HUNCH 2

Targeting the immune checkpoint for treatment of metastatic triple negative breast cancers.

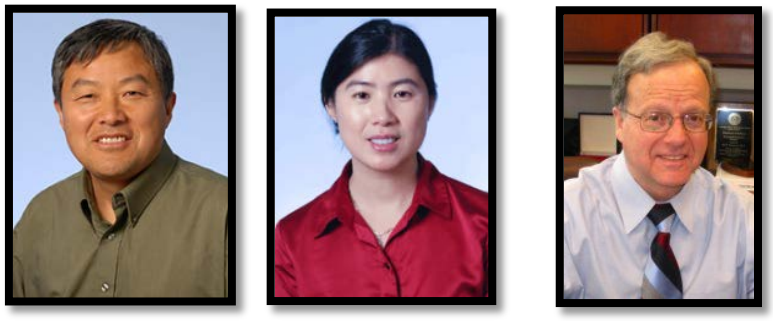
This project was submitted by Drs. Jian-Ting Zhang, Jing-Yuan Liu, and Hal Broxmeyer. Jian-Ting Zhang, PhD, serves as the Andrew and Peggy Thomson Chair in Hematology/Oncology, and his research focuses on drug discovery and cancer treatment resistance. Jing-Yuan Liu, PhD, is an assistant professor of pharmacology and toxicology whose research focuses on drug discovery, and Hal Broxmeyer,PhD, is a distinguished professor in microbiology and immunology who also serves as the co-leader of the Program on Hematopoiesis, Malignant Hematology, and Immunology at the IU Simon Cancer Center.

Metastatic triple negative breast cancer (TNBC) represents one of the most difficult to treat cancers with low survival rate due to lack of effective therapies. Using our own immune system to fight cancer is emerging as a powerful tool in cancer treatment. Tumor cells are "smart" and have a way hiding from the immune system to avoid being killed like a virus or bacteria is when we get sick. Immunotherapy has been shown to be very promising for effective treatment of various solid tumors. The antibody drug pembrolizumab (used since 2014 to treat metastatic melanoma and what Jimmy Carter received) and the drug MPDL3280A target immune checkpoint proteins, PD-1 and PD-L1, and have been tested in metastatic TNBC with promising results.

PD-1 is a protein found on the surface of our body's T cells (the fighters of the immune system) while its partner PD-L1 is expressed on tumor cells. When these proteins link up, the tumor cell becomes invisible to the immune system, which is good for the cancer and bad for the patient. The drugs, pembrolizumab and MPDL3280A work by stopping this interaction and allowing the immune system to "see" the tumor so it can attack it. However, the drawbacks of using these antibodies are potential adverse immune reactions in the patient, inability to stop metastasis to the brain, and the astronomical cost as high as >$1 million a year per patient.

To eliminate these issues, we plan to identify a small molecule inhibitor/chemical drug that will have the same effect as pembrolizumab by repurposing and screening a library containing FDA-approved drugs and drugs that failed phase II and III trials due to lack of efficacy for treating diseases other than cancers. These drugs will be easy to make and have demonstrated safety in humans with cost that would be a small fraction compared with the antibody or cell therapeutics. We anticipate that a potential drug candidate targeting PD- 1/PD-L1 interaction will be generated from this study within the funding period. As the drug will have already been proven safe in humans, we will be able to move quickly to a proof of concept clinical trial.

BUDGET – $99,000



FROM LEFT TO RIGHT, DRS. JIAN-TING ZHANG, JING-YUAN LIU, AND HAL BROXMEYER

HUNCH 4

Combination of Pembrolizumab and Ruxolitinib in PD-L1 + JAK2 amplified TNBC

Hunch 4 was proposed by Milan Radovich, PhD, and Jeffrey Solzak, MS. Dr. Radovich is an assistant professor of surgery whose focus is next-generation sequencing in translational oncology. Jeffrey Solzak works in Milan's lab, and is also a translational researcher whose focus is on personalized medicine.

Therapies that can encourage a patient's own immune system to attack their cancer are emerging as a promising new therapy for a variety of tumor types. Early data presented at the 2014 San Antonio Breast Cancer Symposium demonstrated that immune therapy can be highly effective and durable in a subset of metastatic triple-negative breast cancer patients. Using genomic analyses of 139 triple-negative breast cancers, we've identified that the gene target of immune therapy (known as PD-L1) is amplified (or copied many times over) in 12% of patients. In another cohort of 41 patients, this gene was amplified in 29% of patients. In addition to PD-L1, we found that a nearby activator of tumor growth (known as JAK2) is amplified in these same patients.

Further data unfortunately demonstrates that triple-negative breast cancer patients who have these two amplified genes succumb to their disease much faster than those who do not. FDA approved drugs currently exist that target PD-L1 and JAK2.Though these drugs are approved for other cancers, they are not approved for the treatment of breast cancer. In this hunch, we propose initial testing of the combination of these two FDA approved drugs: Pembrolizumab (which targets PD-L1), and Ruxolitinib (which targets JAK2) in mice bearing a TNBC tumor that harbors the amplification of both of these genes. Positive results from this experiment would be used to support initiation of a Phase I/II clinical trial of these drugs in PD-L1/JAK2 gene amplification-positive triple-negative breast cancers. Our hope is that this combination will provide a new "precision medicine" based drug combination for these aggressive triple-negative breast cancers.

BUDGET – $100,000

DR. MILAN RADOVICH AND JEFFREY SOLZAK, MS