**Lay Summary of Outcomes**

* Paper published in JCI: Szot C et al, Tumor stroma-targeted antibody-drug conjugate triggers localized anticancer drug release. J Clin Invest. 2018 Jul 2;128(7):2927-2943. PMID: 29863500
* Commentary on work published in JCI: McCann et al, Deadly DAaRTS destroy cancer cells via a tumor microenvironment-mediated trigger J Clin Invest. 2018 Jul 2;128(7):2750-2753. PMID: 29863494

This proposal aims to eradicate metastatic breast cancer by using antibody-based therapies to target the tumor microenvironment. Antibodies, often regarded as “magic bullets”, are soluble proteins of the immune system that can be engineered to specifically target other proteins (antigens), including those upregulated in tumors. Antibodies can be armed with cytotoxic warheads to create Antibody-Drug Conjugates (ADCs), potent drugs that have potential to be more selective than traditional chemotherapeutic agents. Antibodies can also be fused to cellular transmembrane spanning receptors on normal human T cells to create Chimeric Antigen Receptor (CAR) T cells. These engineered cells, with guidance from their antibody-based receptor, recognize and kill the cells that display the antigen on their surfaces. Most ADCs and CARs have been designed to target tumor cells directly and are limited to a highly select group of cancer patients. An alternative and complimentary strategy involves targeting the tumor-infiltrating normal cells of the tumor microenvironment, the so-called tumor-associated stroma, as it has become clear that tumor growth depends on the dynamic interaction between tumor cells and non-cancer stromal cells. We previously generated ADCs against cell surface proteins that are widely overexpressed in breast cancers by both the tumor-associated stroma and some tumor cells themselves. Although these ADCs were highly effective against metastatic breast cancer in preclinical studies, we hypothesize that it may be possible to further increase drug activity towards the tumor and simultaneously decrease toxicities through: 1) ADC drug-linker optimization, 2) judicious combination of optimized stromal-targeted ADCs with each other or other anti-cancer drugs, and 3) development of highly specific and tunable tumor stromal-targeted CAR T cells. Through rational engineering of ADCs and CARs, we hope to create novel combinatorial treatment regimens that can be rapidly transitioned from preclinical studies to the clinical development pipeline.