**Cancer Research Coordinating Committee**

*Abstracts for 2021-2022 Awards*

# Table of Contents

*Click on project titles to see full abstracts*

| PI First Name | PI Last Name | Title | Host Campus | Start Date |
|---|---|---|---|---|
| **Olena** | **Vaske** | RNA targets for synovial sarcoma | Santa Cruz | 10/1/2021 |
| **Maxwell** | **Wilson** | Illuminating the fluid connection between Wnt signaling and the centrosome in colorectal cancer | Santa Barbara | 10/1/2021 |
| **John** | **Yoon** | Targeting thermogenesis regulators in pancreatic cancer-associated cachexia | Davis | 10/1/2021 |
| **Peter** | **Zage** | Targeting Novel Signaling Pathways for Neuroblastoma Therapy | San Diego | 10/1/2021 |
| **Weiwei** | **Zhang** | Neurocognitive Processes for Mammographic Detection of Breast Cancer | Riverside | 10/1/2021 |

# 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.

## Role of glycan presentation in head and neck cancer immunoevasion

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

*Abstract*:
Tumor-derived exosomes (TEX) have been increasingly recognized as playing a vital role in tumor progression and immunoevasion. TEXs have emerged as a new and powerful mechanism of communication between tumor cells and their environment with the capability to convey multi-molecular biological messages that modulate the immune system, and play a role immunoevasion. Although the mechanism of TEX-mediated immunomodulation and immunoevasion is not well characterized, there is evidence to suggest that glycosylation has an important role. Due to recent advances in glycomics technologies, we are now able to better measure glycan expression and define glycans structures, which is critical to understanding their function.

Hyper-sialylation mediates tumor progression and immunoevasion. Sialoglycans interact with Siglecs, a family of immune checkpoint receptors. Consequently, Siglec-sialoglycan interactions represent promising immunotherapy targets. However, it is unclear which sialoglycans are the critical ligands that activate Siglecs. It is also unclear what role sialoglycans play in the immunoregulatory properties of TEX, and remains an important gap in knowledge. Since current cancer immunotherapies are effective in only a subset of patients, there is a critical need to identify novel strategies to develop new immunotherapies with improved effectiveness.

My overall objectives are to identify the role of critical sialoglycans in the mechanisms underlying HNC TEX's immunoregulatory properties, and determine the anti-tumor efficacy of TEX sialoglycan inhibitors. My central hypothesis is that HNC-TEX manipulate the immune response to allow immunoevasion and glycomic approaches can identify signaling factors involved. This hypothesis is based on preliminary data suggesting that HNC TEXs express high levels of sialoglycans and polarize macrophages toward an immunosuppressive M2-phenotype. This project's rationale is that identifying the mechanisms TEX use to regulate tumor immunity will enable development of new immunotherapies to improve future treatment of cancer patients.

Specific Aim 1. Identify and define the glycan structures that define TEX.

Specific Aim 2. Determine which specific sialoglycan-Siglec interactions mediate M2 polarization by TEX.The research we propose is significant because it is expected to show that the gut microbiome is a missing key to accurately predicting which patients will receive the beneficial effects of tamoxifen. Ultimately, the results of this research may provide new opportunities to achieve personalized and more effective treatment of breast cancer by accounting for the uniqueness of each patient's gut microbiome.

# Multiparametric 18F-fluciclovine PET imaging in evaluation of recurrent glioblastomas

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

*Abstract*:
Assessment of response to treatment in glioblastoma (GB) is a clinical dilemma. Residual/recurrent tumor could mimic pseudoprogression, radiation necrosis and other treatment-related changes. Although pathological confirmation is the most reliable method to differentiate progressive tumor from treatment effect, it is an invasive method and may not correctly target the viable part of the tumor; therefore, numerous noninvasive methods have been attempted, including several MRI tools , and various PET tracers(1).

Yet, current imaging techniques are often inconclusive. 18F-fluciclovine (Axumin®; Blue Earth Diagnostics), a synthetic amino acid mostly used as a PET tracer in prostate cancer has recently shown value in differencing disease progression and treatment-related changes (2)(3). Its high tumor-to-brain contrast based on the relatively high specificity for neoplastic tissue and the low uptake in healthy brain tissue make 18F-fluciclovine an attractive agent with significantly higher image contrast compared to other amino acid PET tracers(4). Nevertheless, most studies focused on static imaging features, which provide a simple snapshot of radiopharmaceutical concentration within the neoplasms and do not provide sufficient information on tumor perfusion and tracer kinetics that may be important in differentiating active tumor from treatment changes. Dynamic PET imaging utilizing other tracers such as O-(2-[18F]fluoroethyl)-L-tyrosine, $^{11}$C-methionine, and 3,4-dihydroxy-6-[$^{18}$F]fluoro-L-phenylalanine have shown potential in assessment of response to therapy in brain tumors (5)(6)(7). 18F-fluciclovine has several advantages compared to these tracers, including it is already widely available, has appropriate half-life for usage in clinical practice, and FDA approved.

