

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

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Determining Glioblastoma Survival Dependence on Beta2-Adrenergic Receptors

Campus: UCD

Principal Investigator: James Angelastro

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$83,940

Abstract:

Background: Stress causes the release of epinephrine and norepinephrine to activate alpha and beta-adrenergic receptors. Stress also increases tumor progression by activating beta-adrenergic receptors causing epithelial to mesenchymal transition, promoting tumor cell invasion, metastasis, and angiogenesis. Interfering with beta-adrenergic signaling inhibits tumor proliferation and survival. Epidemiological studies revealed that subjects who received beta-adrenergic antagonists for stress reduction showed a lower cancer rate. Combining beta-adrenergic receptor antagonists with the current standard of care therapies creates potent synergism leading to tumor remission. Beta-adrenergic receptors are highly expressed in glioblastomas (GBM) and correlate with poor prognosis.

Preliminary results: Significant cell death occurs by beta2 receptor antagonism and disruption of primarily the beta2-arrestin pathway in three glioma cell lines. Selective beta2-antagonist, ICI 118551 showed, while biased G-protein agonist Salmeterol xinafoate revealed the highest efficacy. Zinterol, a balanced agonist (leading to activation of both G-protein and Beta-arrestin pathways), showed no cell death. Anti-apoptotic protein survivin was downregulated by beta-2-adrenergic signaling interference by salmeterol xinafoate. We hypothesize that (1) disruption of the beta-2-adrenergic signaling or ablation of the beta-2-adrenergic receptor promotes cell death of GBMs/tumorigenesis. (2) The mechanism of GBM death by interfering with beta-2-adrenergic signaling caused by loss of survivin leads to activating proapoptotic caspases.

Aim 1: Determine if tumorigenesis/survival of GBM tumors is dependent on beta-2-Adrenergic receptors. In floxed beta-2-Adrenergic receptor mice, the endogenous neural progenitors will be driven to become gliomas by stereotactic injection of retroviruses expressing platelet-derived growth factor-B and Cre recombinase-estrogen receptor. Only in glioma tumors will beta2-adrenergic receptors be knockout by tamoxifen treatment to test the hypothesis that the resulting tumors could be spatially/temporally regressed by losing their beta-2-AR.

Aim 2: To test the hypothesis that the cellular mechanisms by which loss of- or beta-2-AR-function causes cell death is through downregulation of survivin expression with subsequent activation of caspases.

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Elucidation of novel human mitotic motor activities for cancer therapy and diagnosis

Campus: UCB

Principal Investigator: Georjana Barnes

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Mitotic motor proteins of the kinesin and dynein families generate forces on and within mitotic spindles to faithfully separate chromosomes at each cell division, ensuring genetic continuity necessary for normal health. A hallmark of cancer cells and major driver of the cancer cell evolution that results in proliferation mis-regulation and metastasis, is loss of genetic stability. A major factor in loss of genetic stability is an increase in mitotic errors, which results in aneuploidy. As forces produced by mitotic motors are central to high mitotic fidelity in normal cells, full elucidation of the biochemical activities of human mitotic motors promises to provide insights into how high chromosome separation fidelity is achieved in healthy cells and is lost in cancer cells. Moreover, because cancer cell pathogenesis depends on mis-regulated proliferation, and because cancer cells exhibit enhanced sensitivity to mitotic inhibitors relative to normal cells, newly discovered mitotic motor activities are promising targets for development of new cancer therapies. Indeed, anti-mitotic compounds such as taxol are highly effective clinically. However, these anti-mitotics are dose-limited because they are not specific to mitotic cells. Here, we propose to adopt for human mitotic motors, a powerful biochemical assay system developed and used successfully in the applicant's lab to identify new activities for yeast mitotic motors. This research will build a foundation for future studies to test the hypothesis that these mitotic motor activities are aberrant in certain cancers, and for development of biochemical assays designed to identify novel inhibitors of human mitotic motors for cancer chemotherapy. Such inhibitors would offer a larger therapeutic window than cancer drugs like taxol that target tubulin, because tubulin is not only present in mitotic spindles, but plays sundry roles in every cell in the body and is particularly crucial for function of neurons.

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Role of post-viral lung damage in promoting metastatic outgrowth of cancer cells

