Dr. Prabhjot Mundi

Abstract:

The use of multi-modality treatment approaches has significantly improved outcomes in patients with operable breast cancer. Nonetheless, there are some patients with breast cancer (BC) who demonstrate limited sensitivity to chemotherapy and are at the highest risk for disease recurrence. For these patients, more effective therapeutic options are needed.

Genomic profiling of tumors holds the promise of identifying unique molecular dependencies that can be targeted. The concept of master regulators is predicated on the idea that only a minority of tumors are driven by activating mutations to oncogenes or silencing mutations to tumor suppressors, while the majority of tumors maintain the malignant phenotype through persistently aberrant transcription of a large set of genes, controlled by a select few transcription factors- the so called master regulators. This study will build upon the pioneering work done by investigators at our institution, led by the Califano lab, with systems biology algorithms to analyze large datasets of gene expression profiles in order to accurately reverse engineer genome-wide regulatory network maps and to then identify master regulators in individual tumors.

The aims of this study are 1) to use the MARINa (Master Regulator Inference) algorithm to identify and cross-validate master regulators (MRs) in operable BC patients by analysis of a publicly available large gene expression profile data set (METABRIC) and to then cluster recurrent MRs by BC subtype and clinical outcome information, 2) to identify compounds that effectively reverse the relevant master regulator programs through drug perturbation studies in cell lines, and 3) to use tumor specimens from patients with residual disease after neoadjuvant chemotherapy to perform master regulator analysis and to form patient derived xenograft (PDX) models for prioritized testing of master regulator targeting therapies. Development of PDX models in NOD/SCID mice and subsequent drug testing in these models will be performed by our collaborators at Champions Oncology. Ultimately, we hope that in the future, MR analysis on individual patient tumors could be rapidly translated to the bedside for selecting effective targeted therapies.