To the best of our knowledge, no study has evaluated the usefulness of 18F-fluciclovine dynamic PET in assessing treatment response in GB, utilizing the world's first EXPLORER total-body PET/CT scanner, which offers ultrahigh sensitivity and more accurate tracer kinetic analysis(8).

The aims of this pilot study are (i) to investigate the feasibility of parametric 18F-fluciclovine brain PET imaging in differentiating progressive disease from treatment effect and (ii) to validate the feasibility of the 18F-fluciclovine cerebral perfusion using MRI perfusion imaging as the reference.

## 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.

# Engineered vasculature for long-term culture of tumoroids: in-situ polymerization of scaffolding

*Host Campus*: Santa Barbara
*Lead Investigator*: Emilie Dressaire
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $ 82,416

*Abstract*:
Cancer research has uncovered a small number of fundamental principles that govern the disease's progression, including the formation of a favorable micro-environment. Indeed, tumors induce the growth of blood vessels. The blood flow is essential as it provides sustenance through an influx of nutrients and oxygen and an outflux of waste while contributing to metastasis. Therefore, biomimetic culture environments for cancer research should be vascularized. Engineering a functional vasculature is a mechanical challenge as the vessel walls need to be soft and permeable while retaining their shape under physiological stresses.

The proposed work aims to produce artificial vessels to enable the long-term study of tumoroids in vitro. We will build on the most recent and promising advances in bio-printing that leverage microgels as a printing medium. In microgel particles, cancer cells move and proliferate to form tumoroids whose properties are strikingly similar to those of tumors. However, diffusion limits molecular transport, and the tumoroids stop developing as cells lack oxygen and nutrients. To this day, there is no technology capable of producing a stable, functional vasculature in a microgel bath.

Leveraging our expertise in fluid dynamics through low porosity environments, we are uniquely positioned to tackle this challenge. We will seek to further the fundamental knowledge necessary to develop an artificial vasculature. From an engineering standpoint, a vessel is a hollow tube that allows fluid flow. In microgels, open vessels collapse due to local rearrangements. Our strategy fills the vessels with a scaffolding of solid particles separated by small voids permeable to the flow. The solid particles prevent the collapse of the vessel whose walls remain permeable. To mitigate the challenges of particle transport, we will rely on an emulsion to form the vessels. The emulsion droplets will then be polymerized in-situ to become solid and facilitate the molecular transport to and from the tumoroid.

This seed grant will support our work in a pivotal year. We will demonstrate the printing of a stable permeable channel in microgel through (1) the injection of the emulsion and (2) the in-situ polymerization of the scaffold. With this proof of concept, we will seek extramural funding to further advance cancer research with engineered micro-environments.

## Sum Frequency Generation Imaging of Breast Cancer

*Host Campus*: Irvine
*Lead Investigator*: Nien-Hui Ge
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $75,000

*Abstract*:
Breast cancer, a leading cause of cancer deaths, is among the most frequently diagnosed cancers in women worldwide. Defining a tumor's stage and spatial extent is crucial to planning treatment and evaluating changes associated with therapy and tumor growth. Studying the tumor microenvironment, such as the role of collagen in connective tissue, has been recognized as being important for understanding breast cancer initiation and progression. Although second harmonic generation (SHG) microscopy, a powerful form of microscopy of particular use in imaging tissue disorders, has shown great promise in characterizing collagen structural changes in breast cancer, this technique suffers some limitations because it lacks chemical selectivity under typical operation conditions, making it difficult to determine which molecular parts give rise to the response. There is clearly a need to further develop multimodal multiphoton imaging techniques that can discover and identify biomarkers for cancer diagnosis and prognosis with chemical selectivity, structural specificity, and organizational sensitivity. We propose to explore the capability of a novel method, vibrationally resonant sum frequency generation (VR-SFG) microscopy, in characterizing the chemical, structural, and organizational changes of collagen in breast cancer. We will extract collagen features from VR-SFG images and establish their association with the outcome of ductal carcinoma in situ and invasive breast cancer. Besides exploring the different metrics previously used in SHG as a benchmarking study for VR-SFG, we will devise new metrics based on VR-SFG response because it can probe a wide range of chemical groups and provide detailed information on structural orientation, which is important for revealing changes at the submolecular and supramolecular levels and not accessible from SHG or other techniques. We will delineate the relative merits of different metrics for diagnostic and prognostic applications. The proposed project is significant because once collagen-based VR-SFG is established as a prime indicator of cancer signature, its application and future combination with the modalities of SHG and two-photon excitation fluorescence (a technique that can image the metabolism rate in tissue) will result in new and more effective approaches in cancer research.

