Cancer Research Coordinating Committee

Abstracts for Awards Supported Through California Cancer Research Voluntary Tax Contributions

Table of Contents

Click on project titles to see full abstracts

Cancer Research Coordinating Committee

Abstracts for Awards Supported Through California Cancer Research Voluntary Tax Contributions

PI First Name	PI Last Name	Title	Host Campus/Institution	Start Date
Peter	**Zage**	Targeting Oncogene-Induced Replication Stress for Neuroblastoma	San Diego	10/1/2024
Jack	**Bui**	Self-amplifying mRNA to co-opt anti-viral responses for tumor immune therapy	San Diego	10/1/2023
Naseem	**Esteghamat**	Identifying Disparities in Autologous HCT Utilization for DLBCL in California	Davis	10/1/2023
Kent	**Leach**	Influence of growth hormones and mechanical loading on osteosarcoma progression	Davis	10/1/2023
Karen	**Lindsay**	Exploring pathways for fetal programming of offspring cancer risk through prenatal diet	Irvine	10/1/2023
Yunxia	**Lu**	A feasibility study of remote diet-related small habits intervention in cancer survivors	Irvine	10/1/2023
Dionicio	**Siegel**	Small Molecule Inhibition of GNAS; Creating the First Targeted Treatments for Appendix Cancer	San Diego	10/1/2023
Jeffrey	**Esko**	Heparan Sulfate Biomarker for Pancreatic Cancer	San Diego	10/1/2022
Matthew	**Hangauer**	Decoding Cancer Acquired Drug Resistance	San Diego	10/1/2022
Gerardo	**Mackenzie**	Evaluation of ketogenic diet strategies for pancreatic cancer-associated cachexia	Davis	10/1/2022
Kara	**McCloskey**	Integrated Model of Cancer, Vasculature, and Immune System	Merced	10/1/2022
Jun	**Sheng**	Flexible Robotic Evacuator for Minimally Invasive Brain Tumor Therapy	Riverside	10/1/2022
Hao-Chuan	**Wang**	Enhancing Online Group Fitness Exercise for Health Improvement for Patients with Cancers	Davis	10/1/2022
Tayloria	**Adams**	Electrical Impedance Spectroscopy for Monitoring the Chemoresistance of Prostate Cancer Cells	Irvine	10/1/2021
Michael	**Campbell**	Evaluating cost effective care for differentiated thyroid cancer	Davis	10/1/2021
Nicholas	**Pannunzio**	Etiology of Ph-like ALL and the mechanisms driving Latinx cancer disparities	Irvine	10/1/2021
Feng	**Qiao**	Cancer therapeutics via small molecule-mediated p53 mutant reactivation	Irvine	10/1/2021
Candice	**Sauder**	Outcomes for premenopausal women with triple negative secondary breast cancer	Davis	10/1/2021
Weiwei	**Zhang**	Neurocognitive Processes for Mammographic Detection of Breast Cancer	Riverside	10/1/2021

Cancer Research Coordinating Committee

Abstracts for Awards Supported Through California Cancer Research Voluntary Tax Contributions

PI First Name	PI Last Name	Title	Host Campus/Institution	Start Date
Dorothy	**Apollonio**	Effects of tobacco and cannabis policy implementation on consumption	San Francisco	10/1/2020
Jeremy	**Chien**	Advancing VCP inhibitors as experimental therapeutics in ovarian cancer	Davis	10/1/2020
Michael	**Hoyt**	Biobehavioral Intervention to Reduce Adverse Outcomes in Young Adult Latinos with Testicular Cancer	Irvine	10/1/2020
Chang-il	**Hwang**	Epigenetic landscape of DNA methylation in pancreatic cancer progression	Davis	10/1/2020
Loren	**Mell**	"Lymphomizing" Treatment of Head and Neck Cancer using Involved Field RT with Chemo-Immunotherapy	San Diego	10/1/2020
Tyler	**Seibert**	A polygenic score for prediction of aggressive and fatal prostate cancer in multi-ethnic populations	San Diego	10/1/2020
Zuzanna	**Siwy**	Label free, high throughout detection and separation of individual breast cancer stem cells	Irvine	10/1/2020
Elysia	**Alvarez**	Patterns of Care and Outcomes in AYAs with Germ Cell Tumors	Davis	1/1/2020
Lee	**Bardwell**	Novel Links Between Wnt Signaling, Centrosomes, and Cancer	Irvine	1/1/2020
J. Sebastian	**Gomez Diaz**	Detecting tumor-specific exosomes on a chip	Davis	1/1/2020
Selma	**Masri**	Linking the Circadian Clock and Cancer	Irvine	1/1/2020
Sha	**Sun**	Downregulation of XIST in Ovarian Cancer and Its Mechanisms	Irvine	1/1/2020
Sora	**Tanjasiri**	Samoan Healthy Eating and Active Living (HEAL)	Irvine	1/1/2020
Carolina	**Arias**	Unveiling targets for treating malignancies of viral origin	Santa Barbara	1/1/2019
Siddharth	**Dey**	Studying tumor heterogeneity using single-cell epigenomics	Santa Barbara	1/1/2019
Douglas	**Kellogg**	Control of cell growth in normal and transformed cells	Santa Cruz	1/1/2019
Pradip	**Mascharak**	Improving outcome of cancer chemotherapy with CO	Santa Cruz	1/1/2019

Cancer Research Coordinating Committee

Abstracts for Awards Supported Through California Cancer Research Voluntary Tax Contributions

PI First Name	PI Last Name	Title	Host Campus/Institution	Start Date
Laura	**Romo**	Think Biology: Healthy Teen Lifestyles and Cancer Prevention	Santa Barbara	1/1/2019
Jin	**Zhang**	Photothermal Therapy of Oral Squamous Cell Carcinoma	Santa Cruz	1/1/2019
Scott	**Atwood**	Recurrent GLI mutations in drug-resistant skin cancer	Irvine	1/1/2018
Robert	**Canter**	Outcomes in Stage IV Cancer Patients with Bowel Obstruction	Davis	1/1/2018
Frederic	**Chedin**	R-loop Driven Oncogenic Translocations in Prostate Cancer	Davis	1/1/2018
Celia	**Goulding**	Repurposing a toxin-immunity pair to selectively kill cancer	Irvine	1/1/2018
Michael	**Kent**	The Role of p21 Phosphorylation at S123 in Tumor Suppression	Davis	1/1/2018
Kai	**Kessenbrock**	Studying breast cancer initiation in single cell resolution	Irvine	1/1/2018
Noriko	**Satake**	Leukemia Stem Cells in B-Cell Acute Lymphoblastic Leukemia	Davis	1/1/2018
Szu-Wen	**Wang**	Novel cancer metabolite-triggered drug delivery	Irvine	1/1/2018
***Stella**	**Tommasi**	Investigating the carcinogenicity of e-cig	USC	7/1/2016
***Celia**	**Kaplan**	Lung Cancer Screening: The Views of Patients and Physicians	San Francisco	7/1/2015
***Dian**	**Yang**	Genomic approaches to identify SCLC biomarkers	Stanford	7/1/2015
***Xiaohe**	**Liu**	CTCs for early detection and characterization of lung cancer	SRI	12/1/2014
***Michael**	**McNitt-Gray**	Ultra Low Dose, Effective CT for Lung Cancer Screening	Los Angeles	8/1/2013
***Lori**	**Sakoda**	Shared Genetics of COPD and Lung Cancer	Kaiser	8/1/2013
***Rod**	**Lew**	Alliance for Data Dissemination to Achieve Equity (ADEPT)	APPEAL	5/1/2011

**Awards funded through Tobacco-Related Disease Research Program*

Altering germline BRCA2 mutant RNA to restore protein function

Campus: UCSD
Principal Investigator: Corina Antal
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $95,000

Abstract:
Breast cancer gene 2 (BRCA2) is a tumor suppressor that plays a crucial role in safeguarding genomic stability by repairing DNA double-stranded breaks through homologous recombination. Germline mutations in BRCA2 disrupt its function and compromise this repair mechanism, leading to the accumulation of genetic alterations, thus significantly increasing the risk for breast cancer. Currently, the primary recourse for reducing cancer risk associated with BRCA2 mutations is prophylactic surgery or chemoprevention. Consequently, there is an urgent need for less life-altering preventive strategies for those at risk. In germline BRCA1/2 carriers, cancer cells utilize alternative mRNA splicing to bypass deleterious germline BRCA1/2 mutations to restore function and confer therapeutic resistance to genotoxins. We propose an innovative approach to mimic this natural phenomenon, leveraging gene therapy strategies to modulate splicing of mutant BRCA2 pre-mRNA in order to restore functional protein expression and mitigate cancer risk. In Aim 1, we aim to restore BRCA2 function using antisense oligonucleotides (ASOs) that induce exon 10 skipping to bypass pathogenic variants within this exon. BRCA2 exon 10 harbors ~11% of pathogenic germline variants and it has been shown that deletion of this exon retains 81% of BRCA2 homology-directed repair function. Our lead ASO demonstrates >95% exon 10 skipping in proof-of-concept studies and demonstrates an increase in BRCA2 expression. In Aim 2, we will induce cryptic splice site usage to restore BRCA2 function utilizing small nuclear RNAs (snRNAs) programmed to bind non-canonical splice sites within exon 11, which harbors the majority of pathogenic germline variants. We identified two noncanonical splice sites within exon 11 that retain critical functional domains. We will optimize and validate the effectiveness and specificity of our targeting approach in transformed and non-transformed BRCA2 mutant cell lines, including primary fibroblasts we derived from a BRCA2 carrier. Functional in vitro and in vivo assessments will be employed to assess the therapeutic potential of our lead candidates. Completion of the proposed studies will establish a foundation for this approach, potentially paving the way for the clinical evaluation of innovative prophylactic strategies tailored for BRCA2 mutation carriers.

Investigating the role of tissue-derived extracellular vesicles in cancer origin and progression

Campus: UCSB
Principal Investigator: Marley Dewey
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
The extracellular matrix (ECM) provides critical mechanical and biological cues which can impact the start and progression of cancer. Recently, a new biological component has been discovered residing in the ECM, termed matrix-bound nanovesicles (MBVs). MBVs are a type of extracellular vesicle (EV), or lipid nanoparticle carrying functional nucleic acid and protein cargo, secreted by all cells for cell-cell communication. There is strong evidence supporting the role of other EVs in cancer progression and metastasis, such as liquid-EVs (derived from blood, conditioned cell culture medium, others); however, due to the newly discovered nature of MBVs, we lack a clear understanding of the role of MBVs in cancer. The goal of this proposal is to determine differences between cancerous MBVs and liquid-EVs, how culture conditions such as stiffness influence EV production, and the influence of cancerous MBVs on cancer origin and progression. We hypothesize that as a component of the ECM, MBVs will be different from liquid-EVs and will significantly promote cancer progression through different mechanisms than liquid-EVs. While we propose to examine the influence of osteosarcoma-derived MBVs, these results can be broadly applicable to any tissue-resident cancer. We will accomplish this in the following aims:
Aim 1: How does oncogenic cargo change across EV types and microenvironment culture conditions? We will isolate MBVs from the ECM and liquid-EV from conditioned cell culture medium from MG-63 cells cultured on 2D well plates, 3D collagen gels (soft), and 3D mineralized collagen gels (stiff). We will then perform proteomics on these EVs to determine differences between MBVs and liquid-EVs.
Aim 2: Do MBVs from cancer cells promote cancer-associated lung fibroblast and mesenchymal stem cell differentiation? MBVs and liquid-EVs isolated from Aim 1 will be added to mesenchymal stem cells and lung fibroblasts to examine whether mesenchymal stem cells and fibroblasts differentiate towards cancer-associated fibroblasts on exposure to MBVs, and if these cells secrete pro-tumorigenic cytokines.
Impact: This would be one of the first studies to examine the impact of MBVs on cancer origin, one of the first to examine how culture conditions influence cancerous MBV cargo, and these results will contribute to our understanding of the role of EVs and the ECM in cancer.

Kinase-Ribosome Interactions: A New Strategy to Target mRNA Translation Dysregulation in Cancer

Campus: UCD
Principal Investigator: Christopher Fraser
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
The dysregulation of mRNA translation is common in cancer, where increased protein synthesis supports rapid cell growth and proliferation. Targeting the translation machinery has become a potential cancer therapy. Translation dysregulation promotes cancer through two main mechanisms: 1) enhancing the translation of cancer-promoting factors (e.g., c-Myc, Cyclins, MCL-1, SNAIL) and 2) upregulating metabolic proteins that help cancer cells adapt to nutrient and oxygen shortages.
The recruitment of mRNA to the ribosome is coordinated by eukaryotic initiation factors (eIFs). A key factor, eIF4F, binds to the 5' end of mRNA to facilitate its recruitment. eIF4F activity is regulated by two major signaling pathways: 1) the mechanistic target of rapamycin complex 1 (mTORC1) and 2) the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway. Growth signals and stress also activate the MNK1 kinase, which phosphorylates eIF4F, boosting translation of mRNAs that promote cell survival and metastasis (e.g., c-Myc, MMP3, MMP9, Snail, Cyclin D1).
Dysregulation of mTORC1 and MNK1 in cancer has driven efforts to target these kinases in chemotherapy. However, a comprehensive understanding of how these kinases regulate translation remains elusive, largely because their interactions with the ribosome and associated eIFs are not yet fully understood. This knowledge gap stems from the lack of quantitative assays to study kinase-ribosome interactions. By elucidating these interactions, we aim to uncover novel therapeutic strategies for targeting these kinases in cancer.
To achieve this, we have developed a unique purified reconstituted system for human translation initiation that uses fluorescently labeled components. Using this system, we will develop fluorescence-based assays to monitor MNK1 activation and binding to the ribosome and eIFs. We will test resulting interaction models using cancer models in collaboration with Davide Ruggero at UCSF. Our work, supported by a CRCC seed grant, will form the basis for an NCI R01 proposal to expand our studies to mTORC1 and other protein kinases. Ultimately, our goal is to understand how protein kinases interact with the ribosome, opening new avenues to target them for cancer treatment.

Deciphering the bioelectrical signatures of cancer cells

Campus: UCLA
Principal Investigator: Yu Huang
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
Cancer cells demonstrate distinct electrical properties compared to normal cells, while the ensemble data from cells or tissues usually masked the important nuances essential in understanding the bioelectrical signatures of different cancer cells or cancer cells at different stages. The objective of this proposal is to develop a generic electrochemical transport spectroscopy platform that can be used to accurately probe, monitor and regulate the electronic properties of cancer cell, leading to in-depth understanding of cancer bioelectricity and the exploitation of the new knowledge for novel targeted cancer treatment.

Targeting p300/CBP to inactivate cancer-associated fibroblasts in pancreatic cancer

Campus: UCD
Principal Investigator: Chang-il Hwang
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $95,000

Abstract:
Pancreatic cancer is one of the deadliest human cancers, with survival rates remaining alarmingly low despite advances in treatment. A significant challenge in treating pancreatic cancer is its dense desmoplastic stroma, a fibrous network surrounding the tumor. This stroma acts as a physical barrier that blocks drug delivery and fosters an immunosuppressive environment, rendering immunotherapy largely ineffective. As a result, targeting the tumor's stroma has emerged as a promising strategy to improve drug access and reshape the tumor microenvironment for enhanced therapeutic outcomes. While our research has previously focused on the epigenetic alterations in pancreatic cancer cells, we are now expanding our efforts to understand the tumor microenvironment, particularly cancer-associated fibroblasts (CAFs). CAFs play a critical role in the development of the tumor stroma. When activated, these fibroblasts undergo dramatic epigenetic changes that contribute to the growth and progression of pancreatic cancer. In our recent study, we identified a novel approach to revert CAF activation by targeting key epigenetic regulators. Specifically, we found that epigenetic drugs, such as p300/CBP inhibitors, can inactivate CAFs, thereby reducing the formation of desmoplastic stroma and potentially improving the tumor's response to therapy. This work not only highlights a new avenue for targeting the stroma in pancreatic cancer but also underscores the importance of understanding epigenetic mechanisms in the tumor microenvironment.

Refinement and usability of e-support for pancreatic cancer patients

Campus: UCI
Principal Investigator: Jacqueline Kim
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $95,000

Abstract:
Pancreatic cancer is often found at an advanced and incurable stage. The burden of this disease and its treatment are substantial and the threat of mortality can trigger significant distress in patients, who have markedly elevated suicidality. Timely information and psychological support are critical in order to alleviate distress and to support decision-making. However, many healthcare systems are under-resourced to provide adequate support. Patients may also be unable to regularly attend supportive care sessions because of the demands of their treatment or personal circumstances. New modalities of early psychoeducation and psychological support are required to meet the needs of patients with pancreatic cancer. We propose to narrow the gaps in the unmet needs of patients by examining the feasibility of an e-intervention that combines existing psychoeducational and psychotherapeutic interventions designed for patients with pancreatic cancer; the 'Living Well with Pancreatic Cancer' psychoeducation and the e-version of 'Managing Cancer and Living Meaningfully' (CALM) psychotherapy. We will (Aim 1) conduct focus groups with 6-10 healthcare professionals from the UC Pancreatic Cancer Consortium to refine the e-intervention. Then, we will (Aim 2) test the feasibility of asynchronous e-training of e-counselors across consortium sites (UCI, UCSF, UCSD), and (Aim 3) evaluate the usability of the e-intervention with 10 pancreatic cancer patients across the consortium sites. Results from the study will result in an e-intervention that enhances patients' capacity for self-management, coping and emotional processing, communication with loved ones and healthcare providers, planning for the future, and utilizing community supportive resources. A community advisory board comprised of pancreatic cancer-related organization members and pancreatic cancer survivors and caregivers will inform the research, with effort to represent California's demographic diversity. Findings will provide data for larger NIH, DoD, or PCORI grant submissions for further intervention refinement if necessary, or a randomized controlled trial. Ultimately, this research will inform the development of accessible psychosocial support for patients with pancreatic cancer nationally.

