UC Cancer Research Coordinating Committee 2024 Competition Results
2024-25 Awards List by Abstract

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Identifying cancer-associated fibroblasts in glioblastoma and defining their pro-tumoral effects

Campus: UCSF
Principal Investigator: Manish Aghi
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Glioblastoma (GBM) is a devastating brain tumor lacking effective treatments. Recent evidence has suggested that the growth and treatment refractoriness of GBM derives in large part from the dynamic interplay between tumor cells and supportive cells in the tumor microenvironment. Along those lines, my lab has intriguing data using single-cell RNA-sequencing to identify cells in GBM that express canonical cancer-associated fibroblast (CAF) markers, have CAF morphology, and transcriptomically resemble CAFs from other cancers rather than other stromal cells with similar surface markers such as pericytes. These findings challenge conventional thinking because, while the existence of CAFs in many systemic cancers and their pro-tumoral effects were demonstrated over two decades ago, CAFs had been assumed to be absent in GBM given the lack of normal fibroblasts in the healthy brain. Using spatial transcriptomics, we also demonstrated that these CAFs are enriched in the perivascular niche (PVN) of GBM close to GBM stem cells (GSCs), where they increase GSC proliferation. GBM CAFs also promote pro-tumoral effects on macrophages in GBM. Here, we will build on this intriguing data by investigating our central hypothesis that the GBM PVN is a unique regional microenvironment in which GSCs recruit circulating marrow-derived progenitors that differentiate into CAFs that alter GSCs and their microenvironment in a pro-tumoral manner that promotes therapeutic resistance. We will investigate this hypothesis through three aims: Aim 1 – Determine the origin of CAFs in GBM and the mechanism of their recruitment to the GBM perivascular niche; Aim 2 - Define the immunosuppressive effects of CAFs on T-cells in the GBM microenvironment and the mechanisms of these effects; and Aim 3 - Characterize the role of CAFs in GBM resistance to standard cytotoxic therapies. We will use transcriptome-based lineage trajectory prediction algorithms and murine transplantation models to define the lineage of GBM CAFs, functional immune cell assays to assess the impact of GBM CAFs on immune cells in the microenvironment, and mouse models to delineate the impact of CAFs on GBM therapeutic resistance. Our work will challenge conventional thinking by showing that CAFs exist in GBM, where they are not merely bystanders but active participants in the growth and treatment refractoriness of the tumor.

Determining mechanisms of anti-tumor synergy elicited by innate immune agonist cancer therapies.

Campus: UCI
Principal Investigator: Thomas Burke
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Therapeutically activating innate immunity in tumors can elicit profound anti-cancer responses in a variety of indications. Drugs that target the innate immune protein STING elicit potent anti-cancer responses in mice, and >15 STING agonists entered clinical trials in the past 10 years. However, in 2023 the first trial results showed a lack of efficacy. The emerging challenges in the field are now to increase efficacy of innate immune agonists while maintaining tumor-specific T cell responses.
We recently discovered that STING agonist efficacy is dramatically enhanced when used in combination with agonists of Toll-like receptors (TLRs), another class of innate immune receptors. We found that a single combination dose can elicit complete responses in >80% of mice bearing established B16-F10 melanomas, as compared to 25% with monotherapy. Mice that cleared primary tumors developed resistance to tumor cell rechallenge. This demonstrates that the challenges of efficacy and T cell priming can be overcome through STING+TLR agonist combination therapy.
However, key questions regarding the mechanisms of synergy are unanswered, including: what cytokines and cell types are required for the anti-tumor synergy elicited by STING+TLR agonists? Understanding this mechanism will aid future clinical studies on innate immune agonist therapies for cancer.
We propose in Aim 1 to determine the role for immune cells in the anti-tumor response to combination therapy. We will use flow cytometry to measure T cell activation and the abundance of immune cell types including neutrophils, macrophages, and dendritic cells. To determine the requirement for these cells in the anti-tumor synergy, we will deplete CD8, CD4, and NK cells and measure tumor volume after therapy. This will determine the cellular mechanisms of anti-tumor synergy. Then in Aim 2, we will identify the cytokines required for eliciting synergistic anti-tumor responses to STING+TLR combination therapy in vivo. IL-12 and TNF-a are upregulated in response to STING+TLR agonist co-administration, but their necessity is unknown. We will neutralize these cytokines and measure tumor volume after therapy. Together, this work will determine the cytokines and cell types required for STING+TLR agonist synergy, advancing the field and paving the way for clinical trials with combinations of innate immune agonists.

