Capturing the natural antibiotic'ome: Developing Nature's EVOlved AntiBIOTIC Collective

Naturally evolved antibiotics are our primary mode of treating drug-resistant pathogens. Although individual antibiotics do succumb to resistance via pressures they place on organisms, the producers of these agents innovate through modular antibiotic drug (bio)synthesis programs to naturally thwart drug resistance mechanisms. Moreover these same antibiotic drug biosynthesis programs, are now revealed to construct other agents that perturb microbial physiology apart from killing (i.e. blocking resistance). The evolutionary constraints that have produced these evolved genetically encoded natural drugs are difficult to envision but their specificities, dynamic actions, multi-pronged functions have clearly rendered them as privileged molecules. Much research has defined the codes embedded within these natural small molecule biosynthesis programs and surprisingly these codes and rules are largely followed across all known organisms that generate polyketide and nonribosomal peptide molecules. In addition to the cracking of the nonribosomal and polyketide codes, further facilitating their genomic-based identification is the clustering of genes associated with the synthesis of a particular molecule-type (natural product/antibiotic) and a collinear pattern used in their synthesis. Collectively, these natural principles and rules have now created an exceptional opportunity to drive the detection and discovery of these molecules using a genomic start point. New transformative approaches to antibiotic discovery are needed, and the research in this proposal will lead to disruptive innovation, and a major departure in how historically antibiotics have been found and investigated. With our unique approaches we will enrich in agents with new modes of action, and those with a high likelihood of synergizing with clinically used antibacterials. The following aims are designed to provide this forward-looking view of how to treat antibiotic resistant bacteria:

AIM 1) Uncover the secondary metabolomes of antibiotic producers and define antibiotic chemical-chemical interactions and synergy.

AIM 2) Interrogate the bioproduction of ***antibiotics from genomically identified unexplored microbes using metabolomics***

AIM 3) Test naturally evolved drugs against secretion systems and serum resistance systems of gram negative/drug-resistant organisms

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