Identification of Combinations of Targets for Claudin-Low Triple Negative Breast Cancer Reversion

Madeleine S. Gastonguay1, Lauren Marazzi1, Paola Vera-Licona, PhD.1

1. University of Connecticut Health Center for Quantitative Medicine

Triple negative breast cancer is a heterogeneous subtype of breast cancer characterized by the lack of oestrogen, progesterone, and HER2 receptors. Claudin-low triple negative breast cancer (CL TNBC) is a subtype of the disease displaying a low expression of tight junction proteins Claudin 3,4, and 7, as well as the cell adhesion molecule E-Cadherin. These tumors are prone to the epithelial to mesenchymal transition as well as exhibiting stem-cell characteristics, but unlike most tumors, they are characterized by low proliferation rates. This leads to high rates of metastasis and decreased response to cytotoxic drugs, resulting in a poor prognosis and the need for new treatment options.

Although tumor reversion is a rarely explored therapeutic approach, it has been observed both *in vivo* and *in vitro* over the past century. This project aims to take a dynamical systems approach to identifying combinations of therapeutic targets for claudin-low tumor reversion *in silico*. In this work, an intracellular signaling network consisting of 116 nodes and 259 edges was constructed with multi-omics data for the CL TNBC cell line MDA-MB-231. Then driver nodes of the network were identified using structure-based control theory for nonlinear systems, and a topological signal flow analysis was implemented to estimate the attractor landscape of the network. Lastly, *in silico* perturbation screenings were run to identify putative concerted targets for CL TNBC reversion.