

Wrestling With Cancer: Komen-Funded Researcher Identifies Achilles Heel



Like the mythical Greek hero Achilles, whose heel was his only vulnerable spot, researchers believe that cancer cells also have certain weaknesses that can be exploited. The difficulty is finding them. However, a recent Komen-supported research project, led by Thomas Westbrook, Ph.D, has identified such a weakness. Dr. Westbrook and his team at Baylor College of Medicine in Houston, TX, have identified a set of proteins, called SUMO enzymes, which are necessary for the survival of certain breast cancers, and are being developed as an exciting new therapeutic target.

Calling All Genes

The past 30 years have brought about revolutionary changes in our understanding of breast cancer, and have led to the identification of well-defined molecular drivers of breast cancer (e.g. ER for ER-positive cancer and HER2 for HER2-positive cancer). The development of drugs against these drivers has led to successful therapies for many breast cancer patients. However, there are many breast cancers that become resistant to these therapies or for which these therapies are ineffective, highlighting the need to identify new therapeutic targets.

A Cancer Cell Addiction

As with many types of cancer, a major challenge in devising effective targeted therapies for breast cancer is the identification of relevant targets – particularly those that affect cancer cells, while leaving normal, healthy cells unaffected. For a given subtype of breast cancer, the choice of targets will depend on the particular genes and pathways that support its cancerous phenotype. Some current targeted therapies are directed at blocking oncogenes – genes that promote breast cancer. Cancer cells often rely on oncogenes for their growth and survival, a phenomenon known as oncogene addiction. Unfortunately, cancer cells can “rewire” the pathways needed for their growth and survival, escaping this addiction and making the therapies that target them ineffective. This is, in part, because cells have developed a back-up plan – if one gene is mutated and not working properly, another, normal gene can often compensate. As a result, cancer cells become dependent not only on the oncogenes themselves, but also on the pathways that compensate for the defect. This phenomenon is called non-oncogene addition. Such pathways represent ideal therapeutic targets, because cancer cells – but not normal cells and tissues – become uniquely dependent on them.

Partners in Crime

Dr. Westbrook and his research team have been trying to figure out which pathways breast cancer cells are dependent on, as blocking them could lead to powerful treatments. Conventional molecular and genetic methods are limited in their capacity to identify non-oncogenic pathways, as these technologies are aimed at identifying abnormal genes and not the normal genes that cancer cells have become dependent on. Moreover, we don't know the function of most genes in the human genome, so we can't predict which genes are the best culprits. To overcome these limitations, Westbrook uses a technology he helped to develop – called genome-wide RNAi screen – which identifies all genes that impact tumor growth. Using this technology, one can find genes (and possible drug targets) that are lethal only to cells that harbor the cancer-causing mutation (addicted oncogene). Healthy, non-cancerous cells are spared.

Addicted Oncogene	Gene X	Cell Survival
+	+	😊
+	-	😊
-	+	😊
-	-	☠️

A Lethal Weapon

Myc **SUMO** **Cell Survival**

+	+	😊
+	-	😊
-	+	😊
-	-	☠️

Dr. Westbrook is interested in finding genes that are synthetically lethal with a gene called Myc, an oncogene that is mutated in approximately 25% of breast cancers and is associated with triple negative breast cancer (TNBC) and a poor prognosis. “We wanted to attack a problem that would have a large translational impact”, says Westbrook. Using the genome-wide RNAi screen, Westbrook and his colleagues identified a protein called SUMO activating enzyme (SAE2) - a molecule that helps attach small SUMO proteins to other proteins. SUMO proteins are attached and detached from other proteins, such as Myc, to modify their function. Dr. Westbrook found that breast cancer cells that harbor the Myc mutation have also become dependent on these SUMO proteins. Thus, drugs

that inhibit the addition of SUMO proteins - by targeting SAE - could effectively kill cells with the Myc mutation.

“This is an exciting finding because this enzyme, SAE, is not redundant (it doesn’t have a back-up plan)”, adds Westbrook. Therefore, it has the potential to be a highly effective target for new therapeutics.

What’s Next?

Dr. Westbrook is currently pursuing collaborations to translate his discovery to the clinic. He and others are developing and testing small molecule inhibitors of SAE, in preclinical models. The hope is to develop SUMO-targeted therapeutics as quickly as possible so that they can be tested in humans in Phase I clinical trials.

What Does It Mean for Patients?

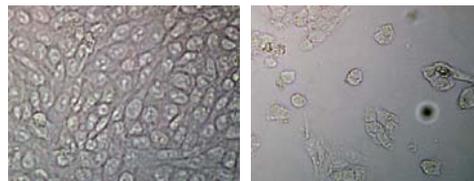
Despite three decades of research, there is no effective method to inhibit Myc. Dr. Westbrook’s findings could have a substantial impact for women whose breast cancers harbor a Myc mutation, particularly women with TNBC for whom there are no effective therapies and outcome is poor. Approximately 20 % of breast cancers are triple negative, which disproportionately affects African Americans and younger women. Studies estimate that African American women are twice as likely to be diagnosed with TNBC as white women, and nearly half of TNBC occur in women under 50. Myc mutations also occur in a number of other aggressive breast cancers such as invasive ductal carcinoma, early recurrence node negative breast cancer, and BRCA1 mutated breast cancers.

However, breast cancer may not be the only cancer impacted by Dr. Westbrook’s research. Many other cancers, including lung and prostate, also contain Myc mutations. Thus, targeting the SUMO process is likely to be effective for the treatment of numerous types of cancer.

The findings from Dr. Westbrook’s Komen-funded research were published in the highly esteemed journal, *Science*.

Kessler et al. A SUMOylation-Dependent Transcriptional Subprogram Is Required for Myc-Driven Tumorigenesis. *Science*. 2012 Jan 20;335(6066):348-53.

Cancer cells with Myc mutation **Myc mutated cells treated with an inhibitor of SAE**



Images of Myc-mutated cancer cells demonstrating Myc-synthetic lethal interaction with SAE. When SAE is inhibited, Myc mutated cancer cells are killed.

It's Not the First Time

This is not the first Achilles heel identified by Westbrook and his research team. With the help of Komen funding, Westbrook has also indentified PTPN12 – a tumor suppressor that is mutated in over 60% of TNBC cases and in some estrogen receptor-positive breast cancers. In a normal cell, PTPN12 suppresses the development of cancer by interacting with and inhibiting multiple oncogenes, including HER2 and MET, which are also frequently mutated in breast cancer. Based on his findings, Dr. Westbrook is developing a combined therapy approach that will effectively target both PTPN12 and the oncogenes it controls, using already existing therapies that target these genes. A Phase I/II clinical trial for combined therapies is being planned, and Dr. Westbrook hopes to start accruing patients to the trial in the coming year.

This work has been published in the highly esteemed journal *Cell*.

Sun et al. **Activation of multiple proto-oncogenic tyrosine kinases in breast cancer via loss of the PTPN12 phosphatase.** *Cell*. 2011 Mar 4;144(5):703-18.

Behind the Scenes



For Dr. Thomas "Trey" Westbrook, cancer research is both a professional and personal passion. "Much of my family had to go through the process of fighting cancer," says Westbrook. "I have known for a long time that I wanted to address the fundamental problems in cancer – to take what we can learn [about cancer] and use this [knowledge] to help people" he adds.

Dr. Westbrook is a geneticist at heart – his research focuses on applying novel genetic technologies to identify new therapies for human breast cancer. Dr. Westbrook uses what's called a functional genomics approach – like the genome-wide-RNAi screen – to identify sensitivities in cancer cells and ways to exploit