# A COMMUNITY MOVEMENT TO DEFEAT CANCER

Established in 2017, the UCI Anti-Cancer Challenge brings like-minded people together to defeat cancer. Participants ride, run and walk to raise awareness and funds for promising research by the UCI Health Chao Family Comprehensive Cancer Center. Corporate partners underwrite event costs, ensuring that 100% of participant contributions go to promising pilot studies and early-phase clinical trials. Since 2017, over 9,300 participants have registered to raise funds for cancer research, with thousands of friends and family members showing up to support them on the day of the event. Our peer-to-peer challenge has raised more than $2.6 million for cancer research and consistently ranks among the Orange County Business Journal's top five fundraising run/walks.

## UCI Health Chao Family Comprehensive Cancer Center

At the UCI Health Chao Family Comprehensive Cancer Center, we work to prevent, manage, and cure cancer to help all people live healthier, longer lives. We are fighting center on all fronts through our basic science and clinical research. Our cancer center members — drawn from more than 32 departments and seven UCI schools — are organized into three research programs: Biotechnology, Imaging & Drug Development; Systems, Pathways & Targets, and Cancer Control. These programs provide an interactive and collaborative infrastructure for cancer discovery, clinical investigations (including early-phase and investigator-initiated trials) and population-based research.

As one of only 52 elite National Cancer Institute-designated comprehensive cancer centers in the nation, and the only one based in Orange County, we treat more patients with cancer — and more complex cases — than any other healthcare provider in our region.

## UCI Health

We are UCI Health: a devoted team of nationally regarded physicians and nurses, researchers and clinicians, educators and students united by a single calling — to improve the lives of the people in our community and beyond. As the only academic health system in Orange County, our multifaceted organization is dedicated to the discovery of new medical frontiers, to the teaching of future healers and to the delivery of the finest evidence-based care.

In 2020, UCI Health cared for 7,268 new cancer patients. As UCI Health continues to expand, more people with cancer are gaining convenient access to the expert care provided by the UCI Health Chao Family Comprehensive Cancer Center.

Cancer services will also be offered at UCI Medical Center — Irvine. Located on the university's north campus, this complex will house a 114-bed hospital, with an emergency department and outpatient care center offering comprehensive care for cancer. Specialty services will include comprehensive care for cancer, neurosciences, orthopaedics and spine. There, UCI Health cancer specialists can more easily collaborate with campus partners to develop evidence-based, health-and-wellness practices, optimizing therapies and helping our patients join the ever-increasing ranks of Orange County cancer survivors.

# RESEARCH PORTFOLIO

## Track 1: Pilot Project Awards

Track 1 awards are for basic and translational pilot project proposals, with an endpoint of a competitive, peer-reviewed extramural grant application. With these awards, researchers seek to understand how cancer cells differ from normal cells and answer the questions of how cancer cells develop, grow and spread. As promising molecules, gene targets or biomarkers are discovered, the goal is to move them from the laboratory bench into clinical studies — Anti-Cancer Challenge track 2 projects — for further testing as potential therapies for cancer treatment.

## BASIC & TRANSLATIONAL RESEARCH

Cancer Center researchers collaborate to perform basic cancer research to understand how cancer cells differ from normal cells and to provide answers on how cancer cells develop, grow and spread.

Through this work, promising molecules, gene targets or biomarkers are discovered, which then move to translational research for further testing ofpotential drugs for cancer treatment.

Target cells or tissues are first tested in vitro (meaning “in glass”) then in vivo (”in living organisms”) to collect information about how the drug works.

## CLINICAL RESEARCH

Promising drugs are filed with the Food and Drug Administration before entering a clinical trial to be tested on cancer patients.

Before a clinical trial can begin at UCI, it is rigorously reviewed at several levels:

- Multidisciplinary teams of doctors, surgeons and scientists, called Disease-Oriented Teams (DOTs), ensure trials are of high scientific quality and importance.
- Institutional Review Board assures the safety and welfare of the participants are protected.

# Track 2: Early-Phase Clinical Trial Awards

Track 2 awards are for early-phase clinical research projects that serve to determine whether new treatments do what they are expected to do, assess their safety and potential side effects or evaluate whether they work. The goal is to move these projects into interventional, investigator-initiated treatment trials.

## PHASES OF CLINICAL TRIALS

**PRECLINICAL PHASE**

Phase 0 studies are exploratory studies that often use only a few small doses of a new drug in a few patients.

- Tested in a small group of volunteers: less than 15
- Find out if the drugs do what they are expected to do
- How the drugs are absorbed or act in the body

**PHASE 1**

Phase 1 trials find the best dose of a new treatment with the fewest side effects.

- Tested in a small group of volunteers: 15 to 20
- Designed to decide how a new treatment should be given
- To see how a new treatment affects the human body and fights cancer
- Can take several months to complete

**PHASE 2**

Phase 2 trials continue to evaluate safety.

- Tested in larger groups of volunteers: 25 to 100
- Designed to determine if a drug or treatment has an affect on a certain cancer
- Can take about two years to complete

**PHASE 3**

Phase 3 trials compare a new drug or treatment to standard-of-care.

- Tested in a much larger group of volunteers: hundreds to several thousand
- Trials assess the side effects of each drug or treatment and evaluate which works better
- Patients are randomly assigned to receive either the new treatment or the best existing treatment
- Volunteers are followed for several years

**PHASE 1–3: TEN TO FIFTEEN YEARS**

**PHASE 4**

Phase 4 trials, the final phase, asks new questions about standard treatments.

