



Drug, or treatment, resistance is a common problem for women with breast cancer. For some, treatment works initially, but then gradually becomes ineffective as the tumor finds a way to evade the therapy. Researchers have long been studying how to overcome treatment resistance, which is key to reducing breast cancer deaths. In breakthrough studies, Komen-funded scientists have not only discovered a way that treatment resistance can develop, but also a potential way to prevent it.

Komen Scholar Dr. Ramon Parsons at The Icahn School of Medicine at Mount Sinai, and Komen-funded investigator Dr. Gary Johnson at The University of North Carolina School of Medicine, have both independently discovered a potential combination therapy, using a class of drugs called BET bromodomain inhibitors, which can overcome resistance to some therapies.



The Therapy Detour

Breast cancer cells depend on specific proteins and “pathways” to grow and survive. Treatments that target these proteins and pathways can reduce the growth of cancer cells and temporarily stop the spread of the disease. But breast cancer cells are clever. They eventually learn to outwit the drug and begin growing again, often by using other proteins and pathways.

Pathways can be thought of as roads, and proteins as traffic signs along the road. Cells must pass through the signs to continue along the pathway. If the cell hits a roadblock (like a therapy that targets the protein), it cannot continue down that pathway. But eventually the cancer cell finds a detour around the roadblock by using another pathway, and continues to grow again.

Cancer Cell Traffic Jam

There are many different cell pathways involved in treatment resistance. Drs. Parsons and Johnson study different pathways, but they are both looking at the same group of proteins these pathways have in

common. Rather than using drugs against individual proteins in each pathway, they decided to target a “master switch,” a family of proteins called BET bromodomain proteins that control many different growth pathways. Researchers believe that drugs that block BET proteins should also block several growth pathways at once and prevent the tumor from finding a detour.

Dr. Johnson is testing compounds that inhibit the BET proteins in a novel combination therapy to treat HER2-positive breast cancer. Therapies that target HER2, like lapatinib, initially work well for some patients, but they eventually develop resistance. In a collaboration of 20 University of North Carolina researchers, Johnson showed for the first time that a BET bromodomain inhibitor could prevent the onset of resistance to drugs such as lapatinib in breast cancer cells. Johnson’s team tested several BET inhibitors, including one currently in clinical trials to treat blood cancers and a specific type of leukemia.



“Breast cancer cells can learn to adapt so that they become resistant to treatment. Komen funding made it possible for us to design a method to make tumor cells sensitive to treatment. Using this discovery, our goal is to make treatments durable and lasting for breast



cancer patients,” says Johnson.

Dr. Parsons’ work focuses on the PI3K pathway, one of the most-often mutated pathways in breast cancer. Drugs that target PI3K, called PI3K inhibitors, have been successful in treating breast cancer in clinical trials. But many of these patients become resistant to PI3K therapy. Because BET regulates the PI3K pathway, Dr. Parsons was able to combine drugs that target both PI3K and BET, essentially blocking all tumor growth and killing the tumor.

“Susan G. Komen was instrumental in providing resources to investigate ways to treat cancers that are highly resistant to PI3K inhibitors. This study should stimulate clinical trials testing the targeting of BET inhibitors and PI3K in patients with breast cancer,” adds Parsons.

What It Means for Patients

Drug resistance occurs in almost all types of breast cancers and treatments. Finding ways to prevent it is key to reducing breast cancer mortality. The studies from Drs. Parsons and Johnson highlight promising results showing that combining a BET inhibitor with other treatments that target a specific pathway may provide a longer-lasting response, prevent the development of drug resistance, and provide a greater benefit to patients. Both Dr. Parsons and Dr. Johnson, with his UNC collaborators, are currently working to replicate their findings and study the effects of BET bromodomain inhibitors on different breast cancer subtypes, such as triple-negative breast cancer. The researchers believe these types of combination therapies are essential to preventing therapy resistance.



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