Defining mechanisms of YAP-driven high-grade complex karyotype sarcoma development

Campus: UCD
Principal Investigator: Janai Carr-Ascher
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Sarcomas are a rare, heterogeneous, and understudied group of connective tissue cancers with varying genetics, histologies, and patient demographics. Within sarcomas, few therapeutic targets have been identified and those tested in clinical trials demonstrate limited efficacy. As a result, people with sarcoma have a 65% five-year survival rate despite aggressive multimodality treatment with surgery, chemotherapy, and radiation. Increasing our understanding of sarcoma biology, discovering new therapeutic vulnerabilities, and identifying opportunities for targeted therapies will improve patient outcomes.
We have developed a robust pre-clinical model that allows for the study of sarcoma development, growth, and metastasis across complex karyotype subtypes. Using this system, we identified oncogenic drivers of sarcoma development including Yes-associated protein (YAP). YAP amplification is observed across human sarcomas and was also observed in our pre-clinical model. YAP is a transcriptional regulator of the Hippo pathway that, in conjunction with coactivators controls development, differentiation, and cancer in context and cell specific manners. During the development of YAP driven tumors, we observed increased activity of Enhancer of Zeste 2 (EZH2). This protein is a key component of the polycomb repressor complex 2 (PRC2) that methylates histones at H3K27 and recruits methyltransferases resulting in a closed chromatin state. We hypothesize that EZH2 is required for the development and progression of YAP driven sarcomas. In this study, we will define the interaction between YAP and EZH2 during transformation and determine if therapeutic targeting of YAP and EZH2 is a feasible clinical strategy.
The era of targeted treatments and immunotherapy ushered in significant improvements in overall survival for patients with cancer. Despite this, the prognosis of high-grade complex karyotype sarcomas has remained stagnant. Inhibitors of YAP and Hippo signaling are under development and in clinical trials. Tazemetostat, an inhibitor of EZH2 is FDA approved for epithelioid sarcoma and follicular lymphoma. This study will be the first to investigate the role of YAP and EZH2 in complex karyotype sarcomas and validate these as therapeutic targets. The pre-clinical data from this study will inform future clinical trials for this aggressive and heterogenous tumor type.

Targeting Bladder Cancer with Intravesical and Systemic NECTIN4-directed Therapies

Campus: UCSF
Principal Investigator: Jonathan Chou
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Bladder cancer (BC) is the 2nd most common genitourinary malignancy and 6th most common cancer in the US, leading to an estimated 16,000 deaths in the US per year. Unfortunately, patients who develop metastatic BC (mBC) have a poor 5-year survival of ~15%. Recently, an antibody-drug conjugate (ADC) targeting the surface protein NECTIN4 (enfortumab vedotin, EV) was approved, validating NECTIN4 as an important target in mBC. Although EV monotherapy has a response rate of 44%, resistance invariably develops to the ADC. Interestingly, our preliminary and unpublished data demonstrates that NECTIN4 expression is retained on the surface of EV-resistant cells (that we generated in the lab) as well as in patient biopsy samples post-EV resistance (measured by immunohistochemistry). Therefore, we hypothesize that additional strategies to target NECTIN4 using CAR T and radioimmunotherapies (RIT) are rapidly needed, and will be efficacious both in EV-naïve and EV-resistant settings. However, to date, neither of these therapeutic modalities have been approved for bladder cancer patients. In this proposal, we will develop these two approaches and perform rigorous preclinical evaluation using 3 in vivo model systems: 1) an orthotopic bladder tumor model; 2) a subcutaneous patient-derived xenograft (PDX) model; and 3) a lung metastasis model. Our study will also use unique PDX's developed at UCSF from minority patients (an important understudied population) and models of EV resistance that we created in our lab. If our results are positive, we plan to translate our findings into an investigator-initiated clinical trial, and will have two non-overlapping opportunities to do so – one with the CAR T and the other with the RIT. As a translational genitourinary medical oncologist and lab-based investigator, I have extensive experience leading pre-clinical studies of novel agents in the lab and running investigated-initiated clinical trials at UCSF. I am also fortunate to work with a fantastic team, so that we can translate findings from the bench to the bedside and back again. Overall, this application represents an important step in developing novel NECTIN4-targeting strategies, with implications that may extend beyond bladder cancer to other NECTIN4-positive tumor types such as breast, ovarian, lung and pancreatic cancers.

