2018 DISCOVERY GRANTS

Every dollar funds life-saving cancer research

In just five years, Padres Pedal the Cause has donated over $7 million dollars to fund collaborative discovery research at the best cancer institutions in San Diego. Scientists at Moores Cancer Center at UC San Diego Health (MCC), Salk Institute for Biological Studies (Salk), Rady Children's Hospital-San Diego (Rady), and Sanford-Burnham Prebys Medical Discovery Institute (SBP) have initiated 42 translational cancer research projects for all types of cancers, including pancreatic, breast, brain, pediatric, skin, lung, colorectal, gastrointestinal, ovarian, and endometrial. This year, thanks to the efforts of more than 3,000 riders, sponsors, volunteers and donors, Padres Pedal donated $2.4 million to fund 11 Discovery Grant projects. **Congratulations to the 23 principal investigators and their teams who are leading San Diego's fight against cancer.**

CREATING SUICIDE CELLS IN NON-RESPONSIVE TUMORS

Inducing Cytosolic Chromatin Fragments in Cancer Cells to Turn Cold Tumors Hot

Investigators: Jack Bui, MD, PhD (MCC), and Peter Adams, PhD (SBP)

Immune therapy is a method to treat cancer using the body's own immune system. This method works because immune cells such as T cells can infiltrate a tumor mass and specifically destroy cancer cells. For some patients, the T cells can also seek out and destroy cancer cells that have metastasized throughout the body. Additionally, the T cells survive even when the cancer cells have been destroyed and thus can prevent recurrence of cancer. Thus, immune therapy has the potential to produce durable, long-lasting cures for cancer. Unfortunately, not all patients respond to immune therapy. In particular, some patients have "cold" tumors that do not contain many immune cells. These tumors resist immune therapy by preventing the infiltration and/or accumulation of T cells in the tumor mass. This grant seeks to discover new ways to make a cold tumor "hot." Specifically, we wish to manipulate the cancer cell to force it to make proteins such as cytokines that recruit immune cells. In essence, our research will turn cancer cells into "suicide cells" that act as beacons for anti-tumor immune cells. We envision that our therapy will amplify and broaden the efficacy of current immune therapies and provide long-lasting remissions for a large swath of cancer patients.

SEQUENCING SINGLE CELLS OF PEDIATRIC BRAIN TUMORS

Transcriptomic and Epigenomic Profiling to Reveal Tumor-Infiltrating Lymphocyte and Microglia Functional Phenotype and Clonality In Pediatric Brain Tumors

Investigators: Anusha Preethi Ganesan, MD (Rady) and P. Vijayanand, PhD (La Jolla Institute)

Brain tumors are the leading cause of cancer-related mortality in children. Despite medical and surgical advances in cancer treatment, a significant proportion of pediatric brain tumors remain incurable and newer treatments are urgently needed. Numerous lines of evidence support a potentially important role for T cell-mediated immunosurveillance of the CNS in mediating protection against cancer. Immunotherapies that boost the anti-tumor responses of T cells have shown promise in many adult cancers, however, translation of their clinical success to pediatric tumors is hindered by a lack of understanding of the tumor immune microenvironment within these tumors. The goal of this project is to define the molecular players and mechanisms involved in anti-tumor immune response in pediatric brain tumors. We will undertake an unbiased and comprehensive approach to define transcriptomic and epigenomic profile of purified tumor-infiltrating lymphocytes (TILs), microglia and other immune cell subsets in a well-characterized cohort of pediatric patients with brain tumors. Utilizing state-of-the-art genomic tools such as single-cell RNA sequencing, ATAC-sequencing and histone ChIP-Seq, we will evaluate the TIL functional phenotype, TCR/BCR sequence and clonality in pediatric brain tumors. In addition, similar analysis in tumor-associated microglia and other key immune cell subsets will unravel their co-regulatory relationship and tumor regulatory mechanisms. Integrated bioinformatics analyses of these datasets will reveal novel immune pathways that may be targeted in immunotherapeutic strategies against pediatric brain tumors.

