**PUBLIC/LAY ABSTRACT**

Antibody-drug conjugates are a new and rapidly expanding class of cancer therapeutics, in which a chemotherapy drug such as deruxtecan is chemically linked to an antibody that recognizes a protein present mostly or exclusively on cancer cells. Thus, the drug is also delivered mostly to cancer cells only, theoretically increasing its efficacy and minimizing side effects. One such antibody-drug conjugate, sacituzumab govitecan (Trodelvy, Gilead), was recently approved by the Food and Drug Administration for metastatic triple negative breast cancer (TNBC) and urothelial cancer, and is currently being assessed in other tumor types. As with other cancer treatments, resistance is observed, especially in advanced/metastatic cases. In this project, we propose to (**1**) investigate why some patients respond to antibody-drug conjugates while others do not, and (**2**) to investigate whether antibody-drug conjugates can be combined with other drugs to overcome resistance. We expect that our studies will help us maximize the population of patients who can derive benefit from antibody-drug conjugates or their combinations. More importantly, our studies will help us limit the use of antibody-drug conjugates (or their combinations) only to those patients who are likely to benefit, and, conversely, avoid futile treatment among patients who are unlikely to respond—our long-term goal is to give *the right drug to the right patient*.

Our overall theory is that a patient's response to antibody-drug conjugates is determined by at least two molecular features: the presence of the protein recognized by the antibody, and the presence of a molecule that sensitizes the patient to the attached drug. To test our theory, we will investigate the efficacy of sacituzumab and a new experimental drug (Dato-DXd) in breast cancer tumors with or without TROP2, the protein recognized by the antibodies in these antibody-drug conjugates, as well as in tumors with or without SLFN11, a protein previously known to sensitize tumors to irinotecan, the drug conjugated to the antibodies. Similarly, we will study breast cancer patients at MD Anderson who have already received sacituzumab to identify genetic characteristics that could determine whether a patient will or will not respond to the treatment. Similarly, we will investigate whether the drug decitabine, which increases production of TROP2 and SLFN11 in cells, can also increase sensitivity to sacituzumab and Dato-DXd. Finally, we will test whether the drug azenosertib, a new inhibitor of wee1, can also be used to maximize the efficacy of sacitizumab and Dato-DXd.

This project will be led by Dr. **Funda Meric-Bernstam**, Chair of the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center, in collaboration with Dr. **Senthil Damodaran**, Associate Professor in Breast Medical Oncology (with joint appointment in Investigational Cancer Therapeutics) and **Dr. Marcos Estecio**, Associate Professor in Epigenetics & Molecular Pathogenesis. We have put together a multidisciplinary team with expertise in personalized cancer treatments and drug development, with full access to the vast research and clinical resources available at MD Anderson. To ensure that our research evolves with the needs and maximally benefits the lives of metastatic breast cancer patients, we have invited **Gail Barr**, an experienced patient advocate, to join our project.