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.

Evaluation of Hepatocellular Carcinoma care capacity in Tanzania

Campus: UCD
Principal Investigator: Cameron Gaskill
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $84,900

Abstract:
Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality in sub-Saharan Africa (SSA). Pathogenesis is driven by high rates of viral hepatitis, untreated cirrhosis, and limited access to HCC screening and treatment. Globally, 2.5% of patients with cirrhosis will develop HCC each year. With adequate resources around 40% of diagnosed HCC patients will receive curative surgical resection, local ablation, or transplant, however in SSA less than 1% of patients receive such treatment. In Tanzania, there is a national effort to improve early diagnosis and treatment of HCC. Despite this, the multidisciplinary liver tumor board (MDTB) at the Muhimbili National Hospital (MNH) notes that treatment rates for localized HCC are less than 25% of expected. Access to treatment and resources are limited outside of the largest hospitals and care recommendations vary by location, resulting in delayed, disjointed, and uncoordinated care.
The landscape for HCC care in Tanzania is unknown. We hypothesize that lack of established referral pathways and treatment guidelines contribute to deficient treatment rates. To address the current absence of HCC data and facilitate treatment, we aim to perform the following: 1) Perform a national assessment of HCC diagnostic and treatment resources, including screening infrastructure, surgical and locoregional capacity, systemic treatment availability, and access to supportive care, 2) Implement a national virtual liver cancer tumor board to strengthen multidisciplinary care and coordination, and 3) Develop contextualized and resource-specific treatment guidelines for liver cancer in Tanzania with assessment of impact using a retrospective patient cohort.
Nation liver cancer care capacity assessments will be performed at all major public medical centers to identify available physical and human resources. The virtual tumor board will be distributed nationwide for optimal provider engagement, with implementation success measured by participation and effect on care recommendations. Resource-specific treatment guidelines for liver cancer in Tanzania will be developed on expert consensus. This proposal is part of a larger effort to improve cancer care in SSA and will provide valuable baseline data leading to future capacity building and intervention-driven research.

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Controlling tumor metastasis via the gut microbiota

