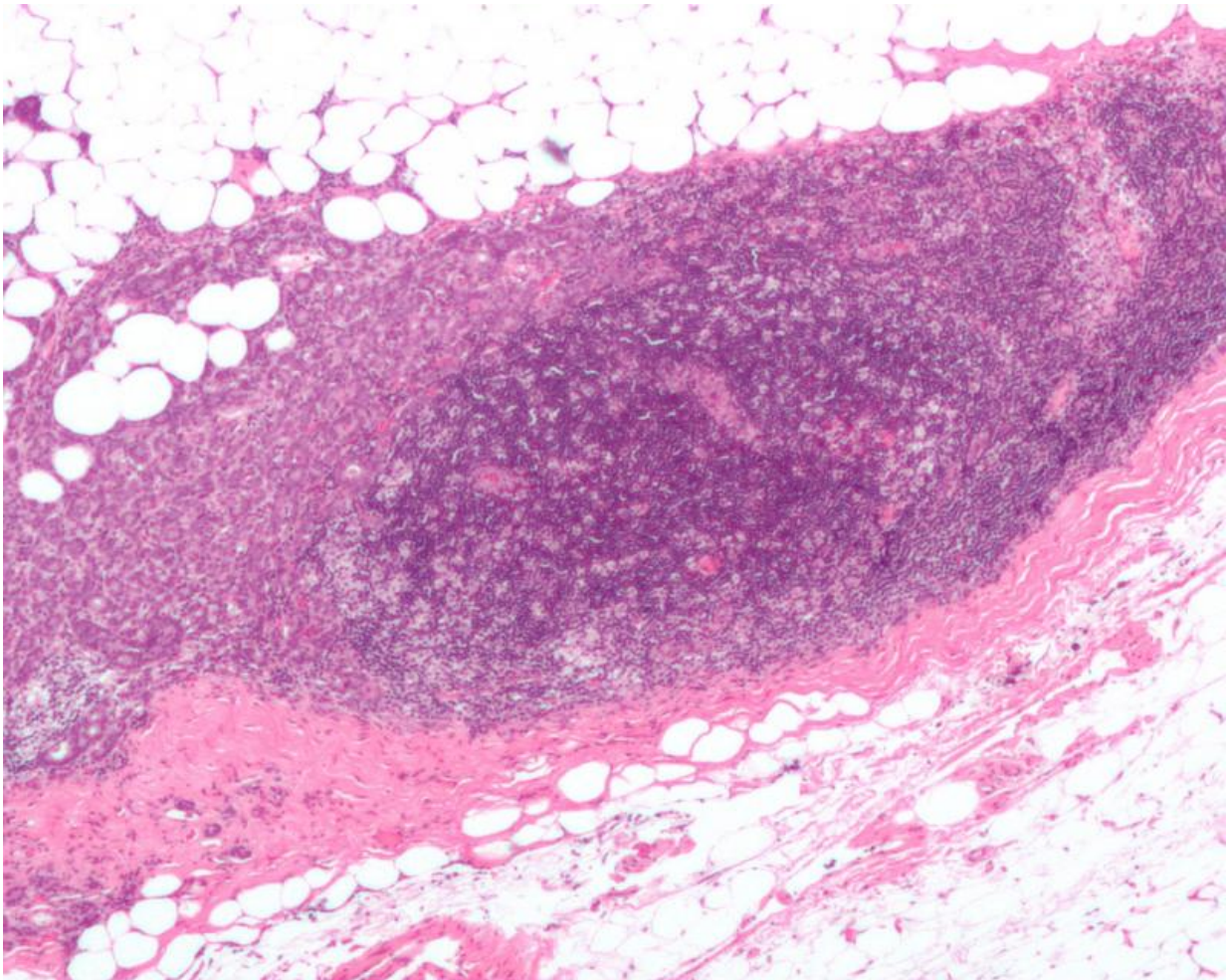


# Breast cancer study suggests new potential drug targets and combinations

January 14 2016

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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

The largest analysis of breast cancer cell function to date suggests dozens of new uses for existing drugs, new targets for drug discovery, and new drug combinations.

The authors say the study results, published online January 14 in the journal *Cell*, will be seized on by labs worldwide to identify new drug candidates in other kinds of cancer, as well to pinpoint mechanisms by which cancer cells resist treatment.

