**Lay Outcomes**

One of our goals for this past year was to establish a model system where circulating tumor cells (CTCs) are shed from human breast tumors that are grown in animal models and can be collected and analyzed by modern sequencing technologies. CTCs are an indicator of active metastases and perpetuate metastatic breast cancer by allowing tumor cells to spread to multiple organs (for example from bone to lung/liver/brain). This is important as to our knowledge no models exist where estrogen receptor (ER) positive breast cancers shed cells into circulation and can be manipulated for experimentation. From our initial data we have now identified that a similar population of CTCs exist in our animal model as in patient blood samples. That is, they show a similar pattern of gene expression.

Our initial experiments measuring blood counts in animals on common forms of endocrine therapy have yielded interesting results. Animals given tamoxifen show a significant drop in platelet counts while animals given fulvestrant show a significant increase in platelet counts. This is important as we know chronic use of these drugs impacts blood cells. Loss of platelets (thrombocytopenia) is a major complication of many cancer drugs and increases danger of bleeding. High platelet count (thrombocytothemia) increases risk of blood clots and is hypothesized to potentially assist in further spread of metastatic cancer cells. We have found that animals given tamoxifen have decreased platelet counts while those given fulvestrant (faslodex) increase platelets.

We have also shown that our patient-derived breast tumor lines that we made resistant to estrogen withdrawal, tamoxifen, and fulvestrant, grow in animals that are maintained on the respective drugs. We will now use these systems to determine changes that occur specifically in the CTCs and the platelets under chronic endocrine therapy. This is important as CTCs only live in the bloodstream for a short time (minutes-hours) and we do not know how systemic therapy impacts their features. Further we will now measure simultaneous impact of long term therapy on both CTCs and platelets.

Dr. Sartorius has presented this information on behalf of the team at several public seminars including the American Association for Cancer Research Annual Meeting (2023), International Association of Breast Cancer Researchers (2023), and is scheduled to present at the Metastatic Breast Cancer Research Conference in August 2023. Dr. Kabos presented at the San Antonio Breast Cancer Symposium (2022) and Dr. Brechbuhl has presented portions of this data at local University of Colorado-AMC seminars. The group is working towards larger grant submissions on metastatic breast cancer based in part on results from ongoing work under this award.