Campus: UCI
Principal Investigator: Matthew Griffin
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Metastasis requires cancer cells to evade the immune system while circulating and colonizing distal sites. Therefore, the basal activation level of the immune system may determine the rate of successful metastases in individual patients and could be a viable therapeutic target to slow cancer progression. Our recent work has suggested that the gut microbiota is a potent source for immune stimulatory molecules and that an individual's microbiota can correlate with their responsiveness to cancer immunotherapies. Thus, we hypothesize that the microbiota's capacity to generate specific, immune active metabolites may more broadly affect cancer progression including the successful formation of new metastatic sites.
This one-year, pilot project will focus on two aims. First, we will examine whether increasing the processing of bacterial cell wall in the gut can control the metastatic progression of melanoma. This will be accomplished using our previous model to orally supplement the gut microbiota with specific microbes or enzymes and will be applied to the established murine model of melanoma metastasis using intravenous injection of B16-F10 cells. Second, we will define host factors caused by increased enzymatic activity in the gut that may function as both biomarkers and causal agents for immune activity against circulating and newly colonizing tumor cells. Here, we will use targeted mass spectrometry to quantify muramic acid in murine blood samples after supplementation as a proxy readout for circulating cell wall fragments. We will also use flow cytometry and single-cell RNA sequencing to quantify and characterize a population of bacterial cell wall-responsive CX3CR1+Ly6Clo patrolling monocytes as a cellular biomarker and a potential effector cell population for reduced metastasis.
These studies align with our laboratory's broader goals (1) to define the mechanisms of immune activation by the gut microbiota during cancer progression and treatment and (2) to develop enzyme- and probiotic-based methods to selectively augment host immune responses as single agents or in combination with other cancer therapies. If successful, this work will provide direct evidence that modulation of enzymatic capacity in the gut – that is, the overall ability to selectively produce metabolites – can alter immune-mediated protection against metastasis.

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.

Targeting the Myc oncoprotein

Campus: UCSF
Principal Investigator: Daniel Johnson
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Aberrant overexpression of the c-Myc (Myc) oncoprotein, a transcription factor, is estimated to be involved in approximately 70 % of all human cancers. Yet, despite it's profound importance, there are no clinical agents that directly target and inhibit Myc. Efforts to develop small molecule Myc inhibitors have been hindered by a lack of suitable binding pockets on the protein. Hence, Myc, like other transcription factors, has been considered "undruggable". We propose to take an entirely different approach to develop a Myc inhibitor. Our approach will be based on the mechanism of Myc action and our prior success in developing a novel inhibitor of the "undruggable" transcription factor STAT3. Myc exerts it's effects by first heterodimerizing with Max. Myc/Max then recognizes a unique, consensus DNA response element found in the promoter regions of Myc target genes. Following binding to these response elements, Myc/Max induces the transcription of target genes that promote oncogenesis and resistance to chemotherapy, radiation, and immunotherapy. STAT3 oncoprotein similarly recognizes it's own unique DNA response element. We previously generated a potent, selective, and well-tolerated STAT3 inhibitor that mimics the STAT3 DNA response element, and is called cyclic STAT3 decoy (CS3D). CS3D is a 15-bp double-stranded DNA molecule that is cyclized at both ends with hexaethylene glycolyl linkers. CS3D binds STAT3 and competitively inhibits STAT3 binding to the promoter region of target genes, shutting down expression of these genes. CS3D inhibits the proliferation of cancer cells and the growth of xenograft tumors following systemic delivery. We hypothesize that cyclic oligonucleotide decoys can be developed to target and inhibit Myc/Max. Three Aims are proposed. In Aim 1 we will generate and optimize cyclic oligonucleotide decoys targeting Myc/Max and the functional capacity of the cyclic decoys to bind Myc/Max will be determined. The optimal length and the specificity of each cyclic decoy will also be determined. Aim 2 will determine the ability of an optimized Myc/Max cyclic decoy to inhibit Myc-mediated transcription using Myc/Max reporter constructs and a scrambled sequence version of the cyclic decoy as a control. Aim 3 will investigate the growth inhibitory and pro-apoptotic properties of the Myc/Max cyclic decoy in Myc-dependent cells.

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.

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Control of cell cycle entry

Campus: UCSC
Principal Investigator: Douglas Kellogg
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $73,079