Campus: UCSC

Principal Investigator: David Boyd

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

The proposed research will explore a new direction in my lab investigating how post-viral lung damage and inflammation affect dormancy and metastatic outgrowth of cancer cells. Metastasis accounts for the majority of cancer related deaths and therapeutic strategies that can prevent or reduce metastatic burden are urgently needed. The lung is the most common site of metastasis in several cancers such as breast, lung, colon, melanoma, bladder, prostate and kidney. Recent studies have shown that cancer cells guide the creation of a pre-metastatic niche to exit cellular dormancy and proliferate to form metastatic lesions. Cancer cells achieve this by secretion of specific cytokines that promote an immune suppressive phenotype in the secondary organ. However, the role of the secondary organ in creating the metastatic niche is underappreciated. Moreover, it is unclear if and how previous injury through respiratory infections and pulmonary fibrosis can influence the growth of metastatic cancer cells in the lung. Among individuals hospitalized for severe respiratory viral infections, such as influenza and SARS-CoV-2, 25 - 50% of patients experience persistent respiratory symptoms due to chronic effects of lung tissue damage. Our research has demonstrated that these infections induce distinct fibroblast activation states that drive immunopathology during acute infection and promote pulmonary fibrosis following clearance of the infection. We have also developed a clinically relevant and well characterized influenza model in mice that allows us to study persistent inflammation and pulmonary fibrosis at chronic, post-viral stages of disease. Working in collaboration with the Sikandar lab at UC Santa Cruz, we have optimized this model to study breast cancer metastasis following viral infection. We are uniquely positioned to ask the following questions: 1. Does prior respiratory viral infection promote metastasis of breast tumor cells to the lung tissue? 2. Do inflammatory lung fibroblasts activated following severe viral infection promote metastatic niches for tumor cells? Using a combination of in vivo and in vitro assays we will test our working hypothesis that damage to the lung by viral infection resulting in persistent inflammation and fibrosis creates a metastatic niche promoting proliferation of breast tumor cells.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Discovery of novel apoptosis control pathways in AML

Campus: UCSF

Principal Investigator: Benjamin Braun

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$85,000

Abstract:

Acute myeloid leukemia (AML) is an aggressive form of cancer that occurs in both children and adults. Treatment requires intensive chemotherapy, months-long hospitalization, and often bone marrow transplant. Despite this, relapses are common, and cure after relapse is rare. Better therapies for AML are sorely needed. Because we have reached the limit of what conventional approaches can offer, progress will depend on our discovering new, biologically rational approaches to this disease.

We have chosen to approach this problem systematically by surveying the entire genome for new ways to kill AML cells. Virtually every form of cancer therapy kills tumor cells using a common biochemical pathway called apoptosis. Cancer drugs cause some form of cellular damage or stress, and this triggers the process of apoptosis to kill the cell. A gene called TP53 plays an important role in this process. TP53 acts as a sensor of cellular injury, and it triggers apoptosis when damage reaches a certain threshold. Mutations that disable TP53 make cells less prone to apoptosis, allowing them to persist despite treatment. TP53 mutations are therefore highly associated with relapse in AML and most other forms of cancer.

We reason that new therapies might emerge from a broad survey of apoptosis regulation across the genome. We have conducted preliminary experiments studying a different type of cancer (rhabdomyosarcoma). We adapted cutting-edge CRISPR technology to identify genes that regulate BIM, one of several key proteins involved in the apoptosis process. Having validated this approach, we now plan to study AML with a broader version of this novel technology.

With recent advances, we are now poised to study multiple proteins that work together in apoptosis. Some promote cell death (BAD, BID, BIM, and BAX), while others are protective (BCL2, BCL-XL, and MCL1). Studying this protein family as a whole will be more useful than focusing on BIM alone, because apoptosis reflects the combined action of these components. In essence, we will identify pathways that increase pro-death proteins and reduce survival proteins in a panel of AML cell lines. By comparing cells that have a mutation in TP53 to cells with normal TP53, we will discover ways to trigger apoptosis regardless of TP53 status. This will suggest potential new therapies for the most difficult, resistant forms of AML.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Self-amplifying mRNA to co-opt anti-viral responses for tumor immune therapy

Campus: UCSD

Principal Investigator: Jack Bui

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$65,000

Abstract:

When viruses infect people, successful elimination of the virus results in the generation of immune cells called memory T cells that persist for years. These memory T cells stand poised to recognize the virus and fight subsequent infection with the same virus. In order to provide optimal protection, memory T cells patrol the body and look for infected cells by examining whether cells have viral pieces, or peptides, on the cell surface. For example, memory T cells that have formed during the COVID-19 (Coronavirus disease 2019) pandemic can recognize pieces of the spike peptide of SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2), the virus that causes COVID-19. Spike-specific memory T cells will kill any cell that expresses viral spike proteins.

Recent findings have shown that memory T cells even patrol tumor tissue. Of course, since tumor cells are not infected with virus, the virus-specific memory T cells that patrol tumor tissue will not harm the tumor cells. Our preliminary studies have found that administration of viral peptides into tumor tissue will make tumors resemble virus-infected cells, resulting in activation of virus-specific memory T cells that can kill the tumor; however, the effect is transient since the viral peptides undergo rapid degradation and clearance. If this response can be augmented and sustained, it could represent an innovative non-toxic approach to tumor immune therapy.

In order to make tumor cells resemble infected cells, we propose to deliver self-amplifying mRNA vaccines into the tumor. These vaccines, similar to Moderna or Pfizer's mRNA vaccines, will result in the production of spike peptides by tumor cells, rendering them immunogenic. Anti-COVID-19 responses will be directed towards the tumor and release tumor antigens to prime tumor-specific responses. We will test our approach using mouse models of viral infection and blood from COVID-19 patients known to have memory T cells specific for spike peptides. If successful, our approach could work in a majority of the world's population given the incredible T cell memory that has emerged from the COVID-19 pandemic.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Dissecting the Role of Myeloid Derived Suppressor Cells in Resistance to IL-15 Immunotherapy in Dogs

