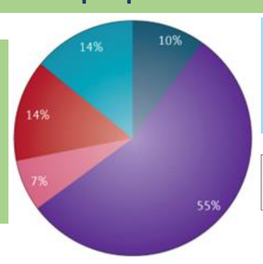
Harnessing Machine Learning and 3D Spheroid Cultures to Identify Biomarkers for Combating Drug Resistance in Breast Cancer

Introduction

Cancer is the 2nd leading cause of death globally, 10 million people die annually (2019)

Our World in Data

Reasons for Failure of Clinical Trials (2021)



Oncology Clinical Trials Investment Every Year: $10.8 billion
Overall Success Rate of Clinical Trials: Only 3.4%

(UICC.org, Wong et al 2019, Market Analysis Report 2020-2027)
Harrison, RK, Nature Reviews, 2016

Problems	Unmet Needs	Solutions
• Cancer is detected at a late stage resulting in low survival rates • Drug resistance / Relapse • Large datasets but lack of new therapeutic targets • Testing in clinical trials is expensive	• Methods to efficiently identify target genes • Modeling to identify drugs that can target the identified genes • Careful selection of targets to test in clinical trials	• Machine learning methods to identify the most promising genes from large datasets • Lab testing using new 3D model to identify drug efficacy in-vitro

Goals and Hypothesis

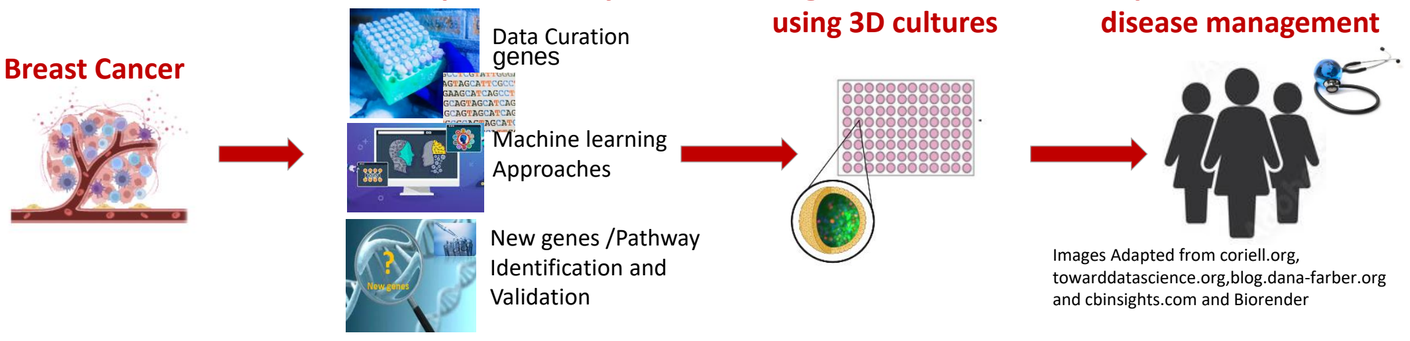
Motivation: Improve diagnosis for cancer subtypes, treatment options, and disease management for cancer patients

Engineering Goals: 1) Establish a Machine Learning Model with > 85% accuracy to identify specific treatment options for drug resistance.

2) Develop an accurate lab testing model to test the efficacy of targets

Hypothesis: Identification of biomarkers of drug resistance may lead to new targetable pathways for the treatment and can improve treatment strategies in patients

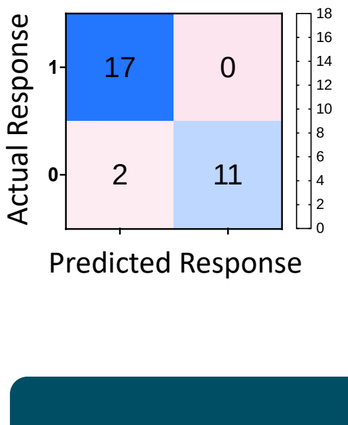
Proposed Functional Targets Testing Workflow