## In vivo CAR and TCR cancer immunotherapy using in vitro reconstituted virus-like particles

*Host Campus*: Los Angeles
*Lead Investigator*: William Gelbart
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $75,000

*Abstract*:
Gene therapy delivering ex vivo T cell receptors (TCRs) or chimeric antigen receptors (CARs) has revolutionized oncology. Two CAR therapies targeting CD19 on B cells to cure previously fatal B cell leukemias and lymphomas are FDA approved. But barriers remain to harnessing T cell gene therapy to its full potential. Clearing solid tumors has been unsuccessful, as they require more persistent and vigorous immunity, given a large local tumor burden that creates a hostile microenvironment. And up to now TCR/CAR therapies have involved: leukapheresis; massive ex vivo expansion of T cells to condition them for transduction in large numbers; lentiviral delivery of a TCR/CAR gene; and infusion. This process drives T cells to abnormal differentiation and exhaustion, reducing functional capacity and limiting survival. Additionally, the requirement for huge numbers of T cells risks cytokine storm and insertional oncogenesis.

An ideal alternative approach for TCR/CAR gene therapy would include: in vivo gene delivery under physiologic conditions that do not alter cell function; ability to control the number of transduced cells so that therapy can be ramped up gradually and maintained to persist long term; and avoidance of permanent modification of the genome that risks oncogenesis.

We are pursuing such an approach in a collaboration combining expertise from two research groups. Dr. Gelbart has developed RNA delivery technology using in vitro reconstituted virus-like particles (VLPs): capsid modification allows cell targeting, and packaged RNA serves as mRNA. In particular, we propose in vivo TCR/CAR gene delivery targeted to T cells via CD3 engagement. Cells transduced in situ would be unmanipulated and fully functional, and the process could be repeated and titrated to control numbers of transduced T cells over time. Because there is no genomic modification and RNA is transient, this approach would avoid risks of cytokine storm and oncogenesis. Dr. Yang, whose group has extensive experience in TCR and CAR manipulation, will collaborate with Dr. Gelbart to develop VLP technology to deliver genes for TCRs/CARs, providing proof-of-concept that T cells can be functionally retargeted, in vivo, via this approach.

KEY WORDS: T-cell therapy; T-cell receptors (TCRs); chimeric antigen receptors (CARs); in vivo T-cell transformation; targeted virus-like-particles (VLPs)

## The Role of Alternative pre-mRNA Processing in Colon Cancer

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

*Abstract*:
Recent work has documented that changes in alternative pre-mRNA processing associate with colorectal cancer (CRC), suggesting that aberrant pre-mRNA processing may contribute to tumorigenesis. As a first step towards understanding CRC, it is crucial to understand the biology of the organ the cancer develops in. The inner mucosal layer of the intestine is comprised of an array of different epithelial cell types, which are organized in crypt structures. At the base of each crypt are non-quiescent epithelial stem cells that rapidly differentiate into progenitor cells. To determine how the transcriptome and proteome keep pace with rapid differentiation, we developed a new cell sorting method to purify mouse colon epithelial cells. We showed that alternative pre-mRNA splicing and alternative polyadenylation dominate changes in the transcriptome as stem cells differentiate into progenitors. By contrast, as progenitors differentiate into mature cell types, changes in mRNA levels rather than different isoforms dominate the transcriptome. These observations demonstrated that during the first steps in loss of stemness, the most notable change in the transcriptome are changes in mRNA isoform production via alternative splicing events and/or alternative polyadenylation. Considering that the disruption of cellular differentiation and the promotion of rapid proliferation is a crucial step in initiating carcinogenesis, it is likely that CRC may originate from an inability of crypt stem cells to initiate the necessary alternative pre-mRNA processing programs that guide terminal differentiation. Therefore, we hypothesize that defects in alternative pre-mRNA processing contributes to the origin of CRC. To demonstrated that that the lack of differentiation-specific alternative pre-mRNA processing is an early hallmark of CRC, we plan to define the transcriptomes of colon stem cells and daughter cells harvested from a CRC mouse model. Furthermore, to demonstrate that equivalent alternative pre-mRNA processing changes accompany differentiation of human CRC cells, we will analyze the transcriptomes of CRC crypt organoids derived from human patients in the context of stemness and metabolically-induced differentiation. Throughout this project we will rely on our expertise in cancer biology, RNA biology, and bioinformatics to obtain new insights into gene expression patterns in CRC.