Campus: UCD

Principal Investigator: Robert Canter

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Osteosarcoma (OSA) is a rare and difficult-to-treat cancer for which outcomes have stagnated over the last 40 years. Despite great success in other cancers, current immunotherapies have shown minimal efficacy in human OSA, underscoring the need for novel immunotherapies for these aggressive cancers. Dogs are outbred companion animals that develop spontaneous cancers in the setting of an intact immune system, allowing for the study of complex immune interactions during cancer therapies while also addressing endpoints of efficacy and toxicity. Importantly, dog OSA shows remarkable homology to human OSA. We have exciting data that a subset of dogs with bulky pulmonary metastases from OSA can show tumor regression after only 14 days of inhaled recombinant human (rh) IL-15, including dogs with dramatic responses lasting 1 year. However, we have also observed that if we administer rhIL-15 after surgery in an earlier stage of disease, rhIL-15 is ineffective and appears to worsen outcomes, suggesting a tumor-promoting effect of rhIL-15 in the post-surgical setting. We now have provocative preliminary data that myeloid-derived suppressor cells (MDSCs) express the IL15 receptor alpha (IL15RA), suggesting these immunosuppressive cells may be able to sequester IL-15 and limit the anti-tumor activity of natural killer (NK) and memory T cells. Since surgery is known to induce IL-6, TGF-beta, and GM-CSF secretion, which all promote MDSC expansion, we hypothesize a link between surgery, MDSC expansion, and resistance to IL-15 immunotherapy.

We will evaluate our hypothesis with the following specific aims:

Aim 1: Evaluate circulating MDSC levels post-surgery, hypothesizing an MDSC expansion triggered by increases in myelopoiesis cytokines (IL-6, TGFB, and GM-CSF). MDSCs will be phenotyped as lineage negative CD11b+CD14-MHCII-. Readouts will include flow cytometry, multiplex ELISA, and RNA sequencing from multiple time points, including pre-surgery, post-surgery, and post-immunotherapy.

Aim 2: Evaluate circulating NK and MDSC levels in relation to clinical outcomes. We hypothesize that patients with greater increases in MDSCs will show lower numbers and cytotoxicity of NK cells with shorter survival time. Readouts will include numbers/ function of NK cells stratified by peak and fold change in MDSC levels with correlation to survival time.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Elucidating the function of BET proteins in the G2-M cell cycle transition

Campus: UCSD

Principal Investigator: Arshad Desai

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$85,000

Abstract:

Fundamental cellular pathways are rewired in cancers to drive their inappropriate proliferation. This rewiring enhances cancer growth but can also generate vulnerabilities to therapeutic interventions. To enable cell proliferation, cancers frequently deregulate key transitions in the tightly-controlled cell division cycle. Prior work has focused on developing therapeutic agents that target uncontrolled entry into the DNA replication phase of the cell cycle in cancers (the G1-S transition). In this proposal, we will develop an unexpected observation that implicates BET (Bromodomain and ExtraTerminal domain) proteins in promoting entry into mitosis after completion of DNA replication (the G2-to-M transition). BET proteins harbor two domains that recognize acetylated lysine residues and are emerging targets for cancer therapy based on their involvement in numerous chromatin-related functions, including transcriptional regulation and protection from DNA damage. Employing a live imaging assay for quantitatively monitoring mitotic entry in single cells, we have observed a role for BET proteins in promoting the G2-to-M transition. BET inhibition delays mitotic entry in cancer-derived and non-transformed, immortalized cell lines. In a specific colorectal cancer-derived cell line, BET inhibition strongly synergizes with inhibition of the mitotic kinase PLK1 to block mitotic entry. The proposed work will investigate how BET proteins contribute to mitotic entry, testing specific hypotheses related to transcriptional regulation, DNA damage, and the mitotic entry circuit. The proposed effort represents an entirely new research area for the group, which has historically focused on chromosome segregation, centrosome function, spindle assembly, and checkpoint function during mitosis. Successful execution of the project has the potential to advance understanding of the cellular functions of BET proteins and of the control of mitotic entry in human cells, while also revealing whether there are opportunities for targeting the G2-M transition of the cell cycle, as has been done for the G1-S transition, in specific cancer contexts.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Identifying Disparities in Autologous HCT Utilization for DLBCL in California

Campus: UCD

Principal Investigator: Naseem Esteghamat

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$74,929

Abstract:

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

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

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

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Developing inhibitors targeting glycine decarboxylase

