Bringing Back Nature to Drug Discovery
Natural Molecules in an Antibacterial Program

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The research and development of antibacterial agents have enjoyed immense success over the past 50 years. Availability of antibacterial drugs, improved hygiene and the overall awareness of bacterial infections have contributed to a tremendous decline in bacterial infections since the 30's. It is also a well-known fact that molecules from nature have provided a vast majority of these antibacterial compounds. Either providing pure source compounds or scaffolds for medicinal chemistry modifications in order to expand the spectrum or potency, natural products have provided well over 50 antibacterial drugs over the past 20 years. However, with the shifting priorities in pharmaceutical business and the under-appreciation of drug resistance by bacteria, an impending danger looms for a shortage of new chemical entities for antibacterial compounds. Moreover, the total abandonment of natural products in drug discovery research, a platform that achieved so much success in the past, only adds to a bleak future for any new antibacterial agents coming on line in the next 10 years.

The discovery and initial development of new antibiotics have shifted to the backs of small entrepreneurial companies in the United States. The entrepreneurial approach to discovery has led to a plethora of creativity in strategies, selection of novel targets and integration of genomic information in creating a few new antibacterial candidates. Built on a combinatorial platform, the list of candidates is small. What is needed is the integration of natural products into this pipeline. The abandonment of natural products by most industrial groups is a mistake. An SAR template generated by a natural product discovery platform has and still can provide a successful starting point for medicinal chemistry. The path to discovery and the best prospects for success in an antibacterial program must integrate natural products in to the program.

Sequoia Sciences was founded to deliver to the drug discovery process a structurally diverse library of natural products isolated from plants. The proprietary design of this library allows the screening of these compounds at optimal HTS concentrations without non-drug-like interferences. In order to facilitate the rapid identification of potential leads, Sequoia has built an analytical process that can facilitate the rapid isolation and structure elucidation of active compounds. We have applied our proprietary chemistry procedures and innovative technologies in our internal antibacterial program, discovering a variety of compounds that show promising inhibition of bacterial biofilms and are synthetically accessible.

In an NIH funded collaboration with Montana State University's Center for Biofilm Engineering, Sequoia has discovered new inhibitors of bacterial biofilms. During research under this collaboration, novel compounds have been identified that demonstrate biofilm inhibition in *Pseudomonas aeruginosa* (PA01) and multiple strains of *Escherichia coli*, including uropathogenic clinical strains isolated from patients with urinary tract infections. Through collaborations at Washington University School of Medicine and the University of Connecticut, this biofilm research was expanded to include multiple species of bacteria and micro array data.

This talk will discuss a specific example of a set of compounds that were discovered from our natural product collection that exhibits remarkable activity against uropathogenic clinical strains of *E. coli*. Detailed will be the scientific strategy that Sequoia employs in order to uncover the chemical diversity in natural products that has gone untapped in plants. Expanding upon known advanced analytical technology, the techniques that Sequoia has employed to accelerate the drug discovery process from a natural product source will be explained in detail. Overcoming the challenges in working with natural products, both the failures and successes will also be shared. It will be obvious to the audience how Sequoia has been able to generate a robust supply of natural product compounds to drive this research project.