## Identification of novel Clic1 inhibitors for the treatment of cancer

*Host Campus*: San Diego
*Lead Investigator*: Christina Jamieson
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $75,000

*Abstract*:
CLIC1 is overexpressed in most tumors including prostate cancer, muscle-invasive bladder cancer, pancreatic adenocarcinoma, glioma. Elevated CLIC1 expression correlates with poor prognosis. The peculiarity of CLICs, in particular of CLIC1, is it is mainly present as a cytosolic protein under physiological conditions and transiently expressed in the cell membrane during stress conditions. In prolonged stress conditions, the functional expression and the membrane activity of CLIC1 is no longer transient but becomes chronic and thus represents a unique pharmacological target. The integral membrane form of Clic1 is an active ion channel and transports Cl– into the cell as well as stimulates increase reactive oxygen species (ROS) production. These changes in intracellular localization and channel function, uniquely associated with malignant transformation offers a unique target for cancer therapy, likely able to engender specificity with reduced side effects. Moreover, studies have shown Clic1 inhibition, by a specific inhibitor, IAA94 reduces ROS production, decreased intracellular chloride levels and lowers cell motility and invasiveness of cancer cells. From the standpoint of developing new anti-cancer agents for preclinical evaluation IAA94 provides the ideal starting point as it was initially developed in 1987 as a diuretic but was not optimized for specific chloride channel activity. It has a good toxicity profile and established ADME/PK attributes. With an abundance of high-resolution crystallographic structures computational modeling of Clic1 shows clear opportunities for improvements in potency and selectivity over other chloride channels though medicinal chemistry optimization of IAA94. These new IAA94 analogues will also be designed and tested for ADME/PK attributes allowing in vivo assessment for anti-cancer activity. Compounds will be tested in established models of prostate cancer to determine cellular localization and functional effects on proliferation. Following iterative cycles of model-build-test (in vitro) the assessment of improved Clic1 inhibitors in vivo will be used to validate our proposal that this structural class of compounds provides new lead compounds with anti-cancer activity and a good toxicological profile. In summary, Clic1 inhibition is an exciting therapeutic strategy with great potential in a broad spectrum of cancer types.

## Leveraging single-cell transcriptomics to discover mechanisms of immune surveillance

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

*Abstract*:
The immune system not only attacks cancers—the basis of immunotherapy—it can stop them from starting. This process of "immune surveillance" is not well understood, but is attracting growing attention, as studies show that many normal tissues bear a high burden of oncogenic mutation, which is kept from progressing to malignancy.

A superb system for studying this process is the fruit fly, Drosophila. Flies do not normally get cancer (they don't live long enough), but oncogenic mutations can be introduced into individual cells of larvae and, depending on the mutation, the initially overgrowing cells are either killed, or brought back under control, so that the affected tissue appears normal (analogous phenomena have also been observed in mice). If an immune cell known as the hemocyte is eliminated, however, the same transformed cells will grow out of control (i.e. turn into cancer). The hemocyte is the fly homologue of the mammalian macrophage, and recent studies suggest that it enforces growth control at least in part through release of a ligand that is the fly homolog of TNF-alpha, a signaling molecule produced by activated human macrophages and implicated in immune surveillance.

One of the least understood aspects of immune surveillance is how hemocytes/macrophages know which cells to target. Studies suggest that localized overgrowths disturb both tissue mechanics and the organization of molecules that mark cell polarity, but exactly how hemocytes—which are rare, free-living cells—recognize the sites of such disturbances is unknown. We propose to leverage fly genetics and single cell transcriptomics to address this question. Specifically, we will generate scattered groups of cells mutant for the tumor suppressor gene scribble, in larval wing imaginal discs; cells bearing such mutations are normally eliminated but grow into tumors if hemocytes are absent. We will use single-cell RNA sequencing to identify transcripts encoding molecules, especially secreted and cell surface signaling molecules, that are differentially expressed by mutant cells and/or their neighbors. We will subject validated findings to functional analysis by siRNA-mediated knockdown. The results have the potential to elucidate evolutionarily conserved pathways of immune surveillance that might be difficult to find by other means.

## Role of cytoplasmic polyadenylation element binding protein 3 (CPEB3) ribozyme in cancer

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

*Abstract*:
Regulation of mRNA translation plays an essential role in cellular differentiation and proliferation. Dysregulation of post-transcriptional control and translational machinery have been implicated in malignant tumor development. One of the mechanisms to govern translation is cytoplasmic polyadenylation, and recent evidence suggests that this process modulates gene reprogramming associated with cancer progression. Cytoplasmic polyadenylation element binding proteins (CPEB1-CPEB4) are sequence-specific RNA-binding proteins that act as a translational regulator to control poly(A) tail elongation of target mRNAs, and subsequently contribute to phenotypic changes in cancer cells. Among CPEBs, aberrant expression of CPEB3 has been shown in several types of cancers, including hepatocellular carcinoma, cervical cancer, colorectal cancer, and glioma. Importantly, a self-cleaving hepatitis delta virus (HDV) ribozyme was identified in the CPEB3 gene. While we have previously uncovered the role of CPEB3 ribozyme in memory formation in mice, the regulation of CPEB3 ribozyme in transcriptional machinery implicated in cancer cells remains unexplored. Given the fact that CPEB3 acts as a tumor suppression gene, and downregulation of CPEB3 promotes cancer progression, we hypothesize that CPEB3 ribozyme might regulate CPEB3 expression and subsequently modulate tumorigenesis.