Campus: UCSB

Principal Investigator: Yang Hai

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Glycine decarboxylase (GLDC) is a mitochondrial pyridoxal-5'-phosphate (PLP)-dependent metabolic enzyme breaking down glycine into carbon dioxide, ammonia, and a C1 building block. GLDC function is critical to tumor-initiating cells in non-small cell lung cancer (NSCLC), and it has been proposed as a promising drug target for lung cancer treatment. In spite of the urgent need to develop new lung-cancer chemotherapeutics, currently there is no GLDC inhibitor available that could allow researchers to validate the hypothesis regarding GLDC as an anti-cancer drug target. In this project, we aim to bridge this knowledge gap to develop first GLDC-selective inhibitor(s). First, we will design mechanism-based inhibitors by harnessing the unique reactivity of aminoxy group towards PLP cofactor and mimicking GLDC's unique substrate lipoylated H-protein. We will use a "cap-linker-binder" modular approach to rapidly create a library of aminoxy-based inhibitors and map out the structure-activity relationship. Secondly, to further improve this first-generation of GLDC inhibitors, we will use a structure-guided approach. Since crystal structures of human GLDC are available, we will leverage the existing structure-determination protocols to study the crystal structure of GLDC-inhibitor complex. Moreover, as the protein-protein interaction between GLDC and H-protein is unknown, we will also use affinity-probe and chemoenzymatically modify H-protein in order to stabilize GLDC-H protein complex for structural characterization. This co-crystal structure will provide critical insights for designing peptide-inhibitors that can block the substrate entrance tunnel of GLDC. Furthermore, it also provides an opportunity to develop protein-protein interaction inhibitor or molecular glue-like inhibitors. Thirdly, as a complementary approach, we will also perform a phenotypical-screening experiment to identify drug leads de novo. For example, we will use the phage-display technique to screen a large library of cyclic peptides and identify the initial peptide scaffolds or sequences that can bind to GLDC and also inhibit its activity. We expect our study will provide new mechanistic insights for modulating GLDC activity, and provide the first-in-class GLDC inhibitors, and pave the way for future in vivo study and pre-clinical investigations.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Targeting Metabolic Vulnerabilities of Chemoresistant Pancreatic Cancer

Campus: UCI

Principal Investigator: Christopher Halbrook

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Pancreatic ductal adenocarcinoma (PDA) is projected to become the second leading cause of cancer-related death by 2030. This is largely driven by a lack of effective treatment options. The majority of PDA patients receive conventional chemotherapy, and while some initially respond to the standard of care therapies, most do not maintain a durable response or rapidly develop chemoresistance. This project aims to overcome resistance to gemcitabine, one of the most widely used cytotoxic agents in PDA therapy. Improvement of gemcitabine chemotherapy combinations represents an immediately translatable clinical benefit to PDA patients.

To develop methods to overcome gemcitabine resistance, we have generated models of chemoresistance in syngeneic murine PDA lines and assembled a library of pancreatic cancer patient-derived organoids with an array of responses to gemcitabine. Through transcriptional profiling, we identified several mechanisms of metabolic reprogramming in our gemcitabine resistant models. Further characterization revealed several potential metabolic vulnerabilities, including the mevalonate pathway. We have generated preliminary data showing that approaches targeting the rate-limiting enzyme of the mevalonate pathway, HMG-CoA reductase, are significantly more potent in gemcitabine resistant PDA cells than in the respective parental counterparts. Downstream rescue experiments have demonstrated that the main impact is through loss of geranylgeranyl pyrophosphate levels, however, further investigation will be needed to provide additional mechanistic details.

The research in this proposal will determine the potential of combining gemcitabine treatment with inhibition of the mevalonate pathway to treat chemoresistant PDA. We will use both immune-competent murine allografts and patient-derived organoids as preclinical models. In addition, we will examine the impact of other identified metabolic targets that can potentially be used to overcome the acquisition of gemcitabine resistance. Finally, we will test if the approaches to overcome gemcitabine chemoresistance are also effective against PDA cells that are resistant to other clinically deployed therapies. These approaches have potential for rapid translation, and the data generated in this proposal can be used to inform clinical trial designs here at UCI.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Cell therapy for muscle atrophy following irradiation in Rhabdomyosarcoma

Campus: UCI

Principal Investigator: Michael Hicks

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

There are more than 80 types of sarcomas, including Rhabdomyosarcoma, that develop within connective tissues or skeletal muscle, which if left untreated are lethal. Radiation therapy combined with surgery is the standard-of-care for sarcoma treatment; however, radiation causes severe, permanent damage to the surrounding tissues including depletion of the skeletal muscle stem cells required for maintenance and repair. Because sarcomas disproportionately affect young people (11% of all adolescent cancers), patients that survive radiation will experience muscle atrophy and reduced mobility over their lifetime.

We have a strategy to generate skeletal muscle from human pluripotent stem cells (hPSCs) with the ability to build new muscles following transplantation. Since hPSCs can be readily obtained from patients from any genetic background and expanded indefinitely, we have an opportunity to provide a robust cell therapy to reconstruct tissues for sarcoma survivors. We hypothesize that transplanted hPSC derived skeletal muscle will prevent muscle atrophy and loss of muscle function after surgery and irradiation in Rhabdomyosarcomas.

Aim 1. Generate a Rhabdomyosarcoma mouse model to evaluate the effects on muscle stem cell repair and function. We will perform allogenic transplant of bioluminescent-expressing human sarcoma cells into quadriceps of mice to induce tumor formation. Tumors will be subject to surgical removal and/or radiation therapy at multiple time points. We will evaluate endogenous muscle stem cell's ability to regenerate functional muscle at treated tumor sites.

