Drug resistance is a major obstacle in the effective treatment and long-term survival of breast cancer patients. While anti-hormone therapies, such as tamoxifen, have significantly improved survival, many women who initially respond well to these drugs develop drug resistance over time, leaving them with limited treatment options. However, research from Komen Scholar and Promise Grantee, Dr. Matthew Ellis, Professor of Medicine at Washington University in St. Louis, Missouri shows promising results that could lead to the development of new therapies to prevent drug resistance.

Hormone therapies have been used for the past 30 years to treat estrogen receptor-positive (ER+) breast cancers, the most common type of breast cancer. These therapies, like tamoxifen or aromatase inhibitors, stop the growth of ER+ breast tumors by blocking the effects of estrogen (anti-estrogen), a hormone that drives tumor growth. Unfortunately, ER+ tumors can eventually become resistant to these therapies, and as a result may continue to grow, come back after an initial response to the treatment (recurrence), or spread to other parts of the body (metastasis). Drug-resistant breast cancers almost always result in a poor prognosis. Understanding what causes resistance is an important and critical step in developing better therapies and preventing breast cancers from recurring or spreading.

**Finding the Right Model**

Studying drug resistance is challenging because scientists do not have an experimental model system that accurately mimics the complexity of human breast cancer. Many research studies can be done using breast cancer cells that are grown in the lab or by using mice that have been genetically altered to develop breast cancer. However, these methods have many limitations and often do not behave like breast cancer in patients. These problems are the reason why some experimental drugs may work in pre-clinical studies (non-human laboratory studies), but fail in clinical trials (studies in humans). With grant support from Komen, Dr. Ellis and his collaborators developed an improved experimental model to study human breast cancer and determine whether this system could accurately mimic human breast cancer.

More importantly, Dr. Ellis used the model system to investigate unanswered questions in the field, such as why some breast cancers become resistant to therapy. The model is called “patient-derived xenograft” or PDX. Dr. Ellis used the PDX model to identify genetic differences in individual breast tumors. Using this genetic information, Dr. Ellis could also determine which drugs most effectively

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1 Animal models designed to mimic human diseases allow scientists to study complicated questions in human biology that cannot be studies in humans. The Food and Drug Administration (FDA) requires that any new pharmaceutical compound be tested on at least two different animal models to be considered for approval for use in humans. Therefore, some investigators must conduct animal testing in order to comply with FDA regulations for drug development. In order to be eligible for Susan G. Komen research grant funding, investigators must provide safe and ethical animal care methods from the Institutional Animal Care and Use Committee (IACUC) and must ensure all procedures are in compliance with National Institute of Health and (NIH) and U.S. Department of Agriculture (USDA) regulations.
treated the tumors. Over nearly ten years, with Komen and other grant support, Dr. Ellis and his research team created over 50 PDX models representing a range of different human breast tumors. These studies resulted in a collection of different PDX models that are linked to clinical information about individual human breast tumors, such as tumor size, stage of disease, hormone or receptor status (e.g. ER+ or HER2), treatment history, and patient outcome. Dr. Ellis and his colleagues believe that these PDX models can be used to unlock the mystery behind resistance to hormone therapies. “Because the PDX mimic the same clinical, genetic and biological characteristics of the original [human] tumor, we can delve deep into the causes of the clinical problem we’re studying, such as drug resistance,” Dr. Ellis explains. “In essence, we could conduct [the equivalent of] phase II clinical trials in mice before testing drugs in humans.”

Accelerating the Path to Better Therapies

Using PDX models with drug-resistant, advanced or metastatic ER+ breast cancer, Dr. Ellis and his colleagues set out to learn why certain breast cancers become resistant to anti-estrogen therapies. They found that drug-resistant tumors had genetic changes in a gene called ESR1, and these changes appeared to drive resistance. His studies also show that genetic alterations in ESR1 may be used as a biomarker to predict which patients could develop drug resistance to hormone therapies during treatment. “These are profound studies,” notes Dr. Ellis. “If you understand the nature of the resistance problem you can develop drugs that prevent resistance from occurring, or identify patients who are not likely to respond to a particular therapy.” Dr. Ellis hopes his work with the PDX model will ultimately pave the way for more personalized treatment approaches for breast cancer patients.

What’s Next?

Dr. Ellis and his team continue to add to the number of PDX models available, including different breast cancer sub-types such as HER2-positive (HER2+) breast cancers. With an ever-expanding library of PDX models, researchers will be able to find the one model that will most closely match the individual patient to be treated. Clinicians will be able to test multiple treatment regimens in the PDX model before they are given to patients, allowing doctors to optimize the treatment plan that the patient will ultimately receive.

But Dr. Ellis also recognizes that to find a cure for the disease, a true collaborative effort will have to take place. And that is why he has made the PDX models available to the scientific community. Numerous researchers are currently using the model to study critical questions about breast cancer that doctors face every day in clinical practice, such as drug resistance and metastasis, as well as the testing of new drug combinations.
What it Means for Patients

More than 170,000 women will be diagnosed with ER+ breast cancer this year alone. Resistance to hormone therapy is reported in almost half of ER+ breast cancer patients, and no cure is currently available. Because resistance can lead to recurrences and in some cases metastasis, finding ways to effectively treat or prevent drug resistance to hormone therapies is critical. Dr. Ellis’ promising model could rapidly translate into improved patient outcomes in the clinic. His studies suggest that the PDX model may be used to not only discover new therapies for treating drug resistant breast cancer, but also allow for the customization of patient treatment plans. He and others in the field believe that the power of his new approach is that it allows researchers to explore clinical questions, tailored to a very specific set of patient data. “The ultimate goal,” explains Dr. Ellis “is to provide individualized therapy tailored to the specific biology of a patient’s tumor. The PDX models represent a natural model system to test promising new therapies.”

A Compassion to Cure

Matthew Ellis’ inspiration to become a doctor came out of a lifelong sense of compassion, as well as a desire to help people – a passion, spurred by the suffering of a neighbor who died from childhood leukemia. As a young oncologist in the United Kingdom, Dr. Ellis was moved by the numbers of women dying from breast cancer. However, he remained encouraged by the advancements of research: the development of tamoxifen, a targeted therapy for ER+ breast cancer, and the discovery that cancers were caused by changes in genes. Dr. Ellis felt compelled to pursue research in addition to his medical practice. As a physician-scientist, Dr. Ellis’ breast cancer research is driven by his clinical experience – what he calls “patient-focused research.” Today, Mathew Ellis is a leader in the use of genomic approaches to increase our understanding of breast tumor biology. He has been a Komen grantee since 2007 and is currently a member of the Komen Scholars, a group of leading scientists, clinicians and advocates who are recognized for their contributions in the field of breast cancer research and are dedicated to the mission of Susan G. Komen. “My role as a Komen Scholar, guiding the charity to make the wise investments, is how we can achieve a cancer-free world in our lifetime, with lots of energy and a lot of thought. I am happy to be a part of this wonderful institution.”