PADRES PEDAL THE CAUSE
FUNDED GRANTS

2020 Grant

TYPE OF CANCER FUNDED	AWARDEES	
Prostate	**Dr. J. Kellogg Parsons**	UC San Diego Health
	Dr. Rana McKay	UC San Diego Health
	Dr. Christina Jamieson	UC San Diego Health

CLINICAL TRIAL: A Phase 1B, Nonrandomized Trial Investigating Docetaxel Combined with Cirmtuzumab in Patients with Metastatic Castration

Metastatic castration resistant prostate cancer (CRPC) is a lethal disease that claims 30,000 lives annually in the U.S. Although current approved drugs will slow the growth of metastatic CRPC, development of drug resistance—and cancer progression—is inevitable. It is therefore imperative to develop new treatments to improve survival. As we learn more about the factors driving progression of metastatic prostate cancer, we have discovered that the Wnt signaling pathway is activated in these patients. The Wnt pathway possibly confers resistance to standard drug treatments, including hormone therapy and chemotherapy. Prior attempts to target this pathway have been unsuccessful. Cirmtuzumab, a ROR1-binding monoclonal antibody which inhibits the Wnt pathway, is a compelling new drug with the potential to treat CRPC by blocking Wnt activity. Cirmtuzumab was developed at UCSD by Drs. Kipps, Jamieson, and Carson. Studies are underway in chronic lymphocytic leukemia and breast cancer. We hypothesize that the addition of cirmtuzumab to docetaxel, a chemotherapy drug, will be safe and effective for patients with metastatic CRPC. To test this hypothesis for the first time, we propose a clinical trial of cirmtuzumab combined with docetaxel in men with prostate cancer. To better understand mechanisms of drug resistance, and which patients might benefit most from cirmtuzumab, we will perform molecular analyses of cancer tissue and blood samples throughout the study. This multidisciplinary, collaborative effort harnesses the expertise of clinical and laboratory scientists at UCSD; and if successful, may reveal a new and unique drug to improve survival for patients with CRPC.

INSTITUTIONS
UC San Diego Health

2020 Grant

TYPE OF CANCER FUNDED	AWARDEES	
Pancreatic	**Dr. Alexandra Newton**	UC San Diego Health
	Dr. Andrew Lowy	UC San Diego Health

TEAM SCIENCE AWARD: Protein Kinase C as a Novel Biomarker and Target in Pancreatic Cancer

Pancreatic cancer remains one of the deadliest and most aggressive types of cancer, with a five-year survival rate of 9%. We recently discovered that the levels of two proteins predict survival outcome. One protein, PKC, is a tumor suppressor and the other protein, PHLPP1, is its negative regulator that controls how much PKC is present. We found that in pancreatic cancer, high PHLPP1/low PKC correlated with poor prognosis: in a cohort of 105 patients, none survived longer than five years. But 50% of patients with low PHLPP1/high PKC survived longer than 5 years. This proposal Aims to set the stage for clinicians to one day use a pancreatic cancer patient's PHLPP1/PKC levels as a predictor for prognosis, and for researchers to develop new therapeutic drugs that inhibit PHLPP1 and boost PKC as a means to treat the disease.

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2020 Grant

TYPE OF CANCER FUNDED	AWARDEES	
Myeloid Leukemia	**Dr. Tannishtha Reya**	UC San Diego Health
	Dr. Edward Ball	UC San Diego Health
	Dr. Rafael Bejar	UC San Diego Health