Abstract:
The decision to enter a new round of cell division is amongst the most consequential decisions in the life of a cell. Entry into the cell cycle occurs only when sufficient growth has occurred and only when there are sufficient nutrients for further growth. In animal cells, cell cycle entry is controlled by growth factors, which ensures that cell division occurs at an appropriate time and place. Defects in the signals that control cell cycle entry are a primary cause of cancer.
The mechanisms that initiate cell cycle entry are poorly understood. The critical molecular event that drives cell cycle entry is expression of late G1 phase cyclins. Decades of work in both yeast and mammals led to a canonical model in which initiation of cell cycle entry occurs entirely via activation of late G1 phase cyclin transcription. In this model, a cyclin expressed in early G1 phase activates a cyclin-dependent kinase (Cdk), which then phosphorylates and inactivates a repressor protein that inhibits transcription of late G1 phase cyclins. In mammalian cells the repressor is the tumor suppressor Rb. In yeast, the repressor is Whi5. This model has been highly influential and has guided the field for decades, despite the existence of numerous observations that are difficult to reconcile with the model. Moreover, recent tests of the model in both yeast and mammalian cells have shown that the model is inadequate and inaccurate. The critical molecular events that initiate cell cycle entry remain largely unknown, which means that the mechanisms by which oncogenic signals influence cell cycle entry also remain unknown.
The goal of our work is to discover conserved molecular mechanisms that control cell cycle entry, which could lead to transformational breakthroughs in our understanding of how cell cycle entry is initiated, how it is influenced by oncogenic signals, and how cancer cells develop resistance to new drugs that target cell cycle entry.

Targeting Cancer Cells with Carborane Salts for Photodynamic Therapy

Campus: UCR
Principal Investigator: Vincent Lavallo
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $95,000

Abstract:
In collaboration with professors Richard and Sophia Lunt at Michigan State, we have identified an extraordinary class of chemical entities that allow for highly selective and non-toxic breast cancer cell targeting system that has potential for infrared activated photodynamic therapy. The preliminary discovery was serendipitous but the PI is trying to acquire funding to pursue this important finding. Photodynamic therapy (PDT) has emerged as a promising targeted treatment for cancer. However, current PDT is limited by low tissue penetration, insufficient phototoxicity (toxicity with light irradiation), and undesirable cytotoxicity (toxicity without light irradiation). Recently, Sophia and Richard Lunt introduced a novel platform for tuning the toxicity of near-infrared (NIR) light activated photosensitizers (PSs) through counterion pairing in organic salts, achieving greater tissue penetration, improved phototoxicity, and minimal cytotoxicity. It turns out that using this approach, but with special molecules called carborane anions developed in Lavallo's lab, unprecedented higher potency and efficacy against primary breast tumors as well as metastatic breast cancer cells has been observed. Sophia Lunt has characterized their cellular
uptake, organelle localization, generation of reactive oxygen species (ROS), suppression of pro-metastatic pathways, and activation of apoptotic pathways using metastatic breast cancer cell lines. Further she has shown that Lavallo's molecules have the ability to create PSs that stop tumor growth in vivo using an orthotopic mouse model of breast cancer to an unprecedented level. The newly developed lead PS formulation introduces a potent therapeutic approach against aggressive breast cancer cells while decreasing side effects in healthy cells. This seed grant funding will be used by Lavallo's group to create libraries of commercially unavailable carborane salts and provide them to the Lunt groups for elaboration and exploration of structure activity/toxicity relationships of the therapeutics. Lavallo's lab is traditionally a synthetic/fundamental/battery inorganic group that has never participated in cancer research previously.

Enhancing CAR-T Therapy by Targeting PP2A in Glioblastoma

Campus: UCSF
Principal Investigator: Rongze Olivia Lu
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $95,000

