Improving Immunotherapies for Advanced Metastatic Breast Cancer

Effective treatments to permanently eradicate late-stage metastatic breast cancer do not exist. This proposal aims to accelerate METAvivor's vision to end 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 patient 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.

Currently, four different ADCs and two CARs are approved for clinical use in the US and many more are in clinical development. Most ADCs and CARs have been designed to target tumor cells directly and are limited to a highly select group of cancer patients - for example trastuzumab emtansine, a clinically approved ADC targeting HER2 to treat patients with HER2-positive breast cancer, or Kymriah, a CD19 CAR approved to treat CD19-positive leukemias. 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. One advantage of this approach is that stromal cells are genetically more stable than the tumor cells, which may help prevent the development of drug resistance which is commonly seen with drugs targeting tumor cells. Another advantage is that cellular targets of tumor-associated stroma may be overexpressed in most, if not all, primary breast tumors as well as their metastases. We recently generated ADCs against two cell surface proteins, CD276 and TEM8, that are widely overexpressed in breast cancers by both the tumor-associated stroma and some tumor cells themselves. Remarkably, in preclinical studies ADCs against these targets extended the survival of mice with widespread established breast cancer metastases. We also determined that stromal-targeted ADCs could be engineered to destroy tumors through different and distinct mechanisms. TEM8 CAR T cells were also found to be highly effective against metastatic breast cancer. Based on these data 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. In a preliminary study two stromal-targeted ADCs with distinct warheads and killing mechanisms were combined to treat breast cancers grown in mice. Strikingly, while low-dose ADC individual therapies only delayed tumor growth, combination therapy was able to eradicate approximately half of the tumors in the study.

By optimizing ADCs and combining them with each other and other agents with distinct cell-killing mechanisms it may be possible achieve substantially increased potency at reduced drug doses. Stromal-targeted CARs may also be effective in BC therapy, and their selectivity for cell killing may be improved by genetically engineering T cells that require two targets for activation. Because the targets of our immunotherapies are widely expressed in all types and stages of breast cancer we have examined, these therapeutic agents have high potential for improving survival of all forms of breast cancer, notably those which have already metastasized. 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.