, showing that the macrolide part occupies the macrolide binding site in the ribosomal exit tunnel, whereas the quinolone moiety establishes new interactions with the tunnel. Macrolones efficiently inhibit both the ribosome and DNA topoisomerase *in vitro*. However, the primary cellular target of chemically distinct macrolones differs dramatically. In contrast to macrolide or fluoroquinolone antibiotics alone, dual-targeting macrolones are less prone to select resistant bacteria carrying target site mutations and also fail to activate inducible macrolide resistance genes. Furthermore, because some macrolones engage Erm-modified ribosomes, they retain activity even against strains with constitutive erm resistance genes.

Host: Axel Innis, ARNA laboratory