Abstract:
Glioblastoma (GBM) is one of the most aggressive cancers without cure. Chimeric antigen receptor (CAR)-T cell therapy is a powerful strategy for cancer treatment that offers new opportunities for patients with malignant gliomas. However, there are several barriers that possibly dampen the efficacy of CAR-T cell therapy for glioma, including the intrinsic nonimmunogenic phenotype of glioma cells and their immunosuppressive tumor microenvironment (TME). To solve this problem, we have established murine orthotopic GBM models for optimizing IL13Rα2 CAR-T cell therapeutic parameters for clinical translation through collaboration. The immunocompetent syngeneic mouse models of GBM, and murine-CAR-T cells more precisely recapitulate patient glioma tumors and will provide essential information regarding the effect of therapies on the TME. For effective CAR-T therapy against GBM, it has been shown that activation of endogenous T cells and anti-tumor TME is required.
Protein Phosphatase 2A is heterotrimeric, consisting of scaffolding (A), regulatory (B), and catalytic (C) subunits that interact to form a functional holoenzyme. We were the first to demonstrate that inhibiting PP2A enhanced immunogenicity of glioma cells to induce sensitivity to tumor specific T cells mediated killing and reprogrammed the TME toward anti tumor. We demonstrated that LB-100, small molecule inhibitor of the conserved catalytic subunit of PP2A (PP2Ac), synergizes with PD1 blockade in multiple in vivo tumor models including GBM7,8. These results led to a phase I/II clinical trial testing LB100 in patients with recurrent GBM (NCT03027388) and a combination trial with anti-PD-1 in ovarian clear cell carcinoma (NCT06065462). Elucidating the role of PP2Ac within different cell types of the TME in regulating tumor sensitivity to CAR-T therapy is critical to inform rational combination in future clinical trials.
We hypothesize that inhibition of PP2Ac will overcome the barriers for CAR-T cell therapy in glioma TME, and combination of IL13Rα2 CAR-T cell therapy and PP2A inhibitor will be a potential novel combination treatment for brain tumors. Successful completion of this project will provide preclinical insights to initiate novel clinical trials of combining PP2A inhibitor with IL13Rα2 CAR-T therapy.

Investigating the biogenesis of histone mRNAs during normal and aberrant cell proliferation

Campus: UCR
Principal Investigator: Jernej Murn
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $95,000

Abstract:
Regulation of histone biosynthesis during the cell cycle is critical for coordinating chromatin assembly, DNA replication, and gene transcription. Overproduction or underproduction of histone protein can result in replication stress and genome instability that contribute to the development of cancer. The supply of histone proteins is primarily regulated at the level of replication-dependent (RD) histone mRNA production, a process that is tightly coupled to the phase of the cell cycle but remains incompletely understood. Here, we propose to investigate the mechanism of RD histone mRNA transcriptional termination, an enigmatic aspect of histone biogenesis with particular relevance to cancer formation.
RD histone mRNAs are the only eukaryotic mRNAs in animal cells that lack poly(A) tails, ending instead with a conserved stem-loop structure. The genes encoding all five RD histone proteins are clustered in metazoan genomes, and transcription and pre-mRNA processing factors required for histone mRNA biosynthesis are organized into a nuclear body (the histone locus body or HLB) that assembles at these gene clusters. Because of their close proximity to one another, transcription of each RD histone mRNA copy has to terminate shortly after the stem-loop; delayed termination akin to that seen with most polyadenylated mRNAs can lead to aberrant replication stress, aberrant gene transcription, and chromosomal instability, which are signature hallmarks of cancer.
In our preliminary studies, we found that acute depletion of RNase MRP - a ubiquitous and essential endonuclease known largely for its critical role in maturation of rRNAs – specifically affects termination of RD histone mRNA transcription. Here, we propose to investigate the requirement for the endonuclease activity of RNase MRP in RD histone mRNA termination and delineate the direct and indirect mechanisms by which compromised activity of RNase MRP could lead to deregulated production of histones and cancer development. This study will address one of the least understood aspects of histone gene regulation and shed light on the elevated risk of cancer development in patients with mutations in RNase MRP.

