

## **METAvivor Final Report**

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PI Name: Brad St. Croix

Co-applicant name (if applicable):

Grant title: Improving therapy for metastatic breast cancer through targeting of tumor stroma

The goal of the proposed studies was to improve therapies for late-stage metastatic breast cancer through the development of antibody-drug conjugates (ADCs) against the tumor microenvironment. 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. For example, 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. By conjugating fully-human antibodies to small molecule drugs, we have created new stromal targeted ADCs that may have enough specificity to selectively target the tumor microenvironment for the treatment of breast cancer. The ADCs have now been tested against various breast cancer models and have shown promising data in preclinical studies. The ADCs killed both cancer cells and tumor vasculature, eradicating large established tumors and metastases, and improving long-term overall survival in mouse models. In addition, the ADCs have been evaluated in preliminary toxicology studies where they showed limited, if any, off-target toxicity. The results of this work have been published in *Cancer Cell* and *The Journal of Clinical Investigation* (see citation above). Commentaries associated with both manuscripts have also been published (Khan KA and Kerbel RS, A CD276 Antibody Guided Missile with One Warhead and Two Targets: The Tumor and Its Vasculature. *Cancer Cell*. 2017 Apr 10;31(4):469-471 and McCann JV, Null JL, Dudley AC. Deadly DAaRTS destroy cancer cells via a tumor microenvironment-mediated trigger. *J Clin Invest*. 2018 Jul 2;128(7):2750-2753). Our laboratory will continue to build our preclinical data set and are actively seeking research collaborations or licensees for further development and clinical translation of these promising therapeutic agents.