PADRES PEDAL FUNDED GRANTS

JUNE 2020
Thank you for supporting Padres Pedal the Cause and our mission of accelerating cures for cancer by funding collaborative research among San Diego’s top cancer research institutions and care providers! Our community once again demonstrated record setting growth in 2019, raising $3.1 million and bringing our lifetime raise to over $13.1 million. We are pleased to share a summary of each of the nine grants selected for funding from our 2019 raise. In the pages that follow, learn about the innovative and collaborative research taking place right here in San Diego. We appreciate your support of the vision that unites us: a world without cancer.

**PADRES PEDAL FUNDED PROJECTS – JUNE 2020:**

| Project #1: Medulloblastoma | John M Crawford, MD – Moores Cancer Center / Rady  
|                           | Robert Wechsler-Reya, PhD – Sanford Burnham Prebys |
| Project #2: Neuroblastoma   | Shweta Joshi – Moores Cancer Center  
|                           | Andrew Sharabi – Moores Cancer Center |
| Project #3: All Childhood Cancers | Hari K. Narayan, MD, MSCE – Moores Cancer Center / Rady  
|                           | Saro Armenian, DO, MPH – City of Hope  
|                           | Sun Choo, MD – Moores Cancer Center / Rady |
| Project #4: Neuroblastoma   | Peter Zage, MD, PhD – Moores Cancer Center/ Rady  
|                           | Tony Hunter, PhD – Salk Institute  
|                           | Pablo Tamayo, PhD – Moores Cancer Center |
| Project #5: Pancreatic Cancer | Ronald M. Evans – Salk Institute  
|                           | Gregory Botta – Moores Cancer Center |
| Project #6: Gastric Cancers | Pradipta Ghosh, MD – Moores Cancer Center  
|                           | Michael Bouvet, MD – Moores Cancer Center  
|                           | Garth Powis, PhD – Sanford Burnham Prebys |
| Project #7: Lung Cancer     | Hatim Husain, MD – Moores Cancer Center  
|                           | Nicholas Cosford, PhD – Sanford Burnham Prebys  
|                           | Reuben Shaw, PhD – Salk Institute |
| Project #8: All Cancers     | Susan Kaech – Salk Institute  
|                           | Stephen Schoenberger – La Jolla Institute  
|                           | Sandip Patel – Moores Cancer Center |
| Project #9: Pancreatic Cancer | Rebekah White – Moores Cancer Center  
|                           | Dannielle Engle – Salk Institute  
|                           | Herve Tiriac – Moores Cancer Center |
A pilot trial to test the benefit of real time drug screening to determine individualized treatment plans for children and young adults with relapsed or refractory medulloblastoma

Medulloblastoma is the most common malignant brain tumor in children. Although significant advances have been made in treating medulloblastoma, many patients still die from the disease, and those who survive suffer severe long-term side effects from therapy. Patients who relapse have extremely poor outcomes, and new approaches to treating them are particularly important. We propose to carry out a unique clinical trial in which we take tissue from a patient’s tumors at the time of surgery, sequence it to identify mutations that may be causing the tumor, and also test the sensitivity of tumor cells to drugs that have been used against other cancers. Using this approach, we hope to identify more effective therapies for each patient. Our previous studies have demonstrated the feasibility of performing sequencing and drug testing on patient samples and have shown that these analyses can provide insight into possible therapies. Our proposed trial will test whether this type of analyses can be done in a clinical setting, whether results can be used by a panel of experts to make recommendations for therapy, and whether these recommendations are beneficial for patients. If our approach is successful it will improve outcomes for relapsed MB patients and provide a new paradigm for personalized therapy of other pediatric cancers.
Elucidating the role of Syk kinase and Syk inhibitors combined with radiation therapy in neuroblastoma

Neuroblastoma is a cancer that develops in certain types of nerve tissues and is responsible for more than 15% of all childhood cancer deaths. Despite aggressive treatments including chemotherapy, radiation, and immunotherapy, the five-year survival of children with high risk neuroblastoma is only 40-50%. We are proposing a targeted strategy to make immunotherapy and radiotherapy more powerful in this cancer. In a study performed in mice, we found that Syk kinase controls the response of immune cells called macrophages. When cancer cells start growing in body, macrophages get recruited into the tumor and try to kill and destroy cancer cells, but very soon these macrophages get educated by cancer cells to promote tumor growth and to suppress the activity of other immune cells, especially T cells. This change in phenotype of macrophages does not allow the T cells to enter the tumor and it also interferes with the success of immunotherapy. Similarly, after radiotherapy, macrophages hinder the activity of T cells which leads to tumor relapse. Our studies have shown that inhibiting the action of Syk kinase caused macrophages and T cells to mount a continued response against pediatric tumors grafted onto mice. Moreover, we found that combination of Syk inhibitors with checkpoint inhibitors improved survival of mice grafted with pediatric tumors. Since macrophage response is suppressed in pediatric cancer patients, these results might be translated into therapy against neuroblastoma and can be combined with conventional radiotherapy and checkpoint inhibitors to improve survival of these children.
Improved echocardiographic diagnosis of anthracycline-related cardiac dysfunction using global longitudinal strain