The evolution of cancer in planarians

Campus: UCM
Principal Investigator: Nestor Oviedo
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $95,000

Abstract:
Arguably, one of the least understood aspects of cancer is how normal cells acquire cancer features. This process of malignant transformation endows some cells with extraordinary properties to avoid surveillance mechanisms, skip cell death, and proliferate indefinitely. Most cases of cellular transformation occur as tissues replace old and damaged cells with new ones. However, tissue renewal is challenging to analyze as it tends to happen simultaneously in many tissues that turnover at different rates for many years. In humans, for example, cellular turnover is continuous throughout the lifespan, deploying billions of cells daily to renew tissues such as blood, epidermis, and gastrointestinal epithelia. A significant limitation in the field is the lack of experimental models to analyze systemic tissue renewal and malignant transformation simultaneously. A predominant view explaining the progression of malignancy claims that the deregulation of tumor suppressors induces DNA damage that is present at the early stages in almost all cancers.
We propose a paradigm shift by introducing a simplified experimental model to enable in situ analyses of cellular transformation during tissue renewal. The planarian flatworm continuously renews about 40 tissue types throughout the body, and we developed the first planarian cancer model by inhibiting PTEN, the second most inactivated gene in human cancers. PTEN-mediated cancer in planarians aggressively elicits a phenotype that resembles mammalian carcinogenesis. It takes less than two weeks to observe neoblast over-proliferation, tissue invasion, and the formation of lethal tumors. However, how malignancy arises and evolves during tissue renewal in planarians is unknown. We aim to leverage the integration of systemic tissue turnover and PTEN function to address the earliest manifestations of malignancy and identify the cells driving the cancer phenotype. Preliminary results demonstrate that DNA damage underlies cellular transformation that is detectable after a few hours of PTEN inhibition. The results also suggest that disrupting neural transcription factors essential for neurogenesis can prevent malignancy. We propose to analyze mechanisms of cellular transformation and the evolution of the cancer phenotype in planarians.

Seeing the obscure for non-small cell lung cancer radiotherapy

Campus: UCLA
Principal Investigator: Dan Ruan
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Locoregional failure (LRF) is a frequent challenge in patients treated with radio-chemotherapy for locally advanced non-small cell lung cancer. LRF has been observed in about 45% of ablative radiotherapy recipients in the recent PACIFIC trial. These indicate that remission rate may be reduced by either local boosting in the definitive radiotherapy or focal salvage treatment. These failure patterns also allude to the criticality in ensuring that the ablative dose has been actually delivered to the intended treatment volume, a question to be answered with sophisticated monitoring that is currently absent.
In this project, we propose to work with the widely accessible x-ray based on-board imaging (OBI) system. As X-ray collapses attenuation information along the beam direction, there is depth uncertainty and compromised conspicuity of the tumor target. Furthermore, the OBI is configured at a fixed angle to the treatment megavoltage beam, so its view angle is passively determined by the treatment trajectory, and typically does not offer the best visibility for tumor target or surrounding tissue context. The suboptimal region-of-interest (ROI) visibility is further compounded with the obstruction of high attenuating structures such as the rib(cage) along the x-ray beamline, drowning important lung texture. To facilitate both online monitoring of the thorax anatomy, and spatiotemporal dose integration as quantitative evidence for adaptive SBRT, we will tailor neural field learning development with x-ray physics and geometry to (1) develop a physics and geometry informed view toggler to translate an online acquired OBI x-ray image to a clinically favorable angle with high GTV and context conspicuity (2) develop a virtual rib removing network to reveal the lung texture, and (3) Expand view toggler to full volumetric synthesizer to generate spatiotemporal anatomy for radiation dose accumulation. Success of this project will fill in the knowledge and clinical gap in fully monitoring the thorax dynamics during lung radiotherapy treatment, which has hindered the development and utilization of real-time adaptive control. Accurate spatiotemporal dose accumulation not only provide informed prescription adaption but also provides more accurate actual dose to support radiobiological and outcome analysis to improve treatment regimen design.

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.