- Begins after a drug or treatment is approved by the FDA and made available to the public
- Trials evaluate the long-term benefits, side effects and how well the drug works when used more widely
- Data collected on the drug or treatment's risks, benefits and optimal uses

# 2021 Track 1: Pilot Project Awards

## Effects of Dietary Methionine Restriction on Splicing in Tumors

Investigator

**Peter Kaiser, PhD,** *Department of Biological Chemistry,* School of Medicine

Immune checkpoint inhibitors are some of the most promising emerging therapies for cancers. Unfortunately, due to insufficient immunogenicity of some tumors only a fraction of cancers responds to current therapies. This project tries to increase tumor immunogenicity through specific diets that increase production of aberrant proteins in tumors to activate the anti-tumor immune response.

## Defining Genomic Instability in Early Onset Colorectal Cancer in Us-Born Hispanics

Investigator

**Nick Pannunzio, PhD,** *Department of Medicine—Hematology/Oncology,* School of Medicine

Colorectal cancer (CRC) is the third most diagnosed cancer in the United States. Though CRC cases in older adults have decreased, the incidence of CRC in young adults, ages 15-39, is on an alarming rise especially in Hispanics. The cause of this rise in young adult CRC cases is unknown, but is linked to environmental and dietary factors, which are known to disrupt the circadian clock that controls sleep cycles, diet, and metabolism. The goal of this proposal is to interrogate the role of the circadian clock in CRC and to define how disruption of circadian rhythms impacts young adult CRC, specifically in Hispanics.

## Identifying Approaches to Effectively Target Metastatic Pancreatic Cancer

Investigator

**Christopher Halbrook, PhD,** *Department of Molecular Biology & Biochemistry,*
School of Biological Sciences

Pancreatic cancer is a devastating digestive disease. Most patients are diagnosed with metastatic disease, and the few who qualify for removal of the primary lesion typically experience recurrence in secondary sites. As a result, nearly all patients die with metastatic disease. The site of pancreatic cancer metastasis is the liver, and research contained within this proposal will provide new insights into the effectiveness of methods to harness the immune system to target liver metastatic lesions.

## Understanding and Addressing Cancer Survivorship Needs for Filipino-Americans in Los Angeles and Orange Counties

Investigator

**Sora Park Tanjasiri, DrPH, MPH,** *Department of Epidemiology and Biostatistics,* Program in Public Health

Research aimed at understanding how social support and quality of life impacts the physical and mental health of cancer survivors have primarily focused on those affected by breast cancer, and only a subset investigated certain Asian American subpopulations. Filipino Americans account for the third-largest Asian American subgroup in the U.S., but only a limited number of studies, if any, have explored factors that affect the health-related quality of life and the long-term health care needs of Filipino American cancer survivors. This pilotstudy will use interviews with Filipino American cancer survivors and leaders in the community to explore the cancer-specific treatment and survivorship needs of Filipino Americans in Southern California and will contribute to the limited literature that focus on the unique unmet needs and psychosocial preferences of this understudied population. Findings will be used to develop supportive care interventions that improve quality of life factors for Filipino American cancer survivors.

## Identifying Early Diagnosis Markers and Therapeutic Targets of Kidney Tumors in Young Tsc Patients

Investigator

**Gina Lee, PhD,** *Department of Microbiology & Molecular Genetics,* School of Medicine

The kidney is an essential organ that eliminates harmful wastes from the blood into the urine and reabsorbs important nutrients. The tumor formation in the kidney, therefore, affects not only kidney function but also damages all other critical organs, causing lethal consequences. Using our state-of-the-art tissue surgery and chemistry techniques, we will determine how tumor-bearing kidneys affect kidney function and the whole body. We will also identify potential blood markers for early detection of kidney tumors by analyzing numerous patient samples obtained from the non-profit kidney tumor research foundation and UC Irvine's cancer center. Our studies will reveal clinically important information about kidney tumors to facilitate the development of new drugs and diagnostic tools.

## Functional Characterization of the Hippo Pathway in Cancer

Investigator

**Wenqi Wang, PhD,** *Department of Developmental and Cell Biology,* School of Biological Sciences

The Hippo pathway has been established as a tumor suppressor pathway, whose deficiency is frequently observed in human cancers. In this proposal, we will focus on the Hippo pathway mutations identified in human cancers and investigate their effects on Hippo signaling. Completion of this proposed study will enrich our understanding of the Hippo pathway in human cancer development and allow us to reveal novel regulation and function for this key signaling pathway.

## Quantification of Irreversible Electroporation Outcomes Based on Longitudinal Monitoring of Hybrid Functional/Structural Variations of Hcc Microenvironment

Investigator

**Zhouli Zhang, PhD,** *Department of Radiation Oncology,* School of Medicine

Irreversible electroporation (IRE) utilizes powerful electrical fields using a high-voltage direct current to induce several holes in the cell membrane and irreversibly damages the cell's homeostasis mechanism, leading to instant cell death. How this process contributes to disease progression and how tumor microenvironment changes post-treatment affect its outcomes are areas of intense study. We propose to use first-of-its-kind cutting-edge technology developed at IVFOI-CFCCC, namely PMI to measure the changes in oxygenation levels and hemoglobin concentration globally throughout the tumor before, longitudinally after IRE in a rat liver tumor model.

## Vascularized Microtumor as a Drug Testing Platform for Peritoneal Carcinomatosis

Investigator

**Maheswari Senthil, MD,** *Department of Surgery*

Peritoneal Carcinomatosis is a form of cancer in which a tumor growing in organs like colon, rectum, stomach, appendix etc. spreads to the lining of the abdomen, namely the peritoneum. The treatment of PC is challenging, as standard-of-care cancer treatments are ineffective and are not customized to match the tumor behavior and biology. Hence, new treatment combinations are necessary to improve survival in PC, however progress in this area has been impeded by lack of pre-clinical tumor models that closely mimic the behavior of tumors in humans. We have extensive experience in creating vascularized microtumors and propose to develop a PC-specific version that is suitable to study the mechanisms of PC and assess response to various treatment combinations.