Due to high survival rates and long life expectancy after a childhood cancer diagnosis, there is a large and growing population of nearly 500,000 childhood cancer survivors in the United States, a majority of whom were exposed to anthracycline chemotherapy. Although highly effective at treating cancer, anthracyclines damage the heart and result in high rates of heart dysfunction and heart failure in survivors. Childhood cancer survivors are periodically screened for the development of heart dysfunction. However, standard ultrasound-based heart function screening measurements are inaccurate and may fail to correctly diagnose a substantial percentage of affected individuals. More accurate screening methods are needed.

We propose to study the role of global longitudinal strain, a more sensitive ultrasound-based measure of heart function, in the diagnosis of heart dysfunction in childhood cancer survivors. Using a comparison to heart function measured by magnetic resonance imaging (the most accurate method available), we will determine whether global longitudinal strain can aid in screening procedures in survivors. **In the short-term, our study has the potential to improve heart function screening accuracy in childhood cancer survivors. In the long-term, we intend to build upon these results in future studies that combine the most accurate ultrasound-based methods to optimize early detection and treatment of heart failure in childhood cancer survivors.**
Novel pathways regulated by NME1 in neuroblastoma

Children with aggressive neuroblastoma tumors have poor rates of survival and cure despite intensive treatment, and new therapies are needed. Treatments that block the actions of important proteins and pathways in neuroblastoma tumors are likely to be more effective with fewer side effects. We have identified an association between the levels of the NME1 gene and the rates of survival of children with neuroblastoma. We have also identified an association between the levels of the NME1 gene and signaling pathways that potentially control neuroblastoma cell growth and spread, suggesting that NME1 may be a good candidate target for new neuroblastoma treatments. We propose to determine the genes and pathways in neuroblastoma cells that are controlled by NME1 and to explore how NME1 expression levels and activity affect neuroblastoma tumor cell 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.
Peptide targeted delivery of epigenetic therapies in pancreatic cancer

Pancreatic cancer is a devastating disease with few effective treatments. Moreover, recent immunotherapy approaches that have been remarkably successful in certain cancers have failed in pancreatic cancer. This poor performance of current therapies is in large part due to the presence of a complex cellular support network or stroma that surrounds the tumor. Importantly, the presence of the stroma compromises the immune response as well as drug delivery to the tumor. Cancer associated fibroblasts (CAFs) are major contributors to this stromal response, and as such, approaches that reduce the activities of CAFs may improve the effectiveness of existing therapies. Towards this end, we have promising findings that the epigenetic drug OTX can reduce the tumor supporting and immune suppressive actions of CAFs. However the adverse side effects of OTX are prohibitive.

Here we will explore whether targeting technologies that focus drug delivery to the pancreas are able to reduce the adverse effects of OTX, and whether the therapeutic effects of this combination therapy are sufficient to enable immunotherapies. In addition, we will explore whether the existing targeting approach can be modified to selectively target the critical CAF population. These studies will be undertaken in mouse models that accurately mimic human disease, where the effects of therapy combinations on disease burden and ultimately survival will be measured. The potential of these studies to improve the effectiveness while simultaneously reducing the adverse effects of existing therapies, as well as to sensitize pancreatic cancer to immunotherapies, could profoundly increase patient survival.
Precision interception of gastric cancers

A team of researchers comprised of engineers, cancer biologists, and physician-scientists have joined forces to intercept the devastating disease that is Gastric Cancer (GC). GCs often present as advanced disease and kill silently. Fortunately, this disease has well known triggers, e.g., the cancer-causing bug, Helicobacter pylori (Hp) and some poorly understood, but definite pre-cancerous states that are typically not treatable by surgery but could be specifically intercepted with medical treatment. Currently, no such treatment exists; this team seeks to change just that.

