One of the biggest challenges in the treatment of breast cancer is the development of resistance. A drug that initially works well will stop being effective. Many newly diagnosed breast cancers are estrogen receptor (ER) positive. The cancer will initially respond to drugs that target the estrogen receptor but unfortunately, over time, these drugs stop working due to alterations (or mutations) in the cancer cells.

Many ER positive cancers have initially responded to a class of drugs known CDK4/6 inhibitors. However, many cancers stop responding to these drugs over time. Sarat Chandarlapaty at Memorial Sloan Kettering has recently identified mutations in two genes that play a critical role in the development of resistance (RB1 and FAT1). Mutations in FAT1 and the pathway it controls lead to an increase in CDK6 which causes a decrease in the effectiveness of the CDK4/6 inhibitor drugs. This development, and future developments, are possible largely through the cataloging of data and the identification of genetic changes that occur at a cellular level. This information leads to the next crucial step of developing new therapies to overcome resistance.

<https://www.mskcc.org/blog/researchers-identify-origin-resistance-new-class-breast-cancer-drugs?utm_source=Twitter&utm_medium=Organic&utm_campaign=121018bc&utm_content=Research>

Nikhil Wagle, MD, and his laboratory at Dana-Farber Cancer institute have also advanced the understanding of drug resistance. Dr. Wagle sought to identify mechanisms of resistance that cause ER+ breast cancer to stop responding to commonly used treatment, including tamoxifen and aromatase inhibitors. His research found that when treated with hormone therapy, ER+ metastatic breast cancer develops mutations in the human epidermal growth factor receptor 2 (HER2) that were not present in the original tumor. This is important because by blocking the effects of the HER2 mutation, resistance to treatment in ER+ metastatic breast cancer was overcome.

<https://www.dana-farber.org/newsroom/news-releases/2018/her2-mutations-can-cause-treatment-resistance-in-metastatic-er-positive-breast-cancer/>

Dr. Wagle’s laboratory has also supported the work of Dana-Farber colleagues Geoffrey Shapiro, MD, PhD and Seth Wander, MD, PhD in further advancing the understanding of drug resistance. They identified resistant cells that did not contain a mutation, but became resistant by spreading the trait to neighboring cells by “transporters” know as exosomes. They further found that resistance could be overcome by stopping treatments for periods of time and then restarting. Future work will hopefully lead to the identification of these exosomes in blood tests which may help identify resistance early on.

Most recently, Dr. Wagle has continued to explore resistance mechanisms in ER+ breast cancer via a genome-scale function screen, which allows over 10,000 genes to be studied in order to determine if their expression leads to treatment resistance. In addition, Dr. Wagle’s laboratory performed whole exome sequencing in biopsies of patents with ER+ metastatic breast cancer who developed resistance to ER-specific therapies. Collectively, this work, which was presented at the annual American Association for Cancer Research Conference, demonstrates that treatment resistance can be overcome through a combination therapy that targets both the ER and FGFR pathways.

<https://www.biorxiv.org/content/10.1101/605436v1>

Current research has identified some acquired mutations that develop during the course of treatment as well as communication amongst cells, both of which ultimately lead to resistance. The identification of these means of resistance allows for a better understanding of metastatic breast cancer and the development of new medications, or combination of current medications, to overcome resistance and improve treatment response.