In our preliminary studies from analysis of The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC), we have found that CPEB3 expression is correlated with survival in low-grade glioma, melanoma, liver hepatocellular carcinoma, and lung adenocarcinoma. The proposed pilot study aims to elucidate whether the CPEB3 ribozyme plays a role in tumor development and progression. In Aim 1: We will investigate CPEB3 ribozyme self-cleaving activity and identify whether the ribozyme facilitates full-length mRNA processing and protein expression in cancer cells. In Aim 2: We will determine tumor suppression effects of CPEB3 by inhibiting CPEB3 ribozyme, and understand the underlying mechanisms associated with cancer metastasis through post-transcriptional regulation by CPEB3. Our study will unveil the biological function of CPEB3 ribozyme in cancer, and provide insights into therapeutic interventions.

## Role of Immunological Experience Shaping T Cell Reactivity in Tumors

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

*Abstract*:
Mice have been invaluable in discovering fundamental tumor immunology principles, model processes, and test anti-cancer immunotherapies at a pre-clinical stage. However, laboratory mice are usually kept in specific pathogen-free (SPF) conditions resulting in limited immune stimulation, while humans are exposed to natural pathogens and commensals throughout life. Such a different "immunological experience" has extreme consequences on the maturation of the immune system. SPF mice resemble newborn humans in that naïve T cells predominate, and tissue-resident adaptive immunity has not developed. Some of the immunomodulatory drug tests conducted in SPF mice have been dramatically misleading. For instance, SPF mice failed to predict the cytokine storm ensuing the administration of CD28 superagonist in humans, which could only be reproduced in immune-experienced mice after patients experienced life-threatening side effects. This application for a pilot grant through CRCC hypothesizes that immune experience increases CD8+ T cell reactivity within tumors. In contrast, modifications in T regulatory (Treg) cell reactivity may be absent or present. Tipping the balance towards CD8 reactivity would facilitate tumor rejection, especially after PD-1 immunotherapy. We will test this hypothesis by combining two state-of-the-art technologies. We have cutting-edge capabilities and experience in measuring TCR-mediated activation in tumor-associated CD8, CD4, and Treg cells in living mice using intravital multiphoton microscopy. We will combine this with C57BL/6 mice rederived to feral mice (wildling mice) to harbor the natural microbiome, mycobiome, and virome while being inbred and on a common genetic background. We collaborate with Prof. Rehermann of the NIH to import wildling mice to UCI and have an approved IACUC protocol to use them. We will first measure tumor-associated CD8+ and Treg cell reactivity in SPF as compared to wildling mice. We will then establish a correlation between tumor CD8+ and Treg cell reactivity in wildling mice and enhancement of their function and cancer rejection, either spontaneous or induced by PD-1 blockade. Our investigation will help identify the most suitable mouse model to study T cell immunology in cancer and shed light on the connection between immune experience and the quality of T cell responses to tumors.

## Investigating the roles of alternative RNase P and MRP subunits in stem and cancer cells

*Host Campus*: Riverside
*Lead Investigator*: Jernej Murn
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $75,000

*Abstract*:
Normal cell homeostasis requires control over the fine balance between differentiation and proliferation. Cancer arises when this balance tilts in favor of proliferation. The accompanying block in differentiation of cancer cells is often characterized by their immortalization and their propensity to self-renew. These hallmarks of cancer cells are shared to a significant extent with the self-renewing population of stem cells, which give rise to more specialized cell types during embryonic development and in the adult.

In our preliminary survey of molecular traits associated with fast-expanding, non-differentiated cells, we found that the RNA-binding protein Rpp25, a canonical subunit of ribonuclease P (RNase P) and its evolutionary descendant, RNase MRP, is abundantly expressed in mouse embryonic stem cells (ESCs), but is curiously missing in most mammalian somatic tissues. This observation is unexpected given that RNases P and MRP are ubiquitous and essential endonucleases that are critical for maturation of tRNAs and rRNAs, respectively. By contrast, we find that a paralog of Rpp25, a heretofore unstudied RNA-binding protein, Rpp25L, is broadly expressed and appears to be a dominant alternative subunit that replaces Rpp25 in somatic cells. Phenotypic analyses of Rpp25-null ESCs reveals their impaired colony formation and increased propensity towards spontaneous differentiation, whereas Rpp25L-null ESCs appear phenotypically normal. Markedly, akin to ESCs, Rpp25 is highly expressed in several human cancers, most notably melanoma, whereas its paralog shows no significant changes in expression. These results suggest non-overlapping roles of two alternative subunits of RNases P and MRP, with Rpp25 supporting fast expansion and undifferentiated state of stem and cancer cells. Here, we propose to 1) determine the impact of paralogous subunits on processing of tRNA and rRNA precursors, 2) define the effect of Rpp25 and Rpp25L on protein translation, and 3) investigate autonomy of the effects of Rpp25 in normal and cancer cells. This study will shed light on the alternative composition of these ancient 'housekeeping' ribozymes and their regulation of the balance between cell proliferation and differentiation, with general implications for cancer development.