This team is deploying a new set of mathematical tools for finding precise drugs that prevent GCs and utilizing human stem-cell based disease models for target validation. The team has already created the first-ever map of how GCs begin and has defined the most important steps of GC progression that could be precisely intercepted with drugs. **Going forward, their goal is to validate ~3-6 new drugs, some aimed for prevention and others for halting metastatic disease.**

**There are 2 reasons why this team is likely to succeed where others have failed:**

First, when it comes to drug discovery in GC, this team employs precise and unbiased AI-based approaches to expose previously unknown and undefined intermediate stages before GCs and reveal how to stop progression.

Second, when it comes to drug testing, this team has developed human models that are reverse engineered with the GC-causing bug, the stomach lining and the immune cells to mimic the human “stomach-in-a-dish”. These human-relevant models are expected to enable rapid translation of discoveries.
Examination of inhibitors of the ULK1 autophagy kinase as therapeutics in non-small cell lung cancer

Lung cancer is the number one cause of cancer deaths per year, causing more deaths annually than colon, breast, and prostate cancer combined. One of the reasons underpinning the high mortality rate of lung cancer is the rapid development of therapeutic resistance to chemotherapies, as well as resistance to targeted therapies in those select patients for which genetically targeted therapies are applicable. ULK1 is a key enzyme in a cellular process known as autophagy. Autophagy is normally used in cells to survive starvation conditions by recycling internal stores of nutrients, but autophagy gets upregulated in tumor cells, especially in response to therapy. We hypothesize that autophagy allows lung cancer cells to evade cell death in response to chemo- and targeted therapies, causing resistance. We have very recently developed new orally available small molecule inhibitors of ULK1, which we have shown suppress autophagy and work without toxicity in animal models. Here we propose to test our new ULK1 inhibitors in the first-of-its-kind study for the treatment of lung cancer, and further to specifically to see if they will re-sensitize human tumor samples to standard therapies. We believe autophagy inhibitors have unique promise against a broad set of lung cancers, when used in combination with existing therapeutics.
Neoantigen-specific T cell responses in exceptional responders to immunotherapy in non-small cell lung cancer

A breakthrough in cancer treatment is drugs aimed to revitalize our immune system to attack cancer, also known as immunotherapies. However, the majority of patients are non-responders or their cancer develops resistance months after initially responding to therapy (progressors). A few patients on the other hand, are ‘exceptional responders’ who experience complete cures with tumors melting away within months. In order to find a “true” cure for cancer, it is critical to understand why some patients’ tumors completely regress and others do not. This pilot project will address this question in a way that has not been investigated before by comparing the immune responses induced between ‘exceptional responders’, ‘progressors’ and ‘non-responders’.

By definition, tumors are created by mutations that allow it to outgrow normal tissue. These mutations create ‘neoantigens’ that could potentially induce immune reactions. Many have tried to identify biomarkers that correlate with positive outcomes, but no study has systematically compared the number or quality of tumor-reactive T cells across these groups to correlate with clinical outcome. We have a time-series of blood samples collected from more than 20 patients with metastatic lung cancer treated with a form of immunotherapy called KEYTRUDA (pembrolizumab) who vary in their responses to treatment. Importantly, we have cryopreserved many T cells from each patient that we can use to enumerate tumor-reactive T cells between patients with different outcomes. This type of analysis may provide the best understanding of patient responses to immunotherapy to date.
### PROJECT FOCUS

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### AWARDEES

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**Defining the mechanisms of pancreatic cancer susceptibility in patient-derived organoid models**

Pancreatic cancer (PDA) is a deadly malignancy. Most PDA patients are diagnosed with late-stage disease and no longer benefit from surgery, the only curative treatment for this disease. Early detection would greatly increase the number of patients who receive this life-saving surgery. Unfortunately, diagnostic tests with the necessary specificity for pancreatic cancer are not available. This is due in part to the difficulty in discriminating between pancreatic cancer and pancreatitis. Pancreatitis is a common type of pancreatic inflammation that resolves naturally in most patients and has a low mortality rate. However, it shares several features with PDA, including the development of fibrotic scar tissue, making it difficult to distinguish between patients with pancreatitis and PDA. We propose to make models from pancreatitis patients that will enable in depth comparison to a collection of models already generated from normal pancreas and pancreatic cancer patients. This will facilitate the discovery of biomarkers that are unique to pancreatic cancer and can be used for early detection.

Several populations exhibit elevated risk for developing pancreatic cancer. Patients with chronic pancreatitis are at 3.5-fold higher risk than the general population and patients with hereditary pancreatitis have a 40-55% lifetime risk of developing PDA. However, the underlying cause of this increased risk is largely unknown. To develop prevention approaches for this at-risk patient population, we need a better understanding of why they have increased susceptibility to cancer. Therefore, we will use the models we generate from pancreatitis patients to uncover the source of pancreatic cancer risk.