HUNCH 1

A Novel Epigenetic-PARP Inhibitor Combination to Inhibit Metastasis in Triple Negative Breast Cancer

This proposal brings together two unique areas of research to improve therapies available for triple negative breast cancer (TNBC), a highly aggressive form of breast cancer that occurs in 15-25% of patients. Although many patients with TNBC initially respond to chemotherapy, relapse and spread of the disease to other parts of the body including the lungs, liver and brain is common. The first research area this hunch will utilize is epigenetics, or the process by which cells control their function. Epigenetics describes the cellular proteins that tell genes what to do, where to do it, and when to do it. This is how cells in the body can be so different even though they all have the same DNA. Cancer cells take advantage of this process and turn on genes in cells that stimulate growth, while turning off genes that regulate and control growth. If we understand the process of epigenetics, we could utilize it in treatment, turning off what cancer has turned on. Another important area of research this hunch will encompass is PARP inhibitors, a new class of drugs that treats cancer through accelerating DNA repair. These treatments have proven to be very effective with less side effects for the patients. However, they are only effective in women with the BRCA genetic mutations. This project explores whether combining the principles of epigenetics with PARP inhibitor treatment will allow these promising therapies to be effective for women without the BRCA mutations. The research team has already conducted preliminary work with this combination, and further funding will allow them to use the combination to treat mice with breast cancer. The goal of this hunch will be to acquire data to launch a clinical trial determining if this combination could be a viable treatment for women with TNBC who do not have a BRCA mutation.

HUNCH 2

Identification of “Tumor Compaction Factor X” in a Bone Microenvironment for Preventing Bone Metastasis from Breast Cancer

Bone is a common site for breast cancer to move and is often the first site where a recurrence of breast cancer is identified. In addition to being common, bone metastasis causes great pain for many patients with metastatic disease, reducing their quality of life. This hunch hopes to answer the questions: Why does breast cancer frequently metastasize to bone? Does bone emit a special chemical signal that attracts breast cancer cells? Can we block this signal and protect bone? This team of researchers has recently conducted real-time filming of bone-tumor interactions, which have shown that osteocytes, the most abundant type of bone cells, interact with and cling to breast cancer cells like a magnet. An experiment using osteocyte cells and breast cancer cells demonstrates that this attraction seems to be induced by an unknown secretory protein factor from osteocyte cells. In this project, the researchers will first identify the chemical and biological nature of the protein that bone cells are releasing, using mass spectrometry, a highly sensitive technique for characterizing chemical compounds. Identifying this instrumental protein should explain why breast cancers tend to home in on the bone. Once the protein is determined, that knowledge could be used to develop novel treatments for preventing bone metastasis. Determining this protein may also significantly improve the efficiency of drug delivery, as treatments could be tailored to target bone-seeking cancer cells. Collectively, the researchers expect that this pilot project will open a new avenue to prevent metastatic breast cancer.
HUNCH 3

Increasing the Tumor Penetration of Cancer Drugs to Improve the Treatment of Metastatic Tumors.

In order for cancer drugs to eliminate breast cancer metastases effectively, the drugs need to target the right mechanisms driving the tumor growth and get to every cancer cell in the tumor. Our current efforts to personalize treatments have focused on tailoring therapies based on 1) the mechanism driving the tumor, and 2) how the patient’s body gets rid of the drug; however, much less is known about how to predict, or manipulate, the ability of the drugs to penetrate to all parts of the tumor cell. This is, in part, due to the difficulty in getting additional tumor samples from women while they are taking the anti-cancer drugs for both logistical and safety reasons. Therefore, this unique team of researchers, encompassing experts in drug therapies, genetics, and imaging, has created artificial tumor models that allow them to visualize how drugs get to the tumor and what facilitates them getting into the tumor at a high-enough concentration. This project will allow the research team to analyze these tumor models to explore better means of delivering drugs, selecting the right drugs for a patient based on how drugs are penetrating their unique tumor, or determining if a combination drug would allow therapies to reach the tumor more efficiently. By applying genomic technologies to these models, the research team also expects to identify the reasons why some tumors are able to prevent the drugs from penetrating their cells, so we can eventually block those mechanisms. The goal of this project will be to understand how clinicians can better deliver existing therapies so they are more effective for patients.