## Elucidating Epigenetic and Metabolic Mechanisms Underlying Sex Differences in Cancer Development

Investigator

**Mei Kong, PhD,** *Department of Molecular Biology and Biochemistry*

According to American Cancer Society, cancer will affect 1 in 2 men and 1 in 3 women in their lifetime in US. Thus, sex differences in cancer incidence are apparent but remain poorly understood. Identifying specific genetic factors contributing to the differences in cancer incidence between men and women will eventually help drug development and prevention strategies that take a patient's sex into consideration. This proposal aims to define the roles of a sex-chromosome associated gene in directly affecting cancer development and aggressiveness in male and female cells.

# 2021 Track 2: Early-Phase Clinical Trials

## An Optimal Dose Finding Study of N-Acetylcysteine in Patients with Myeloproliferative Neoplasms

Investigator

**Angela Fleischman, MD, PhD,** *Department of Medicine—Hematology/Oncology*, School of Medicine

Myeloproliferative Neoplasm (MPN) is a chronic blood cancer characterized by uncontrolled production of blood cells. MPN patients have an increased risk of blood clots, accordingly treatment for this disease focuses on reduction of blood clotting risk. MPN patients have chronic inflammation which is responsible for the debilitating symptoms such as fatigue, headache, and severe itching that MPN patients suffer from. Although patients with early stage MPN can expect a relatively normal lifespan the disease can progress to myelofibrosis which is a bone marrow failure state, or acute leukemia which has a dismal prognosis. There are currently no treatments which prevent progression or cure MPN besides bone marrow transplant. We have recently found that the anti-oxidant supplement N-Acetylcysteine (N-AC) protects an animal model of MPN from blood clots. Moreover, we have found that N-AC blocks the production of inflammatory proteins by immune cells from both normal controls and MPN patients. These findings suggest that N-AC could have multiple benefits in MPN patients, including reduction in blood clots, reduction in inflammation, and improvement in symptoms. We will now test the impact of N-AC on symptom burden, inflammatory protein levels, and markers of blood clots in a group of MPN patients. Moreover, it is possible that long-term treatment with N-AC could prevent progression of MPN through its anti-inflammatory or antioxidant effects. We anticipate that this initial clinical trial will lead to much larger studies that could establish N-AC as an easily accessible, low risk, low cost therapy in patients with MPN.

## Electroacupuncture for the Management of Cancer-Related Cognitive Impairment in Adolescent and Young Adults — a Pilot Clinical Trial

Investigator

**Alexandre Chan, PharmD, MPH,** *Department of Clinical Pharmacy Practice*

Adolescent and young adult (AYA) cancer survivors often experience cancer-related cognitive impairment (CRCI) which can lead to functional impairment at great economic, emotional, and social cost. Effective treatments are currently lacking for managing CRCI, and we aim to investigate the efficacy of electroacupuncture (EA) as a rehabilitation strategy to improve cognitive function and quality of life in AYA cancer survivors. The long-term goal is to optimize EA as an evidence-based integrative health treatment modality in managing AYA cancer survivors' well-being.

## A Feasibility Study for Application of AI to the Study of Integrative Oncology

Investigator

**Edward Nelson, MD,** *Department of Medicine—Hematology/Oncology,* School of Medicine

The diagnosis of cancer is frightening, disruptive, and fraught with symptoms and side effects and many patients with cancer, 10% to >75% in the literature, seek out and use complimentary and/or alternative medicine (CAM) modalities. Essentially all individual cancer practitioners have patients who have benefited from one or more CAM modalities. Traditional or allopathic medicine is diagnosis and specific symptom driven; whereas, CAM is viewed as being more holistic and CAM providers often "prescribe" multiple modalities for a patient. The multimodality approach of CAM along with the difficulties in establishing valid controls and identifying patients likely to benefit from a given modality has led to the study of CAM being insufficiently rigorous to result in adoption of CAM by mainstream medicine. With our College of Heath Sciences focus on Integrative Health, we propose a feasibility study to utilize artificial intelligence (machine learning) to be able to handle the multiple data streams that will be necessary to overcome the above major challenges in studying CAM, to provide an infrastructure for rigorous research into CAM modalities, to identify where and for whom these modalities should be recommended.

# 2020 Track 1: Pilot Project Awards

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

Investigators

**Klemens Hertel, PhD,** *Department Microbiology & Molecular Genetics,* School of Medicine

**Marian Waterman, PhD,** *Department Microbiology & Molecular Genetics,* School of Medicine

Alternative pre-mRNA processing is a hallmark of many colon cancer genes, suggesting that aberrant pre-mRNA processing may contribute to the formation of tumors. This study proposes to determine if defects in alternative pre-mRNA processing contribute to the origin of colorectal cancer. The information obtained from this study will enable a more in-depth analysis identifying alternative processing signatures that promote tumor growth and progression. Trial results are likely to provide novel screening, outcome prediction and therapeutic possibilities.

