Biological Design Dissertation Defense

Systems Biology Approaches to Discover Mesothelioma Therapies

School for Engineering of Matter, Transport and Energy

Sierra Wilferd

Advisor: Christopher Plaisier, PhD

Abstract

Diffuse pleural mesothelioma (DPM) is a devastating lung cancer most commonly diagnosed at an advanced stage with a poor prognosis for patients. Therapies available to patients after diagnosis currently include surgical resection, radiotherapy, immunotherapy, and chemotherapy. However, these therapies only prolong life for about a year and a half on average. DPM patients desperately need effective therapies in the form of drugs, drug combinations, and miRNA-based therapies, that could lengthen overall survival and provide a better quality of life. I hypothesized that focusing on DPM tumor biology would streamline the process for discovering new therapies that will have a lasting impact for patients.

I have applied systems biology methods to mine multi-omic data from patient DPM tumors to discover new therapeutic options. I began by developing a somatic mutation integration pipeline, which created a comprehensive somatic mutational profile of DPM tumors from patient genomic and transcriptomic data. The somatic mutational profile was used in the generation of dpmSYGNAL, a disease-relevant gene regulatory network (GRN) trained on patient tumor multi-omic data. I integrated this GRN with functional genomics screens performed on two low-passage primary DPM tumor cell lines and identified gene vulnerabilities that could be targeted by FDA-approved inhibitors and drug combinations. I also developed a pipeline to integrate miRNA target genes from biotinylated pulldowns with RNA-seq data from a study re-expressing the miRNA hsa-miR-497-5p in DPM cell lines. I determined that the re-expression of hsa-miR-497-5p had early pro-apoptotic effects and inhibited the cell cycle at later time points. The identification of inhibitors, combinations of inhibitors, and a therapeutic miRNA demonstrates that DPM biology can be used as a guide to discover new therapeutics for DPM. .

April 4, 2024; 11:00 AM; ISTB1 227

Zoom Link: https://asu.zoom.us/j/81400834466

Arizona State University