Improving Therapy for Metastatic Breast Cancer through Targeting of Tumor Stroma

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The goal of the proposed studies is to develop improved therapies for late-stage metastatic BC through the development of antibody-drug conjugates (ADCs) against the tumor microenvironment. Monoclonal antibodies, often dubbed “magic bullets”, have revolutionized cancer therapy. Their value lies in their exquisite specificity which, when harnessed appropriately, enables them to selectively accumulate in tumors thereby reducing off-target toxicities. The tumor microenvironment is comprised of extracellular matrix (ECM) and various stromal cell types, many of which play a critical role in promoting the growth and metastasis of breast cancer. Tumor infiltrating blood vessels provide a vital lifeline of nourishment and endow tumors with an escape route for metastatic spread. Cancer associated fibroblasts also promote tumor growth and metastasis by suppressing immune responses and secreting growth factors, chemokines and ECM which stimulate cancer cell proliferation, invasion, and angiogenesis. Although the tumor stroma plays an essential role in promoting tumor growth and metastasis, the tumor stromal cells themselves are not malignant but instead can be considered partners in crime. The idea of using antibodies to deliver cytotoxic agents to the tumor stroma for cancer therapy is widely recognized. However, despite the undeniable appeal of this approach tumor stroma-targeting ADCs remain at the developmental stage. A major obstacle limiting the clinical deployment of such ADCs is the identification of suitable targets with the specificity required to selectively target tumor stroma. In previous studies our laboratory has uncovered a number of cell surface receptors, called Tumor Endothelial Markers, or TEMs, some of which are overexpressed on tumor infiltrating blood vessels and cancer associated fibroblasts. In collaboration with Dr. Dimiter Dimitrov’s group at the National Cancer Institute, we have now developed a panel of fully-human antibodies against TEMs. By conjugating these antibodies to small molecule drugs, we are creating new stromal targeted ADCs that may have sufficient specificity to selectively target the tumor microenvironment for the treatment of breast cancer.