AI-powered discovery of inhibitors for the orphan GPCR BB3, a new target in lung adenocarcinoma

Campus: UCSD
Principal Investigator: Irina Kufareva
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $95,000

Abstract:
Despite advances in targeted therapy, the non-small-cell lung adenocarcinoma (LUAC) remains one of the biggest causes of mortality in the US. The team of co-PI Nicola Smith at UNSW discovered that an orphan G protein-coupled receptor (oGPCR), - the 'bombesin' receptor BB3, - is highly upregulated in LUAC but not in the healthy lung. In fact, BB3 expression is vanishingly low in normal healthy adult tissue, making it a uniquely specific receptor in LUAC. However, how BB3 contributes to LUAC progression, and whether its inhibition is synergistic or deleterious to current LUAC therapies, is unknown. Importantly, as with other oGPCRs, the exploration of this question is hindered by the lack of potent and selective molecular tools and probe compounds targeting BB3 in vitro and in vivo.
To enable pharmacological manipulation of BB3's signaling in organoids and mouse models of LUAC, my team here aims to discover such compounds with the use of structures, computation, and artificial intelligence (AI).
Traditionally, the biggest barriers for computational ligand discovery for oGPCRs have been (i) the lack of high-resolution structures in relevant functional states, (ii) the computational cost of docking for flexible molecules, especially peptides, (iii) the inability of scoring functions to pick out active molecules from large databases when applied to limited-accuracy models, and (iv) the large and ever growing size of the libraries that need to be screened to find even a single hit. These historical challenges can now be tackled, thanks to the AI-powered breakthroughs in (i) protein complex structure prediction, (ii) peptide and chemical design, (iii) complex interaction scoring, and (iv) AI-accelerated virtual screening platforms. Capitalizing on these advances, small molecule and peptide modulators of BB3 will be discovered in silico and evaluated in reporter assays in BB3-expressing cells. The Smith lab will then use the compounds to assess the effects of BB3 perturbation, with and without current LUAC treatments, in a mouse model of carcinogen-induced LUAC and in human LUAC organoids.
The seed funding is requested to support molecular discovery efforts in the Kufareva lab. The funding will help establish the proof-of-concept for the use of BB3-targeted therapies in LUAC and collect critical preliminary data for joint extramural grant applications.

Elucidating the role of cyclin B3 in cancer cell mitosis.

Campus: UCI
Principal Investigator: Pablo Lara Gonzalez
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
This proposal aims to deepen our understanding of how cells control their transition through mitosis and to exploit these mechanisms for the developing of new therapies for the treatment of cancer. Mitosis is a critical step of cell division that ensures the passing of genetic information from one generation to the next. Cancer, a disease characterized by uncontrolled cell division, is often treated by targeting mitosis. Indeed, classical anti-tumor drugs halt the growth of cancer cells by stalling them in mitosis or causing massive chromosome segregation errors, which eventually trigger their death. However, these drugs also affect healthy cells, leading to severe side effects. Therefore, there is an urgent need to identify new, cancer-specific mitotic targets for chemotherapy.
Using the roundworm C. elegans as a model system, our laboratory has made significant progress in elucidating the molecular mechanisms that control mitosis. We have identified a key player in this process, called cyclin B3, which accelerates the rate of embryonic mitoses. Strikingly, when we translated these findings to human cells, we made a surprising discovery: cyclin B3 is critical for the division of cancer cells but not for normal cells. This finding suggests that cyclin B3 represents a new cancer-specific pathway that can potentially be targeted for chemotherapy.
Our proposal will gain insights into the role of cyclin B3 and its associated pathways towards cancer cell mitosis. For this, we plan to elucidate the molecular mechanism by which cyclin B3 contributes to cancer mitosis, as well as to define whether specific types of cancer are particularly dependent on cyclin B3. Finally, we will determine whether cyclin B3 depletion can be used, alone or in combinational therapy, to specifically target cancer cells.
This research represents a new avenue for our laboratory into a more applied approach for cancer research. If successful, our research could lead to the development of a new class of cancer drugs that specifically target the cyclin B3 pathway in cancer cells. These therapies could potentially be more effective and less toxic than current treatments, which may improve patient outcomes.

Impact of Pesticide Exposure on Hematopoietic Stem Cells and Cancer

Campus: UCM
Principal Investigator: Jennifer Manilay
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $95,000

Abstract:
In California's San Joaquin Valley, pesticide exposure is significantly higher than in other areas due to widespread agricultural use, household applications, and potential ingestion of pesticide residues on food. Epidemiological studies suggest a possible link between high pesticide exposure and increased incidences of blood cancers, such as leukemia and lymphoma, which often originate from bone marrow abnormalities. However, these findings are largely correlative, leaving critical gaps in understanding how pesticides directly impact blood stem cells and contribute to disease. Our laboratory focuses on the molecular and cellular processes in bone marrow that support healthy blood and immune cell production, as well as the disruptions that lead to conditions like bone marrow failure (BMF) and cancer. BMF is a severe disease in which blood stem cells are damaged and can no longer generate white blood cells, red blood cells, or platelets, leading to immune deficiencies, severe anemia, and an increased risk of bleeding and infections. Chronic BMF, particularly when initiated by chemical exposures, remains poorly understood. Additionally, long-term damage to bone marrow cells can increase the risk of developing hematological cancers. Despite these risks, research on the effects of pesticides on hematopoietic stem cells and bone marrow health is limited. Our research goal is to investigate how pesticide exposure leads to changes in blood stem cells, contributes to BMF, and increases the risk of cancer. Using advanced techniques such as multiparameter flow cytometry, we will measure changes in stem and progenitor cells, assess mature blood cell levels, and identify signs of anemia. Bone marrow samples will also undergo gene expression analyses and functional tests, including colony-forming assays and long-term transplantation experiments, to evaluate stem cell health and regeneration. Our research will provide critical insights into the harmful effects of pesticides on blood stem cells, bone marrow function, and cancer risk. By identifying specific cellular and molecular changes, this work aims to guide the development of strategies to prevent or mitigate these effects in humans, contributing to improved public health in pesticide-exposed communities and advancing our understanding of the connections between environmental toxins, BMF, and cancer development.

Illuminating PDAC's Dark Proteome to Reveal New Vulnerabilities

Campus: UCI
Principal Investigator: Thomas Martinez
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest major cancers and is projected to become the second leading cause of cancer-related death in the US by the end of the decade. Its poor prognosis is largely driven by a lack of early detection methods, preventing effective interventions before the disease advances. Over 90% of PDAC lesions harbor activating mutations in the KRAS oncogene, most frequent of which is KRASG12D (oncogenic KRAS), which enables constitutive downstream MAPK signaling. Mutant KRAS-specific inhibitors are currently being tested in the clinic with some success, but acquisition of resistance centered on reactivation of MAPK, MYC, and YAP signaling has also been observed. Thus, there is still a need for additional novel proteins that can be targeted in combination with oncogenic KRAS. There is a gap in our knowledge on the role microproteins play in regulating PDAC progression. Microproteins are a recently uncovered class of small proteins composed of less than 100 amino acids that are encoded by small open reading frames (smORFs). While microproteins represent a new and largely unexplored frontier in cancer research, several examples have now emerged that demonstrate microproteins can regulate tumor growth and invasiveness in different cancer types, including PDAC. These results suggest that there are additional PDAC regulating microproteins to be discovered and characterized. To address this possibility, we applied our microprotein discovery platform combining Ribo-seq, RNA-seq, and bioinformatics, to uncover >2,600 oncogenic KRAS-regulated microproteins in a murine model of PDAC with inducible and reversible KRAS G12D expression. The goals of this proposal are to 1) identify oncogenic KRAS-regulated microproteins that mediate PDAC growth, and 2) identify secreted microproteins which might serve as diagnostic biomarkers. This work represents crucial first steps toward our long-term goal of translating key microprotein regulators of PDAC into novel therapeutic strategies and biomarkers for early detection, both of which would substantially benefit patients.

Reconstitution of the molecular forces necessary for mitotic spindle bipolarity

Campus: UCD
Principal Investigator: Richard McKenney
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $95,000

Abstract:
Cellular life relies on the spatial and temporal coordination of molecular networks, where nanoscale biochemical and biophysical interactions produce emergent properties at the cellular scale. A prime example is the mitotic spindle, a dynamic structure essential for accurately segregating sister chromatids during cell division. Defects in spindle assembly or maintenance can cause catastrophic chromosome segregation errors, a hallmark of cancer. Thus, understanding how cells generate molecularly networked structures like the spindle is a central goal in cellular biology.
The McKenney lab seeks to uncover how mechanochemical systems organize and maintain cytoskeletal structures. Using a reductionist approach, we combine biochemical and biophysical methods to study the interplay between molecular motor proteins, such as dynein and kinesins, and microtubules, the dynamic filaments forming the spindle. Our hypothesis is that critical steps in spindle self-assembly, particularly spindle pole focusing and the balancing of opposing forces to generate spindle bipolarity, can be reconstituted from a small number of purified molecular components. Through in vitro reconstitution systems, we aim to decode how these molecules produce the emergent properties of this essential cellular structure and systematically explore the effects of varying molecular complexity.
We propose that spindle self-assembly arises from smaller modules of interacting molecular networks and that purified components can recapitulate the emergent properties of spindle machinery. To test this, we will pursue two specific aims: Aim 1: Reconstitute physiological interactions between dynein and kinesin motors, testing the hypothesis that dynein and kinesin-5 engage in antagonistic interactions to generate spindle bipolarity. Aim 2: Investigate the redundant role of kinesin-12 in spindle pole focusing when kinesin-5 is absent, a pathway enabling cancer cells to evade kinesin-5 inhibitors in clinical trials. This multifaceted approach aims to provide a deeper molecular understanding of mitotic spindle assembly, offering insights into fundamental cellular processes and potential therapeutic targets.

Machine learning enabled deconstruction of malignant potential at clonal resolution

Campus: UCI
Principal Investigator: Stanley Ng
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
Cancer-associated genetic mutations accumulate over time, leading to the outgrowth of cancer-like clones, which has been observed in many adult tissues. For instance, blood-forming stem cells that have acquired fitness-enhancing cancer driver mutations can initiate blood disorders and cancers. Although machine learning methods have been used to identify robust markers of cancer patient outcomes, methods for identifying optimized strategies for targeting individual pre-cancerous and cancer clones, which are the drivers of cancer development and relapse, is lacking. Thus, our team aims to develop innovative gene expression and mutation-based models for elucidating clone-specific treatment response pathway states. Toward this goal, we recently developed a machine learning model of the treatment response pathway for a drug called Mylotarg using gene expression and mutation data to identify Mylotarg-sensitizing agents for optimally eradicating patient-specific leukemia cells. Model-predictions were validated using in-vitro dose response experiments, where we also found that resistant leukemia stem cells could be sensitized to Mylotarg-mediated cell kill. Due to the biological heterogeneity in treatment response pathways, we hypothesize that each disease-driving clone will require individualized treatment strategies for targeted eradication. To test this, we will collaborate with Dr. Angela Fleischman, an expert in blood disorders and cancers at UCI, to generate single-cell gene isoform expression and mutation data from retrospectively collected myeloproliferative neoplasm (MPN) patient samples. The Ng Lab at UCI, which specializes in using statistical learning approaches to infer clonal composition and biomarker development, will use this data to predict clone-specific treatment strategies based on perturbing interferon and Janus kinase signaling pathways, which are commonly targeted in MPN therapies. We will validate model predictions by comparing changes in clonal composition using gene expression and mutational profiling (Ng Lab) before and after clone-specific targeting in-vitro and/or in-vivo (Fleischman Lab). Our work will provide a foundational framework for instructing the design of precision clone-level therapies for targeting individual pre-cancerous and cancer clones in both blood and solid tissues to curb cancer initiation and recurrence.

Synthesis of Nanocomposite Scintillators

Campus: UCLA
Principal Investigator: Qibing Pei
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
Positron emission tomography (PET) is a crucial imaging technique for diagnosing and monitoring various diseases, including cancer. A full body scan can produce the volume distribution of a tumor. However, current advanced PET systems suffer from limited spatial resolution (>4-8 mm) due to constraints in scintillator detectors including low coincidence time resolution (CTR) and low signal-to-noise ratio (SNR) which necessitate complex image reconstruction. To address this challenge, the “10 picosecond PET challenge” aims to develop a Time-of-Flight (TOF) detection system with 1.5 mm resolution, enabling high-SNR imaging without reconstruction. This entails a scintillator with a CTR of 10 picoseconds. Current state-of-the-art scintillators, such as lutetium oxyorthosilicate (LYSO), exhibit CTRs of 200-400 ps, limiting their potential for significant resolution improvement.
We have developed a novel nanocomposite scintillator with preliminary measurements demonstrating the scientific rationale to achieve a CTR of approximately 10 ps. This scintillator exhibits scintillation kinetics far superior than LYSO, but its light yield is much lower than LYSO, impacting the SNR and CTR. This CRCC seed project aims to enhance the light yield of this nanocomposite to be comparable to that of LYSO while maintaining its superior scintillation kinetics. This will be achieved by incorporating luminescent heavy-element nanoparticles to improve gamma-ray stopping power and facilitate efficient photon production. An organic luminescent polymer matrix will be employed to efficiently outcouple photons with fast kinetics. The targeted nanocomposites will be synthesized via bulk polymerization of liquid formulations in a mold to enable cost-effective mass production.
Successful development of this scintillator will not only demonstrate the feasibility of 10-ps resolution PET but also provide critical data to support the pursuit of an NIH grant for full-scale technology development. Our overarching objective is to achieve a TOF-PET with spatial resolution of 1.5 mm, and therefore enables early cancer diagnosis and monitoring. Furthermore, the substantially reduced equipment cost will broaden the access of the advanced TOF-PET to members of socioeconomically disadvantaged community.

Building a geographically diverse cohort to examine the multilevel effect of racism on breast cancer

Campus: UCB
Principal Investigator: Lia Scott
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $84,737

Abstract:
Black women are more than twice as likely to be diagnosed with triple-negative breast cancer than white women, more likely to be diagnosed at a later stage, and more likely to be diagnosed before age 40—earlier than screening recommendations. There is a consensus that age and race play significant roles in the diagnosis of breast cancer, yet with the knowledge we have, disparities persist. If we continue to inadequately address the role of racism rather than race in disparities, we will limit ourselves to the misconception that race reflects inevitable biological differences rather than recognizing that race is a social construct that categorizes people in a hierarchy of privilege. This proposal aims to recruit a diverse cancer epidemiology cohort of women residing in the Bay Area diagnosed with first primary malignant neoplasm of the breast between 2019 and 2024, followed through 2029, with the long-term goal of delineating the multi-level impact of racism on their diagnosis and subsequent outcomes. This group will be pooled with a cohort from metropolitan Atlanta and will serve as a foundation for studies to come focused on quantifying the effect of structural racism at the neighborhood level, interpersonal racism and identify any cross-level interactions on clinicopathologic characteristics at diagnosis and 5-year outcomes. We chose these areas due to their distinct histories with racially exclusionary policies and practices that have lingering effects to the present day. Our study is driven by ecosocial theory of racism and health, that racism is embodied over the life-course and exposure through multiple pathways can be deleterious to one's health. We expect that experiences of interpersonal and structural racism will be associated with early-onset, later stage diagnosis, increased likelihood of triple-negative subtype, and poorer clinical characteristics. Studies often examine the role of structural racism or inequity, at a single level, either the interpersonal or the structural level, whether classified as neighborhood disadvantage, socioeconomic status or other dimensions of structural racism. This work is unique in its aims to link the two levels, examining the role of each level of racism independently and jointly on etiologic heterogeneity and individual level outcomes.

Interrogating an ERK Activity Signature in Non-Small Cell Lung Cancer

Campus: UCD
Principal Investigator: Surbhi Singhal
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $73,419

Abstract:
Non-small cell lung cancer (NSCLC) is a leading cause of cancer death. As a genomically complex disease, many cases of NSCLC are driven by oncogene mutations that activate a key cellular pathway known as the extracellular signal-regulated kinase (ERK) pathway. The pathway plays a crucial role in normal cell growth, but when activated via a somatic mutation, it plays a central role in cancer. While targeted therapies have been developed to block the effects of these oncogene driver mutations, some patients' tumors fail to respond, and disease recurrence is nearly universal. A major unanswered question is how to better predict NSCLC treatment response beyond conventional methods such as genomic sequencing alone. While ERK signaling has been proposed as functional NSCLC biomarker, prior attempts to develop an ERK signaling biomarker have been limited because they relied on individual static measurements. It is known that the dynamic pattern of ERK activity is essential to proper ERK signaling. The proposed study builds on our previous work of a novel ERK activity signature in which ERK activity was multiplexed with immunofluorescence (IF) staining for downstream targets of the pathway. Combining these datasets with linear regression, machine learning, and differential equation models, we developed an IF-based dynamic ERK signature and performed preliminary testing in cancer cell lines. We identified discrete ERK activity signatures, in which non-ERK pathway mutated cells demonstrated organized pulsatile ERK activation, KRAS-mutated cancer cells demonstrated sustained ERK activation, and EGFR-mutated cancer cells demonstrated chaotic ERK activation. We hypothesize these signatures can be used as functional biomarkers in tumor tissue. Our objective is to test these ERK signatures in clinical specimens from patients with KRAS-mutated, EGFR-mutated, and KRAS/EGFR-wild type NSCLC tumors. We will define the differences in ERK signatures in tissue from varied oncogene driven subsets of NSCLC (Aim 1), establish the mechanistic significance of ERK signatures in NSCLC growth and aggressiveness (Aim 2), and determine the relationship between ERK signatures in tissue and clinical outcomes (Aim 3). Our findings will provide critical data to develop a functional ERK signature biomarker that informs treatment responsiveness and resistance to targeted therapies in NSCLC.

Antigen-Specific Strategies for Reinvigorating Exhausted T Cells

Campus: UCR
Principal Investigator: Huimin Zhang
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $84,764

Abstract:
T cell exhaustion is a dysfunctional state in which T cells lose their ability to effectively respond to antigenic stimuli, resulting in diminished anti-tumor immunity. This condition is commonly observed in cancer, where T cells that infiltrate tumors become exhausted due to chronic exposure to tumor antigens and the immunosuppressive tumor microenvironment. T cell exhaustion is characterized by the upregulation of inhibitory receptors (such as PD-1 and TIM-3) and the downregulation of effector functions, leading to a failure in clearing cancer cells. This exhaustion severely limits the effectiveness of current immunotherapies, including CAR-T cell therapy and immune checkpoint blockade. This proposal seeks to develop an innovative strategy to reinvigorate exhausted T cells by using advanced gene-editing technologies to enhance their ability to recognize and attack tumor cells. The primary goal is to design a novel lentiviral platform capable of specifically targeting cancer antigen-specific T cells and delivering CRISPR-based gene-editing tools that reverse exhaustion and restore effector function. Our approach leverages a lentivirus engineered with a VSV-G mutant that does not bind LDLR but conjugates with peptide-MHC (pMHC) complexes, enabling targeted delivery to T cells recognizing cancer-specific antigens. By displaying pMHC complexes on its surface, the lentivirus directs the delivery of CRISPR-Cas9 gene-editing machinery to antigen-specific T cells, promoting the removal of exhaustion markers and reinvigorating their anti-tumor responses. To assess the feasibility and efficiency of this approach, we will generate T cell lines expressing cancer-specific T cell receptors (TCRs) and evaluate their specificity and sensitivity to lentiviral targeting. CRISPR gene-editing efficiency will be measured in these T cell lines and in primary human T cells, with key readouts including enhanced cytokine production, increased cytotoxicity, and improved proliferation. The results of this study will provide critical insights into the potential of lentiviral-mediated gene editing to reverse T cell exhaustion, offering a promising new strategy for improving the persistence and potency of T cell-based immunotherapies in cancer treatment.

