Integrating Machine Learning with 3D Organoid Modeling to Identify Biomarkers to Combat Drug Resistance in Cancer

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Over $10.8 billion is spent each year in various oncology clinical trials. However, only 3.4% of those trials succeed. This is because of the lack of precision in the selection of targets to be tested. Rigorously selecting targets could greatly improve the outcome of these trials. I hypothesized that a machine-learning approach could rapidly identify the genes responsible for drug resistance, which could then be validated in an in-vitro setting to improve the efficiency of clinical trials. I used an active breast cancer clinical trial dataset with 998 patients. Feature selection was performed using the ExtraTreesClassifier. A neural network was trained to predict patient response for each drug with 92% accuracy after applying Bayesian hyperparameter-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 genes. I identified that cancer cells depend on MST1 and ERBB3 in chemotherapy-resistant patients. POLR2L and IGF1R were promising targets to overcome resistance to AKT and HER2 inhibitors. Finally, I established a novel 3-dimensional organoid method by co-culturing cancer and endothelial cells. Flow cytometry and imaging analysis showed that combining IGF1R inhibitor with chemotherapy increased cell death (33%) and reduced organoid growth (25%). Interestingly, many IGF1R pathway members are upregulated in drug-resistance samples, indicating that IGF1R is an attractive therapeutic target. Overall, my parallel experimental validation combined with a machine-learning approach identified new targets to be tested in clinical trials. My approach is applicable to various cancers to improve patients' outcomes.

Awards Won:

Second Award of $2,000

The Scientific and Technological Research Council of Türkiye TUBITAK: 1st Prize Award