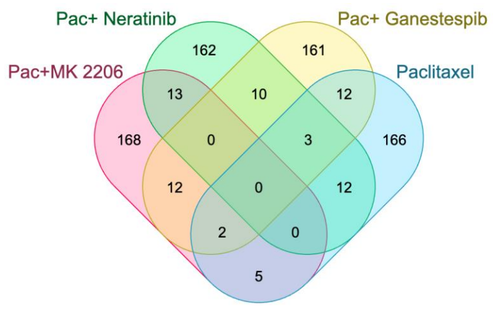
Results: Machine Learning and Computational Analysis

Machine Learning Model Accuracy up to 92%

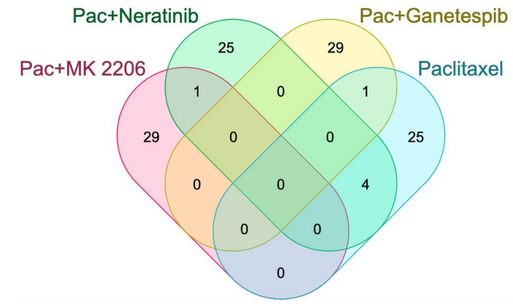
Pac+Neratinib	
Precision	0.857
Recall	1.000
F1 Score	0.923
Accuracy	0.929



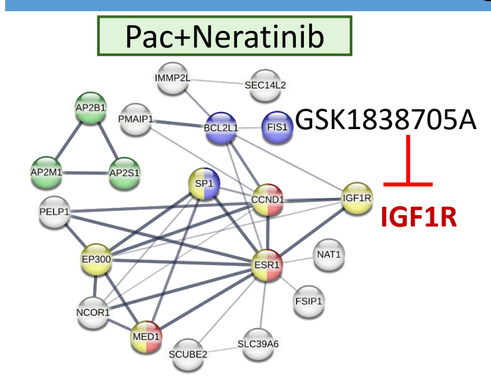
Top 200 genes with the highest Shapely values