Prostaglandin-metabolizing microbial enzymes as novel target of colorectal cancer

Campus: UCD
Principal Investigator: Guodong Zhang
Start Date: 10/01/2025 *End Date:* 09/30/2026 *Amount:* $85,000

Abstract:
Inflammation is a hallmark of many human diseases including colorectal cancer (CRC). One of the most important inflammatory stimulators is prostaglandins, eicosanoid metabolites produced by cyclooxygenase enzymes (COX-1 and COX-2). Human studies consistently support that COX inhibitors, such as aspirin and non-steroidal anti-inflammatory drugs, which block the biosynthesis of prostaglandins, are among the most effective agents for CRC prevention. For example, the CAPP2 randomized trial demonstrated that daily aspirin use leads to a 63% reduction in the risk of developing CRC compared to a placebo. However, because COX enzymes are also expressed in various other tissues where they regulate essential physiological functions, the broad suppression of COX activity by these inhibitors could lead to serious adverse effects, prohibiting the widespread use of COX inhibitors for CRC prevention. Given the critical role of prostaglandins in promoting inflammation and tumorigenesis, identifying novel therapeutic targets to selectively reduce prostaglandin levels in the colon—without disrupting other tissues—is crucial for developing safe and effective strategies to mitigate CRC risk.
The objective of this project is to evaluate microbial β-glucuronidase (GUS) enzymes as a potential target for selectively reducing prostaglandin levels in the colon and mitigating the risk of CRC. Our preliminary data supports that specific microbial GUS enzymes play critical roles in regulating colonic levels of prostaglandins. Because GUS microbial enzymes are exclusively present in the colon, in this project we will test the hypothesis that targeting these enzymes selectively reduces prostaglandins in the colon without affecting other tissues, offering a promising approach to reducing CRC risk with minimal systemic toxicity. Successful accomplishment of the proposed research could establish prostaglandin-reactivating microbial GUS enzymes as novel therapeutic targets or biomarkers for CRC, potentially leading to a significant impact for the treatment or prevention of CRC.

Predicting causal variants in melanoma

Campus: UCSD
Principal Investigator: Emma Farley
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $95,000

Abstract:
All aspects of cancer are driven by changes in gene expression. Enhancers are genomic elements that control the timing, location, and levels of expression of a particular gene or genes, as such, enhancers provide the instructions for gene expression. While there has been extensive focus on protein-coding variants and genomic changes that alter protein-coding regions, how enhancer variants contribute to cancer initiation, progression, metastasis, and response to therapy is poorly studied. Enhancers harbor the majority of variants associated with diseases including cancers, but pinpointing causal variants is a major challenge because they are typically embedded within a sea of inert variants. This gap in our knowledge is stalling efforts to harness the full potential of genomic data to understand and treat cancer. A clear understanding of which enhancer variants contribute to various aspects of cancer is vital to understand the genetic basis of cancer initiation, progression, to develop novel therapeutics, improve diagnosis, and stratify patients for more targeted treatments. In this study, we will pilot a novel approach to identify enhancer variants that contribute to changes in gene expression in melanoma. We are experts in identifying causal variants within enhancers that alter gene expression and cellular identity within the context of the developing embryo. We have found that low-affinity binding sites are critical for precise control of gene expression. The prevalent use of low affinity sites within enhancers creates a vulnerability within genomes whereby SNVs can increase the affinity of binding sites within enhancers causing gain of function gene expression that alters cellular identity. We have demonstrated this in the context of heart and limb development. We now wish to apply this knowledge to gain insight into causal variants that contribute to various aspects of cancer. We plan to initially focus on metastasis, immunotherapy response and drug resistance in melanoma. In our preliminary study we have shown that an affinity optimizing SNVs found in a somatic melanoma eQTL increases expression of DAAM1 and increased cell migration. Successful completion of this project will uncover the contribution of enhancer variants to cancer progression and treatment.

Identifying distinct lymphvascular drivers of tumor initiation and evolution

Campus: UCSD
Principal Investigator: Shiri Gur-Cohen
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
All forms of cancer begin with genetic alterations in otherwise healthy cells. Yet, these alone are insufficient to predict an individual's disease onset and risks, indicating that nongenetic events within the tumor ecosystem ('niches') play a role in unleashing tumorigenesis. Stem cells are the origin of many life-threatening malignancies and are notorious for their tight dependency on the surrounding microenvironment. Despite undisputed importance, our understanding of how the ecosystems that stem cells inhabit direct oncogenic fate flexibility is limited. Equally, it remains a mystery whether early-stage tumor initiation through advanced disease progression is supported by overlapping or distinct niches. These gaps in knowledge can largely be attributed to a dearth of tools and models that capture the oncogenic stem cell identity landscape in intact tissues.
The lymphatic vascular network is an emerging, previously unrecognized niche entity for epithelial stem cells, yet much of the mystery of the lymphatic niches in directing tumorigenesis remains untapped. The goal of our proposed work is to determine how distinct vascular cues drive oncogenic flexibility and tumorigenesis in rare pre-cancer stem cells. Using deep imaging and sequencing approaches in skin squamous cell carcinoma, we discovered that lymphatic vascular insufficiency predisposes to malignant transformation. Detailed temporal volumetric imaging revealed that oncogenic plasticity propelling the transition from benign to metastatic carcinoma is preceded by dynamic lymphatic remodeling. These results raise the intriguing possibility that lymphatic niches evolve during disease progression, directing oncogenic tolerance in tumor-initiating cells while becoming a significant barrier to cancer treatments. To fill these knowledge gaps, we aim to determine how vascular circuits shape oncogenic tolerance in mutated yet untransformed cells in concert with their evolving niches, and to identify non-mutational drivers that build the pro-metastatic niche using our newly developed enhancer-based proximity sensor technology. Our innovative approach will define how vascular circuits shape the stem cell oncogenic landscape. A successful outcome of these studies holds promise for the development of therapeutics that block early cancer progression and pave the way to combat advanced metastatic disease.

AI based discovery of novel T cell therapies for diverse immunogenetic backgrounds

Campus: UCSC
Principal Investigator: Vanessa Jonsson
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $94,961

Abstract:
The pursuit of novel T cell targets that unleash potent anti-cancer immune responses is hindered by the lack of scalability of traditional wet lab techniques — imposing burdensome costs and inefficiencies on immunotherapy target discovery. While T cell therapies have brought about a transformative impact on cancer treatment, their effectiveness is limited to a few cancer types, and has struggled to be applicable to individuals with diverse immunogenetic profiles. There is an urgent need to shift our focus towards automated target discovery, with the aim of reaching a broader patient population.
The overall goal of this project is to propel the discovery of targets for novel T-cell therapies and expand their use in patients with diverse immunogenetic backgrounds by deploying AI-driven tools to analyze high throughput RNA sequencing data. My lab has recently developed an AI-driven framework and two pivotal datasets, containing 2 million publicly available single T cell transcriptomes, with matching T cell receptor data, and experimentally validated T cell antigen specificity data, extracted from 265 cancer patients, across 30 cancer types. This framework aims to accelerate the discovery of novel T cell therapies for cancer, promising faster and more cost effective development, with broader accessibility to diverse patient populations. Notably, ours is the only known methodology capable of automating the design of T cell therapies using data from an individual's adaptive immune system, without knowledge of their cancer genome.
We harnessed our AI-driven framework and database to discover a novel T cell therapy that can target two key cancer antigens: insulin like growth factor 2 mRNA binding protein 2 (IGF2BP2), prevalent in multiple cancer types, and associated with poorer patient survival, and well known target, melanoma antigen recognized by T-cells 1, (MART1). In collaboration with Dr. Powell at the UPenn, we are testing this newly discovered immunotherapy for clinical translation. We propose to leverage our framework for the discovery of: 1) multispecific T cell therapies simultaneously targeting multiple cancer antigen(s) and 2) T cell therapies applicable to populations with diverse immunogenetic backgrounds. The CRCC funding will allow us to discover and gather preliminary data on additional targets that will be leveraged to obtain NIH funding.

Targeting RNA splicing in B-cell acute lymphoblastic leukemia

Campus: UCD
Principal Investigator: Noriko Satake
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
The proposed project is built upon our prior transcriptomic studies that led us to a new area of research studying the role of RNA splicing in cancer. SF3B1 is a core component of the spliceosome and an essential protein in the RNA splicing process. Mutations in SF3B1 are a common cause of RNA dysregulation in multiple carcinomas and myeloid malignancies, and targeting the spliceosome has been evaluated in preclinical models and clinical trials. On the other hand, aberrant expressions, not mutations, of SF3B1 are common in cancers, including sarcomas and lymphoid malignancies, suggesting the role of RNA splicing can be different in different cancers.
Recently a study on aberrant RNA splicing and its potential as a therapeutic target in T-cell acute lymphoblastic leukemia was published. Aberrant RNA splicing has also been reported in B-cell acute lymphoblastic leukemia (B-ALL); however, its role and therapeutic potential are not yet known. Our preliminary studies in B-ALL suggest that leukemia-initiating cells (LICs) that we discovered use unique RNA splicing as a survival mechanism and are sensitive to SF3B1 targeting. Therefore, targeting leukemia cells, including LICs, has the potential to eradicate leukemia at its root. LICs are believed to be the reason for disease relapse, and relapsed diseases still have very poor outcomes. Our project has the potential to overcome the significant challenges of treating relapsed diseases.
We hypothesize that SF3B1 selectively regulates apoptosis-associated genes, and inhibition of SF3B1 induces cell death in B-ALL cells. We will investigate the role of SF3B1 in B-ALL cell survival, particularly in LICs. We will investigate the therapeutic potential of SF3B1 inhibition, with or without another drugs, both in vitro and in vivo, using our well-established, patient-derived high-risk B-ALL xenograft models.
Understanding the role of RNA splicing in leukemia cell apoptosis in this project has the potential to lead to novel therapeutics to improve overall outcomes by decreasing treatment failure and relapse and has the potential to minimize negative side effects of current treatments by directing the therapy to LICs. Adolescents and young adults with B-ALL have particularly poor outcomes.

Targeting Oncogene-Induced Replication Stress for Neuroblastoma

Campus: UCSD
Principal Investigator: Peter Zage
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Children with high-risk and relapsed neuroblastoma (NB) need improved therapies, and recurrent cytogenetic abnormalities, such as amplification of the MYCN oncogene, represent candidate therapeutic targets. MYCN amplification is associated with significantly worse survival rates for children with NB, and MYCN amplifications in NB can be found both within the linear genome and on circular extrachromosomal DNA (ecDNA). Amplifications of additional oncogenes in NB tumors, such as CDK4 and MDM2, have also been found on ecDNA, suggesting a broad role for ecDNA in NB pathogenesis. MYCN amplification via ecDNA has been linked to the presence of replication stress (RS), and RS is associated with defects in DNA replication and repair and is an important driver of tumor initiation and progression via induction of chromosomal instability. However, the role of RS and its significance as a potential therapeutic target in NB are unknown. We have established that MYCN-amplified NB cells demonstrate significantly increased sensitivity to inhibition of targets that generate increased RS compared to NB cells without MYCN amplification. We hypothesize that enhanced sensitivity of MYCN-amplified NB cells to induction of RS is due to a lethal increase in levels in RS beyond that induced by ecDNA formation and maintenance. Therefore, we propose to evaluate NB cells and tumors for the mechanisms of vulnerability to RS induction. We will investigate the contributions of MYCN amplification and expression and of ecDNA prevalence and content to sensitivity to RS induction in NB and evaluate the roles of MYCN- and ecDNA-induced RS in NB cell and tumor growth and response to treatment. Our proposed research will identify and validate novel approaches for targeting MYCN in NB via the unique strategy of targeting RS in a cancer cell-specific fashion. The proposed research will also facilitate future clinical trials and commercialization of novel inhibitors capable of inducing RS for treating MYCN-amplified NB tumors in need of less toxic and more effective therapies.

Self-amplifying mRNA to co-opt anti-viral responses for tumor immune therapy

Campus: UCSD
Principal Investigator: Jack Bui
Start Date: 10/01/2023 *End Date:* 9/30/2024 *Amount:* $65,000

Abstract:

When viruses infect people, successful elimination of the virus results in the generation of immune cells called memory T cells that persist for years. These memory T cells stand poised to recognize the virus and fight subsequent infection with the same virus. In order to provide optimal protection, memory T cells patrol the body and look for infected cells by examining whether cells have viral pieces, or peptides, on the cell surface. For example, memory T cells that have formed during the COVID-19 (Coronavirus disease 2019) pandemic can recognize pieces of the spike peptide of SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2), the virus that causes COVID-19. Spike-specific memory T cells will kill any cell that expresses viral spike proteins.
Recent findings have shown that memory T cells even patrol tumor tissue. Of course, since tumor cells are not infected with virus, the virus-specific memory T cells that patrol tumor tissue will not harm the tumor cells. Our preliminary studies have found that administration of viral peptides into tumor tissue will make tumors resemble virus-infected cells, resulting in activation of virus-specific memory T cells that can kill the tumor; however, the effect is transient since the viral peptides undergo rapid degradation and clearance. If this response can be augmented and sustained, it could represent an innovative non-toxic approach to tumor immune therapy.
In order to make tumor cells resemble infected cells, we propose to deliver self-amplifying mRNA vaccines into the tumor. These vaccines, similar to Moderna or Pfizer's mRNA vaccines, will result in the production of spike peptides by tumor cells, rendering them immunogenic. Anti-COVID-19 responses will be directed towards the tumor and release tumor antigens to prime tumor-specific responses. We will test our approach using mouse models of viral infection and blood from COVID-19 patients known to have memory T cells specific for spike peptides. If successful, our approach could work in a majority of the world's population given the incredible T cell memory that has emerged from the COVID-19 pandemic.

Identifying Disparities in Autologous HCT Utilization for DLBCL in California

Campus: UCD
Principal Investigator: Naseem Esteghamat
Start Date: 10/01/2023 *End Date:* 9/30/2024 *Amount:* $74,929

Abstract:

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma, which is fatal without treatment, but potentially curable with current therapies. The standard of care for patients who relapse or have refractory (R/R) DLBCL >12 months after initial treatment is an autologous, or in some instances, an allogeneic hematopoietic cell transplant (HCT). For patients who relapse <12 months after first-line therapy, HCT is still an option, with the addition of chimeric antigen T-cell therapy more recently becoming a standard of care treatment in this setting. Patients often receive second and further lines of chemo-immunotherapy for disease control for R/R DLBCL, but without HCT, all therapies are palliative in nature.

The utilization of HCT in patients with DLBCL remains low for certain patients and can be impacted by multiple factors, such as access to a transplant center and insurance status. Prior studies have found racial/ethnic disparities in the utilization of autologous HCT in lymphoma patients, with Non-Hispanic Black patients undergoing HCT less often than their Non-Hispanic White counterparts and having inferior survival. To date, little is known about the influence of sociodemographic and clinical factors on HCT utilization for patients with lymphoma over time.

In order to identify barriers to care in patients with DLBCL, we propose a retrospective cohort study of all DLBCL patients diagnosed in California from 1992 to 2016 using a novel data linkage from the Center for International Blood and Marrow Transplant Research (CIBMTR), California Cancer Registry (CCR), and statewide hospitalization data. A study in multiple myeloma patients from this linkage has identified that each of the three data sources independently capture HCT utilization, permitting the assessment of utilization of HCT at the population-level. These data sources also include sociodemographic factors (race/ethnicity, health insurance status, neighborhood socioeconomic status, sex, and age at diagnosis) and clinical factors (e.g., chemo-immunotherapy, disease stage, and comorbidities). This study will identify changes in sociodemographic and clinical associations with HCT over time and inform strategies to help to improve HCT rates, which is a curative therapy for patients with R/R DLBCL.

Influence of growth hormones and mechanical loading on osteosarcoma progression

Campus: UCD
Principal Investigator: Kent Leach
Start Date: 10/01/2023 *End Date:* 9/30/2024 *Amount:* $75,000

Abstract:

Osteosarcoma (OS) is the most common primary malignant tumor of bone in children and young adults. Adjuvant chemotherapy and surgical resection has been used to treat OS for decades, with 5-year survival rates of 60-70%. Unfortunately, for those patients with metastatic disease, 5-year survival rates are dismal (less than 30%), motivating the urgent need to understand what triggers the migration of OS cells from the bone into surrounding tissue, and eventually distant metastasis to the lungs.
When studied in monolayer culture, cancer cells are deprived of their native microenvironment and lose the tumor phenotype, making their responsiveness to therapy inaccurate. Animal models, considered essential for cancer research, also fail to accurately predict clinical outcomes. Tumor features have been created in biomaterials to model both the structural and cellular composition of the bone and marrow microenvironments. Mechanical stimuli also play a key role in tissue development and diseases such as cancer. For instance, OS thrives in a mechanically active microenvironment, especially during the teenage growth spurt. This suggests there may be a link between mechanical signaling, bone growth, and tumor formation that merits further study.
We hypothesize that OS progression and metastatic potential will be increased with exposure to pubescent growth hormones and mechanical loading. Murine OS cell lines or MC3T3 pre-osteoblasts will be entrapped in engineered constructs mimicking the composition and structure of bone marrow. Constructs will undergo dynamic compressive loading in a bioreactor for 2 h per day for 7 days in complete media or media supplemented with testosterone, β-Estradiol, or dihydrotestosterone. We will measure changes in bone formation and known metastatic signaling pathways by standard biochemical assays (e.g., PCR, RNAseq, IHC), while metastatic potential will be examined by tracking metastasis to the lungs upon murine subcutaneous implantation. We will also test efficacy of known chemotherapeutic drugs (i.e., doxorubicin) on stimulated constructs both in vitro and in vivo. The results will reveal the synergy of mechanical signaling on tumor growth in the presence of growth hormones and establish the importance of mechanical loading as potential drug targets to slow the growth and metastasis of OS.