PADRES PEDAL THE CAUSE

2018 DISCOVERY GRANTS

Every dollar funds life-saving cancer research

IDENTIFYING THE HIDDEN DRIVERS OF ENDOMETRIAL CANCER

Epigenetic Profiling of Endometrial Cancer

Investigators: Diana Hargreaves, PhD (Salk) and Ramez Eskander, MD (MCC)

Endometrial cancer is the fourth most common cancer in women, and the most commonly diagnosed gynecologic cancer, and is rising in both incidence and mortality. While the prognosis for patient with early stage endometrial cancer is quite good, those presenting with advanced stage or recurrent disease have a more guarded prognosis. Treatment often involves surgery to remove the uterus and other affected organs. Radiation and/or chemotherapy are sometimes required to help improve outcomes. Despite advances in surgical management and therapeutics, the 5-year survival for patients with advanced stage or recurrent disease approaches 50% and represents a significant unmet clinical need. In an effort to improve outcomes, researchers are looking to leverage knowledge of genetic events caused by mutations in the DNA sequence that promote or "drive" endometrial cancer. This approach is limited, however, by the effectiveness of targeted therapies for each "driver" event. Indeed, many genetic drivers are non-targetable. Alternatively, we hypothesize that the epigenetic signature of endometrial cancer will reveal many more genes with potential "driver" activity based not on genetic mutation, but modifications at regulatory sequences affecting gene expression. Our approach is to profile 20 endometrial cancer samples from patients treated at the Moores Cancer Center at UC San Diego Health using next-generation sequencing methods. These data will be used to classify endometrial cancers into subtypes and to identify genes on which each subtype depends. Our goal is to develop a classification system based on epigenetic features that will improve diagnosis and help identify novel treatment strategies for endometrial cancer.

EVALUATING THE CAUSE OF T CELL FUNCTION LOSS

Responses of Melanoma Patients to Checkpoint Immunotherapy

Investigators: Linda Bradley, PhD (SBP) and Gregory Daniels, MD, PhD (MCC)

Advances in immunotherapy for cancer have yielded tremendous optimism that even aggressive cancers, including metastatic melanoma, can one day be cured in the majority of patients. However, many patients fail to respond to current treatments, or their tumors become resistant to treatment. It has been proposed that the T cells that are necessary for tumor eradication become refractory to treatment by the development of progressive loss of function. Thus, there is a critical need to better understand the loss of T cell function in patients and to develop new targets for immune modulation by distinct immune mechanisms. We seek to evaluate the responses of melanoma patient T cells to anti-PD-1 blockade, the frequencies of responsive vs non-responsive subsets of T cells, and the potential for blocking a new T cell inhibitory receptor that we discovered, designated PSGL-1, as a new immunotherapy for metastatic melanoma and other cancers.

INCREASING MINORITY PARTICIPATION IN PEDIATRIC CANCER CLINICAL TRIALS

Development and Implementation of a Peer-Navigation Intervention to Improve Research Literacy in Pediatric Cancer Trials

Investigators: Paula Aristizabal, MD (Rady) and Elena Martinez, PhD (MCC)

Whereas Hispanic children will comprise 33% of the U.S. population by 2060 and have higher incidence of their participation in biomedical research is critically low and they have poorer survival rates than non-Hispanic Whites. Interventions to improve research literacy (capacity to understand and act on information to make decisions about research) and clinical trial participation, particularly for Hispanics, are lacking. The objective of this proposal is to improve research literacy in

parents of children with cancer and increase clinical trial participation, particularly for Hispanics by developing and implementing a culturally and linguistically tailored peer-navigation intervention. By increasing minority participation in clinical trials, we can effectively translate discoveries and treatments equally, and, ultimately, improve equity of survival among diverse populations.