Aim 2. Test transplantation of hPSC skeletal muscle to restore the stem cell pool and muscle function. It's unclear whether the volumetric muscle loss following surgical tumor removal or irradiated tissue remnants, such as extracellular matrices, can support engraftment of muscle stem cells. We will perform cell transplantations at irradiated sites with or without hydrogel plugs to test cell replacement of functional skeletal muscles within the irradiated muscle environment. If successful, our immediate goal would be to leverage pilot funding toward the California Institute of Regenerative Medicine (CIRM) DISC2 Quest grant, which would enable us to pursue an Investigational New Drug Application (IND) for moving forward with translating muscle stem cell therapies for cancer survivors.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Investigating the role of RNA editing induced double-stranded RNA in leukemia initiating cells

Campus: UCSD

Principal Investigator: Qingfei Jiang

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Relapsed pediatric T-cell acute lymphoblastic leukemia (T-ALL) is often refractory to conventional therapy and is associated with a dismal survival rate of less than 25%. Relapsed/refractory T-ALL is often enriched with leukemia initiating cells (LICs), which exhibit enhanced survival and self-renewal capacity. Adenosine deaminase acting on RNA 1 (ADAR1) plays a key regulatory role in hematopoietic stem cell maintenance, the innate immune response, and cancer. We discovered that ADAR1-mediated adenosine-to-inosine (A-to-I) RNA editing is crucial for the maintenance of T-ALL LIC. Preliminary studies revealed that approximately 70% of T-ALL patients exhibit high expression of ADAR1, and this is associated with significantly worse clinical outcome. In addition, inhibition of ADAR1 impairs LIC survival and self-renewal in patient-derived in vitro and in vivo models. An important functions of A-to-I RNA editing is to suppress interferon (IFN)-induced apoptosis by dsRNA sensing and to prevent activation of the innate immune response. Inosine-containing endogenous dsRNA are recognized as “self” by dsRNA sensing pathways to distinguish from invading viral dsRNA. In this manner, ADAR1 prevents activations of dsRNA sensors such as melanoma differentiation-associated protein 5 (MDA5) and protein kinase R (PKR) which in turn trigger the inflammation signals. We were excited to confirm that ADAR1 suppresses inflammation pathways by limit cytosolic dsRNA pool in T-ALL LICs. This occurs through both hyper-editing of IFN-associated RNAs and retention of nuclear dsRNA via RNA editing-independent mechanism. However, whether ADAR1-directed dsRNA sensing pathway contributes to LIC maintenance has never been studied. To test this, we will first determine if ADAR1 knockdown activates aberrant dsRNA sensing by quantify the level and cellular location of dsRNA. In addition, concurrent knockdown of dsRNA sensors (PKR and MDA5) in combination with ADAR1 knockout in LICs will be applied to determine if aberrant dsRNA sensing disrupts LIC self-renewal in patient-derived xenograft mouse models. Mechanistically, we will map dsRNA-containing genes suppressed by either RNA editing or dsRNA binding activity of ADAR1. Together, these studies will establish whether the cellular functions of ADAR1 in LICs depend on the suppression of dsRNA sensing pathways.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Prediction and Prevention of Malignant Transformation in IDH mutant gliomas

Campus: UCLA

Principal Investigator: Albert Lai

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Isocitrate dehydrogenase (IDH) mutant gliomas comprise 35% of adult diffuse gliomas, translating into ~5000 new patients yearly in the United States [1]. IDH mutant gliomas are for the most part distinct from glioblastomas, a type of diffuse glioma that is the most common adult brain cancer. IDH mutant gliomas can be further separated into astrocytomas and oligodendrogliomas based on the absence or presence, respectively, of the 1p19q chromosomal co-deletion. IDH mutant astrocytomas are ~2-3 times more common than oligodendrogliomas. The process of malignant transformation [2], albeit poorly defined and characterized, represents a common transition in which low grade gliomas adopt a more aggressive and treatment resistant phenotype, ultimately leading to death. Malignant transformation is diminished or significantly delayed in many oligodendroglioma patients, and as a result, many but not all, oligodendroglioma patients treated with radiation and chemotherapy can experience long survivals approximating cure. This is not the case for the majority of astrocytoma patients. While astrocytomas can be controlled for intervals ranging from 5-15 years, almost inevitably, astrocytomas will undergo malignant transformation becoming more aggressive and treatment resistant. With improved understanding of the process of malignant transformation, we expect to be able to predict and ultimately prevent malignant transformation. Specifically, we will examine the role of recently available IDH mutant inhibitors now in trials for glioma [3] in altering malignant transformation and whether IDH mutant inhibition has a role in gliomas post malignant transformation. The anticipated approach will be multidisciplinary involving neuro-oncology, neuro-imaging, neurosurgery, and molecular pathology and tumor biology all focused on leveraging the large numbers of IDH mutant patients cared for by the UCLA Neuro-oncology. Over the past 4 months, we have identified >800 IDH mutant patients and begun collecting and organizing clinical, pathological, imaging and tissue resources. We will pursue the following aims: 1) identify predictors of malignant transformation of IDH mutant gliomas, 2) characterize the effect of IDH mutant inhibition on patient gliomas both before and after malignant transformation, and 3) explore mechanisms of malignant transformation in vivo and in vitro.

**UC Cancer Research Coordinating Committee 2023 Competition Results
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Influence of growth hormones and mechanical loading on osteosarcoma progression

Campus: UCD

Principal Investigator: Kent Leach

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Osteosarcoma (OS) is the most common primary malignant tumor of bone in children and young adults. Adjuvant chemotherapy and surgical resection has been used to treat OS for decades, with 5-year survival rates of 60-70%. Unfortunately, for those patients with metastatic disease, 5-year survival rates are dismal (less than 30%), motivating the urgent need to understand what triggers the migration of OS cells from the bone into surrounding tissue, and eventually distant metastasis to the lungs.