Genome-wide maps of c-Myc dependent genetic interactions

Campus: UCLA
Principal Investigator: Desmond Smith
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $85,000

Abstract:
Overexpression of the c-Myc cancer gene drives growth >70% of malignant tumors, including breast, brain and lung. The c-Myc oncogene encodes a transcription factor and thus regulates many other genes. However, transcription factors are difficult targets for which to design drugs.
As exemplified by c-Myc, genetic interactions are at the root of normal and malignant cell growth. Interactions between gene pairs have been cataloged in mammalian cells by combining knockouts created using CRISPR/Cas9 or siRNA and observing the changes in cell growth. However, these piecemeal approaches are laborious and expensive and do not address the >200 million genetic interactions that potentially occur.
An approach that can affordably map the entire array of genetic interactions in normal and diseased cells is urgently needed. We have developed a technology using radiation hybrid (RH) cells that is capable of elucidating with high sensitivity and specificity genes that interact even though they are located at a distance within in the genome. Our approach yields high-resolution, comprehensive maps of interacting gene pairs. RH panels are constructed by lethally irradiating cells so that the DNA shatters. The fragments are then introduced into living cells so that a random assortment, ~25%, of genes are triploid rather than diploid. Statistically significant patterns of co-inherited triploid genes point to the cell's survival mechanism. Most importantly, the fragments are so small that the technique often provides single-gene resolution, revealing with specificity the multiple roles one gene plays within a cell. Our preliminary data shows that low pass genome sequencing of nascent human RH clones (RH-Seq) is an economical approach to constructing interaction maps. The network showed significant overlap with a previous network obtained by us that established the groundwork for the RH approach and showed that coinheritance of distant genes is an important mechanism for cell viability.
Our goal is to map genetic interactions for the entire genome in normal cells and cells that overexpress c-Myc. The result will be a high resolution map of the genetic interactions that drive cell growth in the context of aberrant c-Myc expression, providing new, highly relevant targets for treatment.

LINCing macromolecular crowding and pancreatic ductal adenocarcinoma

Campus: UCD
Principal Investigator: Daniel Starr
Start Date: 10/01/2024 *End Date*: 09/30/2025 *Amount*: $95,000

Abstract:
Nucleoplasmic macromolecular crowding (MMC) is a critical yet often overlooked factor in cancer progression. This proposed research is the first to consider how MMC influences progression in pancreatic ducal adenocarcinoma (PDAC). PDAC patients have a 5-year survival rate below 5%. While the PDAC is primarily driven by genetic mutations in KRAS and tumor suppressor genes, PDAC metastasis lacks recurrent genetic drivers. This suggests that non-genetic factors play a critical role in shaping the disease's progression. Research shows a relationship between MMC and progress in other cancers. We propose investigating how nucleoplasmic MMC influences PDAC progression and metastasis using innovative tools like nucleoplasmic genetically encoded multimeric nanoparticles and 3D PDAC organoid models. Our observations hint at perturbed nucleoplasmic MMC in metastatic PDAC organoids, suggesting a potential role in PDAC metastasis. Furthermore, analysis of existing PDAC organoid RNA-seq datasets has unveiled the up-regulation of nesprin-3, a crucial component of the outer nuclear membrane and the linker of nucleoskeleton and cytoskeleton (LINC) complex, in metastatic PDAC organoids. LINC complexes govern cytoplasmic MMC, nuclear-cytoplasmic transport, mechanotransduction, and chromatin organization. Our proposed experiments will determine whether nesprin-3 regulates nucleoplasmic MMC, offering a promising avenue for targeted therapy against PDAC metastasis. We will address two specific aims: 1) Do changes in nucleoplasmic MMC correlate with PDAC prognosis in 3D pancreatic organoid models? and 2) Do alterations in nucleoplasmic MMC affect PDAC cell metastatic capabilities in vivo? This proposal capitalizes on the synergy of an interdisciplinary collaboration between a developmental cell biologist (Daniel A. Starr), a quantitative cellular biophysicist (G.W. Gant Luxton), and an expert in PDAC and organoid modeling (Chang-Il Hwang). By bridging the gap between genetic and non-genetic factors, our study will provide comprehensive insights into the biophysical properties of the nucleoplasm and their influence on the aggressive traits of PDAC. The potential identification of a novel therapeutic target holds immense promise for addressing the daunting challenge of metastasis in PDAC patients, offering hope for improved clinical outcomes and enhanced quality of life.

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.