ORGANIC SEMINAR

Chemical Grammar of Accumulation in Pathogenic Bacteria with Subcellular Resolution

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Abstract: The Golden Era of antibiotics leveraged naturally abundant small molecules that were readily identified using traditional methods; however, this methodology has proven to be much more difficult to be further mined for new antibiotics during the past several decades. The next phase of antibiotic drug discovery has the potential to be supported by our increasing collection of proteomics, genomics, and metabolomics data that will reveal promising drug targets. Academia and industry could potentially exploit these data sets to design small molecule agents that are potent and of high specificity. To accomplish this, the field fundamentally requires guiding principles describing the molecular determinants of permeation into bacterial cells akin to the Lipinski's rules of 5 (Ro5). I will describe a novel fluorescence assay that measures the accumulation of small molecules/peptides in diderm pathogens based on a minimal tagging modality. Our team systematically (testing established antibiotics with known permeation profiles) and broadly (screening a unique library of small molecules modified with an azide tag) applied this approach to measurably grow our fundamental understanding of the molecular determinants of permeation.

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