UC Cancer Research Coordinating Committee
2025-2026 Awards List by Abstract

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Altering germline BRCA2 mutant RNA to restore protein function

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

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

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

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

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

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

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

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

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Deciphering the bioelectrical signatures of cancer cells

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

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

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

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

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

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Refinement and usability of e-support for pancreatic cancer patients

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

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

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

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

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

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Elucidating the role of cyclin B3 in cancer cell mitosis.

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

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

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Impact of Pesticide Exposure on Hematopoietic Stem Cells and Cancer

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

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

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Illuminating PDAC's Dark Proteome to Reveal New Vulnerabilities

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

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

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Reconstitution of the molecular forces necessary for mitotic spindle bipolarity

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

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

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Machine learning enabled deconstruction of malignant potential at clonal resolution

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

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

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Synthesis of Nanocomposite Scintillators

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

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

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

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

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

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

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

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

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Antigen-Specific Strategies for Reinvigorating Exhausted T Cells

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

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

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Prostaglandin-metabolizing microbial enzymes as novel target of colorectal cancer

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

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