Exploring pathways for fetal programming of offspring cancer risk through prenatal diet

Campus: UCI
Principal Investigator: Karen Lindsay
Start Date: 10/01/2023 *End Date:* 9/30/2024 *Amount:* $85,000

Abstract:

The objective of the proposed research is to investigate the contribution of maternal diet and glucose-insulin homeostasis in pregnancy to offspring cancer risk via dysregulation of the insulin-like growth factor (IGF) axis. Maternal obesity and high birth weight are repeatedly associated with various cancers in children and adults. The IGF axis has been highlighted as a plausible underlying mechanism given that i) IGF-1 and IGF-2 are present in fetal circulation and play key roles in fetal growth and development; ii) IGF-1 is strongly positively correlated with fetal growth and birth weight; and iii) the IGF axis is implicated in the pathogenesis and progression of different types of human cancer such as colon, breast, prostate, lung and leukemia. Early-life efforts for cancer prevention may therefore begin in utero through modulation of the fetal IGF axis, which is thought to be stimulated by circulating glucose and insulin. Maternal diet may be a key modifiable factor via its influence on glucose tolerance.
We propose a prospective observational study of N=80 pregnant women with pre-pregnancy overweight or obesity and diverse racial/ethnic backgrounds, leveraging the high proportion of Hispanic and Asian women who obtain prenatal care at the UCI medical center. Maternal diet in each trimester will be assessed using two 24-hour dietary recalls and the Alternative Healthy Eating Index for Pregnancy will be computed as a measure of diet quality. At 28 weeks' gestation, maternal fasting glucose, insulin, and c-peptide will be measured and the homeostasis model assessment of insulin resistance computed. Maternal glucose concentrations from the standard glucose challenge test will be abstracted from medical record. Neonatal IGF-1, IGF-2, IGFBP-1, and IGFBP-3 will be assayed from cord blood. The separate and combined contribution of maternal diet and glucose-insulin homeostasis to variation in concentrations of cord blood IGFs and IGFBPs will be analyzed, with trimester-specific analysis for the effects of maternal diet. Analyses will be adjusted for maternal demographics, gestational weight gain, infant sex, and gestational age at birth.
It is expected that this study will generate novel preliminary data to test if modifiable gestational exposures may influence offspring IGF axis, representing a possible early-life window for cancer prevention efforts.

A feasibility study of remote diet-related small habits intervention in cancer survivors

Campus: UCI
Principal Investigator: Yunxia Lu
Start Date: 10/01/2023 *End Date:* 9/30/2024 *Amount:* $85,000

Abstract:

The number of cancer survivors in the United States has been rising exponentially, with a projection of 22.2 million by 2030. Adherence to general healthy dietary recommendations, e.g., achieving a healthy body weight, being physically active, and following a dietary pattern rich in whole grains, fruits, and vegetables, has been associated with improved survival and health-related quality of life in cancer survivors. However, previous studies have found low adherence to these guidelines in cancer survivors. Dietary recommendations designed specifically for cancer patients are often based on inclusive, conflicting, or non-existing medical evidence, which is the primary source of confusion and frustration. We intend to design a randomized controlled trial which is an individualized diet-related small habits (DISHs) intervention program for cancer survivors. In the main trial, individual-tailed DISHs will be proposed based on an assessment of DISH perceptions, diet and nutrition status, demographics, and environmental information. The personalized intervention will be implemented remotely through a smartphone App. As more data is collected by the App to train machine learning algorithms (MLA) models, the DISHs intervention will be further modulated individually to increase adherence. The objective of the current study is to examine the feasibility of the main trial. In this study, we will estimate the capability of recruitment of CCCS (clinically cured cancer survivors) in communities through different sources; evaluate questionnaires for measuring DISHs perception and collecting of data that are associated with barriers to unhealthy dietary behaviors; assess questionnaires for measuring adherence of DISHs; investigate the approach to collect biological specimens; evaluate the performance of training the MLA models for personalized DISHs; and ultimately estimate the cost, time and manpower as a whole. The results of this feasibility study will provide solid evidence to design the main trail at the next stage.

Small Molecule Inhibition of GNAS; Creating the First Targeted Treatments for Appendix Cancer

Campus: UCSD
Principal Investigator: Dionicio Siegel
Start Date: 10/01/2023 *End Date:* 9/30/2024 *Amount:* $85,000

Abstract:

The Gα protein GNAS, which encodes for the heterotrimeric G protein Gαs, is the second most frequently mutated gene in mucinous appendiceal adenocarcinoma (AA) (~50% of tumors) and Pseudomyxoma Peritonei (PMP, ~75% of tumors) and third most common in non-mucinous AA (~25% of tumors), making it a promising drug target in this orphan disease. Although classically druggable, no commercially available inhibitors of Gαs exist. Here, we propose an innovative approach to develop and characterize chemical inhibitors of Gαs. Given prior in vitro and in vivo data demonstrating that GNAS knockout is lethal to GNASR201 tumors, there is a high likelihood that chemical inhibition of Gαs will be an effective therapeutic strategy for GNASR201 mutant tumors.
New Treatments are Needed for Appendiceal Cancer, Currently an Orphan Disease.
Appendiceal tumors encompass a rare and diverse group of neoplasms; AA is the most common histologic subtype. Epidemiologic studies based on Surveillance, Epidemiology, and End Results (SEER) data have shown a steady increase in incidence from approximately 0.2 cases per 100,000 in the 1970s, to current estimates of just over 1 per 100,000. In comparison, this is 40-fold less common than colon cancer, which in the US has an incidence of approximately 40 per 100,000. Cases of early-onset AA, defined as diagnosis before age 50, have increased by 24% between 2011 to 2016, and in 2016 represented 40% of all appendiceal cancer. In contrast, the increase in early-onset colorectal cancer (CRC) was only 2.2% for that same time period. Historically, appendiceal tumors have been grouped together with CRCs, and as of 2021 the National Comprehensive Cancer Network (NCCN) guidelines still suggested that appendiceal tumors be treated with chemotherapy similarly to colon tumors. The rarity of AA has made it difficult to conduct clinical trials, and in the absence of trial data, the NCCN guidelines assume biological similarity due to anatomic vicinity, common embryological origin, and common expression of the transcription factor CDX2. However, there is a growing consensus that AA is a clinically and molecularly distinct entity from CRC, and that AA specific therapies (none exist currently) need to be developed. We have discovered two druggable sites on GNAS and have developed small molecule inhibitors targeting the site next to the point of mutation.

Heparan Sulfate Biomarker for Pancreatic Cancer

Host Campus: San Diego
Lead Investigator: Jeffrey Esko
Start Date: 10/1/2022 *End Date*: 9/30/2023 *Amount*: $75,000

Abstract:
Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal types of cancer. This is in part due to difficulties in diagnosing the patients early where intervention would still be effective. Thus, PDAC specific markers that arise early in the disease are in high demand, to develop functional screening methods for early diagnosis. One of the key components to the cancer associated extracellular matrix is a type of carbohydrate, or glycan, called heparan sulfate (HS). HS biology is complex, but it is clear that these molecules accumulate and are structurally altered in many types of cancer. We have found that a unique type of HS, that is found in clinical heparin but rare in healthy tissue, accumulates in early stages of progression to PDAC. This type of HS is called HSAT. Notably, we show that the enzyme that produces HSAT, is elevated in early stages of the disease and correlates with poor disease prognosis. We show preliminary data that HSAT can be detected in PDAC precursor lesions and cancer tissue specimens and that it can be found circulating in the plasma from PDAC patients. We also show preliminary data that HSAT can be used as a target for cancer tracing studies. This project aims to fully investigate the potential of HSAT as a tool for the early diagnosis of PDAC, and potentially pave the way for the investigation of HSAT as a target for directed therapy against PDAC. The discovery of novel markers specific to PDAC has the potential to provide diagnostic and therapeutic strategies to combat this devastating disease, to the benefit of patients worldwide.

Decoding Cancer Acquired Drug Resistance

Host Campus: San Diego
Lead Investigator: Matthew Hangauer
Start Date: 10/1/2022 *End Date*: 9/30/2023 *Amount*: $75,000

Abstract:
The process by which initially drug sensitive tumor cells acquire drug resistance is poorly understood, but it is widely appreciated that the acquisition of resistance-conferring genetic mutations contributes to acquired cancer drug resistance in patients. The molecular mechanisms underlying the emergence of these mutations are not known. We and others have reported on a subpopulation of cancer cells termed “persister” cells, found within every solid tumor type thus far tested, which enter a quiescent pro-survival state in response to therapy and provide a surviving cancer cell reservoir from which overtly drug resistant tumors can subsequently emerge (e.g. Hangauer MJ et al., Nature 2017, 551, 247). These persister cells initially survive treatment through a reversible, non-genetic mechanism of drug-tolerance which is poorly understood. However, during prolonged treatment, it has been observed that a fraction of persister cells acquire new resistance-conferring mutations which allow for outgrowth of drug resistant cancer cells. It is not understood how persister cells acquire mutations. We recently discovered that during oncogene-targeted therapy treatment, persister cells undergo sublethal apoptotic signaling resulting in activation of apoptotic DNase DFFB which induces DNA damage and mutagenesis. While this exciting discovery points toward a potential new paradigm for how targeted therapy can produce mutations in cancer cells, it is not known whether sublethal apoptotic signaling and DFFB contribute to mutagenesis in other treatment modalities including chemotherapy, antibody treatments and immunotherapy. Here, we address these three distinct treatment modalities. In Aim 1, we will determine whether DFFB is required for chemotherapy- or antibody-induced mutagenesis in persister cells and acquired resistance. In Aim 2, we will determine whether DFFB is required for persister cell antigen loss during acquired resistance to CD8 T cell attack. Together, these proposed experiments will start a new direction of research into the role of DFFB in therapy-induced mutagenesis in persister cells and acquired resistance.

Evaluation of ketogenic diet strategies for pancreatic cancer-associated cachexia

Host Campus: Davis
Lead Investigator: Gerardo Mackenzie
Start Date: 10/1/2022 *End Date*: 9/30/2023 *Amount*: $85,000

Abstract:
Ketogenic diets (KDs) are diets characterized by having a high fat content and very low or almost no carbohydrates (sugars). Our proposed research studied the role of a KD in pancreatic cancer (PC). PC is a deadly disease, with limited effective treatments. At the time of diagnosis, around 80% of PC patients suffer from cachexia, a condition that involves progressive weight loss, nutritional deterioration and loss of muscle mass. Therefore, new strategies to improve patients' survival and quality of life are urgently needed. Our proposed research evaluated the role of a KD in PC. In particular, we investigated if a KD could improve the quality of life and help prevent cachexia. We observed that mice (that had PC) fed a strict KD had significantly improved motor mass and function compared to mice fed a control diet. We also evaluated exactly how this happens and whether other KD strategies are useful for PC-associated cachexia. We observed that a KD affected muscle physiology in mice that have pancreatic tumors by affecting cellular mechanisms related to muscle strengths. These included decreased muscle inflammation, and increased activation of the protein eIF2α, which regulates many processes related to muscle generation. These studies, which have been recently published, strongly indicate that a KD might to be a beneficial dietary treatment for PC-induced cachexia. In addition, since strict diets are difficult to maintain throughout cancer treatment, we are currently running a study to test if intermittent feeding of a KD (i.e: feeding a KD for a week following for a week of control diet) can achieve similar effects as observed with the strict KD. This part of the work is currently ongoing. The successful completion of our studies could inform us on whether certain diets, such as the KD, can be beneficial for PC and for mitigate cancer cachexia, which is a major problem experienced by PC patients.

Integrated Model of Cancer, Vasculature, and Immune System

Host Campus: Merced
Lead Investigator: Kara McCloskey
Start Date: 10/1/2022 *End Date*: 9/30/2023 *Amount*: $85,000

Abstract:
Endothelial cells (ECs) are activated to generate new blood vessels that play a key role in supporting the growth and spread of many cancers. However, treatments shown to be highly effective in mice are proving less robust in humans. Three-dimensional microfluidic chips enable recapitulation of the tumor microenvironment with human cancers, human endothelial cells and human immune cells. Establishing a highly angiogenic tumor vasculature perfused with immune cells is needed to accurately reconstruct the tumor pathology. Our laboratory has identified and characterized a unique highly angiogenic ECs from mouse and human embryonic stem cells (ESC). The proposed studies will examine various cancer spheroids' ability to recruit new blood vessels, undergo metastasis, and examine response to anti-angiogenic drugs for treating growing cancers.

Flexible Robotic Evacuator for Minimally Invasive Brain Tumor Therapy

Host Campus: Riverside
Lead Investigator: Jun Sheng
Start Date: 10/1/2022 *End Date*: 9/30/2023 *Amount*: $85,000

Abstract:
The goal of this project is to design, fabricate, and test a flexible robotic evacuator that can be deployed by meso-scale steerable robots inside a brain tumor and controlled to evacuate tumor tissue at multiple locations towards conformal tumor evacuation. Glioblastoma multiforme (GBM) is one of the most challenging cancers to cure. Each year, nearly 12,000 new cases of GBM are diagnosed in the US, with the overall median survival being only 12 to 18 months. GBM rarely metastasizes to other organs; however, standard therapies with surgery via a craniotomy combined with adjuvant radiation and FDA-approved drugs can barely prevent the recurrence of GBM. For recurrent GBM (rGBM), although re-surgery can provide the best survival on select patients, most patients cannot afford re-surgery due to their generally poor health conditions. Thus, minimally invasive techniques arise to address this challenge. Nevertheless, existing tools are straight and rigid, and thus are not adequate to remove large and irregularly shaped tumors. Hence, there is an urgent need to develop a steerable robot that can be introduced through a small burr hole and manipulated throughout the tumor to remove the tumor in a minimally invasive manner. This project aims to develop and demonstrate a flexible robotic evacuator that can be integrated with steerable neurosurgical robots. The device will be made of flexible material so that it can be delivered through the curved channel of a steerable robot. In this project, we will: 1) design and fabricate a flexible robotic evacuator with a capability of aspiration and irrigation, 2) Integrate the evacuator with a steerable robot, and 3) evaluate the functionality of the robot system. With the success of this pilot project, we will pursue a NIH RO1 grant to improve the robot design, develop a planning and control system, and perform in vivo studies on normal and GBM pigs.

Enhancing Online Group Fitness Exercise for Health Improvement for Patients with Cancers

Host Campus: Riverside
Lead Investigator: Hao-Chuan Wang
Start Date: 10/1/2022 *End Date*: 9/30/2023 *Amount*: $85,000

Abstract:
Zumba and similar group-based aerobic exercises have become popular worldwide, engaging approximately 12 million people to attend the fitness dancing parties on a frequent basis. Prior studies showed evidential benefits in mental and physical wellness, as well as quality of life, of such fitness programs among the common public and patients with cancers. Patients with cancers, either on treatment or off therapy, may encounter challenges to attend in-person training due to their illness and mobility constraints, in addition to the current global covid pandemic. Therefore, it's essential to explore online options which offers easy accessibility and inclusiveness of "exercise classes". In terms of personal motivation and social engagement, patients with cancers may also benefit from additional personalization and social support to help them physically catch up with the exercise and socially connect with co-trainees. Our goal in this project is to create a social, accessible and inclusive video-mediated Zumba experience that extends the benefits of group training to the online space (Zumba together!). By enhancing video communication, we will develop a real-time action feedback mechanism and a recommendation mechanism that produces recommendations of training content and co-trainees, both driven by continuous comparison of pose estimations performed by the system using a data-driven machine learning model, with the goal to improve social synchrony and engagement in the virtual program. In this one-year project, we will design and prototype the technological mechanisms and conduct a pilot study with up to 30 health adults to assess the feasibility and benefits of using the enhanced video communication channel for virtual group exercises. The results from this project will be used to apply for an R01 to conduct a multicenter clinical trial targeting young adult cancer survivors and patients undergoing treatment.

Electrical Impedance Spectroscopy for Monitoring the Chemoresistance of Prostate Cancer Cells

Host Campus: Irvine
Lead Investigator: Tayloria Adams
Start Date: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $ 85,000

Abstract:
Prostate cancer is a life altering disease that affects one in six men in the United States. A challenge in treating prostate cancer cells is overcoming their plasticity. Cancer cells have subpopulations of stem cells that can switch phenotypes, converting between chemoresistant and non-chemoresistant cells. In particular, the epithelial mesenchymal transition (EMT) is linked to chemoresistance and the presence of cancer stem cells. EMT is a reversible process in which cells lose their epithelial features and gain mesenchymal features. The goal of this proposal is to monitor EMT to gain a deeper understanding of chemoresistant cells and the time scale at which change occurs. A custom electrode-based microfluidic device will be used to measure dynamic changes in impedance at the single cell level. Electrical impedance spectroscopy is a cell analysis technique that offers a label-free approach for the recognition of cancer cells, their dynamics, and chemoresistance using electric fields.

Our central hypothesis is that impedance is a good candidate for the detection of prostate cancer cells' EMT, which is associated with the presence of cancer stem cells. We have preliminary data that indicates impedance detects: (a) stages of prostate cancer cells, stage 4 (PC-3) and stage 1 (DU145) and (b) phenotype differences in PC-3 and DU145 cells cultured as monolayer (less chemoresistant) versus suspension (more chemoresistant). Also, we have found correlations between impedance and the gene expression of N-cadherin, E-cadherin, and ZO-1 proteins (markers of EMT).

The following aims will be tested, Aim 1: Characterize the baseline impedance spectra and functional profile of PC-3, DU145, LnCAP and patient samples. Aim 2: Modulate the EMT of PC-3, DU145, LnCAP and patient samples using transforming growth factor b (TGF-b), hypoxia inducible factor 1 alpha subunit (HIF-1a), and estrogen receptor alpha (ER-a) and quantify the impedance spectra and functional profile. Impedance measurements will be coupled with cell proliferation, cell cycle analysis, apoptosis, and gene expression assays.

At the end of these studies impedance and membrane capacitance will be quantified and screened as potential biomarkers of EMT. This work will lay the foundation toward the development of potential EMT-specific drug therapies for prostate cancer.

Evaluating cost effective care for differentiated thyroid cancer

Host Campus: Davis
Lead Investigator: Michael Campbell
Start Date: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $ 75,000

Abstract:
Thyroid cancer is one of the most common cancers in the United States and its incidence is increasing. Total thyroidectomy (removal of the thyroid gland) is the predominant treatment for thyroid cancer but carries the risk of hypoparathyroidism because of damage to the parathyroid glands (small organs that lay adjacent to the thyroid and are responsible for calcium homeostasis). Hypoparathyroidism is the most common complication following thyroidectomy and is responsible for the majority of emergency department (ED) visits and readmissions following surgery. The propensity for thyroid cancer to present in young populations, coupled with its good prognosis, increases the importance delivering safe, cost effective care for these patients. Complications of treatment, such as hypoparathyroidism, can debilitate patients for many years, and the economic impacts of these complications must be paid for by society for decades after they are incurred.