Supported by the Goon Family

## Overcoming Barriers to Health-Information Seeking Behavior and Potential for Technology for Childhood Cancer Survivors (CCS)

Investigators

**Gillian Hayes, PhD,** *Department of Informatics,* Donald Bren School of Information & Computer Sciences

**Joel Milam, PhD,** *Department of Epidemiology,* School of Medicine

**Anamara Ritt-Olson, PhD,** *Department of Preventive Medicine*, Keck School of Medicine, University of Southern California

**Lilibeth Torno, MD,** *Pediatric Oncology,* CHOC

**Carol Lin, MD,** *Pediatric Oncology,* CHOC

**Christine Yun, MSN, PNP, CPON,** *Oncology,* CHOC

The purpose of this study is to better understand how to maintain the health of adolescent and young adult (AYA) survivors of childhood cancer. The study will help us track the well-being and health of AYA survivors and understand how they seek needed care after completing cancer treatment. There are three main goals for this study: (1) to interview scientists, researchers, cancer advocates, patients and family members, and cancer care providers about the unique needs of AYA survivors; (2) to use those interviews to identify barriers that affect AYA childhood cancer survivors' connection to chronic after-cancer care; and (3) to run a series of workshops to design technology to help AYA cancer survivors stay healthy.

## Mechanisms of Local Treg Expansion in Melanoma Following PD-1 Blockade

Investigators
**Francesco Marangoni, PhD,** *Department of Physiology & Biophysics,* School of Medicine
**Maki Yamamoto, MD,** *Department of Surgery,* School of Medicine
**Michael Cahalan, PhD,** *Department of Physiology & Biophysics,* School of Medicine

Melanoma is one of the most common types of cancer in Orange County, yet 50% of patients with metastases do not respond to state-of-the-art checkpoint blockade immunotherapy and succumb to the disease. We studied the reasons for therapeutic failure and discovered that checkpoint blockade immunotherapy not only increases the immune response against melanoma, but also enhances the function of other components of the immune system, the so-called T regulatory (Treg) cells, which prevent immune responses from becoming too vigorous. We propose to study the mechanisms that lead to the expansion of Treg cells in melanoma in mice and humans after the administration of checkpoint inhibitors. This investigation will pave the way to more effective forms of melanoma immunotherapy.

Supported by Team Grandma Marcia

## Human Lymphoma Organoids as a Screening Platform for Drug Discovery and Precision Medicine in Non-Hodgkin Lymphoma

Investigators
**Lisa Wagar, PhD,** *Department of Physiology & Biophysics,* School of Medicine
**Ash Alizadeh, MD, PhD,** *Department of Medicine—Oncology,* Stanford University
**Jenna Kastenschmidt, PhD,** *Department of Physiology & Biophysics,* School of Medicine

This study will use tumor samples from patients with Non-Hodgkin lymphoma to generate “organoids,” miniaturized and simplified model systems that can be used to study cancer outside of the human body. We have already demonstrated that we can make organoids from some types of Non-Hodgkin lymphoma and will use these systems to test how well current therapies work for different subtypes of lymphomas. These organoids also provide us with the power to test new therapies, which have the potential to inform treatment strategies on a patient-specific basis.

## Active in Vivo Metabolites of p53 Reactivation Small Molecules

Investigators
**Cholsoon Jang, PhD,** *Department of Biological Chemistry,* School of Medicine
**Scott Rychnovsky, PhD,** *Department of Chemistry,* School of Physical Sciences
**Peter Kaiser, PhD,** *Department of Biological Chemistry,* School of Medicine

This proposal aims to identify active drug-like molecules that restore the body's own anti-tumor mechanism, the tumor suppressor protein p53, which is the most frequently mutated protein in human cancers. Each year in the U.S., about 600,000 new cancer patients are diagnosed with tumors carrying p53 cancer mutants, which are particularly enriched in aggressive, hard-to-treat tumors. We have analyzed and found drug-like molecules in mouse tumor models that are metabolized to highly active p53 reactivation molecules. In this proposal, we seek to identify the chemical structure of these p53 reactivation molecules to develop drugs that restore p53 activity for novel cancer treatment.

## Characterizing the Bioenergetic Shift in Triple Negative Breast Cancer Metastasis

Investigators
**Devon Lawson, PhD,** *Department of Physiology & Biophysics,* School of Medicine
**Dennis Ma, PhD,** *Department of Biological Chemistry,* School of Medicine
**Kai Kessenbrock,** *PhD, Department of Biological Chemistry,* School of Medicine

Among the major causes of breast cancer-related deaths are late diagnosis, drug resistance and metastasis. We have discovered that cancer cells change the way they make energy during metastasis, which is when cancer cells spread from the original tumor to a secondary distal site. This trial will study these changes and establish their importance in metastasis. By revealing vulnerabilities in these cells, we hope to devise new therapeutic strategies in treating metastatic disease.

Supported by Team Wild Heart Gypsy Soul

## Pathophysiological Role of Complement C1q in Glioma

Investigators
**Munjal Acharya, PhD,** *Department of Radiation Oncology,* School of Medicine
**Andrea Tenner, PhD,** *Department of Biochemistry and Molecular Biology,* School of Biological Sciences

Glioblastoma multiforme (GBM) is one of the deadliest forms of brain cancer. A recent gene expression analysis has shown that a higher expression of the brain's immune component —complement C1q—correlates to a reduced life expectancy in GBM patients. Using a genetic knockdown approach, this mechanistic proposal will link the detrimental role of complement C1q in GBM.