CONTROLLING PROTEINS TO ELIMINATE CANCER CELLS

Understanding and Targeting NRF2 in Pancreatic Cancer

Investigators: Michael Karin, PhD (MCC), Andrew Lowy, MD (MCC) and Jorge Moscat, PhD (SBP)

We have identified a protein that is called NRF2, whose expression is elevated in the pancreas of patients suffering from chronic pancreatitis, an inflammatory disease that greatly increases pancreatic cancer risk. Importantly, NRF2 expression remains elevated in established pancreatic cancer. In preclinical studies we found that inhibition of NRF2 expression slows down development of pancreatic cancer in mice subjected to either acute or chronic pancreatitis. These results suggest that developing drugs to lower NRF2 or kill cells with elevated NRF2 may be used to prevent pancreatic cancer in high-risk individuals and may also be effective against established pancreatic cancer. To better understand how NRF2 accelerates the development of pancreatic cancer and provide us with an experimental system suitable for testing of NRF2 targeting drugs, we generated a new mouse model in which the formation of pancreatic cancer is strictly dependent on NRF2. We will use these mice to study how NRF2 controls pancreatic cancer metabolism and determine whether known drugs that inhibit certain aspects of NRF2's tumorigenic activity can be used to prevent pancreatic cancer. We will also asses the therapeutic potential of a new class of prodrugs whose conversion to fully toxic anticancer drugs is NRF2-dependent. We expect such drugs to selectively kill pancreatic cancer cells that possess high NRF2 activity while sparing normal cells in which NRF2 expression is low. These studies will contribute to development of new procedures for prevention and treatment of pancreatic cancer, the deadliest common human malignancy.

BREAKING DOWN TUMOR BARRIERS

Targeting Fibroblast Heterogeneity to Improve Surgical Outcomes in Pancreatic Cancer

Investigators: Ronald M. Evans, PhD (Salk) and Michael Bouvet, MD (MCC)

Currently, the only curative treatment for pancreatic cancer is surgical resection. However, for the majority of patients that undergo surgery, some cancer cells are inadvertently left behind and tumors regrow. The recent development of fluorescence-guided surgery and photoimmunotherapy techniques have tremendous potential to capture these remaining tumor cells and allow surgeons to achieve truly curative resections where patients remain disease free. Importantly, these revolutionary new approaches rely on the delivery of labeled drugs to tumors. One major roadblock for their successful application in pancreatic cancer comes from the presence of a cellular support network (or "stroma") that surrounds the tumor, forming a physical barrier that hides tumor cells and prevents drugs from reaching them. This stromal response is largely driven by a collection of cells known as cancer associated fibroblasts (CAFs). In breakthrough studies, we have found that therapeutically targeting the Vitamin D Receptor (VDR) in CAFs can destabilize this stromal barrier. Here, we will use mouse models that accurately mimic human disease to test if VDR-targeted therapies can aid fluorescence-guided surgery and photoimmunotherapy to improve surgical success rates. In addition, we will use recent advances in single cell genomic analyses to understand precisely how VDR-targeted therapies impact the different types of CAFs that establish stromal barriers for drug delivery. In summary, by combining VDR-targeted therapies with fluorescence-guided surgery and photoimmunotherapy, we believe we are poised to dramatically enhance the success of surgical resection, paving the way for increased patient survival of this deadly disease.

PADRES PEDAL THE CAUSE

2018 DISCOVERY GRANTS

Every dollar funds life-saving cancer research

IDENTIFYING MOLECULES THAT CAN DISRUPT THE GROWTH OF GENETICALLY-ALTERED CANCERS

Targeting a Therapeutic Vulnerability in PTEN-Deficient Brain Tumors

Investigators: Frank Furnari, PhD (MCC) and Geoff Wahl, PhD (Salk)

Glioblastoma (GBM), the most common primary brain tumor in adults, is a highly invasive neurologically destructive tumor with a survival range of 12-15 months, despite aggressive treatment efforts. Like most cancers, gain of function of oncogenes and/or loss of function of tumor suppressor genes are common in GBM, and in addition to bestowing enhanced growth to the tumor, these genetic alterations create collateral dependencies on cellular processes, otherwise known as synthetic vulnerabilities, that can be targeted for cancer therapy. A gene associated with the aggressive nature of GBM is the PTEN tumor suppressor gene, which is affected in ~40% of patients. This proposal aims to leverage this information by establishing a new molecular-based platform designed to rapidly identify molecules able to inhibit the growth of PTEN-deficient GBMs. By focusing on this genetically distinct class of GBMs, this proposal represents a unique personalized therapeutic approach to target an Achilles heel that arises as a consequence of a specific gene mutation.

