

Lay Abstract

This project aims to determine the potential of a new class of drugs called sulfatase 2 inhibitors to treat metastatic triple-negative breast cancer, prolong patient survival and improve their quality of life.

Breast cancer takes the lives of more than two hundred thousand women every year worldwide. In the United States alone more than forty thousand women die from breast cancer every year. This is primarily due to its capacity to spread to other organs, also known as metastasis. Although the prognosis of breast cancer has improved, these gains have been mostly restricted to breast cancers that express estrogen receptors or HER2 receptors. Breast cancers that do not express estrogen receptors or HER2 receptors are called triple-negative breast cancers. These cancers tend to be aggressive from the start, respond poorly to current therapies and are associated with the worst outcomes.

The underlying genetic changes that cause triple-negative breast cancers are complex and varied, often affecting genes that normally function to block the development of cancer. This has made it difficult to successfully treat triple-negative breast cancer, since blocking one specific cell growth pathway is ineffective. While a small fraction of patients benefits from other available treatments such as immunotherapy, for most patients with metastatic triple-negative breast cancer, toxic chemotherapy regimens are the only treatment option.

Even with chemotherapy treatments, cancer cells evolve and adapt to evade the effects of the therapy and become resistant. Thus, patients with the most advanced triple-negative breast cancers must undergo toxic treatments that do not result in the durable control of their cancer and are faced with the prospect of multiple rounds of different chemotherapy regimens with ever-diminishing responses. New treatment strategies that result in long-term control of cancer, that cause fewer side effects are urgently needed for this large population of patients.

Like many other studies, our laboratory has demonstrated that a molecule known as ATP that normally functions as the universal energy currency inside cells, can kill cells when present at high concentrations outside cells. Specifically, we have shown that ATP is released from cells to their external environment when they are treated with chemotherapy. We have also shown that when we blocked the enzymes that degrade external ATP (eATP), cells were more susceptible to the effects of chemotherapy. However, there are a large variety of enzymes that degrade eATP, making it difficult to design medicines that block all these enzymes. Based on previous reports that the presence of sulfate "tags" on large molecules in the tumor environment can interfere with the degradation of eATP, we searched for such molecules that had been previously reported to prevent eATP degradation. We found that a molecule that is present in the external environment of normal cells, known as heparan sulfate, has been reported to prevent eATP degradation. We also found that heparan sulfate interferes with all the classes of enzymes that degrade eATP. Finally, we confirmed that a class of drugs called "sulfatase 2 inhibitors", which maintain heparin sulfate activity, increase the sensitivity of cancer cells to chemotherapy ultimately by increasing extracellular ATP concentrations.

Given that cancer cell growth under laboratory conditions may not perfectly reflect their behavior in human patients, we will evaluate the effects of sulfatase 2 inhibitors in mice, where we will implant human breast cancer cells in the mice and measure the effects of administering sulfatase 2 inhibitors in combination with chemotherapy on the growth of these cells. As these mice lack an immune system to allow the growth of human cells, in a separate group of experiments we will assess the immune system response to sulfatase 2 inhibitors by implanting mouse breast cancer cells in mice that have an intact immune system and study their effects on the growth of the tumors and immune cells of these mice when combined with immunotherapy.

If successful, we may learn that sulfatase 2 inhibitors have potential as novel drugs to improve survival and the quality of life for metastatic triple-negative breast cancer patients. These studies would set the stage for testing the safety of this drug in an additional large mammalian species followed by early-phase human trials immediately following this award period. Further, the findings of these and future studies may provide evidence supporting the use of sulfatase 2 inhibitors in other types of cancer.