When studied in monolayer culture, cancer cells are deprived of their native microenvironment and lose the tumor phenotype, making their responsiveness to therapy inaccurate. Animal models, considered essential for cancer research, also fail to accurately predict clinical outcomes. Tumor features have been created in biomaterials to model both the structural and cellular composition of the bone and marrow microenvironments. Mechanical stimuli also play a key role in tissue development and diseases such as cancer. For instance, OS thrives in a mechanically active microenvironment, especially during the teenage growth spurt. This suggests there may be a link between mechanical signaling, bone growth, and tumor formation that merits further study.

We hypothesize that OS progression and metastatic potential will be increased with exposure to pubescent growth hormones and mechanical loading. Murine OS cell lines or MC3T3 pre-osteoblasts will be entrapped in engineered constructs mimicking the composition and structure of bone marrow. Constructs will undergo dynamic compressive loading in a bioreactor for 2 h per day for 7 days in complete media or media supplemented with testosterone, β -Estradiol, or dihydrotestosterone. We will measure changes in bone formation and known metastatic signaling pathways by standard biochemical assays (e.g., PCR, RNAseq, IHC), while metastatic potential will be examined by tracking metastasis to the lungs upon murine subcutaneous implantation. We will also test efficacy of known chemotherapeutic drugs (i.e., doxorubicin) on stimulated constructs both in vitro and in vivo. The results will reveal the synergy of mechanical signaling on tumor growth in the presence of growth hormones and establish the importance of mechanical loading as potential drug targets to slow the growth and metastasis of OS.

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

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

Campus: UCI

Principal Investigator: Karen Lindsay

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$85,000

Abstract:

The objective of the proposed research is to investigate the contribution of maternal diet and glucose-insulin homeostasis in pregnancy to offspring cancer risk via dysregulation of the insulin-like growth factor (IGF) axis. Maternal obesity and high birth weight are repeatedly associated with various cancers in children and adults. The IGF axis has been highlighted as a plausible underlying mechanism given that i) IGF-1 and IGF-2 are present in fetal circulation and play key roles in fetal growth and development; ii) IGF-1 is strongly positively correlated with fetal growth and birth weight; and iii) the IGF axis is implicated in the pathogenesis and progression of different types of human cancer such as colon, breast, prostate, lung and leukemia. Early-life efforts for cancer prevention may therefore begin in utero through modulation of the fetal IGF axis, which is thought to be stimulated by circulating glucose and insulin. Maternal diet may be a key modifiable factor via its influence on glucose tolerance.

We propose a prospective observational study of N=80 pregnant women with pre-pregnancy overweight or obesity and diverse racial/ethnic backgrounds, leveraging the high proportion of Hispanic and Asian women who obtain prenatal care at the UCI medical center. Maternal diet in each trimester will be assessed using two 24-hour dietary recalls and the Alternative Healthy Eating Index for Pregnancy will be computed as a measure of diet quality. At 28 weeks' gestation, maternal fasting glucose, insulin, and c-peptide will be measured and the homeostasis model assessment of insulin resistance computed. Maternal glucose concentrations from the standard glucose challenge test will be abstracted from medical record. Neonatal IGF-1, IGF-2, IGFBP-1, and IGFBP-3 will be assayed from cord blood. The separate and combined contribution of maternal diet and glucose-insulin homeostasis to variation in concentrations of cord blood IGFs and IGFBPs will be analyzed, with trimester-specific analysis for the effects of maternal diet. Analyses will be adjusted for maternal demographics, gestational weight gain, infant sex, and gestational age at birth.

It is expected that this study will generate novel preliminary data to test if modifiable gestational exposures may influence offspring IGF axis, representing a possible early-life window for cancer prevention efforts.

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

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

Campus: UCI

Principal Investigator: Yunxia Lu

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$85,000

Abstract:

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

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

Magnitude and mechanisms of macrophage plasticity during checkpoint immunotherapy of melanoma

Campus: UCI

Principal Investigator: Francesco Marangoni

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

The plasticity of tumor-associated macrophages (TAMs) governs their transition from pro-inflammatory functions, which oppose tumor growth, to anti-inflammatory functions that promote cancer progression and vice-versa. Leveraging TAM plasticity to promote pro-inflammatory functions holds great promise against tumors. However, the mechanisms that regulate TAM plasticity in vivo have not been studied extensively because of a dearth of appropriate mouse models. To fill this gap, we just generated a mouse strain that allows us to map the fate of IL12b-producing (pro-inflammatory) TAMs towards IL-10-producing (anti-inflammatory) ones.

This application aims to use our new mouse strain to gain insights into the mechanisms of plasticity regulating the stability of the pro-inflammatory function of TAMs in vivo. Our central hypothesis is that the pro-inflammatory activity of TAMs can be induced by immunotherapy but is short-lived because the tumor microenvironment efficiently re-programs them to become anti-inflammatory. In Aim 1, we will determine the sequence and dynamics of TAM functional changes during the transition from pro- to anti-inflammatory. We will also explore the molecular mechanisms that might regulate the loss of the pro-inflammatory state in vivo by running RNA and ATAC sequencing on TAMs sorted based on their function. In Aim 2, we will measure TAM plasticity from pro- to anti-inflammatory phenotypes in tumors with varying degrees of immunogenicity and after the administration of various immune-stimulating therapies.