## 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.

## Small Molecule Targeting of GNAS for the Treatment of Mucinous Adenocarcinoma of the Appendix

*Host Campus*: San Diego
*Lead Investigator*: Dionicio Siegel
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $85,000

*Abstract*:
The Gα protein GNAS is the second most frequently mutated gene in mucinous adenocarcinoma of the appendix (~50% of tumors), an orphan disease with no FDA approved systemic therapy. Genetic studies have confirmed that mutations in the R201 codon of GNAS drive oncogenesis in appendiceal, colon, and gastric adenocarcinoma, as well as Intraductal Papillary Mucinous Neoplasms (IPMN) of the pancreas and Small Cell Lung Cancer (SCLC). Although classically druggable, no commercially available inhibitors of GNAS currently exist. Here, we propose an innovative approach to develop and characterize chemical inhibitors of GNAS. 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 GNAS will be an effective therapeutic strategy for GNASR201 tumors.

Structure based approach to designing the needed modulators of GNAS mutant is a highly promising path to finding drug candidates to treat patients with GNAS mutations. With two of the most druggable pockets identified we will perform a screen against the largest chemical catalog of a billion compounds. The top hits characterized by the neural network force field-based docking score, as well as desirable ADME/Tox characteristics, will be obtained or synthesized and experimentally tested. In parallel, a de novo compounds based on docking predictions, will be synthetized and evaluated. The first hits will be derivatized, synthesized and tested through iterative cycles of model-build-test allowing continued refinement of our pocket targeting small molecules arriving at a set of compounds at the end of this study that will validate our targeting of these sites for selective chemotherapy.

Our previous experience in discovering first in class compounds for newly identified pockets (e.g., recently published inhibitors of CK2 alpha/beta interface, HepC protease inhibitors) is a good illustration of our ability to find drug candidates for this important target. As well as our proven track record synthesizing target small molecules quickly and efficiently. The team is led by a synthetic chemist (Dr. Dionicio Siegel, UCSD) with full support from a computational chemist (Dr. Ruben Abagyan, UCSD) and cancer clinician (Dr. John Paul Shen, MD Anderson Cancer Center).

# Tumor microenvironment-induced epigenomic remodeling promotes persistent invasion

*Host Campus*: Santa Barbara
*Lead Investigator*: Ryan Stowers
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $75,000

*Abstract*:
Breast cancer metastasis, which is responsible for ~90% of breast cancer deaths, is driven in part by mechanical properties of the tumor extracellular matrix (ECM). Tumor ECM stiffness correlates with disease progression, and stiffness per se has been shown to drive proliferation and invasion, even from non-malignant mammary epithelial cells1,2. A firm foundation has been built elucidating how mechanotransduction pathways can alter gene expression and ultimately phenotype3–7. However, it is not well understood how ECM mechanics influence the epigenome; modifications to chromatin that potently regulate gene expression, to give rise to malignant phenotypes. Epigenomic reprogramming could explain why cancer cells maintain their malignant, invasive phenotypes after metastasizing away from the stiff primary tumor.

The overall objective of this proposal is to determine how ECM mechanical properties activate histone deacetylases (HDACs) to induce epigenomic reprogramming and promote persistent breast cancer invasion. My central hypothesis is that mechanosignaling pathways differentially activate HDACs, causing epigenomic changes that promote and sustain malignant traits. Our very recent work indicates that stiff ECM causes misregulation of both lamina-associated chromatin and chromatin accessibility. Further, we showed that chromatin modifiers histone deacetylases (HDAC) 3 and 8 promote malignancy in response to stiff ECM.

Specific Aims

1. Determine the mechanism by which tumor stiffness promotes differential HDAC activity to induce a tumorigenic phenotype in a 3D breast cancer model.

We will use 3D hydrogel matrices with tunable mechanical properties that have been shown to induce a tumorigenic phenotype and standard molecular biology characterization techniques to complete this Aim.

2. Determine the contributions of epigenomic reprogramming to driving persistent invasion.

We will use dynamically tunable 3D hydrogel matrices to vary ECM properties over time to assess the maintenance of the reprogrammed epigenome and the invasive phenotype. We will evaluate the efficacy of HDAC inhibitors in reversing these chromatin modifications and preventing further invasion.

Successful completion of these aims has the potential to identify a novel mechanism driving malignancy and sustaining the invasive potential of metastatic cells.