CELL-BASED IMMUNOTHERAPY TO TARGET AND KILL CHILDHOOD BRAIN TUMORS

Natural Killer Cells for Treatment of Medulloblastoma

Investigators: Dan S. Kaufman, MD, PhD (MCC) and Robert J. Wechsler-Reya, PhD (SBP)

Immunotherapy is emerging as a powerful approach to treating cancer. Most immunotherapies work by increasing the activity of immune cells called T cells, but T cells can only attack tumor cells if the tumor cells display a protein on their surface called MHC-I. In our recent studies of the childhood brain tumor medulloblastoma, we discovered that tumor cells frequently shut off expression of MHC-I, and thereby become invisible to T cells. This raises the possibility that these patients may be insensitive to T cell-based immunotherapy. In contrast, a different type of immune cell called a natural killer cell is not dependent on (and is actually inhibited by) MHC-I, and thus may be better able to kill tumors that do not express MHC-I. In the proposed studies, we will test whether natural killer cells can be used to attack and kill medulloblastoma cells that lack MHC-I. If successful, these studies could markedly increase the numbers of patients who benefit from this type of cell-based immunotherapy.

EFFECT OF GENE EXPRESSION ON TUMOR FEATURES AND SURVIVAL RATES

A Novel Role for Histidine Kinase Activity in Neuroblastoma Pathogenesis

Investigators: Peter Zage, MD, PhD (Rady) and Tony Hunter, PhD (Salk)

Children with aggressive neuroblastoma have poor cure rates despite intensive treatment, and new treatments are needed. Treatments that inhibit important proteins and pathways in neuroblastoma are likely to be more effective with fewer side effects. In our initial experiments, we have identified an association between expression of the NME1 gene and the survival rates of children with neuroblastoma. NME1 can act as a histidine kinase, by adding phosphate to the amino acid histidine in other proteins in neuroblastoma cells, representing a previously undiscovered way for cells to control the function of proteins required for neuroblastoma growth and survival. We propose to evaluate the associations of NME1 expression in tumor samples from children with neuroblastoma with their survival rates and other tumor features, and we will explore

how NME1 functions to affect neuroblastoma growth, survival, and spread. The results of these studies will likely identify new proteins that could serve as targets for new types of treatment, leading to improved success of neuroblastoma therapy and improved chances of survival for children with neuroblastoma.

DEVELOPING NEW MODELS FOR CANCER RISK ASSESSMENTS

Enhanced Breast Cancer Risk Prediction from Imputed Gene Expression

Investigators: Hannah Carter, PhD (MCC) and Graham McVicker, PhD (Salk)

Early detection remains the strongest determinant of long-term disease-free survival across cancer types, however there is a tradeoff between screening for early detection and the risk of false diagnosis and overtreatment. One strategy to optimize this tradeoff is to stratify individuals by genetic cancer risk and to screen more aggressively in high-risk populations. Genetic risk scores have shown some promise for identifying individuals at risk, however, current models use a very simple combination of risk factors and do not account for the complex nature of the underlying biology. In this proposal, we will develop new genetic risk scores that incorporate information about (1) the impact of genetic factors on gene expression, and (2) the relationship between gene expression and disease risk. This proof-of-principle study will be implemented in breast cancer but can easily generalize to a number of cancer types and will provide a framework for future studies of cancer risk biology. The long-term goals of this research are to improve our understanding of the genetic mechanisms that drive cancer risk and to enable accurate identification of high-risk individuals that can benefit from additional screening and prevention.