TEAM SCIENCE AWARD: New Therapies for Myeloid Leukemia

Acute Myelogenous Leukemia (AML) is a cancer marked by rapid and uncontrolled growth of immature cells of the myeloid lineage. Although it is the most common acute leukemia in adults, current treatments, which include chemotherapy and bone marrow transplantation, are largely ineffective, leading to relapse and death in most patients. AML also occurs in children, and pediatric AML has a much poorer outcome than other childhood leukemias. In light of these issues, AML represents a disease with a significant unmet medical need. Given that there have been no new therapies for AML in the last 30-40 years, identifying new approaches to target AML is critically important. At a cellular level, AML is heterogeneous and has been shown to be driven by cancer stem cells. Thus strategies aimed at inhibiting cancer stem cell growth and renewal may target the fundamental propagative abilities of the tumor and allow development of a more targeted therapy. Importantly, AML can often arise from early stage myeloid disorders such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN), thus also providing an opportunity to block its progression at earlier stages. Our goal is to develop a new therapeutic agent that can block growth and progression of these myeloid disorders. To this end we have developed antibodies that target a protein required for AML growth. We will test whether these antibodies can block progression of MDS/MPN to AML and improve outcomes. If successful, these exciting studies could to lead to a new treatment strategy for myeloid leukemia.

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UC San Diego Health

2019 Grant

TYPE OF CANCER FUNDED	AWARDEES
Pediatric	**Dr. Graham McVicker** Salk Institute for Biological Studies **Dr. Jennifer Elster** Rady's Children's Hospital

ACCELERATING KNOWLEDGE OF GENETIC MUTATIONS IN NEUROBLASTOMA

Neuroblastoma is a devastating cancer of the sympathetic nervous system that most commonly affects very young children; 90% of patients are diagnosed by 5 years of age and the highest rate of diagnosis in the first month of life. Neuroblastoma patients are currently stratified into low-, intermediate- and high-risk groups based on their age at diagnosis, pattern of metastases, and the genetic mutations in their tumor. Unfortunately the accuracy of risk stratification is hampered by limited genetic understanding of the mutations that drive disease progression and relapse. Improved knowledge of the genetic mutations that are important for neuroblastoma could lead to advances both in neuroblastoma risk stratification and to new therapeutic approaches. This study will focus on learning how mutations affect genes indirectly by changing their expression instead of the genes themselves. It will identify mutations in neuroblastoma tumors that occurred in the parents or early in embryonic development. **These types of mutations may be more important in neuroblastoma than other cancers because of its extremely early age of onset.**

Accelerating discoveries in pediatric neuroblastoma patients and new approches to treatments.

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salk Where cures begin.

Rady Children's Hospital San Diego

2019 Grant

TYPE OF CANCER FUNDED	AWARDEES
Pediatric	**Dr. Jean Wang** UC San Diego Health **Dr. Richard Kolodner** UC San Diego Health **Dr. Sun Choo** Rady's Children's Hospital

OVERCOMING RESISTANCE TO CURRENT BONE CANCER CHEMOTHERAPY

Ewing sarcoma (ES) is a bone cancer that affects children and young adults. Despite aggressive treatment survival remains poor because of resistance to chemotherapy. This study will investigate a new drug target, FEN1, to overcome resistance to current therapy. FEN1 is an enzyme that helps with DNA replication. Other research has shown that ES cells behave like BRCA- deficient cells, which are known to be hypersensitive to FEN1 inhibition. ES cells are also sensitive to removal of FEN1 by a process that uses CRISPR, a gene editing technology, to knockout genes. Further, ES cells from at least one patient are hypersensitive to the FEN1 inhibitor, SMD2485. This project will provide the necessary pre-clinical data for evaluating FEN1 as a drug target to treat ewing sarcoma.

A collaboration to accelerate new drug targets for ewing sarcoma.

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UC San Diego Health

Rady Children's Hospital San Diego

2019 Grant

TYPE OF CANCER FUNDED	AWARDEES
Pediatric	**Dr. Tony Hunger** Salk Institute for Biological Studies **Dr. Peter Zage** UC San Diego Health

TARGETING NEW TREATMENTS FOR CHILDREN WITH NEUROBLASTOMA

Children with aggressive neuroblastoma have poor cure rates despite intensive treatment, and new therapies are needed. Treatments that inhibit important proteins and pathways in neuroblastoma tumors are likely to be more effective with fewer side effects. We have identified an association between expression of the NME1 gene and the survival rates of children with neuroblastoma, suggesting that NME1 may be a good candidate target for new neuroblastoma treatments. 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 explore how the NME1 histidine kinase affects neuroblastoma tumor cell maturation, 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.**

Identifying new targets for neuroblastoma.