## Chemical Tools for Visualizing the Glycocalyx in Cancer Cells and Tissue with Nanoscale Resolution

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

*Abstract*:
The glycocalyx is a layer of polysaccharide molecules that coats the surface of every cell in the human body. Sialic acids are saccharide components of the glycocalyx that are particularly relevant in cancer. Hypersialylation of the glycocalyx enables cancer cells to evade immune detection and metastasize to new tumor sites. While it is appreciated that increased sialylation correlates with cancer severity, it is not well-understood how the nanoscale organization of the hypersialylated glycocalyx specifically relates to cancer processes. This lack of clarity is due to the paucity of imaging methods that allow in situ glycocalyx visualization with sufficient nanoscale resolution on non-specialist instrumentation. As glycocalyx heights are between tens to hundreds of nanometers, they challenging to resolve on the diffraction-limited fluorescence microscopes that are found in most biology laboratories. Expansion microscopy (ExM) is an appealing imaging modality in this regard, as it enables super-resolution imaging dimensions on commonplace microscopes. ExM is a materials-based (rather than optics-based) approach that physically expands the imaging specimen to achieve super-resolution. Biomolecules of interest in cells or tissues are tagged with fluorophores, then tethered to a swellable hydrogel mesh. Osmotic swelling of the hydrogel physically separates the tagged fluorophores to achieve super-resolution; fluorophores that were initially indistinguishable are physically separated into distinct pixels for improved resolution.

This proposal explores chemical strategies for visualizing the sialic acid glycocalyx using ExM. Aim 1 develops ExM-compatible bioorthogonal probes to selectively tether, expand, and image sialic acid residues. As imaging resolution is proportional to the hydrogel swelling ratio, the major limit to glycocalyx resolution is the swelling factor of the polymer network, which can be tuned via hydrogel chemistry innovations. Aim 2 describes molecular engineering approaches to push the limits of glycocalyx visualization using ExM. Finally, as ExM processing renders samples optically transparent, low-background super-resolution imaging may be achieved on tissue samples that typically suffer from fluorescence scattering. Aim 3 explores the notion of visualizing sialic acids in human breast cancer tissue microarrays using expansion microscopy.

## RNA targets for synovial sarcoma

*Host Campus*: Santa Cruz
*Lead Investigator*: Olena Vaske
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $85,000

*Abstract*:
The proposed work will explore a new research discipline for my laboratory called cancer epitranscriptomics. This discipline is the study of how "spelling" mistakes in the RNA, rather than the DNA, contribute to cancer development. I will examine whether spelling mistakes in the RNA contribute to the development of a specific cancer, synovial sarcoma.

Synovial sarcomas are rare aggressive cancers of the muscle tissue that often affect adolescents and young adults. These cancers are invariably associated with an abnormality of chromosomes 18 and X (translocation t(X:18; p11:q11)), producing a chimeric protein SS18-SSX. While the presence of this chimeric protein ultimately results in abnormal gene regulation (how genes are turned on and turned off), the exact mechanism by which this occurs is still unknown.

Proteins that modify the sequence of RNA have recently emerged as an important class of gene regulators. They act at the level of RNA metabolism and translation and can affect the expression of cancer genes. However, the role of RNA modification defects in the development of synovial sarcoma is completely unknown. I hypothesize that abnormal modifications of the RNA contribute to the gene regulation changes that cause synovial sarcoma development. To address this hypothesis, I will examine the expression of RNA-modifying proteins in synovial sarcomas using the RNA sequence information from over 30 synovial sarcoma tumors, over 12,000 other cancers, and over 100 normal tissues that my laboratory previously assembled. I will then use a technology called nanopore direct RNA sequencing to characterize the landscape of RNA modifications in a panel of 30 synovial sarcoma tumor samples and patient-derived cell cultures. Finally, I will correlate the expression of RNA-modifying proteins to the catalog of RNA modifications to identify synovial sarcoma-specific patterns; I will use these patterns to develop further hypotheses about the role of RNA modifications in tumor development. The preliminary findings generated by this work will enable me to apply for larger grants to fund cancer epitranscriptomics research in my laboratory.

## Illuminating the fluid connection between Wnt signaling and the centrosome in colorectal cancer

*Host Campus*: Santa Barbara
*Lead Investigator*: Maxwell Wilson
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $85,000