The expected outcome of this project is to gain insight into the extent, duration, and potential mechanisms by which the tumor re-programs pro-inflammatory macrophages to become anti-inflammatory, supporting its progression. In the long term, the knowledge we generate will pave the way to new forms of cancer immunotherapy to perpetuate pro-inflammatory TAM functions.

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

Small Molecule Immuno-Oncology: Mechanism-based Inactivators of IL4I1 and AHR-Driven Cancers

Campus: UCR

Principal Investigator: Michael Pirrung

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$79,500

Abstract:

A major advance in cancer treatment has been checkpoint inhibitors like Keytruda, an antibody that overcomes evasion of the local immune response to a tumor by inhibiting interactions of a molecule called PD-L1. Like many cancer treatments, effective responses are observed in only a minority of patients. Another way tumors suppress the immune response in their local environment is producing tryptophan metabolites via the kynurenine pathway. One of its enzymes is indole dioxygenase (IDO), for which inhibitors/drug candidates have been developed (epacadostat, indoximod). These entered clinical study, often combined with checkpoint inhibitors. For the most part, these have not shown desired efficacy, and IDO inhibitors have lost their luster.

Understanding of how tryptophan metabolites suppress the immune response has recently expanded. Their activation of the aryl hydrocarbon receptor (AHR) in T-cells is key. Tryptophan-derived indole-3-pyruvate is a strong AHR activator. The enzyme that produces them is IL4I1. There is a greater correlation of immune suppression by a tumor to indole-3-pyruvate levels than kynurenic acid levels (a product of IDO), and only IL4I1 is needed to make indole-3-pyruvate. Therefore, IL4I1 is a more relevant target to the desired drug effect, overcoming tumor immune evasion. Activation of the AHR in tumor cells also stimulates their proliferation. So preventing AHR activator production has two benefits. The enzymatic mechanism of IL4I1 includes an essential flavin cofactor. Inhibitors of flavin enzymes have a long history in biochemistry. One particularly fruitful approach to targeting them is a classical, now almost forgotten strategy, mechanism-based inhibition. "Suicide inhibitors" typically lead to irreversible covalent enzyme modification. There are marketed drugs with this mode of action against flavin enzymes. While covalent drugs are currently fashionable, and also have success stories in cancer (like ibrutinib), there are distinct advantages to mechanism-based inhibitors. They must be acted upon by the enzyme to reveal a reactive functionality, providing very high specificity. We will take this approach to inhibiting IL4I1 that draws from a vast past literature on mechanism-based inhibition. An effective inhibitor of IL4I1 would be a worthy candidate to study in combination with checkpoint inhibitors for immuno-oncology.

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

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

Campus: UCSD

Principal Investigator: Dionicio Siegel

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$85,000

Abstract:

The G α protein GNAS, which encodes for the heterotrimeric G protein G α s, is the second most frequently mutated gene in mucinous appendiceal adenocarcinoma (AA) (~50% of tumors) and Pseudomyxoma Peritonei (PMP, ~75% of tumors) and third most common in non-mucinous AA (~25% of tumors), making it a promising drug target in this orphan disease. Although classically druggable, no commercially available inhibitors of G α s exist. Here, we propose an innovative approach to develop and characterize chemical inhibitors of G α s. 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 G α s will be an effective therapeutic strategy for GNASR201 mutant tumors.

New Treatments are Needed for Appendiceal Cancer, Currently an Orphan Disease.

Appendiceal tumors encompass a rare and diverse group of neoplasms; AA is the most common histologic subtype. Epidemiologic studies based on Surveillance, Epidemiology, and End Results (SEER) data have shown a steady increase in incidence from approximately 0.2 cases per 100,000 in the 1970s, to current estimates of just over 1 per 100,000. In comparison, this is 40-fold less common than colon cancer, which in the US has an incidence of approximately 40 per 100,000. Cases of early-onset AA, defined as diagnosis before age 50, have increased by 24% between 2011 to 2016, and in 2016 represented 40% of all appendiceal cancer. In contrast, the increase in early-onset colorectal cancer (CRC) was only 2.2% for that same time period. Historically, appendiceal tumors have been grouped together with CRCs, and as of 2021 the National Comprehensive Cancer Network (NCCN) guidelines still suggested that appendiceal tumors be treated with chemotherapy similarly to colon tumors. The rarity of AA has made it difficult to conduct clinical trials, and in the absence of trial data, the NCCN guidelines assume biological similarity due to anatomic vicinity, common embryological origin, and common expression of the transcription factor CDX2. However, there is a growing consensus that AA is a clinically and molecularly distinct entity from CRC, and that AA specific therapies (none exist currently) need to be developed. We have discovered two druggable sites on GNAS and have developed small molecule inhibitors targeting the site next to the point of mutation.

