

## UCSF team finds new approaches to eradicate aggressive breast cancers

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Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Conventional chemotherapy generally fails to eradicate aggressive breast cancers due to the early distant metastasis that can occur in these diseases. Triple-negative breast cancer (TNBC) is a particularly aggressive subtype which has no targeted treatment. It has recently been discovered that the oncogene MYC is elevated in TNBC, opening up promising opportunities for the development of new targeted therapeutic strategies that will allow selective killing of MYC-overexpressing TNBC cells.

With support from a Department of Defense Breast Cancer Era of Hope Scholar Award, Dr. Andrei Goga has taken a multi-faceted approach to identifying new therapeutic targets in MYC-driven TNBCs. In the first part of the study, Dr. Goga's team used a fluorescence activated cell sorting (FACS) assay to isolate disseminated tumor cells (DTCs) from patient-derived xenograft models (PDX) of breast cancer. DTCs are the cancer cells that no longer reside with a primary tumor but occupy a peripheral tissue and may develop metastatic tumors. FACS was used to sort cells based on the expression of human cell marker CD298, allowing for detection of early DTCs as well as DTCs from late stage metastatic tumor-burdened tissues. Gene signatures of isolated cells could then be determined by qPCR.

The Goga team found that metastatic cells from low tumor-burdened tissues had enhanced stem cell-like gene signatures, while those from high-burdened tissues displayed signatures closer to that of the primary tumor. An important difference between cells isolated from low-burden and high-burden areas was whether or not they had entered the cell cycle. Cells from the low-burdened tissues displayed markers of quiescence and dormancy, while those from high-burdened tissues displayed signatures of luminal differentiation, suggesting they had entered the cell cycle and, as a result, expressed an elevated level of MYC. As such, the DTCs from high-burdened tissues proved to be sensitive to the cyclin-dependent kinase inhibitor dinaciclib (Merck).

After a four-week treatment course, DTCs were found in only 1 of 24 drug-treated mice, compared to 11 of 25 vehicle-treated mice. In addition, while the growth of primary tumors in drug-treated animals was slowed, many animals still had significant primary tumors at the endpoint of the study, suggesting that the inhibitory effects of dinaciclib were greater on [metastatic tumors](#) than on primary tumors.

Overall, the results from this study demonstrate that the MYC oncogene is markedly up-regulated compared to the primary tumor, in a subset of metastasis. Treatment with CDK1/2/5/9 cell cycle inhibitors can deplete disseminated, tumor-initiating [cells](#) and that treatment with dinaciclib may prevent [metastatic breast cancer](#) by eliminating DTCs with elevated MYC expression. This is an important finding, as clinical trials of dinaciclib for the treatment of various cancers are already underway.

In the second part of the study, using a targeted metabolomics approach, Dr. Goga's team identified fatty acid oxidation (FAO) intermediates as being significantly upregulated in a MYC-driven model of TNBC. In the MYC-driven transgenic TNBC model and also MYC over-expressing TNBC PDX models, they found that inhibition of FAO decreased energy metabolism and blocked tumor growth, suggesting that FAO has a critical role for in vivo tumor activity. This represents one of the first studies to investigate the role of MYC in the metabolism of TNBC in vivo, and the results warrant further investigation into the inhibition of FAO as a therapeutic strategy for TNBC patients.

**More information:** Roman Camarda et al, Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer, *Nature Medicine* (2016). [DOI: 10.1038/nm.4055](https://doi.org/10.1038/nm.4055)

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