*Abstract*:
Colorectal adenocarcinoma (CAC) is a deadly cancer with few promising treatment modalities. The overwhelming majority of patient CACs stem from loss-of-function mutations that result in runaway activation of the canonical Wnt signaling pathway and proliferation of gut epithelium. In healthy gut tissue, Wnt pathway activation is tightly controlled by a protein condensate, the Destruction Complex (DC), which degrades the transcriptional co-activator β-catenin and prevents aberrant activation of proliferative genetic programs. Intriguingly, the most common CAC mutation is a large deletion that results in the loss of DC liquid-liquid phase separation (LLPS). While the precise mechanism through which the DC regulates β-catenin is unknown, it is clear that DC function is perfectly correlated with LLPS. Recent work in our lab has uncovered that the centrosome, the structure that orchestrates chromosomal segregation and cell-cycle progression during cell division, nucleates DC droplets consequently regulating droplet volume and localization as a function of the cell-cycle. This finding is the first evidence that DC structure and Wnt signal transduction are directly related to cell-cycle progression and provides a potential mechanism of CAC progression. The present proposal thus seeks to elucidate this novel relationship by addressing the following questions: 1) What role does centrosome nucleation of DC proteins play on Wnt signal transduction? 2) How do they change in response to cell cycle progression, and 3) How do the biophysical properties of the DC compare between healthy and CAC tissues? Using optogenetic tools that allow us to control the DC LLPS with light we will map the DC phase diagram and signaling output in live, single cells. We will then characterize DC dynamics and Wnt signaling function in cell cycle synchronized cell populations. These experiments will then be repeated in a patient-derived CAC epithelial cell line bearing the common loss-of-function mutation that inhibits condensate formation. By understanding the connection between the biophysical properties and signaling outcomes of the Wnt pathway and their connection to cell cycle progression, in wild-type and cancer cells, we will support the development of therapeutics that more precisely target the pathological mutations that lead to cancer.

## Targeting thermogenesis regulators in pancreatic cancer-associated cachexia

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

*Abstract*:
A majority of patients with advanced cancer develop a condition called cancer cachexia, leading to severe weight loss that cannot be treated by simply increasing food intake. Cancer cachexia diminishes physical function and quality of life and is estimated to directly account for 20% of cancer-related deaths. At present, there is no effective therapy. Cancer cachexia is especially prominent in pancreatic ductal adenocarcinoma (PDA), which carries a poor prognosis and is projected to become the second leading cause of cancer-related death in the U.S. by 2030. A vast majority (80%) of patients with PDA have lost more than 10% of body weight at the time of diagnosis and the more pronounced the degree of cachexia, the worse is the chance of survival. Recent research indicates that a major driver of weight loss in cancer cachexia is increased energy burning (also called thermogenesis) by specialized fat cells. These energy-burning fat cells become more numerous and active and so more calories are lost. At the same time, regular energy-storing fat cells and muscle shrink. Exactly why this happens and whether restoring fat cells to normal can be beneficial is not known. Our proposed research for this grant deals with two genes that we recently discovered to control the conversion of regular fat cells into energy-burning fat cells. One gene increases the conversion while the other gene blocks the conversion. We proved this by removing each gene to make genetic knockout mice and studying their fat cells. With these knockout mice, we can now test whether blocking the conversion of regular fat to energy-burning fat will reduce the severity of cachexia associated with pancreatic cancer. This could lead to new treatment strategies to combat cancer cachexia.

## Targeting Novel Signaling Pathways for Neuroblastoma Therapy

*Host Campus*: San Diego
*Lead Investigator*: Peter Zage
*Start Date*: 10/1/2021 *End Date*: 9/30/2022 *Amount*: $75,000

*Abstract*:
Children with high-risk neuroblastoma (NB) have poor outcomes despite intensive treatment, and new therapeutic combinations targeted at biologically relevant pathways are more likely to be effective. Amplification of MYCN remains the best-characterized genetic marker of risk in NB and is found in ~25% of all NB tumors and in 50% of high-risk tumors. MYCN amplification correlates with high-risk disease and poor prognosis, and MYCN-mediated signaling networks therefore represent candidate targets for new therapies.

Systems biology analyses have been used to model complex intracellular networks, and therapies based on systems biology-based analyses can both enhance cancer treatment efficacy and minimize side effects and the emergence of treatment resistance. In collaboration with the UCSD Institute for Network Medicine (iNetMed), we have performed systems biology-based analyses using Boolean models to identify invariant gene expression relationships associated with MYCN expression that are relevant in all patients despite inter- and intra-tumoral heterogeneity. Our preliminary analyses have identified a cluster of genes that regulate intracellular signaling that is strongly associated with MYCN expression, suggesting that a coordinated network of intracellular signaling pathways regulated by MYCN are likely associated with NB pathogenesis and represent novel and likely universal candidate therapeutic targets.

We propose to investigate novel therapeutic vulnerabilities in NB tumors by identifying and validating candidate genes associated with MYCN expression in NB tumors, and we will use high-throughput screening studies to identify candidate compounds effective against NB cells via inhibition of MYCN-mediated signaling. We anticipate that targeting MYCN-mediated signaling will be effective against NB and will lead to candidate compounds to be developed as universally effective agents for NB patients. Our proposed studies leverage innovative algorithms and software developed by the UCSD iNetMed and will address a critical gap in our understanding of the mechanisms underlying NB pathogenesis and identify novel targets for future drug development. Therefore, our studies represent an opportunity to identify innovative potential therapeutic approaches for children with NB.

## 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.