Systematic discovery of plant natural products for the development of lung cancer therapeutics

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Natural products have historic utility for treating human illnesses, particularly cancer, infectious diseases, and other therapeutic areas. Although half the FDA-approved natural product drugs are plant-sourced, pharmaceutical companies have reduced their efforts toward discovering plant natural products due to significant bottlenecks in chemical rediscovery and labor-intensive methods. Herein, we develop a systemic discovery pipeline that combines applications of high-content screening assays with mass spectrometry-based metabolomics to establish a rapid method of identifying translatable chemotherapeutics in an *in vitro* H1437 lung adenocarcinoma cancer model.

I have conducted a quantitative high-throughput screen (qHTS) of the Kersten lab's natural product library from 1065 pre-fractionated extracts of the phylodiverse plants from the Matthaei Botanical Garden at the University of Michigan *in vitro*. In my discovery pipeline, cell imaging of the extracted library determines anticancer phenotype and cytotoxicity, mass spectrometry-based metabolomic analysis of bioactive plant extracts allows for rapid dereplication, and computational analysis of cell-painting assays provide a hypothesis for the MOA of lead compounds. Thus far, six bioactive extracts were selected from the preliminary qHTS by their capacity to induce cell death. Bioactivity-guided fractionation of selected plant extracts was isolated by preparative HPLC, then assessed for cytotoxicity against H1437 cells in qHTS format. The chemical novelty of the active fractions is determined by feature-based molecular networking to prioritize unannotated chemistry or existing compounds with unknown mechanistic features. Currently, image-based profiling of the purified fractions is being quantitatively assessed using various machine-learning tools to identify exciting phenotypes. Future studies will employ de novo metabolomic tools such as SIRIUS and Canopus to guide the structure elucidation of lead compounds. This research could revitalize pharmaceutical interest in the medicinal utility of plants and could guide further extrapolations into the mechanism of actions of characterized plant natural products with activity in various cancer models.