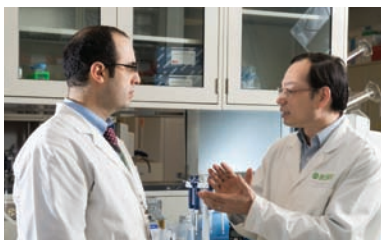
EXPLORING STRATEGIES TO COMBAT BREAST CANCER

As any oncologist can tell you: Cancer is not a monolithic disease. Each person's cancer is individual to his or her genetic signature. Instead of a search for "a cure to cancer," there are now myriad questions specific to each cancer and each person: Which drug combination will work best with the tumor's signature? Which mutated genes create drug resistance?



Researchers Abde Abukhdeir, PhD (left), and Youping Deng, PhD, are both investigating the molecular mechanisms behind the development of breast cancer.

Breast cancer clinicians and basic researchers at Rush University Medical Center tackle the disease from all these angles — from trying to develop a biomarker for early detection to identifying mutations that lead to acquired drug resistance.

Catching the disease in its earliest stages

Youping Deng, PhD, a bioinformatics researcher at Rush, has a vision: Along with checking a woman's cholesterol and glucose levels, a primary care physician could also determine her breast cancer risk — all through the evaluation of lipids in her routine blood work.

"Lipids have already been used as a biomarker to indicate other kinds of disease — diabetes, heart disease — and we know lipids are very important to cancer," Deng says. "But while many lipids have been studied as a class, few studies have investigated individual lipid species as biomarkers using metabolic lipid profiling and bioinformatics, and even fewer for breast cancer specifically."

Using a combination of around 16 lipids, Deng and his colleagues developed a lipid signature they believe could be used to predict breast cancer. In an initial study looking at 53 cancer patients and 20 benign patients, they were able to detect breast cancer with a sensitivity of 92 percent, and an accuracy of around 94 percent, using this lipid signature. Their next step is to seek additional validation with more samples and to combine the signature with microRNA to improve accuracy.

Deng and colleagues also apply this methodology to investigate signatures for lung and prostate cancers.

Finding the mutations and the mechanisms behind them

As groundbreaking as Herceptin was, only 20 percent of patients are especially sensitive to Herceptin as a single agent. For basic researchers like **Abde Abukhdeir, PhD,** this relatively low response rate is a call to action. Working with a research model that recapitulates in the lab genetic alterations that occur in the patient, Abukhdeir's goal is to first identify the genetic alterations that may be the cause of this resistance. These alterations can serve as markers that predict which patients should receive therapy. More important, these genetic alterations can serve as novel targets for new therapies that may be able to overcome Herceptin resistance.

Abukhdeir can test this model against samples from patients given only Herceptin, without chemotherapy. As one of the investigators leading the initial Herceptin trials, **Melody Cobleigh, MD,** a medical oncologist at Rush, collected patient samples throughout the trials, including samples from patients treated with Herceptin alone. "Dr. Cobleigh has samples that no one else in the world has, or can ever have," says Abukhdeir. "This is gold. So once we identify the genes that are the most likely culprits for resistance, we can use Dr. Cobleigh's samples to look at how frequently this occurs in actual patient samples."

Targeting pathways

As a pilot study, Abukhdeir is also taking all the drugs commercially available that target PIK3CA, the most frequently mutated oncogene in breast cancer, and testing them on breast cancers that harbor mutations on other genes within the same pathway. The goal: to see whether drugs that address specific mutations will also affect the entire pathway.

If drugs that work on specific gene mutations can be shown to work on a pathway, patients with rare mutations that currently have no targeted therapies available may one day have more individualized options. "If you add up all the gene mutations within a pathway, it adds up to a significant number," he says. "That's what I'm most excited about: trying to identify the best patient population for targeted therapies, and at the same time expanding the repertoire of drugs available."

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— Youping Deng, PhD, researcher

The missing link in cyclin D1 overexpression?

Clinicians know that the protein cyclin D1, a critical component of cell proliferation, overexpresses in several cancers: pancreatic, prostate, lung and breast cancers and leukemia. In fact, more than 50 percent of breast cancer cells have cyclin D1 overexpression.

The missing link, however, is what causes this overexpression. **Di Chen, MD, PhD,** a biochemist at Rush, and his colleagues hypothesize that overexpression occurs because of a defect in sumoylation, a posttranslational modification involved in various cellular processes, including apoptosis. In initial studies, Chen's group has found repeatedly that sumoylation leads to ubiquitination, a process in which the regulatory protein ubiquitin is attached to proteins and labels them for destruction, and then protein degradation — thereby allowing for normal regulation of cyclin D1.

Taking this hypothesis to the next level, Chen and his colleagues hope to find agents that will stimulate ubiquitination. One potential agent: arsenic trioxide, a highly toxic anticancer agent currently used to treat leukemia. Chen is working with a colleague from another institution who is developing material to enable safer, local delivery of arsenic trioxide for the treatment of breast cancer.

Inheriting a hidden mutation

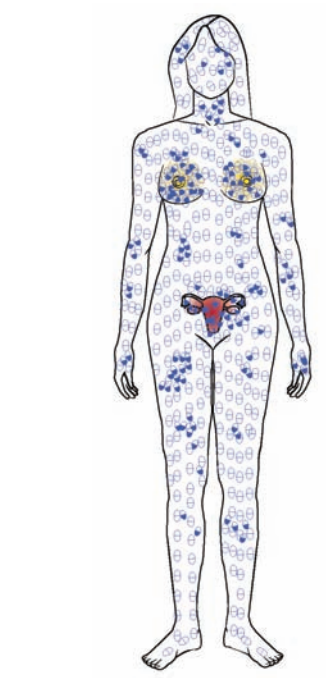
As a medical oncologist who specializes in inherited susceptibility to cancer, **Lydia Usha, MD,** is testing a novel hypothesis about the origin of cancer in relatives of BRCA mutation carriers. She suggests that patients who have a known BRCA 1 or 2 mutation in their families but test negative for it by blood testing, and later develop a tumor consistent with hereditary breast and ovarian cancer syndrome, may in fact have the familial BRCA mutation present in their tumor. Usha hypothesizes these patients had BRCA-positive chimeric cells in their body since birth because their mother or gestational twin transferred these cells to them during pregnancy. "If we confirm this hypothesis, the implications can be far-reaching," says Usha. "There is no explanation for these BRCA phenocopies. Patients are counseled that they do not have an increased risk for cancer, and that is not necessarily true."

The implications could apply to treatment as well as prevention. Some new therapeutic approaches currently being studied for cancer that specifically target BRCA mutations, such as PARP inhibitors (see p. 4), are not offered to patients who test negative for the mutations; however, if this hypothesis is correct and they have hidden BRCA mutations in their tumor, these patients might benefit from these new anticancer treatments as well.

And the potential of chimeric cells might not be limited to cancer: "There are no known diseases associated with chimerism, and if it comes across as a potential mechanism for predisposition to disease, that would be very new and could have potential for other diseases."

To learn about clinical research on breast cancer, see p. 4.

A Woman With BRCA-Mutant Chimeric Cells



Lydia Usha, MD, a medical oncologist who specializes in cancer genetics, is currently testing this hypothesis: Patients with known BRCA 1 or 2 mutations in their family but who test negative for it and later develop tumors consistent with hereditary breast and ovarian cancer may have BRCA-positive chimeric cells that were transferred to them during gestation.