## Real-Time Dosimetric Measurements for FLASH Radiotherapy with Acoustic Emission

Investigators

**Liangzhong Xiang, PhD,** *Department of Radiological Sciences and Department of Biomedical Engineering,* Henry Samueli School of Engineering

**Charles Limoli, PhD,** *Department of Radiation Oncology,* School of Medicine

The goal of this application is to enable the safe and efficient clinical translation of a new cancer therapy called FLASH radiotherapy (FLASH–RT). This therapy involves the ultra-fast delivery of radiation treatment at dose rates several orders of magnitude greater than those currently used in routine clinical practice. Ultra-fast dose rates allow normal tissue tolerance levels to be exceeded, with a greater probability of tumor control and little or no normal tissue damage. Due to its extremely high dose rates, clinical translation of FLASH–RT is hampered by the lack of real-time dosimetry, which is necessary for ultimate clinical translation and accurate dose measurements within deeper tissue volumes. This proposal aims to investigate radiation-induced acoustic imaging (RAI) as a promising image-guidance modality for real-time deep tissue dose measurements during FLASH–RT. Successful completion of this seed grant will allow us to validate and test in vitro and in vivo experiments in a future clinical trial.

# 2020 Track 2: Early-Phase Clinical Trials

## Use of Levocarnitine for Asparaginase Hepatotoxicity for Acute Lymphoblastic Leukemia Patients

Investigator

**Van Huynh, MD,** *Pediatric Oncology,* CHOC

Acute lymphoblastic leukemia (ALL) is the most common cancer seen in pediatrics. Unfortunately, chemotherapy for ALL often causes liver toxicity; the frequency of this known side effect is increased in overweight or obese patients of Latino heritage. For this study, pediatric, adolescent and young adult patients with ALL will be given oral levocarnitine as a supplement during initial treatment to determine if the incidence of liver toxicity can be reduced or eliminated.

## Assessment of Clonal Hematopoiesis as a Predisposing Factor for Severe COVID-19 Infection

Investigator

**Angela Fleischman, MD,** *PhD, Department of Medicine—Hematology/Oncology,* School of Medicine

One of the challenges of the current COVID-19 pandemic is identifying those who are at risk for developing severe and deadly outcomes from the disease. We predict that people with a common pre-cancerous state called clonal hematopoiesis of indeterminate potential (CHIP) will be associated with worse outcomes from COVID-19. CHIP is more common in older populations (affecting more than 10% of people over age 70) and leads to an exaggerated inflammatory response, which may mean that people with CHIP have excessive inflammation in response to COVID-19. To test this, we will screen COVID-19 positive patients at UCI for CHIP to determine if they are more likely to have severe outcomes.

Supported by Kingston Technology

## Immunotherapy Combined with Stereotactic Ablative Radiotherapy for Patients With Advanced or Metastatic Sarcoma

Investigators

**Jeremy Harris, MD, MPhil,** *Department of Radiation Oncology,* School of Medicine
**Jennifer Valerin, MD, PhD,** *Department of Medicine—Hematology/Oncology,* School of Medicine
**Steven Seyedin, MD,** *Department of Radiation Oncology,* School of Medicine

In general, soft tissue and bone sarcomas are rare types of cancers that are aggressive and do not respond well to chemotherapy. Researchers have also tested the effectiveness of immunotherapy treatments for these types of cancers, but without much success.
By combining the immunotherapy drug pembrolizumab with a type of high-dose radiation therapy called stereotactic ablative radiation therapy (SABR), we hope to improve the effectiveness of immunotherapy for these patients. The goal of our study is to determine the early data needed to open a larger study at multiple University of California sites.

Supported by the Kong Family

## Targeted Therapy in Addition to Salvage Chemotherapy for Patients with Primary Refractory AML as a Bridge to Allogeneic Stem Cell Transplantation

Investigators

**Deepa Jeyakumar, MD,** *Department of Medicine—Hematology/Oncology,* School of Medicine
**Pamela Becker, MD, PhD,** *Department of Medicine—Hematology/Oncology,* School of Medicine
**Stefan Ciurea, MD,** *Department of Medicine—Hematology/Oncology,* School of Medicine
**Argyrios Ziogas, PhD,** *Department of Medicine — Epidemiology/Statistics,* School of Medicine

Patients with newly diagnosed acute myeloid leukemia (AML) who do not respond to initial chemotherapy have shorter survival rates. For these patients, the only option for long-term survival is to change chemotherapy (called “salvage”) successfully by undergoing a stem cell transplant from a suitably matched donor. This pilot study will examine the addition of an oral inhibitor targeting certain AML subtypes to a standard triple-drug salvage chemotherapy regimen to see if the combination is tolerable and effective. This study will also examine how well these patients are able to reach transplantation and the overall results of this approach.

Supported byTeam Benjamin & Wagner

## Sequential Systemic Therapy Plus Intraperitoneal Paclitaxel in Gastric/GEJ Cancer Peritoneal Carcinomatosis

Investigators
**Maheswari Senthil, MD,** *Department of Surgery,* School of Medicine
**Farshid Dayyani, MD, PhD,** *Department of Medicine—Hematology/Oncology,* School of Medicine

Gastric cancer is an aggressive cancer associated with a very high mortality rate. Over 30% of patients have stage IV cancer at the time of their diagnosis, due to the high predisposition of gastric cancer to spread to the lining of the abdominal cavity. This metastatic disease is called peritoneal carcinomatosis (PC). Intravenous chemotherapy alone is not sufficient to treat PC. We propose to use a combination approach in which, after a few months of intravenous chemotherapy, patients will be treated with chemotherapy instilled directly into the abdominal cavity. We believe that this combination approach, in addition to consolidation surgery in select patients, will improve survival rates for those with gastric PC.

