Drug Targeting: Repurposing FDA therapeutic drugs to treat triple-negative breast cancer

PROBLEM
To address the limited treatment options for patients diagnosed with triple-negative breast cancer, we have taken a drug targeting strategy. Repurposing FDA approved drug for triple-negative breast cancer could be a powerful approach to discover new therapeutics that might improve patient survival outcome.

BACKGROUND
The development of cancer is a multistep process of sequential genetic alterations in oncogenes and tumor-suppressor genes, making it extremely challenging to find a cure for cancer. In the case of breast cancer, patients diagnosed with triple-negative breast cancer (15-20%) have the worst survival outcome. It is characterized by having no or low expression level of three genes: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2) which makes it more difficult to develop therapeutic agents.

OBJECTIVE
1. To develop patient-derived triple-negative cell lines from surgical tissue samples from breast cancer patients.
2. To identify and repurpose FDA approved therapeutic drugs to treat triple-negative breast cancer.

METHODS
Residual tissue samples from triple-negative breast cancer surgery were processed and the dissociated cells were grown in a defined tissue culture medium containing supplements. The triple-negative primary cell lines were authenticated and checked for contaminations by a CRO. A panel of FDA approved drugs were tested on the primary cell lines to identify potentially new therapeutic drugs for investigation. Molecular and cellular assays including cell proliferation and cytotoxicity were used to determine the effect of the drugs on the cells.

RESULTS
Figure 1. Drug cancer targeting platform. There are 4 steps in this process.

- Surgical patient-derived primary cells
- Immunofluorescence analysis of the patient derived primary cells
- Interactome FDA-approved drug associated with cell signaling pathways
- Patient-derived primary cells
- Next FDA drugs for further investigation to improve patient outcomes

- Cell proliferation
- Phosphorylation assays
- Apoptosis
- Cytotoxic
- Epigenetic alterations

Figure 2. Triple-negative patient-derived cell culture growth curve.

Figure 3. Triple-negative patient-derived cell morphology.

CONCLUSIONS
We have successfully established a triple-negative breast cancer patient-derived primary cell line. This is the first triple-negative cell line established at Aurora Hospital. The primary cells grow in clusters and were negative for the three known receptors (ER, PR, HER2) but positive for cytokeratin 5 by immunocytochemical staining. We have identified several new FDA approved drugs that inhibits triple-negative patient-derived cells from growing. Selected drugs are being further investigated for their mechanism(s) of action in cell signaling pathway and to improve patient care.

REFERENCES

ACKNOWLEDGEMENTS
1. The research was funded by Aurora Cancer Care Research, Aurora Research Institute and Aurora Health Care.
2. Aurora Biorepository and Specimen Resource Center for Tissue Acquisition.