The purpose of this study is to use California Cancer Registry (CCR) and Office of Statewide Health Planning and Development (OSHPD) databases to: 1) assess the incidence of hypoparathyroidism in patients undergoing thyroidectomy for thyroid cancer and determine factors, including racial/ethnic and socioeconomic disparities, associated with hypoparathyroidism and 2) calculate hospitalization and ED costs associated with hypoparathyroidism

To accomplish these objectives, we will identify patients with thyroid cancer who underwent a thyroidectomy between 2005 - 2018 in California using the CCR. Hospital readmission and ED discharge diagnoses will be obtained from the OSHPD databases. Patient data from the CCR and OSHPD will be linked to evaluate the incidence, risk factors, treatment disparities, and costs associated with hypoparathyroidism following thyroidectomy for thyroid cancer. We expect the findings of this study will provide the data to help establish programs to assure quality, equitable thyroid cancer care for all patients in California, including the economically underserved and racial/ethnic minorities.

Etiology of Ph-like ALL and the mechanisms driving Latinx cancer disparities

Host Campus: Irvine
Lead Investigator: Nicholas Pannunzio
Start Date: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $ 84,990

Abstract:
Philadelphia chromosome-like B cell acute lymphoblastic leukemia (Ph-like ALL) is an ALL subtype that disproportionately affects the Latin community and is characterized as having a poor response to therapy, a high risk of relapse, and a peak onset in adolescents and young adults. While lacking a BCR-ABL fusion, nearly 65% of Ph-like ALL cases carry a rearrangement in the cytokine receptor-like factor 2 (CRLF2) gene located on both X and Y chromosomes, the most common being a chromosomal translocation with the immunoglobulin heavy chain locus (CRLF2-IgH) resulting in increased and uncontrolled expression of CRLF2 that correlates with reduced survival. CRLF2 rearrangements are significantly higher in patients of Latin descent, indicating this is a high-risk group for Ph-like ALL and that understanding the molecular mechanisms driving CRLF2 rearrangements would greatly benefit prediction and diagnosis of Ph-like ALL. Our recent analysis of over 2,000 translocation breakpoints in human patients revealed that DNA double-strand-breaks (DSBs) that initiate the CRLF2-IgH translocations can occur within a 25 kb region upstream of the gene but are enriched 36-fold in a 311 bp cluster region and involve the B cell-specific mutator activation-induced cytidine deaminase (AID). Tight clustering of breakpoints indicates a non-random mechanism underlying DSB formation and elucidation of this mechanism would fill a crucial knowledge gap regarding the etiology of Ph-like ALL. Our central hypothesis is that CRLF2 DSBs occur through a defined mechanism that involves abnormal AID levels in an early pre-B cell stage and altered epigenetics that makes AID a more potent mutator and DSB initiator. Our hypothesis will be tested by pursing two specific aims: (1) Use our novel molecular assay to determine the mechanism of CRLF2-IgH translocations and (2) Compare the genomic DNA from B cells of Latino and non-Latino populations for genetic and epigenetic risk markers linked to CRLF2 rearrangements. This work is significant as it will this allow us to both address cancer disparities in the Latino community and develop novel diagnostics applicable to several B cell malignancies in wider population studies.

Cancer therapeutics via small molecule-mediated p53 mutant reactivation

Host Campus: Irvine
Lead Investigator: Feng Qiao
Start Date: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $ 75,000

Abstract:
About 600,000 new cancer patients in the United States are diagnosed each year with tumors expressing mutated p53. These cancers express full length p53 that has lost tumor suppressor activity but acquired gain-of-function oncomorphic properties that provide selective advantage to cancer cells. The large number of affected cancers make p53 an exquisite target for cancer therapy. However, therapeutic approaches require reactivation of mutated p53, which in itself is challenging. Reactivation of mutant p53 is possible through both intragenic second site mutations and small molecules that induce a conformational change and stabilize an active conformation of p53 hotspot mutants. We have developed a compound series that binds mutant p53 and thereby restores DNA binding activity of mutant p53 in a reconstituted purified in vitro system. Furthermore, cell proliferation is halted, and apoptosis is induced in a p53 mutant dependent manner. Importantly, growth of tumors carrying p53 mutants is blocked by this compound series in animal models. These compounds provide strong support for feasibility to develop drug-like molecules that can restore tumor suppressor activity in p53 hotspot mutants. However, these compounds act in the micromolar range and moving from these preclinical successes towards the bedside requires more lead compound series with diverse chemistry, and most importantly, a better understanding of the mechanisms underlying p53 mutant reactivation as well as the identification of key features that determine potency of tumor suppression in the reactivation process. We propose to develop such mechanistic understanding by detailed characterization of p53 hotspot mutant reactivation by small molecules as well as second site mutations. The proposal will generate molecular understanding of key features that allow reactivation of tumor suppression activity of p53 cancer mutants. Such understanding will help the identification of new p53 reactivation lead compounds in the future. The therapeutic concept of p53 mutant reactivation could transform treatment for many cancer patients, but lack of experience with reactivation drug development makes it difficult to achieve this goal. Building detailed molecular knowledge about the reactivation process will overcome these current roadblocks.

Outcomes for premenopausal women with triple negative secondary breast cancer

Host Campus: Davis
Lead Investigator: Candice Sauder
Start Date: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $ 75,000

Abstract:
In the adolescent and young adult (AYA; 15-39 years) female population, breast cancer (BC) is the most common cause of cancer-related death. Overall, in premenopausal women under 50 years of age, BC is more likely to be tumor marker receptor negative (estrogen, progesterone, and human epidermal growth factor 2 receptor negative, i.e. triple negative), of higher grade, and diagnosed at more advanced stages--all factors associated with worse survival. In addition, multiple studies have shown that the AYA population has the highest absolute excess risk for secondary malignancies of any age group, including most commonly BC. Our prior work comparing primary and secondary BCs in premenopausal women has identified that secondary BCs present at earlier stages and tend to be lymph node negative. However, even with diagnosis at an earlier stage and accounting for tumor receptors and grade, being diagnosed with a secondary BC was associated with worse survival compared to a primary BC. Non-Hispanic Black women experience the worst prognosis after both primary and secondary BC.

Traditionally, early stage BC is treated with different adjuvant therapies than more advanced staged BC. Chemotherapy is used less frequently, as is radiation. However, because early stage secondary BC has worse survival than early stage primary BC, treatment for secondary BC may need to differ or be more aggressive. Currently there are no guidelines that define or differentiate treatment for primary and secondary BC, leading to the important question of whether differences in treatment contribute to the survival disparities. Additionally, no study to date has assessed treatment, especially chemotherapy regimens utilized in young women with primary and secondary BCs, to determine treatment differences and the impact on survival.

We propose extracting treatment data, including chemotherapy regimen data via the text fields, from the California Cancer Registry for premenopausal women diagnosed with triple negative BC, a significantly increased aggressive form of BC found in both the primary and secondary BC population. By determining the impact of these regimens on BC survival overall and by race/ethnicity and age group, we will identify areas for intervention to improve outcomes and reduce survival disparities in premenopausal patients with secondary triple negative BC.

Neurocognitive Processes for Mammographic Detection of Breast Cancer

Host Campus: Riverside
Lead Investigator: Weiwei Zhang
Start Date: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $ 85,000

Abstract:
Understanding the nature of medical expertise in cancer diagnostics imaging could be fundamental for cancer diagnostics, clinical training, and development of computer aided detection programs. This project is aiming at directly assessing the characteristics of underlying neurocognitive processes for medical expertise in cancer diagnostics imaging. Specifically it is hypothesized that two dissociable cognitive processes (discrete processing of focal lesions and continuous holistic processing) jointly support mammogram diagnostics, the dual-process hypothesis. We will use a combination of novel behavioral paradigms, individual differences, computational, and MRI methods to assess three key predictions of the dual-process hypothesis. First, expertise in mammogram reporting (e.g., mammographers as opposed to medical students) should manifest more in "gist" information, as opposed to focal information, that can be extracted from mammogram images. Second, processing of holistic mammogram image features should occur earlier than detection of local signs of cancer. Third, acquisition of the processing of holistic mammogram image features should manifest in the Fusiform Face Area of the brain, but in asymmetrical way. The project will develop a novel Hierarchical Bayesian method to assess dissociable cognitive processes underlying mammogram reporting (Aim 1), which will used in conjunction with a novel experimental paradigm to assess the neural mechanisms (Aim 2) for mammogram reporting. Some pilot data collected in a NIH funded Medical Perception Lab at the 2019 Annual Conference of Radiological Society of North America has provide preliminary support for the central hypothesis.

We have developed an interdisciplinary team with the experimental, computational/analytic, neuroimaging, and clinical expertise for the proposed research. The UC CRCC seed grant will support the team to develop subject recruitment mechanism for the targeted enrollment of the specific subject populations, collect pilot data, and establish feasibility for future grant applications. The long-term goals of the project are to further our understanding of medical expertise, to provide the theoretical footing for computer aided medical diagnostic programs, and to develop medical training components that target the core neurocognitive processes.

Effects of tobacco and cannabis policy implementation on consumption

Host Campus: Davis
Lead Investigator: Dorothy Apollonio
Start Date: 10/1/2020 *End Date*: 9/30/2021 *Amount*: $ 51,454

Abstract:
Between 2016 and 2018, California changed multiple policies addressing substance use by legalizing recreational use of cannabis, increasing the minimum age of legal access for tobacco to 21 years, regulating electronic nicotine delivery systems as tobacco products, and expanding access to treatment. The extent to which cannabis policies would be implemented was left to local governments, and varies significantly within the state, with some counties banning retail sales while others allow broad commercialization. As a result, the public health impacts of these changes have been difficult to assess. In particular, stricter tobacco control policies intended to reduce cancer risk may be affected by increased access to cannabis, leading to increased co-use, tobacco-to-cannabis substitution, or both at once in different subpopulations. In this pilot study, we propose to classify tobacco and cannabis policies in California counties and identify associated consumption patterns. We hypothesize that local policies can be classified by the degree to which they restrict access and subsidize treatment, and that policies that do so are associated with reduced consumption of both tobacco and cannabis. We propose the following aims: 1) Map local tobacco and cannabis policies in California and classify their comprehensiveness; and 2) Determine the association between local policies and tobacco and cannabis consumption patterns. We will collect policy data for California counties using data collected by the American Nonsmokers Rights Foundation (ANRF; tobacco) and the Orange County Register (cannabis). We will classify local policies by the degree to which they restrict access to and subsidize treatment for tobacco and cannabis, including treatment policies for co-use. Using data from the 2018 California Health Interview Survey (CHIS), we will analyze the association between local policies and health outcomes: 1) past-month tobacco and cannabis use; 2) modes of use (e.g. smoking, vaping, edibles, dissolvables); and 3) co-use of tobacco and cannabis, (both single-occasion and concurrent). California’s choice to devolve implementation of cannabis policies to local governments makes it possible to determine how substance use policies interact to change consumption, and will inform governments within and outside California seeking policy interventions to prevent cancer.

Advancing VCP inhibitors as experimental therapeutics in ovarian cancer

Host Campus: Davis
Lead Investigator: Jeremy Chien
Start Date: 10/1/2020 *End Date*: 9/30/2021 *Amount*: $75,000

Abstract:
Protein quality control (PQC) pathways are important for protein and organelle homeostasis and essential for the fitness of cancer cells in the face of genomic instability, thus creating a cancer cell dependency. Components of PQC, such as heat shock proteins, also provide an adaptive response to cancer therapy and contribute to resistance. Therefore, PQC represents a point of vulnerability for cancer cells and a therapeutic target to potentiate the efficacy of current cancer therapies. Underscoring this point is a series of reports indicating that various components of PQC are identified as synthetic lethal targets in cancer cells. Among them, valosin-containing protein (VCP, also known as p97 AAA-ATPase) was identified as a lineage-specific dependency gene in ovarian cancer. VCP participates in various cellular functions of protein and organelle homeostasis, and we have shown that VCP inhibition induces ER stress, the terminal unfolded protein response and cytotoxicity in ovarian cancer cells. A previous clinical lead, CB-5083 (CB), inhibits VCP activity in nanomolar concentrations and produces cytotoxicity in over 300 cancer cell lines at low micromolar concentrations. Despite promising in vitro and in vivo anti-cancer activities, a recent first-in-human Phase I clinical trial with CB was stopped due to off-target effects on PDE6, a protein critical for phototransduction, which manifested as ocular side effects. We propose to circumvent the off-target issues using two approaches: (1) nanoformulation of CB to optimize delivery to tumor tissues and (2) the development of CB derivatives as VCP degraders. In the first approach, we will use hydrophobic porphyrin that forms the drug-loadable core with PEG forming the lipid-soluble micelle. Pegylated cross-linked nanoparticles (NPs) are pH-sensitive due to the presence of a Schiff base. In the acidic tumor microenvironment, smaller NPs are released due to the cleavage of the cross-links, thereby limiting drug delivery to the eye. In the second approach, we will synthesize the CB-based VCP degraders using drug design called proteolysis-targeting chimera (PROTAC). These PROTAC molecules can be designed such at it will specifically target VCP but not PDE6 for degradation. These two approaches will overcome current clinical limitations of CB.

Biobehavioral Intervention to Reduce Adverse Outcomes in Young Adult Latinos with Testicular Cancer

Host Campus: Irvine
Lead Investigator: Michael Hoyt
Start Date: 10/1/2020 *End Date*: 9/30/2021 *Amount*: $85,000

Abstract:
Testicular cancer (TC) diagnosis and treatment, especially given its threat to sexuality and reproductive health, can be distressing in young adulthood. In fact, the prevalence of depressive symptoms in TC exceeds the general population, and young Latino men are at high risk for adverse outcomes after treatment. In fact, the majority of young adult cancer survivors will experience impairing, distressing, and modifiable physical, behavioral, and psychosocial adverse outcomes that persist long after the completion of medical treatment. Yet, few targeted, tailored, culturally-relevant interventions exist to assist young Latino survivors in re-negotiating life goals and regulating cancer-related emotions and none focus on reducing cancer burden via biobehavioral mechanisms. Young or “emerging” adulthood is marked by goal attainment. Chronic illness experienced as “off time” in the lifespan interrupts goal pursuits and threatens valued life directions. As young adults return to goal pursuits, re-entry to post-cancer life can be a critical point in the survivorship trajectory. Behavioral intervention at this time is well positioned to confer longer-term impact. Emergent from our group’s preliminary research, we developed and pilot-tested Goal-focused Emotion-Regulation Therapy (GET) as a behavioral intervention to enhance self-regulation through improved goal navigation skills, sense of purpose, and ability to regulate emotional responses in young adults with TC. Responsive the need for feasible, effective, and scalable interventions that meet the need of ethnic minority men, 25 Latino young adults (ages 18-39) with TC will receive 6 sessions of GET. This pilot study aims to establish feasibility, clinically-meaningful (not statistically significant) change, and guidance for cultural adaptation. We predict that GET, and our ability to detect meaningful change, will be feasible in Latino young adult TC survivors. We expect GET to be associated with reduced distress and reductions in adverse biobehavioral indicators (dysregulated stress hormones, elevated inflammation). We also expect that greater endorsement of culturally-relevant factors (i.e., familism, simpatia, acculturation/acculturative stress, machismo/caballerismo) will condition the impact of GET on primary and secondary outcomes and that qualitative data will identify culturally-relevant adaptation.

Epigenetic landscape of DNA methylation in pancreatic cancer progression

Host Campus: Davis
Lead Investigator: Chang-il Hwang
Start Date: 10/1/2020 *End Date*: 9/30/2021 *Amount*: $85,000

Abstract:
Pancreatic cancer is one of the deadly human malignancies, owing in part due its early onset of metastasis. Key driver mutations for pancreatic cancer metastasis have not been identified, and alteration of epigenetic pathways has been suggested as a potential mechanism. We have established the innovative pancreatic cancer organoid cultures derived from both patients and genetically engineered mouse models. Pancreatic organoid cultures are amenable for genetic manipulations and suitable for high throughput 'omics' approaches, allowing us to dissect the underlying molecular mechanisms. Using the pancreatic organoid models, we have reported that epigenetic reprogramming as a potential factor in pancreatic cancer metastasis. Two major epigenetic changes are histone modifications and DNA methylation. Previously, we have extensively profiled the key histone modifications in pancreatic cancer organoids. However, another key epigenetic regulation, alterations of DNA methylation landscape remains to be determined in pancreatic cancer progression. Here, we propose to profile genome-wide DNA methylation in both human and mouse pancreatic organoid models and identify functionally important epigenetic changes of DNA methylation in metastasis. We have performed the Reduced Representation Bisulfite Sequencing (RRBS) in the murine organoid models for pancreatic cancer. We will investigate how DNA methylation pattern changes in pancreatic cancer progression (normal, PanIN, tumor and metastasis). In addition, we will intersect DNA methylation data with transcriptional profiles and key histone modifications in the promoter and enhancer regions. This will provide mechanistic insights in how differential DNA methylation contributes to gene expression and disease progression. To determine the effect of the differential DNA methylation in individual genes, we will employ CRISPR-dCas-DNMT or -TET system to methylate or demethylate specific regions of interest, respectively. This will enable us to identify functionally important DNA methylation for pancreatic cancer metastasis. In sum, the proposed study will elucidate the epigenetic landscape of DNA methylation in pancreatic cancer progression using pancreatic organoid models. Furthermore, genes associated with differentially methylated regions can be exploited for the development of novel diagnostic and therapeutic strategies.

