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

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Claudin-Low Triple Negative Breast Cancer (CL TNBC) has high relapse and low survival rates. Due to the tumors’ decreased response to cytotoxic drugs, alternative therapeutic strategies should be explored. One such strategy is tumor reversion, the biological process by which tumor cells lose a significant fraction of their malignant phenotype. Tumor reversion has been observed for over a century. It has also been achieved both *in vitro, in vivo,* and *ex vivo.* In particular, tumor reversion has been achieved in vitro with the CL cell line MDA-MB-231, and in vivo in a mice xenografted with MDA-MB-231 cells. This project aims to apply optimal control theory to identify *in silico* combinations of therapeutic targets for Claudin-Low tumor reversion. An intracellular signaling network was reconstructed with multi-omics profile data for MDA-MB-231. Then a structure-based attractor-based control method for nonlinear dynamic systems was applied to the network to identify driver nodes. The attractor landscape of the network was estimated using a topological signal flow analysis. This analysis was also used to run *in silico* screenings on perturbations of the driver nodes to predict the resulting attractors. Combinations of nodes whose concerted perturbation resulted in the system shifting from the tumorigenic basin of attraction to the normal-like basin of attraction were deemed putative concerted reversion targets. Through this methodology we have been able to identify several potential combinations of targets that may shift the cell from a tumorigenic to a normal-like phenotype and that will be further validated in future work.