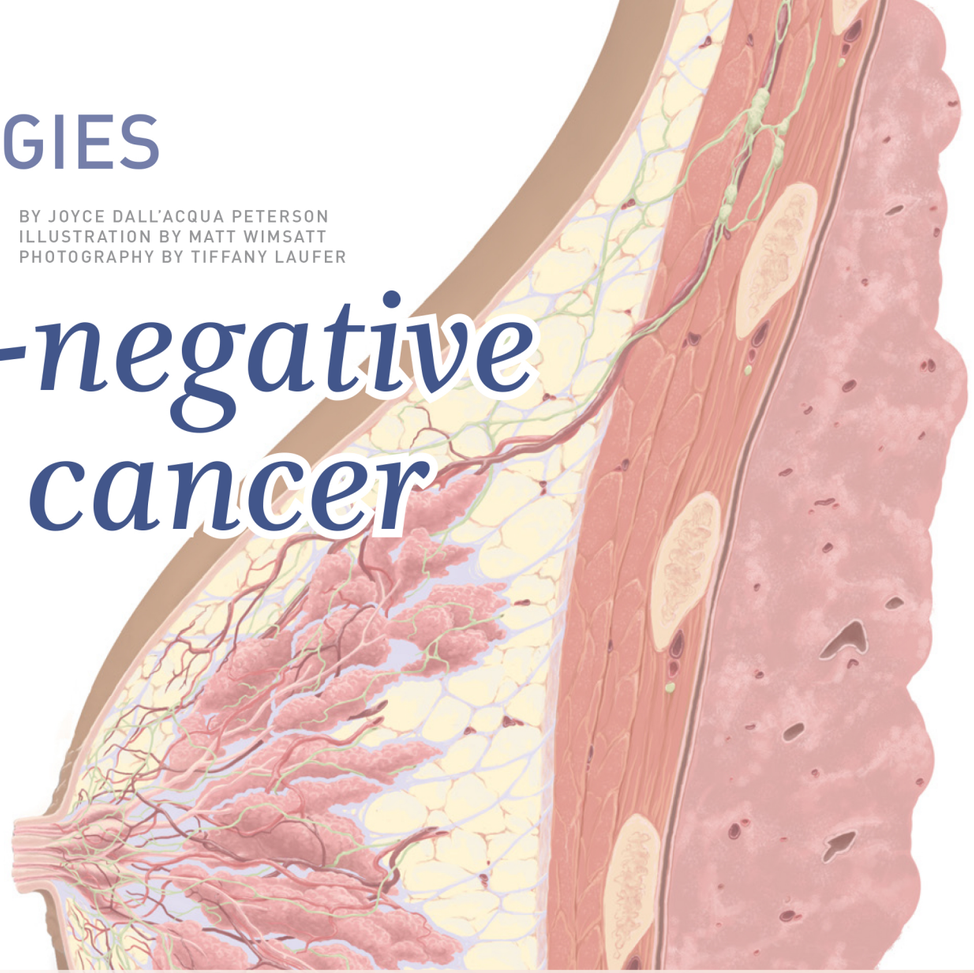
NEW STRATEGIES FOR TACKLING *triple-negative breast cancer*

BY JOYCE DALL'ACQUA PETERSON
ILLUSTRATION BY MATT WIMSATT
PHOTOGRAPHY BY TIFFANY LAUFER



Research at JAX has uncovered a molecular "fingerprint" that could lead to better outcomes for TNBC patients.

Researchers at The Jackson Laboratory are on a fast track to identifying better treatments for patients diagnosed with a particularly deadly type of breast cancer.

Triple-negative breast cancer (TNBC) does not respond well to hormonal therapy, and patients face a lack of tailored treatment options.

"It's the worst breast cancer to have today, the fastest-growing, the most metastatic," says JAX President and CEO Edison Liu, M.D., whose lab is focused on TNBC.

To this end, the Liu lab is pursuing three main objectives: establishing a cohort of genomically and clinically characterized TNBC samples; determining TNBC-specific drug responses; and understanding the exact mechanisms leading to the emergence and tumor formation of this cancer.

A gift from the Scott R. MacKenzie Foundation is funding the ongoing work of Liu's lab in this area, with the ultimate goal of identifying a potentially curative regimen for the cancer.

Last year Liu announced the discovery of a molecular "fingerprint" that is characteristic of TNBC as well as other deadly cancers of women, including serous ovarian cancer and endometrial carcinomas.

This configuration, which they call a "tandem duplicator phenotype," is the result of mutations that cause faulty DNA replication during cell division.

Liu and his team showed that TNBC and other cancers with the tandem duplicator phenotype respond to a specific chemotherapy, cisplatin. The researchers observed strong responses in both cell culture and in patient-derived tumors implanted in mice, with some of the mice showing no detectable cancer whatsoever after treatment.

None of the tumors without the trait showed any response to cisplatin.

The findings, Liu says, "provide the possibility for characterizing approximately 40 percent of these tumors by a genome-based tandem duplicator score and treating them with the best drug possible, providing more precision and effectiveness."

Francesca Menghi, Ph.D., an associate research scientist in Liu's lab who collaborated in the tandem duplicator phenotype research, wants oncologists to have a much larger array of therapies available for their TNBC patients.

Based on the genomic configurations and defects of specific tumors, and the lines of therapy of interest to the clinician-oncologists with whom she collaborates, Menghi says they have compiled a list of about 20 single agents or combinations — all of which are already approved by the Federal Drug Administration — to test for effectiveness.

"Our preliminary data in the lab would suggest that certain tumors with specific genomic profiles will be more responsive to certain drugs," Menghi says.

Not only will the resulting study reveal which drugs and combinations work best on individual tumors, she says, "but also, when we find treatments that work well, we will go back in and figure out why — what the mechanisms are."

These studies in the Liu lab are possible thanks to the advent of patient-derived xenograft (PDX) trials in special mice that can host (and not reject) human tumors. Fragments of a patient's tumor can be reproduced in these mice, and researchers can use the models to explore the basic biology of any cancer.

Moreover, PDX models are ideal for testing multiple cancer drugs simultaneously, both by themselves and in combination, and for gleaning insight into chemotherapy responses. PDX drug trials offer a clinical-trial roadmap for piloting treatments for patients with similar tumors or molecular profiles. They are also a powerful system for understanding the mechanisms of treatment resistance — one of the most serious obstacles to successful chemotherapy — and for devising strategies for overcoming that resistance.

The PDX approach has gained significant traction in the cancer research community due to its increased precision in measuring drug response.

"Better combination therapies mean we could turn triple-negative breast cancer from a death sentence into a chronic but manageable disease," says JAX Professor Carol Bult, Ph.D., the scientific director of the JAX PDX program.

For a patient facing a TNBC diagnosis, she says, "That would be everything."

JAX Associate Research Scientist Francesca Menghi wants oncologists to have a much larger array of therapies available for their triple-negative breast cancer patients.