"Lymphomizing" Treatment of Head and Neck Cancer using Involved Field RT with Chemo-Immunotherapy

Host Campus: San Diego
Lead Investigator: Loren Mell
Start Date: 10/1/2020 *End Date*: 9/30/2021 *Amount*: $82,500

Abstract:
Current standard treatment for most advanced head and neck cancers involves combined chemotherapy and radiation therapy. Newer treatment approaches are incorporating immunotherapy, specifically PD1:PD-L1 checkpoint inhibitors, into the standard treatment paradigm. Standard radiation fields cover both the primary tumor plus "elective" radiation to areas of potential regional spread, especially to lymph nodes, even though many patients do not actually have disease present in the nodes. Large radiation fields result in significant acute and long-term morbidity, particularly difficulty swallowing, which can lead to feeding tube dependence and risk of aspiration. In the setting of concurrent immunotherapy, it is not clear that such large fields are required. For example, in the treatment of lymphoma, successive advances in the quality of systemic therapy have permitted both lower radiation doses and, importantly, smaller field sizes (i.e., Involved Field Radiation Therapy, IFRT), drastically decreasing the morbidity of radiation therapy. Moreover, treatment of healthy nodes with radiation could actually be harmful by interfering with the effectiveness of immunotherapy, which is trying to stimulate the anti-tumor immune response and depends on functional lymph nodes. However, prospective trials are needed to confirm that it is safe to treat head/neck cancer patients with IFRT and that this does not lead to excessively high rates of recurrence, which to our knowledge has not been tested. Therefore we propose to treat a pilot cohort of 12 patients with IFRT (radiation directed only at visible disease on positron emission tomography) plus immunotherapy with standard chemotherapy (tri-weekly cisplatin), and prospectively assess for rates of disease recurrence. Secondly, we will collect novel information on swallowing function using quantitative imaging techniques in collaboration with speech and language pathology, and will collect serial blood specimens for comparison with data from previous trials using standard radiation.

A polygenic score for prediction of aggressive and fatal prostate cancer in multi-ethnic populations

Host Campus: San Diego
Lead Investigator: Tyler Seibert
Start Date: 10/1/2020 *End Date*: 9/30/2021 *Amount*: $75,000

Abstract:
When detected in its early stages, prostate cancer is curable, but it still causes over 350,000 deaths per year. Screening with a blood test to measure prostate-specific antigen (PSA) leads to earlier detection and has been shown to reduce cancer deaths. However, PSA testing of the entire male population leads to many false positives and many diagnoses of slow-growing cancers that are unlikely to cause significant problems. A test is needed to help physicians decide whether a given patient would benefit from screening—and what age to start that screening. Such personalized decisions might be made by measuring each man's genetic risk for aggressive forms of prostate cancer. A genetic score (called a polygenic hazard score, or PHS) has been developed and tested in a dataset of thousands of men. The PHS was strongly associated with aggressive prostate cancer. While promising, the PHS was developed and validated with only data from men of European ancestry, reflecting data availability at the time.

We have obtained access to a large, multi-ethnic dataset, through collaboration with the international PRACTICAL consortium. We propose here to test the original PHS to see whether it performs well in a new dataset and whether performance is affected by race/ethnicity. Rather than self-reported race/ethnicity, we will use genetic ancestry (European, African, or Asian) determined by the individual's own DNA. We will evaluate whether PHS is associated with age at diagnosis of aggressive prostate cancer and with lifetime risk of death from prostate cancer. PHS will be compared to family history and other risk factors for prostate cancer. Our preliminary results suggest that the original PHS works in men of multiple racial/ethnic backgrounds, but performance is best in genetic Europeans.

After formally testing the original PHS in each genetic subgroup, we will use the multi-ethnic data to optimize the score for each genetic ancestry. We will do this by searching for genetic markers within each genetic ancestry that are associated with age of onset of prostate cancer and incorporating them into an enhanced PHS.

Ultimately, PHS could guide personalized prostate cancer screening decisions for men of all races/ethnicities, thus saving lives through early detection.

Label free, high throughout detection and separation of individual breast cancer stem cells

Host Campus: Irvine
Lead Investigator: Zuzanna Siwy
Start Date: 10/1/2020 *End Date*: 9/30/2021 *Amount*: $75,000

Abstract:
Cancer stem cells (CSCs) are a rare cellular subset within a tumor (1-5% but in some tumors only up to ~0.01% of the total tissue) that are believed to be responsible for the metastatic progression of cancer, as well as resistance to chemotherapy and radiation therapies, and disease relapse. As such, the successful isolation of viable CSCs with minimal perturbation and manipulation would enable further understanding of CSC biology, which is necessary for the development of novel therapeutics directly targeting this rare subset of aggressive cells. This is especially relevant to breast cancer where 100% of mortality is due to metastasis. The goal of the proposal is to design a microfluidic platform capable of label-free isolation of viable CSCs breast cancer cells from blood and tissue.

CSCs will be separated based on their unique mechanical properties. Identifying the cells using physical and mechanical properties rather than chemical markers makes the platform independent of an a priori knowledge of cells' surface characteristics, which is often unknown. The microfluidic channel we designed contains a cavity flanked by two narrower regions; at all positions along the channel, the channel width is larger than or comparable to the cells' size. The inhomogeneous pressure gradients and shear stress in such a channel cause multiple deformations of the cell in both directions. The new platform will provide characterization of individual cells and allow finding one-to-one correspondence between a given cell's mechanical properties and the same cell's biological function. Hundreds of cells will be analyzed per second, and 5 mL of cells suspension will be analyzed within 15 minutes.

In Aim 1, the cells (MCF-7 and MDA-MB-231) will be characterized by combined optical and electrical signals analyzed by advanced machine learning approaches. Machine learning algorithms will be applied to find direct correspondence between the optical and electric signals, enabling one to characterize cells' deformation based on electrical recordings only.

In Aim 2 we will develop a platform to isolate individual CSCs that can be subjected to further biochemical analysis.

This work will lay the foundation toward the understanding of CSCs, the cancer stem cell model, and the development of potential CSC-specific drug therapies for the treatment of metastatic cancer.

Patterns of Care and Outcomes in AYAs with Germ Cell Tumors

Host Campus: Davis
Lead Investigator: Elysia Alvarez
Start Date: 1/1/2020 *End Date*: 12/31/2020 *Amount*: $75,000

Abstract:
Germ cell tumors (GCT) are the third most common cancer in adolescent and young adult (AYA: 15-39 years) patients and its incidence is increasing. Survival has increased significantly over the past three decades; however, disparities by stage of disease, age and sociodemographic factors remain. AYA patients with GCTs do not receive uniform care, with providers varying from pediatric oncologists, medical oncologists, urologists, to gynecologists. They also may be treated in community hospitals or specialized cancer centers (SCC: Children's Oncology Group and National Cancer Institute-designated centers). Treatment at SCCs or by pediatric oncologists has been found to improve outcomes in AYAs with certain cancers (i.e. acute lymphoblastic leukemia, Ewing sarcoma), possibly due to clinical trial enrollment and standardized care approaches, but these associations have not been assessed for AYA patients with GCTs. Most of what is known has been obtained through clinical trials, which while important, does not provide a complete "real world" picture of treatment, location of care and survival outcomes in this patient population. Therefore, we propose to undertake a comprehensive, population-based assessment using the California Cancer Registry (CCR) linked with statewide hospitalization data. This database captures information on nearly all patients with GCT in California—allowing us to determine patterns of care for AYA patients with GCTs. We aim to identify the treatment regimens administered and determine differences by location of cancer treatment and treating physician specialty; and examine the impact of guideline concordant care, location of care and treating physician specialty on survival. We hypothesize that guideline concordant treatment will differ by the treating specialty, especially in older AYAs, and that survival in patients with later stage disease will be superior if these patients are treated at SCCs and/or with guideline concordant care. We will accomplish these aims through the use of novel methods to abstract chemotherapy regimens (protocol, specific drugs), provider subspecialty (urology, oncology etc.) and surgical details (biopsy date, resection date, surgical margins) from text fields in the CCR. Findings from this study will identify potential areas for intervention that can improve survival outcomes in AYA patients with GCTs.

Novel Links Between Wnt Signaling, Centrosomes, and Cancer

Host Campus: Irvine
Lead Investigator: Lee Bardwell
Start Date: 1/1/2020 *End Date*: 12/31/2020 *Amount*: $75,000

Abstract:
Normal patterns of Wnt signaling are necessary for tissue development and maintenance, while hyperactive Wnt signaling is implicated in many cancers, especially colon cancer. Indeed, loss of the Wnt pathway negative regulator adenomatous polyposis coli (APC) is typically an early step in the progresson of colon cancers. APC loss results in the stabilization of beta-catenin, which then forms active heterodimers with LEF/TCF (lymphoid enhancer factor/T-cell factor) transcription factors. LEF/TCF target genes promote proliferation, migration, Waarburg-type metabolism, and survival, all of which contribute to malignancy.

Our preliminary experiments have uncovered intriguing new connections between the Wnt signaling pathway and the centrosome, the major organizer of the microtubule cytoskeleton in mammalian cells. Specifically, we have found that LEF/TCF transcription factors localize to the centrosome, where they interact with the centrosomal scaffold protein CEP152, and with the protein kinase PLK4. Futhermore, our preliminary studies indicate that that PLK4 phosphorylates the TCF1 protein and regulates the expression of LEF/TCF target genes. The centrosome is critical for the maintenance of genome integrity, and the PLK4 protein kinase is the master regulator of centrosome duplication, whose over- or under-expression causes tumor-promoting chromosomal instability. Thus, our findings suggest potential new connections between Wnt signaling and the maintenance of genome stability.

We propose a series of experiments to determine the mechanism and functional consequences of the centrosomal localization of LEF/TCF transcription factors, and of the phosphoregulation of LEF/TCF factors by PLK4.

We will determine the domain of CEP152 that binds to LEF/TCF transcriptional factors and the functional consequences of this interaction. In addition, we will map the site(s) of PLK4-mediated phosphorylation of TCF transcription factors, and investigate the functional consequence of this phosphorylation

The potential impact of the studies proposed herein is considerable. Our research could reveal new therapeutic opportunities for targeting the Wnt pathway, unexpected new connections between Wnt signaling and the maintenance of genome stability, and a novel mechanism by which the centrosome may communicate with the nucleus to regulate gene expression.

Detecting tumor-specific exosomes on a chip

Host Campus: Davis
Lead Investigator: J. Sebastian Gomez Diaz
Start Date: 1/1/2020 *End Date*: 12/31/2020 *Amount*: $74,999

Abstract:
Sensitive detection of circulating tumor-associated exosomes (TEXs) and related extracellular vesicles (EVs) may improve strategies for ovarian cancer (OvCa) detection and monitoring because (i) they represent stable and protected biomarkers in blood circulation and (ii) their composition, including surface protein markers, is tissue and pathology-specific. To achieve the best sensitivity for detecting low-frequency TEXs in early stage cancer patients, innovative high-resolution tools are needed. The cornerstone of this multidisciplinary project is to develop an extremely sensitive and affordable on-chip bio-sensing platform able to accurately detect the presence of EVs including TEXs in microseconds, with crucial implications for early detection of OvCa. We have previously demonstrated that our sensor, which relies on a novel transduction mechanism that merges tailored optical and nanomechanical resonances, outperforms at room temperature the sensitivity of the best commercial FTIRs over a narrowband, and here propose to apply this novel technology to bio-sensing for the first time.

To accomplish this objective, we will first isolate circulating EVs using density-gradient ultracentrifugation from human OvCa patient plasma. We are currently collecting more than one hundred plasma samples per week from women suspected of OvCa malignancy through the UCDCC Biorepository resource. Second, we will be capturing EV subsets on our innovative sensors according to multiplexed capture agents like known general exosome-specific and also cancer-exosome-specific molecules, including the recently reported potent OvCa-binding peptide, LXY30. This enrichment method will provide unprecedented sensitivity towards TEX subpopulations. Third, we will use the nanomechanical resonance properties of hundreds of individual detectors, tuned to particular intrinsic EV-specific vibrating frequencies, to label-free sensitively detect small numbers of EVs. Fourth, we will apply custom nanomaterials composed of gold nanoparticles (NPs) and nanorods (NRs) coated with EV-targeting agents to further identify subpopulations of detector-captured EVs. We expect the detected signatures to be significantly more sensitive and specific than the current gold standard diagnostic approach, which may accelerate clinical cancer diagnostic platforms for a wide range of cancers.

Linking the Circadian Clock and Cancer

Host Campus: Irvine
Lead Investigator: Selma Masri
Start Date: 1/1/2020 *End Date*: 12/31/2020 *Amount*: $75,000

Abstract:
The circadian clock controls several physiological, endocrine and metabolic processes that operate to maintain organismal homeostasis. These biological rhythms are self-perpetuating oscillations that are maintained within a 24-hour periodicity and are synchronized by external environmental cues such as light, temperature and food intake. Several lines of evidence undoubtedly suggest that disruptions in circadian rhythms results in numerous physiological disorders, including cancer. At the organismal level, genetic mutations in the circadian clock machinery accelerate tumorigenesis and this has been demonstrated in mouse models of leukemia/lymphoma, hepatocellular carcinoma, lung adenocarcinoma and osteosarcoma. At the molecular level, a crosstalk between the circadian clock and several oncogenic signaling pathways has been reported. Up-regulation of MYC has been shown to disrupt circadian gene expression and therefore perturb circadian glucose and glutamine metabolism in cancer cells. Conversely, the circadian clock has also been shown to target and degrade MYC, thereby inhibiting MYC-dependent proliferation. Additionally, the beta-catenin pathway has been reported to disrupt circadian gene expression, yet how clock disruption mechanistically drives enhanced beta-catenin signaling remains undetermined. We aim to further elucidate the molecular mechanisms related to the bi-directional crosstalk between the circadian machinery and cellular signaling pathways involved in survival and proliferation. Our work has the potential to open new avenues for therapeutic intervention targeting the circadian clock for the treatment of several cancers.

Downregulation of XIST in Ovarian Cancer and Its Mechanisms

Host Campus: Irvine
Lead Investigator: Sha Sun
Start Date: 1/1/2020 *End Date*: 12/31/2020 *Amount*: $75,000

Abstract:
This project aims to elucidate the functional role of cancer-associated long noncoding RNA (lncRNA), in particular, lncRNA XIST (X-inactive specific transcript) in ovarian cancer. Genome-wide association studies in cancer have revealed that more than 80% of cancer-associated genetic variations occur in noncoding sequences of the human genome. In parallel, an increasing number of cancer transcriptomes have also shown thousands of lncRNAs differentially expressed in a variety of human cancers when compared to normal cells. These indicate that understanding lncRNA-associated oncogenic pathways should be an important part of understanding the genetic mechanisms in cancer. The lncRNA XIST has recently been reported to affect cancer metastases and tumor progression. But whether the dysregulation of XIST can directly drive cancer symptoms, what are the XIST-mediated oncogenic pathways, and whether the lncRNA can be therapeutically targeted for cancer biomarkers are unclear. In addition, since XIST is known as the master regulator of X chromosome dosage compensation between XX female and XY male mammals, how XIST is regulated and whether differential expression of X-linked genes may affect female cancer in particular, are notable questions not fully addressed.

Research in my lab has focused on the positive and negative regulators of XIST and, for the first time, reported detailed molecular mechanisms for the function of another lncRNA, Jpx, in activating Xist in mice. To investigate possible mechanisms of XIST regulation in cancer, we have used the cBioPortal for cancer genomics and observed significant downregulation of XIST correlated with higher neoplasm histological grades of ovarian cancer. We hypothesize that XIST, with its activator JPX, can function as tumor suppressors influencing oncogenic pathways related to proliferation and metastasis. We propose to identify the tumor growth relevant pathways in which XIST and JPX are associated within ovarian cancer. We also aim to define the genetic mechanisms underlying the loss of XIST in tumor cells. The outcomes will contribute to the functional annotation of cancer-associated lncRNA and impact future development of RNA biomarkers that may inform cancer diagnosis and treatment.

Samoan Healthy Eating and Active Living (HEAL)

Host Campus: Irvine
Lead Investigator: Sora Tanjasiri
Start Date: 1/1/2020 *End Date*: 12/31/2020 *Amount*: $74,910

Abstract:
Pacific Islanders (PIs) are disproportionately affected by the causes and contributing factors regarding cancer health disparities, as identified nearly 15 years ago by the U.S. Department of Health and Human Services (2004). Cancer is the leading cause of death for PIs, with obesity implicated as a causal factor in the onset of many cancers, including breast, colon, endometrium, esophagus, and kidney cancers. Unfortunately, relatively little is known about how to effectively prevent/reduce obesity among PIs who number 1.3 million in the U.S., 305,202 in California, and 88,050 in the San Francisco bay area. Responding to the National Cancer Institute's call for identifying factors influencing implementation of existing evidence-based interventions into community settings, we propose a multi-level, exploratory, implementation science pilot that applies the Consolidated Framework for Implementation Research (CFIR) to understand the factors associated with the potential adaptation to increase healthy eating and physical activity among Samoans in the bay area. The specific aims are to: 1) explore the organizational pre-implementation factors associated with program adoption among the parishes of the Samoan Congregational Christian Church of American Samoa in the Northern California region. We will conduct key informant (KI) interviews with two leaders from each of 12 parishes (representing 3,000 Samoan members) to understand their perceptions of the barriers and facilitators to EBI adoption; and 2) identify the individual nutritional intake and physical activity levels among members from one parish. We will survey n=70 Samoan adults at this parish to estimate the point prevalence of current diet and physical activity behaviors to inform power analyses in the future R01. The research team is comprised of two academics and two community leaders, all of whom have worked together in the past and have expertise in Pacific Islander health and community-based participatory research. This exploratory study is the essential precursor to the design of a larger implementation study, and the results will inform the development of a larger implementation research proposal in response to the NIH PAR Dissemination and Implementation Research for Health or similar R01 opportunity.

Unveiling targets for treating malignancies of viral origin

Host Campus: Santa Barbara
Lead Investigator: Carolina Arias
Start Date: 1/1/2019 *End Date*: 12/31/2019 *Amount*: $75,000

Abstract:
Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi's sarcoma (KS) and primary effusion lymphoma (PEL), two malignancies predominantly diagnosed in HIV/AIDS and immunocompromised patients. While the advent of antiretroviral therapy has significantly controlled the HIV/AIDS epidemic and has reduced the rates of AIDS-associated KS, infection with KSHV still prevails and causes serious disease in untreated HIV positive individuals and organ transplant patients. Treatment options for patients with severe KSHV-associated malignancies are limited, often involving exposure to chemotherapeutic agents with a wide range of secondary effects and cumulative toxicity. The development of new therapies for the control of KSHV infection in immunocompromised patients with mild to severe KSHV-related malignancies would expand the options for treatment of acute and chronic disease. An aspect of viral infection that remains to be explored for the development of antiviral agents is the strict dependence of viruses on their hosts. The pharmacological inhibition of cellular factors promoting infection or the activation of host pathways impairing viral replication has the potential to pave new avenues for the treatment of infections. This promising approach requires a deeper understanding of host/pathogen interactions at the molecular level. Here, we propose to identify critical cellular factors that are indispensable for KSHV infection, but dispensable for normal cell function, which could be targeted for therapeutic intervention. We will focus on understanding the regulation of viral protein synthesis in cells infected with KSHV. By dissecting the cellular requirements for the synthesis of functional proteins during viral infection, we will reveal potential host targets for the modulation of productive infection. Importantly, recent work showcases the clinical potential of pharmacological modulation of the protein synthesis and folding machinery for the treatment of cancer and other diseases. Our investigations will help pinpoint important host targets for the control of viral infections, offering the opportunity to explore drug repurposing to treat viral diseases, and providing an alternative for the management of KSHV-related malignancies in immunocompromised patients.