Supported by the Kong Family

## Short-Course Radiation and TASOX (TAS102 Plus Oxaliplatin) Chemotherapy in Operable Rectal Cancer

Investigators
**Jason A. Zell, DO, MPH,** *Department of Medicine—Hematology/Oncology,* School of Medicine
**Joseph Carmichael, MD,** *Department of Surgery—Colon & Rectal Surgery,* School of Medicine
**M. Dorna Jafari, MD,** *Department of Surgery—Colon & Rectal Surgery,* School of Medicine
**Jeffrey Kuo, MD,** *Department of Radiation Oncology,* School of Medicine

In this early-phase clinical trial, locally advanced (stage II and stage III) rectal cancer patients will be treated with "short-course" radiation therapy followed by six two-week cycles (three months) of chemotherapy (TAS102 and oxaliplatin) before cancer surgery. This new treatment approach combines the inherent advantages of short course (five days vs. the conventional 5.5 weeks) radiation therapy with a novel combination of chemotherapy drugs that are already approved for advanced or post-surgical colorectal cancer, but not currently used in a pre-surgical setting. The primary measurement of effect will be patients' neoadjuvant rectal (NAR) score, a validated indicator of disease control in stage II and III rectal cancer. Positive results from this trial would lead to a comparison study of this new approach with conventional approaches for the treatment of operable rectal cancer.

## Radiogenomics-Guided Personalized Treatment for Hormonal Receptor Positive Metastatic Breast Cancer and Post-Neoadjuvant Chemotherapy Residual Disease

Investigators

**Lydia Min-Ying Su, PhD,** *Department of Radiological Sciences,* School of Medicine
**Rita Mehta, MD,** *Department of Medicine—Hematology/Oncology,* School of Medicine
**Ritesh Parajuli, MD,** *Department of Medicine—Hematology/Oncology,* School of Medicine
**Peter Chang, MD,** *Department of Radiological Sciences,* School of Medicine
**Daniel Chow, MD,** *Department of Radiological Sciences,* School of Medicine

Many women still die from breast cancer and one possible reason is that the conventional treatment given to patients is not sufficient. The development of targeted therapies, companion molecular/genomic tests and imaging are rapidly transforming the treatment landscape, and can be used to develop a novel radiogenomic strategy to improve treatment outcomes, survival and quality of life. These proposed studies are based on solid supporting evidence and novel technology proven feasible for clinical implementation. If successful, they could be applied to many other cancers. The preliminary results from this pilot project will be used to support the submission of two National Cancer Institute grant applications to demonstrate the feasibility of this radiogenomic research strategy for "precision oncology."

Supported by Monster Energy

## Personalized Therapeutic Cancer Vaccines to Effectively Mobilize Anti-Tumor T Cell Immunity in Non-Small Cell Lung Cancer

Investigators

**Christopher Hughes, PhD,** *Department of Molecular Biology and Biochemistry,* School of Biological Sciences
**Ali Mahtabifard, MD,** *Department of Surgery—Cardiothoracic Surgery,* School of Medicine
**Stephanie Hachey, PhD,** *Department of Molecular Biology and Biochemistry,* School of Biological Sciences

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the U.S. and is disproportionally prevalent in Orange County. We aim to address this disparity and unmet need by producing a cell-based immunotherapy tailored to each individual patient. Our goal is to generate personalized therapies that show greater efficacy than the current standard and that are capable of overcoming treatment resistance in NSCLC.

Supported by Team Grandma Marcia

# 2019 Track 1: Pilot Project Awards

## Novel Inhibitors of Phosphoinositide 3-Kinase (PI3K) That Target Scaffold Protein-Mediated Interactions

Investigators

**Lee Bardwell, PhD,** *Department of Developmental & Cell Biology,* School of Biological Sciences

**David Fruman, PhD,** *Department of Molecular Biology and Biochemistry,* School of Biological Sciences

**James Nowick, PhD,** *Department of Chemistry,* School of Physical Sciences

A potent, cancer-causing gene known as PIK3CA, is oneof the most frequently mutated genes in human cancer. The strategy of this basic science investigation is to interfere with the cellular location of the cancer-causing PIK3CA molecules, rather than inhibit the activity of all PIK3CA molecules in the cell. In this way, it may be possible to maintain efficacy, while limiting toxicity. Another goal is to develop new drug leads for targeting PIK3CA in this novel fashion.

## Melanoma Screening and Staging with a Fiber-optic Device

Investigators

**Per Niklas Hedde, PhD,** *Department of Biomedical Engineering,* Henry Samueli School of Engineering

**Enrico Gratton, PhD,** *Department of Biomedical Engineering,* Henry Samueli School of Engineering

**Anand Ganesan, MD, PhD,** *Department of Dermatology,* School of Medicine

Melanoma is one of the most difficult skin diseases to diagnose and it progresses quickly. A compact and inexpensive fiber-optic device, equipped with a flexible probe that allows examination of difficult-to-access regions of the skin, could help to reduce misdiagnosis of melanoma, the most aggressive and deadliest form of skin cancer. Once developed and tested, the proposed device would bring high-end optical screening methods to the patient to increase diagnosis accuracy, reduce time-to-result and cost, and help to avoid unnecessary surgery.

## Factors Associated with Helicobacter Pylori Screening and Treatment among High-Risk Asians in Orange County: Mixed-Methods Research to Examine Stomach Cancer Disparity

Investigator

**Sunmin Lee, ScD,** *Epidemiology,* Program in Public Health

Asians have unusually high incidence and mortality of stomach cancer, and helicobacter pylori (H. pylori) infection is known to be one of the strongest risk factors for stomach cancer. This study examines factors associated with H. pylori screening and treatment in the high-risk Asian population in Orange County. Findings from the study will be used to design a randomized, controlled study to increase H.pylori screening and treatment and, ultimately, reduce the burden of stomach cancer in the high-risk Asian population.

