Microbes to Medicine
Development of a *Millennial* Drug Discovery Platform

Ashootosh Tripathi, PhD
Research Investigator
Life Sciences Institute, University of Michigan, Ann Arbor, MI- 48109, USA

If discovery of new antibiotics continues to wane while the ability of drug resistant pathogens continues to surge, society's medicine chest will soon lack effective treatments against a multitude of serious infections. To put the situation into context, over the last 30 years no new class of antibiotics has been introduced to mankind.[1] Moreover, the majority of pharmaceutical efforts during the past six decades have focused on the synthetic enhancement of a limited set of unique core scaffolds.[2] From these perspectives, it was envisioned that a more sustainable route to combat antibiotic resistance is the discovery of novel classes of antimicrobials, which would require a greatly improved antibiotic discovery process, and greater access to unique microbial targets. Here, I will describe a robust high throughput antibacterial discovery platform involving key virulence and resistance mechanism as target against both gram-negative (*A. baumannii*) and gram-positive (MRSA) pathogenic microbes, respectively. The success of the approach provided solutions for two major bottlenecks that impede the drug discovery pipeline i.e., identification of novel drug leads and overcoming resistance due to indirect microbial targeting.[3] Moreover, biosynthetic characterization of one of the discovered antibiotic unraveled an unprecedented convergent nature of the gene cluster machinery.[4] This genetic bifurcation was then further explored to biochemically analyze and structurally characterize the substrate scope of a key gatekeeper enzyme. The study led us to isolate novel congeners through targeted precursor incorporation, resulting in production of a potent *Acinetobacter baumannii* biofilm inhibitor.

Irrespective of the discovery approach, there still exists a daunting gap between the detection and efficient identification of new molecular entities. Furthermore, success of any isolation strategy would principally rely on effectively fast and qualitatively accurate de-replication of individual constituents in complex metabolic extracts. Recently, technological advances in high-resolution mass spectrometry (HRMS) and NMR has been at the forefront of molecular identification and de-replication, but these approaches are usually low throughput. To address this challenge, we have developed a unique prototype platform using laser ablation electrospray ionization mass spectrometry (LAESI-MS) coupled with qTOF mass spectrometry. Further information on this novel analytical approach that is being applied for identification of new classes of antibiotics will be discussed.

References

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