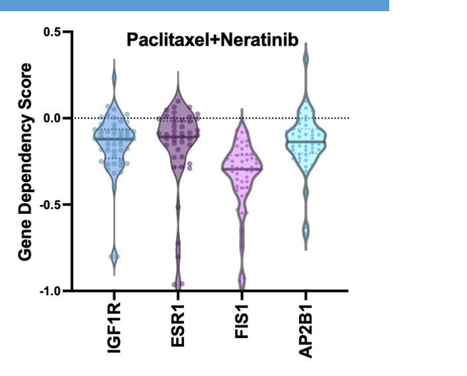


Top 30 differentially expressed genes

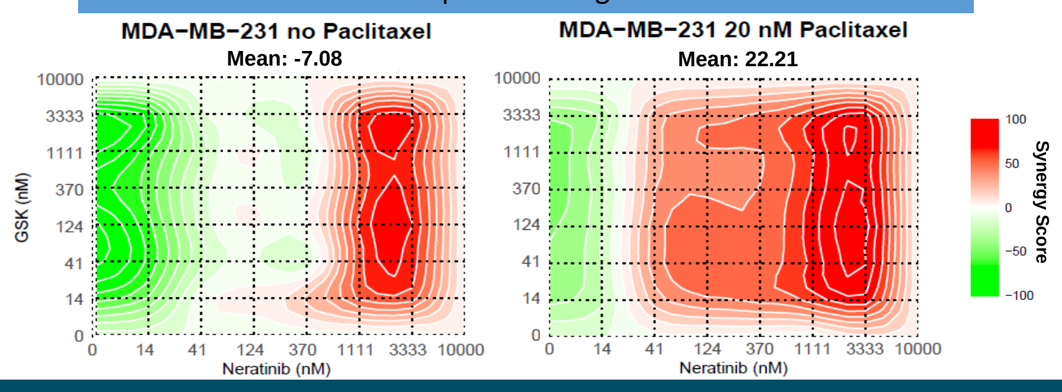


Network and CRISPR dependency analysis identified IGF1R as a new target

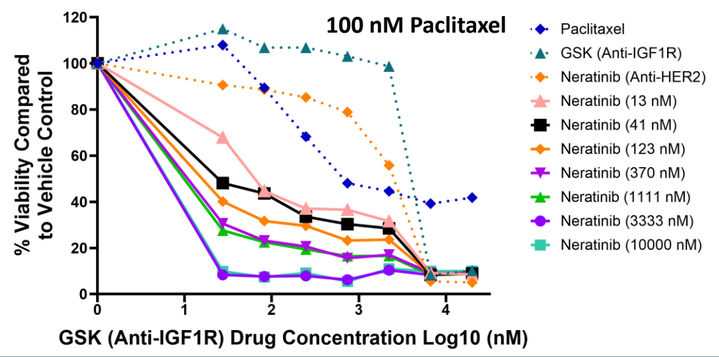




Triple combination: paclitaxel+ anti-IGF1R + anti-HER2 are more effective compared to single treatments