Led by researchers from the NYU Langone Medical Center, its Laura and Isaac Perlmutter Cancer Center, and the Princess Margaret Cancer Centre in Toronto, the team reached its conclusions by combining genetic analyses of more breast cancer cell types than studied previously, new statistical methods, and comparisons with databases of molecular signatures and the effects of anti-cancer drugs.

"This study represents the largest survey yet of how the genetic changes in [breast cancer cells](#) interfere with pathways critical to their growth and survival, pathways that might be targeted by combinations of new or existing drugs" says lead study author Benjamin Neel, MD, PhD.

"Our new statistical approach represents an improvement on earlier methods that were unable to link the webs of genetic changes in cancer cells to the complex functions on which they most depend," says Neel, director of the Perlmutter Cancer Center.

Unlike earlier algorithms, the new statistical model was able to identify several previously known genes that are essential for specific breast cancer subtypes (e.g., HER2, estrogen receptor/ER, HER3).

Better detection and therapy have led to greater than 85 percent 5-year survival in breast cancer, yet half of those affected still die from their disease. Limits on treatment success so far reflect a lack of

understanding of the complex networks of molecular changes that enable most cancers to persist in the face of treatments that address any single disease mechanism.

## **Newfound Patterns to Drive Future Treatment**

For many years, labs worldwide have conducted large-scale genomic studies seeking to identify the many genetic changes that contribute to breast cancer. While such studies have yielded information on which genetic changes are found in different types and subtypes of cancer, they have been less successful in determining which of these changes are critical to cancer cell proliferation and survival, or how these changes might be exploited by therapies.

To complement genomic studies, many labs in recent years had turned to shRNA "dropout screens," which shut down each gene in a cancer cell one by one to see which are most important to its survival. Most past studies, however, did not examine enough cell lines to capture the landscape of diverse changes seen across breast cancer as a whole.

The current study performed shRNA screens on 77 breast cancer cell lines, a large enough sample to represent the many sub-types of this disease. The research team then applied their newly designed statistical technique, the si/shRNA Mixed-Effect Model (siMEM), to score the results of the cell-line genetic knockdown studies, identifying candidate genes most vital to cancer growth. They also compared the results against information in large databases on cancer genetics, protein interactions and [genetic changes](#) seen in cancer cells when drugs are effective or not.

The combined methods created newfound signals in the data more closely tied to impact on cancer cell traits and did a better job screening out false positives. The study identified a number of candidate genes previously unknown to play a role in breast cancer cell survival. In

addition, the team found clusters of genes that were required in cells that were either sensitive or resistant to 90 anti-cancer drugs.

Among the new and potential "druggable" targets identified for triple negative breast cancer, the most deadly form of the disease, were signaling proteins linked by past studies to brain tumors (EFNB3 and EPHA4), proteins that regulate cell growth pathways (MAP2K4, MAPK13), and a protein known to drive inflammation (interleukin 32).

The data also suggested for additional study dozens of new, potential drug combinations for the treatment of breast cancer subtypes, including RAF/MEK and CDK4 inhibitors, EGFR inhibitors and BET-inhibitors with epirubicin and vinorelbine, and PLK1 inhibitors with AKT inhibitors.

While the new method suggests pathways for further study in every breast cancer subtype, the authors chose one for additional analysis to show the potential of the work to guide the field. Further experiments validated BRD4 as a gene essential to the survival of most luminal/HER2+ cancer cells, as well as a subset of triple negative breast cancer cells.

BRD4 is a member of the BET (bromodomain and extra terminal domain) family, which helps regulate many genes important for cell growth, and the target of a drug class called BET inhibitors, currently in clinical trials for leukemia. The study results suggest that BET inhibitors might also be useful for some types of [breast cancer](#), that resistance to these drugs may be influenced by mutations in gene for the enzyme phosphatidylinositol 3-kinase, and that this resistance might be countered by combining BET inhibitors with the drug everolimus.

"Very few patients today get a whole genome sequence analysis done on their [cancer cells](#), and the few that do typically receive little medical

benefit from the results," says Neel. "The ultimate goal of researchers worldwide is to finally understand each cancer cell's wiring diagram well enough to clarify both the molecular targets against which therapeutics should be developed and the patient groups most likely to respond to any treatment."

Provided by New York University

Citation: Breast cancer study suggests new potential drug targets and combinations (2016, January 14) retrieved 23 April 2024 from <https://medicalxpress.com/news/2016-01-breast-cancer-potential-drug-combinations.html>

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