JOHNS HOPKINS
MEDICINE
KIMMEL CANCER CENTER

Leisha Emens, M.D. / Ph.D.

For the past 15 years, The Judith A. Lese Breast Cancer Foundation has supported the work of Leisha Emens, M.D., Ph.D. at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Dr. Emens will be joining the UPMC Hillman Cancer Center in Pittsburgh, Pennsylvania. Her new role will be Professor of Medicine, Co-Leader Hillman Cancer Immunology & Immunotherapy Program; Director of Immunotherapy in the Women's Cancer Research Center; UPMC/Hillman Cancer Center and Magee Women's Research Institute.

Dr. Emen's research, which was supported by the Judith A. Lese Foundation, pertains to the development of treatment strategies that can increase the numbers of breast cancer patients who can respond and benefit from the transformative potential of immunotherapy.

The treatment approach utilizes immune checkpoint blockade together with a new vaccine approach to increase the numbers of T cells – a major contributing factor to immunotherapy. Dr. Emens and her lab have been testing a drug injected directly into a patient's tumor, which acts as a personalized vaccine by activating the STING pathway in the tumor. This vaccine method of STINGing the tumor creates swelling and inflammation much like a bee sting, creating an immune response highly specific for unique features of the patient's tumor. Preclinical data shows that creating T cells by STINGing the tumor, taking the parking brake off with PD-1/PD-L1 blockade, and giving some gas with an OX-40 drug increases responses from 20% to about 60%.

Evanthia Roussos Torres, M.D. / Ph.D.
Instructor, Cancer Immunology & Breast & Ovarian Cancer Program

Evanthia Roussos Torres, M.D./PhD. currently serves as an Instructor of Oncology within the Cancer Immunology and Breast and Ovarian Cancer Program at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center. Prior to her time at Johns Hopkins, Dr. Roussos Torres received her MD/PhD from the Albert Einstein College of Medicine of Yeshiva University in New York, before going on to complete her residency in internal medicine at the Hospital at the University of Pennsylvania. She completed her fellowship training in Oncology here at Johns Hopkins where she now serves as a member of the faculty.

As a physician scientist, Dr. Roussos Torres' work is done in collaboration with Elizabeth Jaffee, M.D., and focuses on development of animal models for use in investigation of immune based therapies in both HER2 positive, triple negative and lobular mouse models of breast cancer. Her work investigates rational combinations of checkpoint inhibitors with epigenetic and other targeted therapies to determine how to improve efficacy of immunotherapies and their mechanisms of action. Dr. Roussos Torres' translational research is focused on immuno-oncology in high risk breast cancers. Overall, Dr. Roussos Torres is interested in dissection of the specific mechanisms involved in response to checkpoint inhibitors with the goal of understanding how to transform the breast tumor microenvironment into an immune responsive microenvironment and bring immunotherapy into the clinic for patients with breast cancer.

Imagine if your own body could seek out and destroy breast cancer!

Cancer immunotherapy is a new treatment approach that can make this happen.

Cancer immunotherapy has now become part of the standard of care for cancers like melanoma, lung cancer, and bladder cancer. These tumors frequently harbor T cells, which act like smart bombs to seek out and destroy cancer. However, inside tumors these T cells are often restrained by specific checkpoints that put the brakes on them. The main checkpoint responsible for this is the PD-1/PD-L1 checkpoint. We now have multiple drugs that disable the PD-1/PD-L1 checkpoint, releasing the brakes on T cells so they can kill cancer. These drugs have been approved for use by themselves or with chemotherapy in several tumor types, and benefit about 20-30% of treated patients. The reason cancer immunotherapy is changing the game is that responses can last a long time due to the ability of the immune system to "remember".

Despite the promise of immunotherapy, progress in breast cancer is lagging behind other cancers. Three reasons are that breast cancers tend to harbor fewer T cells, and unlike other cancers, breast cancer is less likely to contain a lot of mutations that can be easily recognized by T cells, and finally breast cancers tend to have a lot of immune cells that block T cells from working. Even so, we are now seeing signs that targeting the PD-1/PD-L1 checkpoint can work in breast cancer patients:

- About 5% of patients with metastatic triple negative breast cancer (mTNBC) can respond.
- If the mTNBC is PD-L1+, about 10-13% of patients can respond.
- If PD-L1+ mTNBC is treated with immunotherapy first, about 23-25% of patients can respond.
- If patients are lucky enough to respond, they have much longer survival than expected.
- Adding chemotherapy to PD-1/PD-L1 blockade increases the responses from ~10% to ~40%.

Our goal is to develop treatment strategies that can increase the numbers of breast cancer patients who can respond and benefit from the transformative potential of immunotherapy.

An approach we are taking is to use immune checkpoint blockade with a new drug that lifts the influence of suppressive immune cells within the tumor. We have been testing a drug, called entinostat, which is given by mouth and decreases the potency of the suppressive cells within the tumor. When this drug is paired with the drugs that target the checkpoints PD-1 and CTLA-4, we see that the tumor is more responsive to the PD-1 and CTLA-4 blockade. The suppressive cells in the surrounding tumor environment are less potent and thus, the immune cells that are capable of getting rid of tumor cells can infiltrate the tumor more readily. This drug combination is being studied in mouse models of breast cancer as well as in patients. Our preclinical data show that entinostat affects the gene expression of pathways that control the function of these suppressor cells and we are working to better understand this intervention so it can be honed to optimize treatment for patients.

Future Directions

A novel finding from our preliminary data is the discovery that following treatment with entinostat and checkpoint inhibitors that target PD-1 and CTLA-4, suppressor cells within tumors have a dampened effect. We discovered that one potential way in which this combination therapy leads to changes in the function of these suppressor cells is through the regulation of a gene called *STAT3*. *STAT3* is a gene that is known to affect immunity and thus targeting this gene more specifically has the potential to improve response in patients. We also know that entinostat affects many other genes and therefore possibly causes unnecessary side effects. Therefore, if we can find ways to more specifically control *STAT3* we may be able to achieve the same altered function of the suppressor cells with fewer side effects for patients.