

# LIGHTING A NEW PATH IN BREAST CANCER RESEARCH

**S**IGNALING PATHWAYS IN CELLS WORK LIKE ELECTRICAL CIRCUITS with switches turning them on and off, says Todd W. Miller, PhD, an associate professor of molecular and systems biology. “Positive inputs make them go, and negative inputs make them stop,” he says. Switches often take the form of receptors for proteins, fats, or other compounds in the cell’s environment that bind the cell to make it function.

With breast cancer cells, two-thirds of tumors are switched on by the hormone estrogen, which causes cancer cells to grow. Treating them often involves giving the patient an anti-estrogen drug to suppress that growth.

However, in one-third of those cases, even after a tumor is surgically removed, the cancer recurs even though patients continue taking anti-estrogen drugs such as tamoxifen. “This means those cancer cells are hiding out in the body and we know very little about how they survive or how to kill them,” Miller says.

His mission is figuring out how to kill breast cancer cells by manipulating the complicated signals that turn their growth on and off. This complexity is what initially attracted Miller to biology. “Other sciences like physics or chemistry were bounded by hard and fast rules, but biological systems are so infinitely complex it feels like there is more room for exploration.”

As a graduate student at the University of Albany (NY), he initially studied neuroscience, but became discouraged by the difficulty of growing new brain cells to develop treatments for neurodegenerative diseases. He shifted his focus to breast cancer, a disease he thinks may still be curable by killing malignant cells. “Conceptually, it is much easier to develop strategies to kill cells rather than restoring lost cells and connections.”

The trick to treating cancer is in killing malig-



Rob Strong

nant cells while saving healthy ones, which is why doctors attack the signaling pathways that stop cancer cells from growing. Working with mice, Miller’s lab uses animals with estrogen receptor-positive (ER+) breast tumors, and subjects them to anti-estrogen treatment to see what happens in the tumor cells. “The tumors shrink, but they never completely go away,” he says. “You can’t feel them anymore, but when we dissect the mice, there are still residual cancer cells.”

Examining these dormant cancer cells more closely, Miller’s team determined their metabolism had been altered: the signaling pathways were inverted compared to those of growing tumor cells. For example, metformin, a drug commonly used to treat cancer, stimulates the enzyme AMPK slowing down the growth of tumors, but residual tumor cells need AMPK to survive. “The metabolism is flipped,” Miller says. Per these findings, the same drug that may help block a tumor could also increase the chance of recurrence after that tumor is removed. Because of that, timing may be crucial when administering drugs.

Miller is experimenting with another treatment to stop the growth of ER+ tumors: estrogen. His team found that while estrogen can make ER+ breast tumors grow, it can also stop their growth. He speculates that there may be an ideal range of estrogen in which ER+ tumors thrive. “If you go below that range, they will

stop growing, but if you go above that range, they will die,” he says.

Estrogen therapy may be particularly helpful in older women, whose estrogen levels have dropped after menopause, and in women treated with long-term anti-estrogen therapy. “It’s possible,” says Miller, “that cancer cells adjust to those lower levels of estrogen, and then die when exposed to an influx of estrogen.”

Miller co-developed a clinical trial to determine whether there are biomarkers that can help identify which tumors might be particularly susceptible to estrogen therapy—a treatment that, compared to other more expensive treatments, is affordable.

The ease of conducting clinical trials in a hospital environment was one of the factors that drew Miller to Geisel in 2012. “My research is highly translational,” he says. “Dartmouth offers good opportunities to partner with physicians to set up and run early-stage trials.”

Depending on the results of those trials, Miller’s research could help personalize treatments to more effectively target a patient’s cancer. “Ultimately,” says Miller, “we want to improve treatment options and patient outcomes not just by creating new drugs, but by identifying which tumors will respond to which treatments, and spare people from ineffective therapies.”

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