Studying tumor heterogeneity using single-cell epigenomics

Host Campus: Santa Barbara
Lead Investigator: Siddharth Dey
Start Date: 1/1/2019 *End Date*: 12/31/2019 *Amount*: $75,000

Abstract:
While mutations and copy number variations in the genome are known drivers of cancer, there is increasing evidence that dysregulation in epigenetic marks such as DNA methylation (5-methylcytosine or 5mC) and disruption of the 3-dimensional organization of chromosomes within the nucleus of a cell play a critical role in the progression of tumors. In addition to these complex genome-wide transformations, tumors are also characterized by dramatic cellular heterogeneity that remain one of the major challenges in the effective treatment of cancer. However, it remains unclear how the epigenome influences tumor heterogeneity. This is because current measurements are typically made from a bulk population that fail to capture the cell-to-cell variability in 5mC or genome organization and the resulting gene expression heterogeneity. Further, while bulk studies in tumor cells have shown that large blocks of hypomethylation in 5mC appear to correlate with regions of the genome that interact with the nuclear periphery (known as lamina-associated domains or LAD), these experiments cannot distinguish if these profiles occur in the same cell or unrelated cells. Therefore, it remains unknown if a causal relationship exists between 5mC and genome organization, and how dynamic changes in such epigenetic features regulate cellular phenotypes. To overcome the technical challenges in addressing these questions and to understand how dysregulation in 5mC and genome organization together alter gene expression in tumor cells, we propose the following aims: (1) Develop a novel single-cell sequencing technology to simultaneously quantify 5mC, LAD organization and mRNA from the same cell. Integrated measurements of both the epigenetic features and the transcriptome will allow us to directly correlate 5mC to LAD structure and how they combine to regulate gene expression in a single cell. (2) Employ a recently developed model of tumor progression in intestinal organoids to study how simultaneous reprogramming of 5mC and LAD organization directly influences the dynamics of aberrant gene expression by the sequential introduction of mutations in APC, P53, KRAS and SMAD4 genes. This seed grant will lay the foundation for further systematic exploration into the potential mechanisms that mediate the cross-talk between 5mC and genome organization and its influence on gene regulatory networks.

Control of cell growth in normal and transformed cells

Host Campus: Santa Cruz
Lead Investigator: Douglas Kellogg
Start Date: 1/1/2019 *End Date*: 12/31/2019 *Amount*: $66,094

Abstract:
Cancer cells show severe defects in control of cell growth and size, yet the underlying causes are unknown. The long-term goal of our work is to discover how control of cell growth and size works in normal cells, and how it goes wrong in cancer cells. With this knowledge, we hope to identify novel vulnerabilities of cancer cells that can be exploited to improve therapies. Our work thus far has focused on budding yeast, since it provides a simple and powerful system in which to discover fundamental mechanisms of cell size control. In our recent work, we discovered that a highly conserved signaling network that surrounds TOR kinase complex 2 (TORC2) controls both cell growth and cell size. The network includes tumor suppressors, as well as numerous kinases directly involved in critical oncogenic signaling pathways. Our discovery that cell growth and size are controlled by a conserved signaling network that is known to be disrupted in cancer suggests that we are close to solving the mystery of why cancer cells show such severe defects in control of cell growth and size. We are now poised to translate our discoveries into vertebrate cells. We will test the hypothesis that key functions of the TORC2 network that we have discovered in yeast are conserved in vertebrates, and that they play important roles in oncogenic signaling. Successful completion of the Aims will provide fundamental new insights into the functions of important oncogenic signaling proteins, as well as insights into the poorly understood functions of the vertebrate TORC2 network.

Improving outcome of cancer chemotherapy with CO

Host Campus: Santa Cruz
Lead Investigator: Pradip Mascharak
Start Date: 1/1/2019 *End Date*: 12/31/2019 *Amount*: $75,000

Abstract:
Recent studies have indicated that moderate doses (>250 ppm) of CO cause rapid reduction of some cancer cells (but not normal cell) through cell apoptosis. In addition, CO appears to sensitize cancer cells to chemotherapy. We have recently shown that that small doses of CO from designed CO-releasing molecules (photoCORMs) can be conveniently used to induce apoptosis in human breast cancer cells cells in a dose-dependent manner through controlled CO release. We now plan to determine whether such co-administration of exogenous CO increases the efficacy of chemotoxic drugs in the treatment of solid cancers (consequently minimizing treatment-related adverse events). We will utilize in-vitro and in-vivo models of breast and ovarian cancer for our investigation towards assessing the effects of exogenous CO applications. (1) We will determine the optimal concentrations of photoCORMs in diminishing cell proliferation of breast and ovarian cancer cells in-vitro and in xenograft models, in the presence of various doses of commonly used chemotoxic drugs, and (2) We will investigate the detailed mechanism(s) of CO-mediated inhibition of antioxidant pathways in breast and ovarian cancer cells in-vitro and in xenograft models. In both aims, use of photoCORMs will allow delivery of precise doses of CO and study its effects under very controlled conditions. In a recent paper [1], we have shown that CO delivery from our photoCORMs selectively inhibits cystathionine ß-synthase (CBS, a heme protein) and attenuates the antioxidant capacity of human breast cancer cells. In cancer, CBS plays a significant role in drug resistance; silencing CBS expression could sensitize cancer cells to chemotherapeutics. Our results also demonstrated that exogenous CO delivery significantly increased the chemosensitivity of human breast cancer cells toward both Doxorubicin and Paclitaxel. We therefore plan to further explore the mechanism of CO-induced enhancement of chemotoxicity in both breast and ovarian cancer cells (especially cisplatin-resistant ovarian cancer cells). We believe that along with CBS, there could be other pathways also involved, for example metallothionein (MT) expression. This is a new venture in my research group and we plan to write a RO1 grant once we have more initial results to support our hypothesis. 1. J. Med. Chem. 2017, 60, 8000-8010.

Think Biology: Healthy Teen Lifestyles and Cancer Prevention

Host Campus: Santa Barbara
Lead Investigator: Laura Romo
Start Date: 1/1/2019 *End Date*: 12/31/2019 *Amount*: $66,941

Abstract:
Adolescence is an important life stage during which habits formed may shape trajectories of cancer risk later in life. Negative lifestyle behaviors such as smoking, drinking, use of other drugs, and risky sexual behavior start or peak during these years. Success in helping adolescents engage in self-protective health behaviors that reduces cancer risk depends on the availability of quality instructional materials. The overall goal of this study is to test the efficacy of a novel intervention program on high school adolescents' ability to attain and maintain healthy lifestyle behaviors that reduce cancer risk. We will create a program that utilizes theory-driven teaching practices in the field of science education. The Science of Learning approach posits that accumulated factual knowledge alone is insufficient to have a deep understanding of an area of inquiry. Science facts need to be understood in the context of a contextual framework organized around important core concepts to enable learners to construct explanations about bodily processes. Our curriculum will include a discussion of healthy lifestyles, bodily processes, the biology of cancer, and why certain health behaviors can increase the risk of cancer in adulthood. We will employ a group randomized-controlled-trial design to examine the effects of the newly developed curriculum against a control group of adolescents who are exposed to information about behaviors and cancer risk through standard pamphlets. Pamphlets tend to leave out information about the biology of cancer, bodily process, and their link to behaviors. Summative and formative assessments will be utilized to assess student learning. Misconceptions will be identified. Outcome measures will focus on knowledge gains, intentions, and engagements. The data gathered from this study will be utilized to apply for funding for a large-scale assessment program to develop materials that can be incorporated in high school biology courses. Current collaboration with medical professionals at Cottage Hospital. UCSB faculty collaborations: TBD

Photothermal Therapy of Oral Squamous Cell Carcinoma

Host Campus: Santa Cruz
Lead Investigator: Jin Zhang
Start Date: 1/1/2019 *End Date*: 12/31/2019 *Amount*: $75,000

Abstract:
Actively targeted photothermal therapy (PTT) is a new and highly promising medical modality for cancer imaging and treatment. Oral cancer is the ninth most common cancer worldwide, and its prognosis remains poor in comparison to other cancer types, representing a continuing challenge in biomedicine. We propose to use a novel photothermal agent based on peptide-conjugated hollow gold nanospheres (P-HGNs) to actively target and treat oral squamous cell carcinoma (OSCC). The P-HGNs are designed with optimal size, shape, strong near infrared (NIR) light absorption, conjugation length, and high photothermal conversion efficiency. Instead of using antibody for targeting, we propose to use short peptides to reduce the distance between the HGNs and cancer cell or tissue to enhance heat transport and thereby PTT efficiency. Moreover, peptides, as recognition elements, are highly specific, yet inexpensive to produce, thus improving the translational potential of our constructs. We will conduct in vitro studies to validate the hypothesis that P-HGNs are highly effective for PTT applications, which lays the foundation for future in vivo studies.

Recurrent GLI mutations in drug-resistant skin cancer

Host Campus: Irvine
Lead Investigator: Scott Atwood
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $55,000

Abstract:
Basal cell carcinoma (BCC) are locally invasive skin cancers that affect over 4 million patients a year and are solely driven by activating mutations in the Hedgehog (HH) pathway. Inappropriate HH pathway activation also drives growth of a variety of cancers including brain, pancreatic, prostate, and small cell lung cancer that account for up to 25% of all human cancer deaths. The GLI1 and GLI2 transcription factors drive HH transcriptional output, with current therapies for advanced or metastatic BCCs limited to HH pathway antagonists that target proteins that lie upstream of the GLI transcription factors. Although effective, over 50% of advanced tumors display inherent drug resistance and 20% of tumors that do respond acquire drug resistance, indicating a critical need to understand the nature of drug resistance and to find the next generation of therapeutics. Towards this goal, we have found 110 mutations in GLI1 and GLI2 that may drive drug resistance by mining for recurrent mutations from our drug-resistant BCC patient tumor samples and cross referencing them to previously published tumor datasets across all sequenced cancers in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. We have generated all 110 mutations and plan to stably express all variants in several HH responsive cell lines that include BCC lines ASZ001 and BSZ. We will characterize how each GLI mutation alters HH signaling, cell growth, and protein stability with a goal to identify specific clinically observed mutations that drive pathway activation. Positive hits that increase two out of the three criteria will be assayed for DNA binding, transcriptional activity, tumor growth, and drug resistance to understand how each mutation alters GLI function. So far, we have identified a cluster of mutations that disrupt interaction with the negative regulators PKA and SUFU, which significantly increases GLI activity levels. These results will provide insight on how GLI1 and GLI2 are regulated during HH pathway activation, how this regulation is altered during tumor growth and drug resistance, and will be invaluable in the discovery of future treatments for HH-dependent cancers.

Outcomes in Stage IV Cancer Patients with Bowel Obstruction

Host Campus: Davis
Lead Investigator: Robert Canter
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $55,000

Abstract:
Although patients and clinicians consider oncologic outcome and survival the pre-eminent goals of cancer therapy, quality of life (QOL) and avoidance of therapeutic morbidity, particularly among patients with stage IV cancer, are receiving increasing attention as important goals of care. Consequently, prolonged hospitalizations, intensive care stays, emergency room visits, hospital readmissions, and aggressive therapies, such as chemotherapy and surgery, have come under scrutiny given the increasing emphasis on improved palliative care and QOL for patients near their end of life. These issues create a dilemma for surgeons, as patients with disseminated malignancy (DMa) commonly present with acute surgical conditions, such as malignant bowel obstructions (MBO), for which surgery has historically been the standard of care. The goal of this proposal is to examine the morbidity, mortality and surrogate endpoints for QOL among patients with DMA who present with MBO and are treated medically versus surgically. We hypothesize that surgical management will lead to higher rates of these morbidity/adverse QOL outcomes with correspondingly negligible differences in overall survival. We will test our hypothesis through the following specific aims: Aim 1: To demonstrate that rates of morbidity and associated endpoints (e.g. prolonged hospitalizations) are higher for surgically-managed versus medically-managed DMa patients with MBO. Aim 2: To compare overall survival between the surgically and medically managed cohorts. We will test this hypothesis using the California Office of Statewide Health Planning and Development database, specifically consisting of patients with the diagnosis of DMa and MBO admitted to a California licensed hospital from 2005 to 2010. We will obtain inpatient and emergency visit data to evaluate differences in endpoints (i.e. morbidity, prolonged hospitalizations, ICU stays, readmission, emergency room visits and disposition to nursing facilities) for surgically versus medically-managed patients. In addition, we will use linked death data to examine differences in survival among cohorts. These data will have important implications for patients and surgeons as the data will provide a population-based assessment of the impact of medical versus surgical management on morbidity and survival as well as important metrics of QOL. This research is critical to shared patient and surgeon decision-making for this increasingly common and high risk patient population.

R-loop Driven Oncogenic Translocations in Prostate Cancer

Host Campus: Davis
Lead Investigator: Frederic Chedin
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $53,424

Abstract:
Genomic instability is a hallmark of many cancers. This instability often results in oncogenic translocations such as the well-known MYC-IgH translocation in B cell tumors or TMPRSS2-ERG translocation in prostate cancers. Understanding the mechanisms driving such translocations is of critical importance for future therapies aimed at blocking these events. I hypothesize that co-transcriptional R-loop structures formed upon re-annealing of the nascent mRNA to the DNA template are a critical source of oncogenic translocations in prostate cancer. Building on groundbreaking genomics technologies developed by my laboratory, the first aim of this proposal will be to map sites of R-loop formation in prostate cells and their response to stimulation by androgen signaling. Pilot experiments show that R-loops significantly increase over androgen-responsive genes in response to androgen stimulation. Major common translocation partners such as TMPRSS2, NDGR1 and Kallikrein 3 (KLK3 – also known as prostate-specific antigen, PSA) show particularly strong increases in R-loop formation. The second aim of the proposal will test the hypothesis that co-transcriptional R-loops coincide with double-stranded DNA breaks that often initiate translocations. For this we will leverage the recently published END-seq method to map these breaks in prostate cells undergoing androgen stimulation or not. My group is well-versed in all the genomics techniques necessary for completing this work. We also have strong in-house expertise in computational biology including algorithm development and visualization techniques, necessary to analyze and cross-reference these large datasets. Overall, this proposal offers to leverage key breakthroughs in R-loop mapping developed by my group to the study of cancer initiation mechanisms. This represents a novel research direction for us. Upon completion of this 1-year grant, my goal is to extend this work into a more complete NIH R01 proposal aimed at characterizing mechanisms of genomic instability in prostate cancer.

Repurposing a toxin-immunity pair to selectively kill cancer

Host Campus: Irvine
Lead Investigator: Celia Goulding
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $55,000

Abstract:
One of the great remaining challenges in cancer therapy is the design of therapeutics that will selectively kill cancer cells, but leave healthy cells unharmed. A prevailing method of achieving selectivity comes from designing therapeutics that will bind to extracellular receptors; however, many of these markers are expressed in normal and germ cell tissues. Intracellular metabolic and gene expression profiles in cancer cells are instead drastically different from normal cells. It would therefore be transformative to develop targeted therapies that can 'sense' this intracellular difference, rather than a cell surface marker. Herein, we aim to develop such an approach; one that senses the intracellular environment of cancer cells, thereby triggering their destruction, by engineering a naturally occurring bacterial toxin-immunity complex to 'sense and kill' cancer cells and not normal healthy cells. We will fuse a known bacterial toxin, which is a potent DNase capable of completely degrading human chromosomal DNA, to its cognate toxin-neutralizing immunity protein. The toxin will be activated only by Cathepsin-L protease (CatL), a gene grossly upregulated in many cancer cells. Thus, the toxin will be liberated from the toxin-immunity fusion protein by CatL cleavage that will result in cancer cells death, whereas in healthy cells, which do not upregulate CatL, the toxin will remain fused to the immunity protein and therefore inactive. We will then test our optimized toxin-immunity fusion protein to ensure activation in human cancer cells and cell death, and that it remains inactivation in normal human cells. We shall also discuss potential delivery methods for this novel therapeutic; however experimental testing will out of the realm of this proposal. The final outcome of this design will be a state-of-the-art cancer-cell selective therapy. This initial CCRC study will generate data that will be used as proof-of-principle data for dual or multi-PI R01 NIH funding for anti-cancer therapeutics.

The Role of p21 Phosphorylation at S123 in Tumor Suppression

Host Campus: Davis
Lead Investigator: Michael Kent
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $55,000

Abstract:
The cyclin-dependent kinase (CDK) inhibitor p21, also known as WAF1 and CIP1, is a potent suppressor of cell growth and belongs to the Cip/Kip family of cdk inhibitors. p21 is a target of tumor suppressor p53 and mediates p53-dependent cell cycle arrest in response to DNA damage. Due to its potent role in growth suppression, p21 was originally identified as a tumor suppressor. Interestingly, recent studies also showed that p21 has an oncogenic activity as cytoplasmic localization of p21 promotes cell proliferation. Indeed, accumulation of cytoplasmic p21 is found in several types of cancers and associated with tumor progression and poor prognosis. Together, these studies suggest that depending on its cellular context, p21 could inhibit or promote tumorigenesis. Thus, understanding the mechanism how p21 activity is controlled may open a new avenue to explore p21 as a therapeutic target for cancer treatment. We previously cloned the canine CDKN1A gene and found that like human p21, canine p21 is induced by DNA damage in a p53-dependent manner and modulates p53-dependent cell cycle arrest. Interestingly, canine p21 is expressed as two isoforms due to proline-directed phosphorylation at serine 123 (S123), which can be easily visualized as a slower migrating band than the underphosphorylated canine p21. Interestingly, ectopic expression of mutant canine p21(S123D), in which serine 123 was substituted with phosphomimetic aspartate acid, greatly inhibited cell proliferation as compared to that of canine p21(S123A), in which serine 123 was replaced with non-phosphorylatable alanine. However, the role of serine 123 in p21-mediated growth suppression has not been studied in vivo. Interestingly, our pilot study indicated that the level of S123-phosphorylated p21 was reduced by lithium chloride (LiCl), an inhibitor of glycogen synthase kinase 3 (GSK3). Thus, we hypothesize that posphorylation of serine 123 plays a critical role in p21-mediated growth suppression. To test this, we will determine: (1) whether GSK3 phosphorylates canine p21 at S123; (2) whether S123 phosphorylation enhances canine p21-mediated tumor suppression in vitro and in vivo.

