**Lay Summary**

The overarching goal of this work was to develop a novel immunotherapeutic drug for treating established metastatic breast cancers. Our approach leveraged a type of white blood cells called natural killer cells to eliminate metastatic cancer cells. In this project, we generated the drug called IGF1R-trispecific killer engager (IGF1R TriKE) and it engages NK cells in blood and IGF1R on breast cancer cells and incorporates a signal to aid in survival of NK cells. Our data show that it killed breast cancer cells in the laboratory. It effectively activated NK cells from normal volunteers to kill ER+ breast cancers. Further, it did not affect levels of the marker IGF1R that this drug recognizes on breast cancer cells indicating that the IGF1R will remain on the surface to continue to engage the TriKE. These data suggest that the drug brings NK cells to metastatic breast cancer cells by recognizing this marker and causes killing of metastatic breast cancer cells. Our data also indicate the TriKE can activate NK cells in blood of patients with metastatic breast cancer to kill ER+ breast cancers. We also found that the drug inhibited established metastatic lesions and growth of slow growing ER+ tumors in preclinical models. The success of the IGF1R TriKE in killing metastatic breast cancer cells both in the laboratory dishes and in preclinical models provides proof of principle that a NK cell-based strategy, where the camIGF1R TriKE trains the NK cells to recognize metastatic breast cancers, shows high killing activity across a range of IGF1R positive breast cancers. These finding indicate that continued development of this strategy could provide a novel option for patients living with metastatic breast cancer