Bioinformatics-Guided Natural Products Discovery via Reactivity-Based Screening

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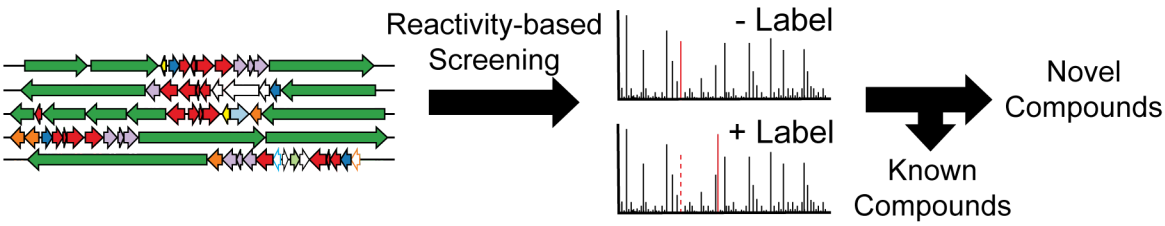
Natural products have been the source of a large portion of clinically used antimicrobial, antifungal and anticancer compounds. Actinobacteria, which have produced many of these drug leads, have been shown by genome sequencing to harbor many more natural product biosynthetic clusters. We employ a combination of bioinformatics prioritization and reactivity-based screening (RBS) toward both the discovery of novel natural products but also towards understanding their biosynthesis. By using bioinformatics prioritization, bacterial strains with the potential to produce electron rich alkene moieties are selected. The active production of novel electron-rich alkene containing natural products is then detected via differential mass spectrometry by reaction with a tetrazine containing probe molecule. This workflow is being used to both discover and characterize the family of polyene containing macrolactams.



Peridinin as a Probe for the Role of Lipid Peroxidation in Disease

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The peroxidation of polyunsaturated fatty acids present in the lipid bilayers of human cells has been correlated with many diseases including atherosclerosis and asthma. However, clinical trials targeting the inhibition of lipid peroxidation have shown little or no benefit, and it is often unclear why these trials have failed. We hypothesized that the atypical carotenoid peridinin, a potent inhibitor of non-enzymatic cell bilayer lipid peroxidation, represents a powerful probe to elucidate the role of lipid peroxidation in disease. In a primary cellular model of atherosclerosis, we found that peridinin attenuated the adhesion of monocytes to endothelial cells, the first step in the pathogenesis of atherosclerosis, showing a key role for lipid peroxidation in this disease. In an acute mouse model of asthma, our preliminary data suggests that peridinin inhibits lipid peroxidation within the airway yet has no effect on the asthmatic phenotype. These results suggest that lipid peroxidation is not a key driver of acute asthma.