Public/Lay Abstract

Developing combinatorial therapeutic strategies for metastatic HER2+ breast cancer

HER2 is a cell surface protein that is overexpressed in around 20% of breast cancers (HER2+ breast cancers). It transmits signals to the cancer cell to promote tumor growth and the spread of cancer cells to other organs (metastasis). Given the critical role that it plays in this breast cancer subtype, multiple inhibitors against this protein have been developed and are currently used in the clinic. These HER2 inhibitors have dramatically improved the clinical outcome of HER2+ breast cancer patients; however, metastatic disease remains incurable and virtually all individuals with metastases relapse from these treatments. Therefore, there is an urgent need to develop more effective therapies that will improve initial responses, significantly delay relapse, and ultimately prolong survival.

We sought to identify additional proteins in the cancer cell that when inhibited, would increase the effect of HER2 inhibitors. We considered a protein named EZH2, which is also overexpressed in the majority (84%) of HER2+ breast cancers, including stage IV. EZH2 makes modifications in the proteins that package the DNA to turn off genes. In contrast, EZH2 inhibitors turn on the expression of multiple genes. Importantly, EZH2 inhibitors have been FDA-approved for other tumor types. In our preliminary studies we found that inhibiting both EZH2 and HER2 significantly enhanced the therapeutic response of HER2+ breast cancers compared to HER2 inhibitors alone. This combination also worked in tumors that are insensitive to HER2 inhibitors. Moreover, this combination induced potent and durable tumor regression in mice with no signs of toxicity or body weight loss.

Our promising therapeutic strategy has the potential to revolutionize the treatment of metastatic HER2+ breast cancer as it could be readily translated to the clinic as a third line therapy to improve survival and reduce mortality. It may also eliminate the need for additional chemotherapy. In this project, we aim to test the efficacy of combined EZH2/HER2 inhibition in metastatic models of HER2+ breast cancer with the goal of translating these results into Phase I/II clinical trials. Importantly, our work could also have broader implications as it could inspire the development of additional EZH2 inhibitor-based drug combinations for other tumor types.

We will also study how EZH2 and HER2 inhibitors work together at the molecular level in HER2+ breast cancer. We have already found that the combination works, in part, by inducing the expression of the gene BMF, which triggers programmed cell death. We will further investigate how these drugs work together to induce the expression of BMF and we will also identify other potential signals that critically contribute to the therapeutic response of the combination treatment. This is important because it could unveil additional therapeutic targets and might help identify which patients will benefit most from this combination treatment.

Finally, we will study mechanisms of resistance to this combination. While drug combinations are an effective strategy to enhance initial responses and delay relapse, it is most likely that relapse will still occur as the residual cells that survive the combination treatment start growing. Therefore, it is essential to 1) identify the signals that enable cancer cells to survive the treatment and 2) design additional therapeutic strategies to target these mechanisms of resistance. One of the main goals of this project is to study how these mechanisms of resistance differ by metastatic site (organ). We hypothesize that metastases at different organs might possess/develop different mechanisms of resistance. Moreover, these altered pathways (specific to each organ) that induce resistance might at the same time constitute additional therapeutic vulnerabilities that can be targeted. Therefore, metastases at different sites might require distinct therapeutic strategies to overcome resistance to combined EZH2/HER2 inhibition and achieve maximal responses. This approach is innovative and could create a paradigm shift in our ability to predict and improve clinical outcomes in individuals with metastatic breast cancer.