**Lay Description of Important Outcomes**

**2021**

The formation and growth of metastatic tumors is the primary driver of breast cancer patient outcomes. Unfortunately, current therapies are rarely effective enough in the metastatic setting. Past work from our lab demonstrated that breast cancers spread through the body in adherent clusters and that they experience significant molecular stresses as they travel through the circulation and arrive in distant organs. Metastasis is a highly inefficient process and most of these cancer cells die soon after leaving the primary tumor. We discovered that a critical mechanism of survival for these cancer cells depends on the protein E-cadherin. This molecule is normally localized on the surface of cells and acts as a form of molecular “velcro”. Our major goal in this project is to identify ways to target cancer cells that rely on E-cadherin for cell survival so that we can prevent the formation of new metastases and shrink or eliminate existing metastases. Progress from year 1:

• Demonstrated that individual human breast tumors can contain cancer cells that use different molecular programs to metastasize to distant organs.

• Identified a critical role for E-cadherin based cell survival in triple negative breast cancer metastasis.

• Used molecular engineering techniques to isolate the specific features within E-cadherin that are required for cancer cell survival.

• Demonstrated that E-cadherin signaling continues to be required as existing metastases grow.

• Developed innovative assays to visualize metastasis formation within the lungs in real-time.

• Developed highly efficient assays to test the ability of large numbers of potential anti-cancer drugs to inhibit new metastasis for formation.

• Developed a new assay to identify the specific molecular requirements for existing lung metastases to grow to life-threatening size.

• Presented our results in eight invited talks, with two more in May 2021.

• Submitted major grants to the NCI and CRUK to enable scale-up of this project

• Submitted a new manuscript on triple negative breast cancer metastasis.

• Our data support the idea of targeted disseminated cancer cells in the adjuvant setting.

**2022 Update**

Used molecular engineering techniques to isolate the specific features within E-cadherin that are required for cancer cell survival.

• Identified that E-cadherin is required for tumor cell survival independent of its molecular adhesion (“velcro”) function

• Developed innovative assays to visualize metastasis formation within the brain in real-time.

• Demonstrated that E-cadherin is required for tumor growth at later stage of metastatic outgrowth

• Developed highly efficient assays to test the ability of a large numbers of potential anti-cancer drugs to specifically inhibit E-cadherin+ metastasis formation.

• Identified that loss of E-cadherin significantly changes mitochondrial function in breast cancer cells.

• Presented our results in thirteen invited talks.

• Submitted major grants to the NCI and multiple foundations.

• Received grants from the NCI (U54CA268083- Project Leader and R01CA266199- Co-Investigator) and Hope Scarves Foundation and Metastatic Breast Cancer Network.

• Submitted three manuscripts (one provisionally accepted, one under review, and one in revision) on the role of E-cadherin in breast cancer metastasis, focusing on triple negative breast cancer.

• Our data continue to support the idea that understanding how E-cadherin mediates cancer cell survival will enable us to suggest new strategies to target disseminated cancer cancer cells in the adjuvant setting.