Reactivity-Based, Genome-Guided Natural Product Discovery

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Natural products (NPs) are, historically, a bountiful source of chemical matter for drug development and understanding of biology—especially for antibiotics and the study of microbial interactions. However, the widespread prevalence of certain NPs among frequently-screened organisms leads to unacceptably high re-isolation and re-elucidation rates in screening campaigns, wasting substantial time and money. With insights gleaned from genome mining (now exceptionally cheap and fast), interest in natural product discovery has been reinvigorated. In particular, biosynthetic gene clusters can be identified readily, and although NP structures can only rarely be fully predicted from genomics, chemical substructure and the presence of certain functional groups can often be confidently inferred.

We report *reactivity-based screening*, a strategy for accelerating the discovery of novel NPs via a combination of (*i*) chemoselective covalent labeling and (*ii*) bioinformatics-based strain prioritization. In this strategy, the genomes of a library of microorganisms are analyzed for the presence of key biosynthetic genes correlated to the presence of certain functional groups. We then employ a chemoselective reaction between a chemical probe and the functional group of interest in the context of bacterial extracts; labeled compounds are revealed by a peak shift in the relevant mass spectra. This technique was used for the discovery of a novel thiopeptide cyclothiazomycin antibiotic and is being expanded to a variety of natural product classes. We have additionally prepared a series of functionalized screening probes bearing reporter moieties aimed at improving the detection of low abundance metabolites in complex extracts. The use of reactivity-based screening has enabled faster discovery rates and also greatly eased structure elucidation of new compounds.