

## **PUBLIC ABSTRACT RATIONALE**

ROS1 is a gene that can break and rearrange or fuse with a partner gene to become highly active and stimulate cancer growth in metastatic cancers. There are FDA approved drugs targeting the ROS1 gene that have provided tremendous benefit for patients living with metastatic cancers. Several of these drugs can easily get into the brain and have shown dramatic tumor shrinkage in the brain metastases of patients with metastatic cancer. Recently, it was shown that inhibiting ROS1 in lobular breast cancers (i.e. cancers with loss of a specific gene called CDH1) would cause these breast cancer cells to die. Additionally, ROS1 has been shown to be potentially important in breast cancer brain metastases. However, we do not know if other mutations other than ROS1 rearrangements or fusions activate the ROS1 gene. Since we already have highly effective drugs targeting ROS1 in metastatic cancers that have minimal side effects, determining how we can leverage ROS1 mutations in metastatic breast cancers is extremely important.

## **RESEARCH GOALS**

Our main goal is to determine the most effective way to provide unique additional treatment options for patients living with metastatic breast cancer. While we will focus our efforts on metastatic breast cancers with ROS1 alterations, we will investigate the potential for ROS1 surface expression in breast cancer brain metastases and metastatic lobular breast cancers – areas that represent significant unmet medical need. We will start our investigation by identifying the incidence and type of ROS1 alterations in metastatic breast cancer and determining which ROS1 alterations activate the ROS1 gene. Additionally, we aim to determine ROS1 expression on specific subsets of metastatic breast cancer specimens, including metastatic breast cancers with known ROS1 alterations, metastatic breast cancer brain metastases, and metastatic lobular breast cancers.

## **ANTICIPATED CLINICAL APPLICATIONS**

Foundation Medicine holds the largest database of mutations in metastatic breast cancer in the world and has agreed to allow us to query their database to identify how often, as well as which types of ROS1 alterations, occur in metastatic breast cancers. Using Foundation Medicine and publicly available databases, we have already identified some specific ROS1 alterations in metastatic breast cancers that may activate the ROS1 gene. We are going to clone the ROS1 mutations and determine if they activate the ROS1 gene. We also have identified a cohort of metastatic breast cancers treated at Duke University. Samples from these patients include metastatic breast cancers with known ROS1 alterations, breast cancer brain metastases, and metastatic lobular breast cancers. A special stain has already been created and validated to determine if ROS1 is positive on the cell surface of metastatic cancers with ROS1 fusions. We will use the identical stain to determine if the Duke University metastatic breast cancer samples are ROS1 positive or not.

## **SIGNIFICANCE TO METASTATIC BREAST CANCER PATIENTS**

Determining which ROS1 alterations activate the ROS1 gene, or determining which metastatic breast cancers express ROS1, could open up a completely new therapeutic approach for patients living with metastatic breast cancer. There are FDA-approved ROS1 inhibitors that are highly effective and can provide years of benefit to patients living with metastatic cancer. Also, several of the ROS1 inhibitors being studied have shown promise in significantly reducing the size of brain metastases. Determining that a subset of metastatic breast cancers have ROS1 gene activation or have high levels of ROS1 surface protein expression could ultimately make a significant impact on the life expectancy of metastatic breast cancer patients. As a first step, this finding could be highly translatable into clinical trials. Our initial studies will provide the basis for pursuing this treatment option and identify patients most likely to respond.