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TYPE OF CANCER FUNDED	AWARDEES
Colorectal	**Dr. Soumita Das** UC San Diego Health **Dr. Svasti Haricharan** Sanford Burnham Prebys **Dr. Pradipta Ghosh** UC San Diego Health **Dr. Debashis Sahoo** UC San Diego Health, Rady's Children Hospital **Dr. Sherry C. Huang** Rady's Children Hospital **Dr. Scott Peterson** Sanford Burnham Prebys

PROTECTING THE GUT AND HALTING COLON CANCER GROWTH

Chronic infections, stemming from an abnormal immune response, fuels inflammation, tissue destruction and DNA damage. Infection-associated inflammation can even initiate and fuel cancers. This grant revolves around the discovery, characterization, disease modeling and harnessing the diagnostic and therapeutic potential of a novel tumor suppressive pathway in the gut that normally protects the gut barrier from the luminal microbes but is lost during the initiation of colon cancers. The combined synergy of several transdisciplinary approaches is used to reveal when and how the microbes may alter host cell properties to ultimately fuel cancer initiation. The grant promises to deliver a therapeutic target/therapy for protecting the gut from these cancer-causing microbes and halt the formation and progression of colon polyps, and to validate a novel set of markers for predicting which polyps in the colons are at highest risk for progressing to colon cancers.

Predicting and halting polyp formation and colon cancer.

INSTITUTIONS

Rady Children's Hospital San Diego

UC San Diego Health

SBP Sanford Burnham Prebys MEDICAL DISCOVERY INSTITUTE

2019 Grant

TYPE OF CANCER FUNDED	AWARDEES
Brain	**Dr. Joseph Ecker** Salk Institute for Biological Studies **Dr. Jeremy Rich** UC San Diego Health **Dr. Jess Dixon** Salk Institute for Biological Studies

DRIVING PROGRESS IN GIOBLASTOMA

Glioblastoma (GBM) is the most lethal malignant brain tumor with a dismal median survival of less than 15 months. GBMs contain heterogeneous cell populations, including a glioblastoma stem cell (GSC) population that drives tumor growth and mediates therapeutic resistance. Cell type heterogeneity is a major contributor to the therapeutic resistance of glioblastoma. The goal of this project is to understand the molecular identity of different cell types in glioblastoma tumors. Using single-cell strategies, the project will reveal the gene regulatory programs that drive the progression of glioblastoma.

Understanding gene regulatory programs to combat gioblastoma.

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2019 Grant

TYPE OF CANCER FUNDED	AWARDEES
All	**Dr. Seth Field** UC San Diego Health **Dr. Michael Jackson** Sanford Burnham Prebys

A NEW PATHWAY TO FRACTIONING CANCER

To more effectively combat cancer, we need new therapies directed at new targets. This project discovered a signaling pathway involving a protein called GOLPH3 that drives a high fraction of cancers that together cause a high proportion of cancer deaths, including lung, breast, prostate, and colorectal cancers. The GOLPH3 pathway is unlike other pathways that drive cancer, and so inhibitors of the pathway provide a unique approach to cancer treatment. Existing data indicate that inhibition of the GOLPH3 pathway preferentially kills cancer. This project has identified a potent inhibitor of the pathway, and proposes experiments to better define its mechanism of action. This will enable further development to produce a compound that would be suitable as a novel therapeutic agent, completely unlike all current therapeutic strategies for cancer.

Understanding pathways that could limit growth of many cancers.

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UC San Diego Health SBP Sanford Burnham Prebys MEDICAL DISCOVERY INSTITUTE