Harnessing Heterotypic 3D Spheroid Culture Method for Pre-clinical Testing of Computationally Identified Biomarkers of Drug Resistance in Breast Cancer

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Over $10.8 billion is spent yearly on oncology trials. Yet, a mere 3.4% of them succeed due to a lack of precision in target selection. Precise selection of targets could significantly improve trial outcomes. I hypothesize that an integrated machine-learning approach with experimental validation using a 3D culture model will be able to predict the drug response and identify markers for drug resistance. I used an active breast cancer clinical trial dataset with 998 patients. Feature selection was performed using the ExtraTreesClassifier. LightGBM predicted patient response for each drug with 94% accuracy after GridSearchCV tuning. SHAP and differential expression analysis prioritized the top 30 out of 16,000 genes. Network and CRISPR dependency analysis identified the functional significance of the identified genes. Interestingly, numerous IGF1R pathway members are upregulated in drug-resistant samples, linked to poor survival in breast cancer patients, suggesting IGF1R as a promising therapeutic target. Next, I tested IGF1R inhibitor synergy with standard-of-care drugs in 147 double and triple combinations, proving better efficacy of triple combinations in 2D culture. Since cancer grows in 3-dimensional form, I established a novel 3-dimensional spheroid method by co-culturing cancer and endothelial cells. Flow cytometry and live cell imaging analysis showed that combining IGF1R inhibitor with chemotherapy increased cell death and reduced spheroid growth over time. This data is validated in three independent breast cancer cell lines. Overall, a machine-learning approach combined with parallel experimental validation identified new targets to be tested in clinical trials. My approach applies to various cancers to improve patients' outcomes.