## Clock-dependent Inflammatory and Metabolic Alterations in Colorectal Cancer

Investigator

**Selma Masri, PhD,** *Department of Biological Chemistry,* School of Medicine

The internal biological clock controls sleep/wake cycles, feeding and metabolism. Disruption of the clock has been reported in several cancer types, including colon cancer. The precise process of clock disruption in colon cancer remains undefined. This research explores how the disruption can promote colon cancer by changing the cues that direct cancer-initiating cells. The goal is to identify new directions to pursue in the search for effective colon cancer prevention strategies that may involve alleviating disruption of circadian rhythms.

## The Burgeoning Cannabis Industry and Availability of Cheap Tobacco in Orange County

Investigator

**David Timberlake, PhD,** *Epidemiology,* Program in Public Health

Smoking is linked to about 80 percent of lung cancer deaths. This project seeks to assess whether the availability and marketing of tobacco products such as cigarillos, blunt wraps and cigar wraps, which are popular among cannabis users, increased as a result of the legalized sales of cannabis for recreational use. The first aim is to assess whether Orange County tobacco retailers, who did not sell these tobacco products in 2016, began to carry them when nearby dispensaries started selling cannabis for recreational use. The second aim is to collect cannabis-themed marketing data from the same tobacco retailers. If the tobacco retailers near cannabis dispensaries now market cigarillos and blunt/cigar wraps with cannabis references, then findings from this project could inform authorities in Orange County about the need for advocating for tobacco regulations such as a minimum pack size for cigarillos.

## Restoring p53 Activity in Human Cancer

Investigators
**Feng Qiao, PhD,** *Department of Biological Chemistry,* School of Medicine
**Peter Kaiser, PhD,** *Department of Biological Chemistry,* School of Medicine

P53 is the most frequently mutated protein in human cancers. Each year, in the US alone, about 600,000 new cancer patients are diagnosed with tumors carrying p53 cancer mutants, which are particularly aggressive and hard to treat. High percentages of ovarian cancers, triple negative breast cancers, pancreatic cancers and lung cancers depend on p53 hotspot mutations. Thus, p53 cancer mutations present an exceptionally attractive therapeutic target. This project seeks to advance approaches to pharmaceutical reactivation of the body's own anti-tumor mechanism, the tumor suppressor protein p53. Pharmaceutical reactivation of mutant p53 in cancer could be truly transformative.

## Dissecting MAP4K Kinases in Cancer Development and Therapy

Investigator
**Wenqi Wang, PhD,** *Department of Developmental and Cell Biology,* School of Biological Sciences

Cancer cells are prone to survive when exposed to extremely stressful conditions including nutrient deprivation, hypoxia, oxidative stress and chemotherapy. Cancer cells are able to take advantage of a physiological process known as autophagy to get around these stresses and fulfill the high metabolic and energetic demands of cell proliferation. Targeting autophagy in advanced cancers shows promising anti-cancer effects; therefore, elucidating the regulation of autophagy can lead to the development of novel therapeutic strategies for cancers. In this pilot project, we dissect a novel metabolic stress signaling that is centered on MAP4K2 and perform a translational study by taking the MAP4K2-autophagy signaling as a target in cancer therapy.

## Developing the Next-Generation Antibody Drug Conjugates

Investigators
**Gregory Weiss, PhD,** *Department of Chemistry,* School of Physical Sciences
**Gultekin Gulsen, PhD,** *Department of Radiological Sciences,* School of Medicine
**Daniela Bota, MD, PhD,** *Department of Neurology,* School of Medicine

Antibody-drug conjugates (ADCs) leverage the high specificity of an antibody to act as a molecular global positioning system combined with the potent anti-cancer activity of an attached cytotoxic drug. Highly effective in the clinic against several cancers, ADCs are valued for their favorable safety profiles in comparison to traditional chemotherapy. However, conventional methods for synthesizing ADCs result in random attachments of drug to antibody, reducing the ADCs' medicinal properties. This project explores a new chemical reaction to more selectively and effectively install drugs on antibody surfaces. The project also aims to create a new class of multi-functional ADCs carrying several small molecules to tumors for simultaneous imaging and treatment, an approach sometimes termed theranostics.

# 2019 Track 2: Early-Phase Clinical Trials

## Phase 2 Study of Cabozantinib Combined with Ipilimumab/Nivolumab and Transarterial Chemoembolization (TACE) in Patients with Hepatocellular Carcinoma (HCC) Who Are Not Candidates for Curative Intent Treatment

Investigators

**Farshid Dayyani, MD, PhD,** *Department of Medicine-Gastroenterology,* School of Medicine

**Nadine Abi-Jaoudeh, MD,** *Department of Radiological Sciences,* School of Medicine

Cancers of the liver are relatively rare in the U.S. Nonetheless, due to their deadly nature, they are among the top five causes of cancer-related deaths in the U.S. When liver tumors grow to more than one to two inches, or when there are more than three tumors in the liver, surgery or transplant is no longer possible. At this point, the goal of treatment is to prolong survival.

Historically, local liver-directed treatment was the only available standard offering some tumor control. Most cancers recurred in less than a year. Advanced liver cancer has a survival of about 10 to 12 months, despite all the new drug developments. Improving patient survival means identifying effective treatment at an earlier stage, before the cancer recurs and spreads beyond the liver.

This project combines standard liver-directed therapy using TACE (transarterial chemoembolization) with a novel combination of dual-immunotherapy drugs (nivolumab and ipilimumab), plus a small molecule inhibitor (cabozantinib). This disrupts vital survival pathways in liver cancer cells and their surrounding stroma (non-cancerous cells that actively support the growth of cancer cells by providing nutrition and suppressing the body's immune system).

This study represents a powerful multipronged approach to attacking liver cancer from multiple angles, with the goal being to minimize resistance and thus maximize tumor shrinkage and long-term survival. The results could establish a new liver cancer treatment option with unprecedented efficacy.