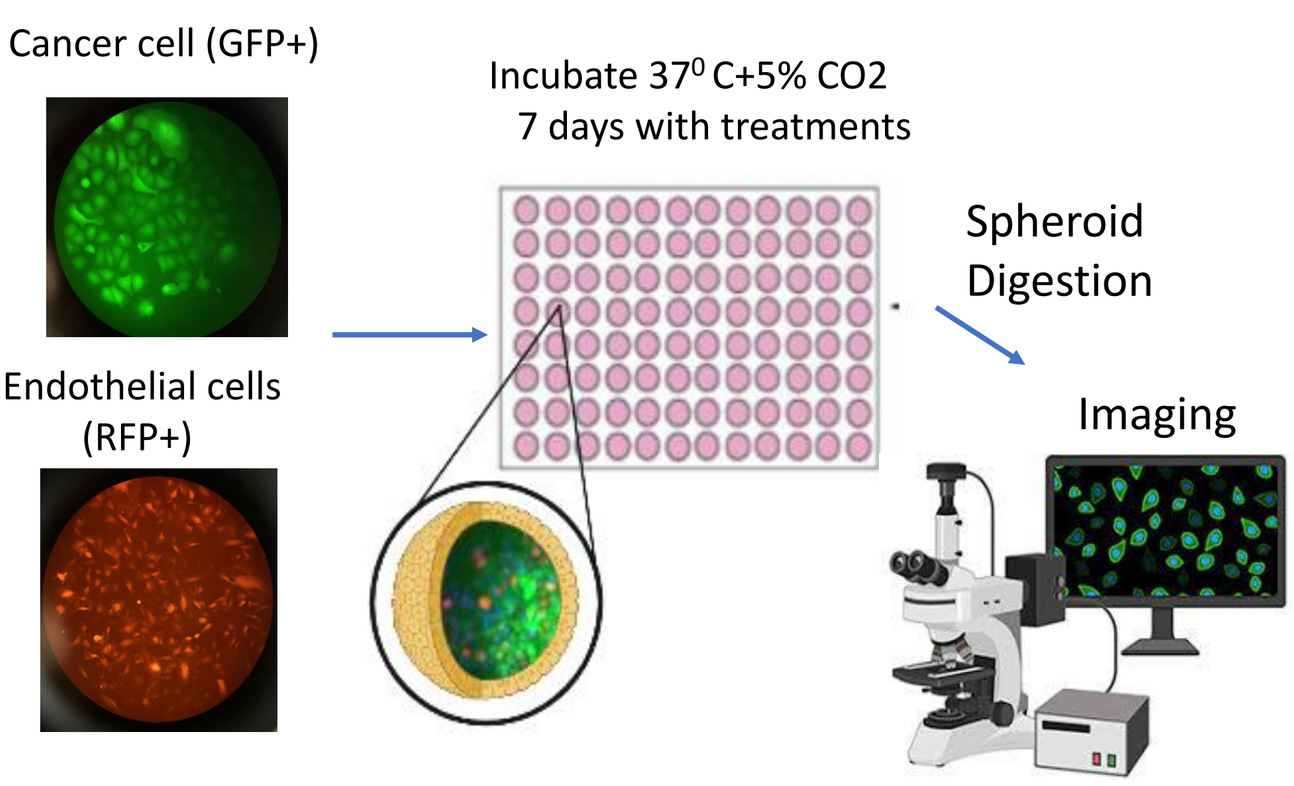


Viability of 4T1 cells treated with triple combination

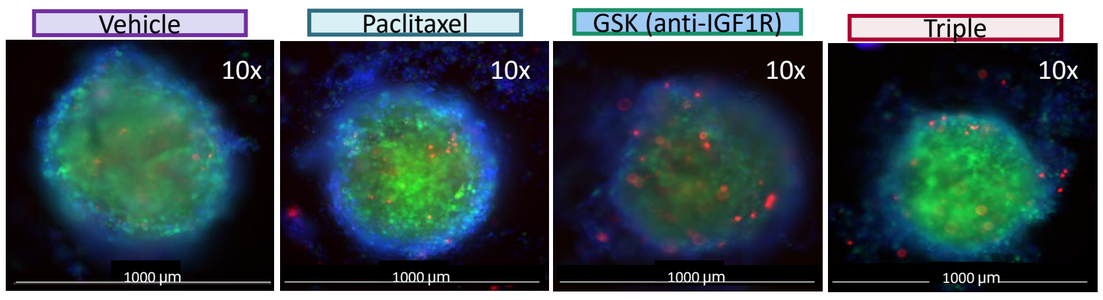


Engineering 3D Spheroids: Wet Lab Validation

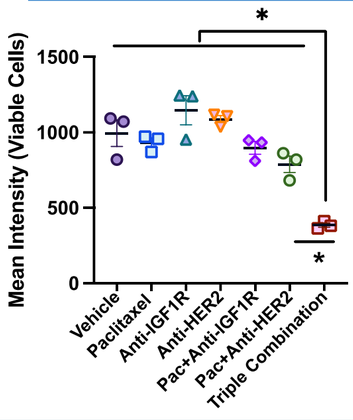
Engineering 3D Spheroid Cultures



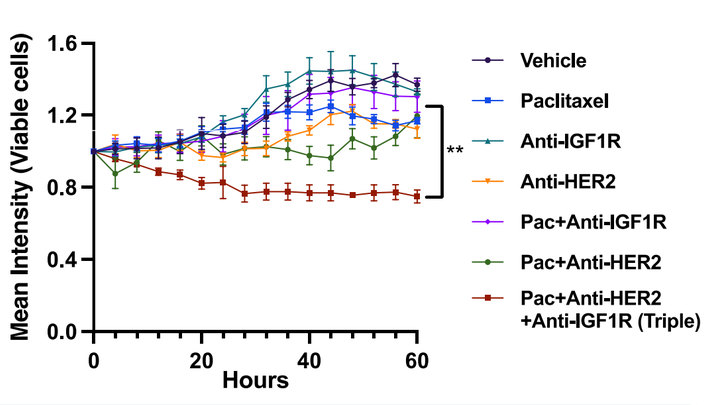
Triple combination: paclitaxel+ anti-IGF1R + anti-HER2 show reduced cell viability overtime



Live Cells' Intensity at Two Weeks



Live cells' Intensity Change Over Time



Takeaways and Future Directions

- **Accomplished Engineering Goal:** ML can predict treatment response with up to 92% accuracy
- **AHA Moment:** Gene signatures for each treatment
- **Favorite Moment:** Seeing 3D models working and validating new targets

More Modeling: Integrate mutation & drug response data to identify new targets

Broaden the Application: Apply ML algorithms to all the cancer types

More Wet Lab Testing: Validate targets using 3D Models

Application to Real World: Work with clinicians to help design clinical trials

All the figures, images, graphs are created/made by Ekansh Mittal if not referenced. Cliparts are taken from Biorender & Canva if not referenced