Studying breast cancer initiation in single cell resolution

Host Campus: Irvine
Lead Investigator: Kai Kessenbrock
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $55,000

Abstract:
Breast cancer is one of the most prevalent forms of cancer in women worldwide. Despite recent advances in understanding the genetic mutations driving breast cancerogenesis, prognosis still remains poor especially due to late diagnosis and subsequent high mortality from metastatic tumor formation. One major scientific roadblock is that most of our scientific knowledge in cancer research is based on averaged ensemble analyses, although heterogeneity within the cell population is a striking feature of many tumors and plays a critical role in driving disease progression and therapy resistance. BRCA1+ carriers have a high risk of developing triple negative basal-type breast cancer, and thus commonly undergo prophylactic radical mastectomy. Studying these tissue samples from BRCA1+ carriers at pre-neoplastic and neoplastic stages offers a unique opportunity to study cancer initiation and progression in a primary human and clinically relevant setting. We hypothesize BRCA1-driven breast cancer leads to the disruption of the normal breast epithelial cell hierarchy and distinct systems-level changes in gene expression signatures not only within the subset of transformed tumor initiating cells, but also within other epithelial cell populations and non-epithelial microenvironmental components. We have established an interdisciplinary research approach utilizing comprehensive single cell RNAseq in combination with cutting edge bioinformatics pipelines to study tumor heterogeneity and to build a cell atlas delineating cancer initiation and progression in single cell resolution. By creating a cell atlas of the human breast in single cell resolution, and interrogating how the system goes awry during tumor initiation, we will identify disease promoting subpopulations, discover novel biomarkers and testable gene signatures to improve cancer early detection, and reveal novel therapeutic targets to prevent breast cancer from progressing into a life threatening condition. Ultimately, this project has the potential to revolutionize cancer genomics and precision medicine by introducing single cell genomics to translational breast cancer research, and thereby providing a first impetus towards the generation of a Single Cell Cancer Genome Atlas (SCCGA).

Leukemia Stem Cells in B-Cell Acute Lymphoblastic Leukemia

Host Campus: Davis
Lead Investigator: Noriko Satake
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $55,000

Abstract:
Leukemia stem cells (LSCs) are the root of cancer and are responsible for treatment resistance and disease relapse. However, LSCs have not been identified in acute lymphoblastic leukemia (ALL), the most common cancer in children. Recently, our group discovered a method to identify and isolate LSCs from primary ALL samples. We demonstrated that the LSCs isolated using our marker have in vivo leukemia-initiating capability and distinct transcriptome profiles. We have identified 1,135 genes that are differentially expressed between LSCs and the counterpart of LSCs, non-LSCs ($p < 0.05$). Of these, 315 genes are upregulated in LSCs. The goal of this project is to identify the gene(s) that regulate the "stemness" of LSCs in ALL. In this pilot study, we will focus on B-cell type ALL (B-ALL), the most common ALL in children. We will identify the genes which are important for LSC maintenance using an in vivo shRNA screening method and leukemia xenograft models with cell lines and primary leukemia samples. We hypothesize that one or more genes play a dominant role in regulating stemness and phenotypic properties of LSCs in B-ALL. The specific aims are to determine 1) the key genes associated with stemness in LSCs and 2) the key genes associated with differentiation in non-LSCs. We will investigate the two counterpart populations (LSCs and non-LSCs) using the same method, which should provide complementary results. We expect to identify potential novel genes (and pathways) which regulate the stemness of LSCs in B-ALL. We will pursue this goal using 1) our well-annotated series of patient-derived xenograft mouse models, 2) our novel LSC isolation technique, and 3) in vivo shRNA screening and targeted gene RNA sequencing. If successful, this project could have a significant impact on the most important challenges in cancer treatment: resistance or recurrence of disease.

Novel cancer metabolite-triggered drug delivery

Host Campus: Irvine
Lead Investigator: Szu-Wen Wang
Start Date: 1/1/2018 *End Date*: 12/31/2018 *Amount*: $55,000

Abstract:
Stimuli-responsive drug delivery strategies are designed to react to changes in conditions, such as pH or temperature, within the microenvironment of tissues or cells. However, often these triggers are not adequately specific, as the conditions can occur at alternate off-target locations, or the differences between diseased vs. normal states are not sufficiently high. This proposed project will develop a novel drug delivery strategy that will target tumors by specifically responding to lactate, a signature metabolite of cancer and a hallmark of the Warburg effect. The Warburg effect has not yet been exploited in a drug release mechanism, so our proposed drug delivery material will introduce a novel means to deliver and release drug cargo to tumor environments with elevated lactate concentrations, and it is likely to be more specific towards cancer than existing approaches. We hypothesize that hydrogels responsive to the Warburg effect can be created by incorporating specifically-engineered lactate-binding proteins within polymeric matrices. The polymer component has been utilized in molecular imprinting, and the unique metabolite "sensor" will be engineered mutants of a protein with natural binding affinity to lactate. A small library of rationally-designed mutants will be created to obtain binding affinities appropriate for response. The protein and its polymerizable inhibitor will be incorporated into the hydrogel polymer, with interactions between the protein and inhibitor serving as reversible cross-linkers. Competitive binding of this material with the lactate in the microenvironment will result in material swelling and drug release. This proposed work will generate proof-of-concept data for future studies in metabolite-responsive drug therapy. Our aims are to: (1) engineer proteins that will competitively bind the lactate metabolite and its monomer inhibitor; (2) fabricate Warburg effect-responsive protein-polymer hydrogels; and (3) examine the hybrid materials' response to the lactate metabolite and the corresponding drug loading/release.

Investigating the carcinogenicity of e-cig

Host Institution: University of Southern California
Lead Investigator: Stella Tommasi
Start Date: 7/1/2016 *Amount*: $396,000

Abstract:
This project will address the overall health impact of electronic cigarette (e-cig) use, which is a major public health concern. E-cigs are increasingly promoted as safe alternatives to conventional tobacco cigarettes or as aids to smoking cessation. E-cigs are rapidly gaining acceptance in the United States and many parts of the world, especially among children and young adults. However, very little is known about the health consequences of e-cig use. The studies described in this “Pilot Research Award” application will investigate, for the first time, the cancer-causing potential of e-cig in a validated mouse model. We will use state-of-the-art DNA sequencing-based techniques, developed in our laboratory (Nucleic Acids Res, 2012) and others’, to investigate the cancer-relevant biological effects of e-cig aerosol, and compare the results to those of cigarette smoke. Using a microprocessor-controlled vaping machine, we will expose mice to e-cig aerosol, harvest their lungs, and measure molecular changes that are known to be associated with cancer. The culmination of the studies described in this proposal is expected to result in data that can help clarify the health risks/benefits of e-cig use relative to cigarette smoking. This information will assist regulatory agencies in making scientifically based decisions on the development and evaluation of regulations on e-cigs and other tobacco products to protect public health and to reduce tobacco use by minors.

Lung Cancer Screening: The Views of Patients and Physicians

Host Campus: San Francisco
Lead Investigator: Celia Kaplan
Start Date: 7/1/2015 *Amount*: $249,475

Abstract:
Lung cancer is the leading cause of cancer death in the U.S. among both men and women. In 2010, results from the National Lung Screening Trial, which compared low-dose computed tomography (LDCT) screening to chest radiography, found a 20% reduction in lung cancer mortality among individuals at high risk who received LDCT. Based on these results, and after evaluating the benefits and harms, the United States Preventive Services Task Force recommended annual lung cancer screening with LDCT scans for high-risk patients. Recently, the Centers for Medicare and Medicaid Services announced the decision to cover LDCT for lung cancer screening. Considering these recommendations, patients, together with their physicians, should weigh currently known benefits with limitations and risks to make an informed and shared decision about being screened.

Any discussion of lung cancer screening should be coupled with culturally and linguistically personalized information about risk and potential benefits, harms, limitations, and associated costs. Although primary care physicians (PCPs) are central to the discussion of lung cancer screening and shared decision making, they may lack tools and information to facilitate these discussions with patients. In addition, patients lack the personalized information to determine their own risk and to evaluate the benefits and harms of lung cancer screening. However, there are no standards for conducting these discussions, particularly with patients of limited health literacy, limited English proficiency or from diverse cultural backgrounds.

Our study will assess the barriers and facilitators of lung cancer screening among a multiethnic population and determine the best methods and messages for communicating risk, benefits, and options for lung cancer screening. We will determine the barriers (psychosocial, financial, system) to physician-patient discussions concerning lung cancer risk and lung cancer screening, and determine what might facilitate those discussions and encourage SDM. We will evaluate patient and PCP perspectives and concerns individually.

We expect our research to provide specific recommendations that will inform an intervention to facilitate patient-PCP discussions about LDCT screening and promote shared decision-making among ethnically diverse patients.

Genomic approaches to identify SCLC biomarkers

Host Institution: Stanford University
Lead Investigator: Dian Yang
Start Date: 7/1/2015 *Amount*: $63,364

Abstract:
Small cell lung cancer(SCLC) is the most deadly type of lung cancer and is associated with heavy cigarette smoking. Although the five-year survival rate is only 15%, the few patients detected with limited-stage disease have a much higher long-term survival. Therefore, it is crucial to identify targets and develop methods that could detect SCLC with high specificity in high-risk patients at early stages of cancer development.

We hypothesized that genes/markers that uniquely label SCLC in the lung would be good candidate for cancer detection. Our preliminary gene expression analysis comparing differences between SCLC lung tumors and normal lung tissue suggests that SCLC tumors have very distinct gene expression profiles with more than a thousand of genes changed their expression level for more than four fold. The defined timeline of tumor development in genetically engineered mouse models of SCLC enables us also to look into even early stage lesions, called hyperplasia. By cross comparison the gene expression patterns among normal lung cells, hyperplasia and SCLC tumors, we will gain a full understanding of early cancer development, but also identify a list of candidate markers for both hyperplasia and tumors. We will query other mouse model of SCLC as well as publicly available human SCLC gene expression dataset to filter our candidate marker list and finalize a list of markers that are generalizable and universal to most SCLC cases. We anticipate getting a list of 10 candidates for further characterization. We will then validate the candidates' expression at protein level using immunohistochemistry on SCLC tumor sections from mouse and human. Given the imperative need for better therapies for SCLC, we will also test whether the candidate markers of SCLC have functional importance during tumor development. We will decrease the candidates' expression by RNAi technology, and monitor the effect on tumor growth in mouse and also effects on proliferation and cell death.

An understanding of the markers that uniquely label SCLC in the lung may allow the clinical development of imaging methods that detect SCLC with high sensitivity and specificity. Functionally important candidates may also be potential drug targets for treating SCLC.

CTCs for early detection and characterization of lung cancer

Host Institution: SRI International
Lead Investigator: Xiaohe Liu
Start Date: 12/1/2014 *Amount*: $351,236

Abstract:
Circulating tumor cells (CTCs) are cells that are released from primary tumors into the bloodstream, thereby contributing to the spread of cancer to other parts of the body. They circulate in very low concentration in the peripheral blood and are not readily detected with conventional technologies. The Holy Grail of cancer diagnostics is the “liquid biopsy”: the ability to use the CTC information available in a blood specimen to diagnose and characterize cancer.

We have developed an innovative technology for rare cell detection called FAST (Fiber-optic Array Scanning Technology) that detects CTCs with high sensitivity and speed. For many years, our laboratory has investigated better ways to detect cancer and personalize and monitor treatments by identifying and characterizing CTCs from multiple cancer types, such as breast, lung and prostate cancers. Our characterization of CTCs analyzes protein biomarkers and genetic traits to provide information about the specific nature of a given patient’s disease and identify potential effective therapies.

The large majority (85–90%) of lung cancers are non-small cell lung cancer (NSCLC), and this aggressive disease has low survival rates. Producing an effective liquid biopsy technique could increase survival and potentially eliminate traditional biopsies, which are not only expensive but are invasive in ways that take an emotional and physical toll on patients.

Our goal is to develop new methods that can accurately detect CTCs from NSCLC with high sensitivity, thereby identifying cancer at a much earlier stage, when treatment can be much more successful. In addition, we propose to develop novel multiplexed assays to characterize molecular targets on CTCs at the single-cell level. These biomarkers will provide extensive, real-time information to allow treatment to be tailored to a patient’s specific cancer. This study is designed to generate data that can be used to pave the way for personalized medicine and better outcomes for NSCLC patients.

Ultra Low Dose, Effective CT for Lung Cancer Screening

Host Campus: Los Angeles
Lead Investigator: Michael McNitt-Gray
Start Date: 8/1/2013 *Amount*: $428,183

Abstract:
Lung cancer is the leading cause of cancer death in both men and women in the United States. The disease has been closely associated with smoking since 1964, when the Surgeon General concluded that tobacco smoke was a cause of lung cancer. Today, smoking is thought to cause up to 80-90 percent of lung cancer cases. Many programs have been successful in limiting smoking (e.g. smoking cessation programs, laws and policies that limit exposure to second hand smoke, etc.). However, lung cancer 5 year survival rates have not improved dramatically in the past several decades. The five-year survival rate for lung cancer currently stands at 15.6 percent as compared to an over 90 percent survival rate for breast, colon and prostate cancers.

In October 2010, the National Lung Screening Trial (NLST) announced it had demonstrated a significant reduction in death rates from lung cancer (and death from any cause) when performing screening using low dose CT. More than 2 years later and despite the success of this trial and the endorsement of many agencies recommending the use of CT in screening in high risk populations (The American Cancer Society, The American Lung Association, The American College of Chest Physicians, the American Society of Clinical Oncology, The American Association for Thoracic Surgery and the National Comprehensive Cancer Network), there has not been widespread adoption of CT screening for lung cancer.

While several reasons for this lack of adoption have been identified, one recurrent reason given is the concern over radiation exposure to a large screening population, even with low dose CT. The scans performed in the NLST were considered to be “low dose” because they used an appreciably reduced scanner output (compared to conventional diagnostic CT scans) to carry out these screening studies. Since the NLST was initiated in 2002, there have been tremendous advances in CT scanner technology, specifically with respect to radiation dose reduction. These include the introduction of automatic exposure controls which adapt the scanner output to the size of the patient (reducing it for small patients, etc.) and novel image reconstruction methods that exploit advances in computing power to reduce image noise and allow image quality to be maintained even when very low doses are used. These developments encourage us that lung cancer screening may be accomplished using CT at doses that are significantly lower than the “low dose” scans used in the NLST.

Therefore, there is a critical need to develop Ultra Low Dose CT scanning methods that bring the radiation dose down to a level close to that of Chest X-rays while maintaining the image quality necessary for lung cancer screening. The purpose of this project is to investigate both methods to perform CT exams at reduced dose levels close to those of Chest X-rays and to evaluate the ability to identify and characterize lung nodules in a screening setting under these ultra low dose scanning conditions. This requires an innovative approach which brings together imaging physics, image reconstruction methods and computer vision techniques with specific emphasis on detection of lung lesions and their boundaries.

Shared Genetics of COPD and Lung Cancer

Host Institution: Kaiser Foundation Research Institute, a Division of Kaiser Foundation Hospitals
Lead Investigator: Lori Sakoda
Start Date: 8/1/2013 *Amount*: $561,107

Abstract:
Why some smokers develop lung cancer, but most do not, remains unclear. Answering this question is critical in improving prevention and early detection of this deadly disease. People with chronic obstructive pulmonary disease (COPD) have a much greater risk of developing lung cancer. Since smoking is the major cause of both COPD and lung cancer, these diseases likely arise from some common biological mechanisms that are activated by tobacco smoke. These mechanisms may be discovered by determining whether genetic characteristics associated with risk for developing COPD are also associated with risk for developing lung cancer. The primary goal of our study is to identify genetic characteristics that jointly contribute to COPD and lung cancer in smokers.

To achieve this, we will identify former and current smokers diagnosed with COPD, with lung cancer, or without either condition as participants from a large, stable, and well-characterized cohort of adult Kaiser Permanente Northern California health plan members. For all participants, survey data on lifestyle and behavioral characteristics, along with extensive genetic data, have already been collected. Genetic data include genome-wide single nucleotide polymorphism (SNP) genotyping and telomere length measures. In analyzing these data, we will first identify genetic characteristics associated with risk of COPD. We will then assess the extent to which COPD-related SNPs identified in this and prior studies and telomere length are associated with risk of (a) both COPD and lung cancer, (b) lung cancer with pre-existing COPD, and (c) lung cancer without pre-existing COPD.

The proposed study will be the most comprehensive examination of shared genetic risk factors for COPD and lung cancer to date. Identifying genetic characteristics associated with COPD and/or lung cancer has the potential to not only improve our understanding of the biological mechanisms involved in both tobacco-related diseases, but also lead to the discovery of new chemopreventive and therapeutic drugs and the development of tailored early detection strategies for lung cancer.

Alliance for Data Dissemination to Achieve Equity (ADEPT)

Host Institution: Asian Pacific Partners for Empowerment, Advocacy and Leadership (APPEAL)
Lead Investigator: Rod Lew
Start Date: 5/1/2011 *Amount*: $481,501

Abstract:
This proposed collaborative project, Alliance for Data dissemination to achieve Equity for Priority populations on Tobacco (ADEPT), will contribute to TRDRP's mission and goals, by helping to understand and translate tobacco use information from California's diverse population through the dissemination and evaluation of high quality, evidence-based data. It will address TRDRP's primary area of tobacco-related health disparities among California's diverse and vulnerable populations including African Americans (AfAms), American Indian/Alaskan Natives (AIs/ANs), Asian Americans (AAs), Native Hawaiians and Pacific Islanders (NHPIs), Hispanic/Latinos (H/Ls), Lesbian, Gay, Bisexual, Transgender (LGBT) and low Socioeconomic Status (low SES) populations. ADEPT will disseminate critical tobacco use data on these 7 diverse and vulnerable populations in culturally and language specific community-tailored format. This will help to increase the understanding of the impact of tobacco use on vulnerable populations and lead to increased mobilization on tobacco control program and policy initiatives. Furthermore, in addition to an individual community-tailoring approach to data dissemination, ADEPT will facilitate a collaborative approach to planning, sharing common strategies and joint event(s) among all 6 priority population groups.