PI: Brad St. Croix, 2020

Public/Lay Abstract:

Effective treatments to permanently eradicate late-stage metastatic breast cancer do not exist. A major challenge in the treatment of late stage, aggressive breast cancer is the heterogeneous expression of targets on tumor cells and the development of resistance to current anti-tumor therapeutics. A recent advance in oncology treatment is the development of antibody-drug conjugates (ADCs) which harness antibodies that recognize specific molecular targets fused to potent cell-killing small molecule warheads. One of the advantages of ADCs is that the payload, upon release in target binding cells, can penetrate nearby neighboring cells in a target independent manner, helping to address the problem of tumor cell target heterogeneity. Importantly, drugs used on modern ADCs, including those which kill cells by damaging DNA, have inherent selectively for tumors which helps safeguard against treatment-induced toxicities. ADCs may also potentiate activity of other therapies, such as immune checkpoint inhibitors. Two clinically approved ADCs, trastuzumab emtansine (Kadcyla) and trastuzumab deruxtecan (Enhertu), target the cell surface receptor HER2 that is amplified or overexpressed in approximately 15-30% of breast cancers. While ADCs like Kadcyla and Enhertu do kill tumor cells, the dose required for complete tumor eradication is often too toxic for clinical use. We propose an alternative or complementary approach for breast cancer ADC treatment that includes targeting of the noncancerous supporting stromal cells of the tumor microenvironment. Because these stromal cells are more genetically stable than tumor cells, ADCs targeting these cells are more likely to evade drug resistance. Another major advantage of targeting tumor-associated stromal cells is that their cellular targets are widely overexpressed in breast cancer, creating broad target populations that could benefit from this therapy. Furthermore, through judicious engineering of these ADCs we hypothesize that it is possible to achieve potent therapeutic responses at lower drug doses, thereby reducing the potential for unwanted side effects. We previously generated ADCs against two cell surface markers called CD276 and TEM8, which are frequently overexpressed on tumor blood vessels and cancer-associated fibroblasts (vital parts of the tumor stroma), as well as tumor cells. These ADCs are capable of significantly extending survival of mice with metastatic breast cancer, even if treatment is started at a late stage of the disease. However, like all ADCs before them, the major current limitation of these ADCs is dose-limiting toxicities. Strikingly, we found that the dose-limiting adverse effects caused by these ADCs is antigen independent, that is not from binding to target-positive cells. Instead, they were caused by 1) instability of the ADC and 2) unintended non-specific binding to target-antigen negative normal cells. The major goal of this study is to prevent these toxicities, by creating new ADCs that can block each of these non-specific interactions. We plan to do this by 1) altering key parts of the antibody backbone to prevent it from binding to so-called Fc-gamma receptors that are present on immune cells, 2) using new methodology to fuse the payload to our antibody, creating a more stable ADC and 3) masking the payload prior to intracellular activation so that the ADC can no longer trigger recognition and removal by immune cells.

Significance and impact: A major limitation of ADCs in clinical development are their dose-limiting toxicities. However, by reengineering our antibody backbones and chemically modifying the biophysical properties of our PBD warhead, we anticipate the creation of advanced next-generation ADCs with substantially improved potencies and reduced toxicities. Because the targets of our stromal ADCs are widely expressed in all types of breast cancer, independent of their stage and subtype, these drugs have potential for improving survival of patients with all forms of breast cancer including that which has already metastasized. The same drug conjugation methodology will also be tested using trastuzumab (an anti-HER2 antibody) to see if the approach can be applied to other antibodies to improve ADC performance across the field. Through rational engineering of antibodies and warheads, we hope to create fully human ADCs that can be rapidly transitioned from preclinical studies to clinical trials within three to five years and radically improve outcomes for breast cancer patients.