

# Breakthrough provides new hope for more effective treatments of HER2+ breast cancer

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Mammograms showing a normal breast (left) and a breast with cancer (right).  
Credit: Public Domain

Ahmad M. Khalil, PhD, knew the odds were against him—as in thousands upon thousands to one.

Yet he and his team never wavered from their quest to identify the parts of the body responsible for revving up one of the most aggressive forms of [breast cancer](#), HER2+. This month in *Breast Cancer Research and*

*Treatment*, Khalil and his colleagues at Case Western Reserve University proved the power of persistence; from a pool of more than 30,000 possibilities, they found 38 [genes](#) and molecules that most likely trigger HER2+ cancer cells to spread.

By narrowing what was once an overwhelming range of potential culprits to a relatively manageable number, Khalil and his team dramatically increased the chances of identifying successful treatment approaches to this particularly pernicious form of breast cancer. The HER2+ subtype accounts for approximately 20 to 30 percent of early-stage breast cancer diagnoses, which are estimated to be more than 200,000 new breast cancer diagnoses each year in this country, leading to approximately 40,000 deaths annually. Several cancer chemotherapy drugs do work well at early stages of the disease—destroying 95 to 98 percent of the cancer cells in HER2+ tumors.

"Eventually though, many of these patients develop resistance to the drugs, and the 2 to 5 percent of the remaining [breast cancer cells](#) begin to grow and cause tumors again," said Khalil, assistant professor in the Department of Genetics and Genome Sciences, Case Western Reserve University School of Medicine. "We want to develop a strategy to target the genes responsible for enhancing HER2 oncogenic activity and increase the chances of eliminating the tumor entirely at the early stages of the disease."

In this study, Khalil, also a member of the Case Comprehensive Cancer Center, and colleagues chose an innovative approach that went beyond merely comparing gene expression in normal and in HER2+ cancer-affected breast tissue. Other scientists tried such a straightforward comparison but found themselves swamped by hundreds and even thousands of gene expression differences. Instead, Khalil designed a study where the offending genes would stand out. He and colleagues compared gene expression differences among HER2+ breast cancer

tissues of uncontrolled HER2 activity with those having greatly diminished HER2 activity. Ultimately their work revealed 35 genes and three long intervening noncoding RNA (lincRNAs) molecules were most associated with the active HER2+ cells.

To obtain special breast cancer tissues in HER2-active and HER2-diminished states, Khalil collaborated with oncologist Lyndsay Harris, MD, who had served as correlative science principal investigator for a clinical trial of the drug trastuzumab, which involved Brown University, Yale University and Cedars-Sinai. Harris, now professor of medicine, CWRU School of Medicine, and director of the Breast Cancer Program, University Hospitals Seidman Cancer Center, obtained the preserved HER2+ breast cancer tissues for Khalil's study from two intervals—before and then during the trastuzumab clinical trial. The drug works by disrupting HER2 activity, which in turn prevents this recalcitrant protein from launching uncontrolled cell growth.

From this collection of HER2+ breast cancer tissue, Khalil and colleagues got to work on determining which genes and other genetic components stood out. First, they applied RNA sequencing and then compared the sequences in tissues collected before trastuzumab curtailed HER2 activity with those collected later when HER2 activity declined sharply. Next, investigators grew the HER2+ breast cancer tissue cells in the laboratory and examined genes prominent in the cell culture (in vitro) model of the disease. Forty-four genes stood out during this portion of the investigation. Finally, Khalil and colleagues obtained publically available RNA-sequence data sets comparing HER2+ breast cancer with matched normal tissue and found that 35 of those 44 genes passed through this third filter.

"In our investigation, we essentially went from thousands of genes and narrowed it down to 35 genes," Khalil said. "A lot of those genes made sense in terms of carcinogenesis. When they become upregulated

because of increased HER2 activity, many of these genes are involved in increased transcription and increased cell proliferation, which are hallmarks of cancer cells."

The investigators applied the same comparative analysis—RNA sequencing, growing cells in culture and inhibiting HER2 protein—to observe the role of lincRNAs. Khalil and colleagues only discovered this special group of RNA genes in humans in 2009, and scientists now are slowly unraveling the mystery of lincRNAs. For this study, investigators uncovered three standout lincRNAs that are modulated in activity when subjected to increased HER2 activity.

"For the first time, we have shown that these lincRNAs can also contribute to this HER2+ breast cancers," Khalil said. "So we added another layer of complexity to the disease with lincRNAs. However, these lincRNAs could potentially open the door for RNA-based therapeutics in HER2+ breast cancer, a therapeutic strategy that has great potential but has not been fully tested in the clinic yet."

The next step for Khalil and his team is to begin assessing which approaches to these genes and molecules have the greatest chance to slow or stop HER2+ cell activity. They can test currently approved compounds or drugs to learn which ones will neutralize these 35 genes and prevent dangerous cell activity.

The researchers have less certain ideas regarding how to approach neutralizing the lincRNAs. Much less is known about how these molecules function, so they will start with antisense oligonucleotide-based therapies and proceed from there.

"We need to find a way to get rid of that 2 to 5 percent of HER2+ breast [cancer cells](#) that is stubborn to current therapies," Khalil said. "It is significant that our study focused on human models instead of mouse

models or just cell culture models. That tells us that these genes are not just important in culture models in vitro, but they are also important in humans in vivo, which is very unique to our study."

Provided by Case Western Reserve University

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