HUNCH 4

Sniffing Breast Cancer and Metastasis

A recent study showed that dogs can identify prostate cancer with better than 97% sensitivity and specificity simply by sniffing urine. Preliminary work conducted by this research team suggests that dogs can similarly detect breast cancer in urine. This project would expand on those findings and allow the team to identify what chemicals the dogs are sniffing, then build an electronic nose to detect those chemicals as a new and potentially improved noninvasive breast cancer screening method. The metabolites associated with the signature smell will be studied to determine their role in breast cancer growth, using that knowledge to design better therapies for breast cancer. Current screening methods, including mammograms, are expensive and if the results are a false-positive patients not only experience psychological impact but also have to undergo unnecessary screening. Analyzing changes in the smell in urine could also lead to a major breakthrough in our ability to predict when breast cancer turns metastatic.
HUNCH 5

Correlative Studies on a Phase I Trial of Gedatolisib Plus PTK7-ADC in Metastatic TNBC: A Clinical Trial Made Possible by 100 Voices of Hope

Triple-negative breast cancer (TNBC) is a devastating disease with poor outcomes and a lack of effective therapies. Typical treatment for metastatic TNBC usually entails administration of a variety of chemotherapies, given as single-agents (or one at a time) for as long as the tumors are kept at bay or are shrinking. Unfortunately, single-agent therapy is not always clinically effective with many TNBC patients progressing through multiple drugs and eventually succumbing to their disease. We have come to learn that resistance to single-agent therapy is common due to these tumors activating what we term: compensatory pathways. Imagine the inside of a tumor cell being a complex electrical wiring diagram. When one node is shutdown with a drug, these tumors can rapidly re-route, activating other nodes that promote tumor growth and survival. Targeting these nodes can be like a game of whack-a-mole. Through extensive preclinical experimental testing, we have demonstrated that when a key survival pathway in TNBC is shutdown with a targeted drug (known as the PI3K pathway) this results in an immediate compensatory activation of another pro-tumor survival pathway known as the Wnt pathway. By targeting both of these pathways, we have demonstrated significant synergistic anti-tumor effects in pre-clinical models. Two therapeutics, Gedatolisib (a PI3K pathway inhibitor) and PTK7-ADC (a drug targeting the Wnt pathway), are attractive for targeting these two pathways. Both of these are experimental drugs being tested as single-agents in clinical trials. We have recently initiated a Phase I clinical trial of combining Gedatolisib + PTK7-ADC in patients with metastatic TNBC. The preclinical data to support the initiation of this trial were made possible by 100 Voices of Hope (Hunch #4). The endpoints of this trial are to determine the safety of the combination and to observe early signals of clinical efficacy as determined by tumor response rate and patient survival. The purpose of the hunch proposed here is to perform additional studies on patient samples from this trial. First, we would like to better understand if we observe in patients what we see in preclinical models, namely the induction of the “whack-a-mole” effect. Second, we would like to determine if there are markers that predict which patients will respond to the combination. The primary outcomes of this hunch are to use this data to support a larger Phase II trial of the combination and advance its clinical development. Our long-term goal is to provide a new FDA-approved cutting-edge treatment for metastatic TNBC patients.

HUNCH 6

A Novel Approach to Suppress Metastasis in ER+ Breast Cancer: Therapeutic Targeting of ARF6 Network

Metastasis remains the leading cause of death in breast cancer patients. Despite the significant improvement in current therapies, about 30% of patients will eventually develop resistance to standard therapies, suffer from distant relapse and succumb to the disease. The overarching challenge is to develop therapies that prevent clinically manifested metastases and eliminate the associated mortality in breast cancer. In order to achieve the goal of reducing the incidence of metastatic disease, drug development needs to target the metastatic process itself. Cancer metastasis is a complex and multi-step process driven by abnormal, deregulated gene networks that converge at places termed “hubs”. This hunch proposes a novel mechanism to target ARF6, a key hub regulating major pathways involved in cancer progression and metastasis. High expression of ARF6 is associated with poor relapse-free survival (RFS) in breast cancer; however, the research team is unaware of any previous studies targeting ARF6 and its pathways in breast cancer. This laboratory has conducted preliminary work that suggests the inhibition of ARF6 causes dramatic death of cancer cells that are resistant to current therapies. This project will further explore the promising preliminary work to establish the use of this inhibitor for the treatment of metastatic breast cancer.

Print Name

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