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

The Warburg Effect is the result of faster ATP production by glycolysis than respiration

Campus: UCB

Principal Investigator: Denis Titov

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Many prokaryotic and eukaryotic cells partially metabolize glucose to organism-specific byproducts instead of fully oxidizing it to carbon dioxide and water, even in the presence of oxygen. This phenomenon, often referred to as the Warburg Effect, was originally observed in tumor cells. The benefit of the Warburg Effect to a cell has been unclear, given that partial metabolism of glucose yields an order of magnitude less ATP per molecule of glucose than complete oxidation. In our recent theoretical study, we proposed that the Warburg Effect stems from the optimization of energy metabolism that allows cells to produce ATP at the highest rate in the presence of excess glucose independent of cell growth rate. By estimating the yield, specific activity, and proteome occupancy of the glycolysis and respiration pathways from published studies in bacteria, yeast, and mammals, we found that for each organism, the data is consistent with glycolysis producing ATP at a faster rate per gram of pathway protein than respiration. However, we could only find a limited number of published datasets for mammalian cells that contain measurements required for our calculations. Here, we propose to perform rigorous measurements of glycolysis and respiration pathway rates per gram of pathway protein in mammalian cancer cell lines to generate additional evidence to support or refute our hypothesis. Our lab has extensive experience performing metabolic flux and proteomics measurements in mammalian cells that will be required for this project, which will allow us to complete the proposed measurement within the 1-year duration of the Seed Grant. Taken together, our study will rigorously test the hypothesis that the Warburg Effect is an expected consequence of the optimization of cancer cell energy metabolism toward maximal energy production rates and might lead to the development of novel anticancer treatments specifically targeting the vulnerabilities of cancer cell bioenergetics.

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

Protoacoustic Image-guided Precision Proton Therapy

Campus: UCI

Principal Investigator: Liangzhong Xiang

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$75,000

Abstract:

Dr. Xiang (Radiology & BME) at UC Irvine is seeking seed funding to support his research focused on developing protoacoustic image-guided precision proton cancer therapy. This project will be a collaborative effort between investigators from UC Irvine, as well as other researchers from University of Oklahoma Health Sciences Center (OUHSC), each bringing their complementary expertise to the table. Dr. Xiang, a pioneer in protoacoustic imaging, will lead the imaging device team, while Drs. Yong Chen and Tyler Gunter at OUHSC, an exceptional expert in proton therapy, will provide expertise in radiation oncology. With the help of this seed grant, the research team will be able to gather the necessary preliminary data to submit an NIH R01 grant to the National Cancer Center (NIH/NCI) in June 2024. The Overall Objective of the planned R01 application is to 1) establish a robust protoacoustic dosimeter for 3D in vivo dosimetry in FLASH proton therapy which is critical for its clinical translation and adoption; 2) develop a strategic alliance of multi-disciplinary (biomedical engineering, radiology, medical physics, and oncology) multi-institutional research team (UCI, and OUHSC), which will accelerate the developments and translation of this novel dosimeter for clinical use in the next 5-10 years. The protoacoustic dosimeter will create a 3D map of the radiation dose delivered to the tumor and surrounding healthy tissue during proton therapy. This will help doctors make sure that the therapy is precise and effective. The new technology we're developing will also make proton therapy less harmful to patients, by reducing the side effects of radiation therapy. During this one-year seed grant, our main focus will be to create a prototype of the protoacoustic/ultrasound imaging technology and gather initial data using a human mimic phantom. This will help us support our R01 proposal and eventually enable us to study the new technology on large animals and conduct a pilot study on patients.

**UC Cancer Research Coordinating Committee 2023 Competition Results
2023-2024 Awards List by Abstract**

Transporter-mediated androgen incorporation into prostate cancer cells

Campus: UCR

Principal Investigator: Naoki Yamanaka

Start Date: 10/01/2023

End Date: 9/30/2024

Amount: \$74,982

Abstract:

Steroid hormones, including sex steroids such as testosterone and estradiol, have diverse biological functions ranging from developmental to pathological effects, such as stimulation of cancer progression. They exert such pleiotropic effects by entering their target cells and activating intracellular nuclear receptors. Due to their lipophilic character, steroid hormones are believed to freely diffuse across cellular membranes in process called simple diffusion. Despite its frequent appearance in physiology textbooks, however, this model has never been experimentally demonstrated in any organism. Indeed, recent studies in our lab have shown that ecdysone, the primary steroid hormone in insects, requires membrane transporters to traverse the plasma membrane. These transporters, named ecdysone importers, all belong to the solute carrier organic anion (SLCO) transporter superfamily, which is highly conserved among metazoans including humans. In the proposed project, we aim to identify potential roles of SLCO transporters in androgen-dependent prostate cancer growth. In preliminary studies, we identified one SLCO transporter that is primarily responsible for testosterone incorporation into human embryonic kidney (HEK) 293T cells, challenging the conventional paradigm that human steroid hormones are incorporated into cells by simple diffusion. As this SLCO is highly expressed in human prostate cancer LNCaP cells whose growth is androgen dependent, we will knock out this SLCO-encoding gene in LNCaP cells using the CRISPR/Cas9 technique and test if their testosterone-dependent growth is significantly affected. We will also examine potential effects of known SLCO inhibitors on the testosterone-dependent growth of LNCaP, aiming to establish a proof of concept that androgen-dependent prostate cancer growth can be pharmacologically manipulated by targeting membrane transporters involved in androgen incorporation.