## A Randomized Clinical Trial to Assess the Impact of a Remotely Administered Mediterranean Diet Intervention on Symptom Burden and Inflammatory Cytokines in Myeloproliferative Neoplasm

Investigators

**Angela Fleischman, MD, PhD,** *Department of Medicine-Hematology/Oncology,* School of Medicine

**Michael Hoyt, PhD,** Program in Public Health

**Andrew Odegaard, PhD, MPH,** *Epidemiology,* Program in Public Health

Myeloproliferative neoplasm (MPN) is an incurable blood cancer, with severe symptoms that are driven by inflammation. A Mediterranean diet reduces inflammation in other diseases, but hasn't been studied in blood cancers. This is a large, internet-based study to test whether a Mediterranean diet reduces symptoms and inflammation in MPN patients.

## Goal-Directed Intervention for Adolescent Cancer Survivors

Investigators

**Michelle Fortier, PhD,** Sue & Bill Gross School of Nursing
**Michael Hoyt, PhD,** Program in Public Health
**Lilibeth Torno, MD,** *Pediatric Oncology,* CHOC Children's

Having cancer can disrupt an adolescent's ability to identify and accomplish life goals. Evidence consistently shows that adult survivors of childhood cancer have lower educational and occupational achievement than their peers. A previously developed intervention known as Goal-focused Emotion-regulation Therapy (GET) was designed to help young adult cancer survivors pursue goals following cancer treatment. This intervention is being adapted for the adolescent cancer population to improve their emotional, physical, educational and occupational functioning after completing cancer treatment.

## Pilot Study for Evaluating the Multiphoton Microscopy Potential for Non-Invasive, Early Diagnosis of Melanoma

Investigators

**Kristen Kelly, MD,** *Department of Dermatology,* School of Medicine
**Mihaela Balu, PhD,** Beckman Laser Institute & Medical Clinic

This pilot project evaluates the potential of an optical imaging technology for non-invasive diagnosis of melanoma. The instrument used in this study was developed at the UCI Beckman Laser Institute & Medical Clinic. It enables rapid acquisition of images with sub-cellular resolution from unprecedented large volumes of lesions. This study is intended to provide key preliminary data that would strengthen an application for funding a clinical trial to evaluate whether the imaging technology can diagnose melanoma more accurately by detecting it early and also reduce the number of unnecessary biopsies.

## Neoadjuvant Combination Therapy with Cabozantinib and Nivolumab in Patients with Muscle-Invasive Urothelial Carcinoma of the Bladder Who Are Cisplatin-Eligible and Are Candidates for Radical Cystectomy

Investigators

**Natallya Mar, MD,** *Department of Medicine-Hematology/Oncology,* School of Medicine
**Edward Uchio, MD, FACS,** *Department of Urology,* School of Medicine

Standard-of-care treatment for non-metastatic bladder cancer consists of up-front chemotherapy, followed by surgical removal of the bladder, or cystectomy. Due to multiple possible side effects of chemotherapy, and in an effort to improve treatment effectiveness, multiple studies replacing chemotherapy with alternative treatments are underway. This is a study of the use of cabozantinib and nivolumab in patients with non-metastatic bladder cancer, with treatment administered for 12 weeks prior to cystectomy. The study examines the efficacy and safety of this drug combination, as well as analyze the genetic and molecular characteristics of tumors from participating patients.

## Feasibility of a Biobehavioral Intervention to Reduce Adverse Outcomes in Young Adult Hispanic Men with Testicular Cancer

Investigators

**Michael Hoyt, PhD,** Program in Public Health

**Lari Wenzel, PhD,** *Department of Medicine,* School of Medicine

Many young adult cancer survivors experience adverse outcomes that persist long after completion of primary medical treatment. These outcomes might include psychological distress and poor psychosocial adjustment, impaired ability to navigate and pursue life goals, persistent treatment side effects, elevated risk of secondary malignancies and chronic illness, or biobehavioral burdens such as enhanced inflammation or dysregulated diurnal stress hormones. Hispanic/Latino young men are at heightened risk for such adverse outcomes. Yet few targeted, culturally tailored interventions exist to help this group renegotiate life goals and regulate cancer-related emotions. None focus on reducing the burden of morbidity via biobehavioral mechanisms.

This study explores the feasibility of Goal-focused Emotion Regulation Therapy (GET) to improve depressive symptoms as well as emotion regulation, goal attainment skills, and career confusion in Hispanic/Latino young adult testicular cancer patients. It is designed to assess whether GET is associated with reductions in biological markers of stress and inflammation. And it looks at whether cultural processes (i.e., familism, simpatia, machismo/caballerismo, acculturation/acculturative stress) underlie change.

## Pilot Study of the Safety and Feasibility of Immediate Postoperative Chemotherapy in Patients with Metastatic Invasive Colonic Adenocarcinoma

Investigators

**Mehraneh Dorna Jafari, MD,** *Department of Surgery-Colon and Rectal Surgery,* School of Medicine

**Alessio Pigazzi, MD, PhD,** *Department of Surgery-Colon and Rectal Surgery,* School of Medicine

**Jason Zell, DO, MPH,** *Department of Medicine-Hematology/Oncology,* School of Medicine

**Weian Zhao, PhD,** Program in Pharmaceutical Science

Many metastatic colon cancer patients choose not to have their tumor removed because they fear the risks of stopping chemotherapy for surgery. This can lead to major complications with the colon tumor; complications that may lead to the same thing they fear the inability to receive chemotherapy. This study explores a protocol that allows the tumor to be safely removed without delaying chemotherapy. It allows for the administration of systemic treatments at the time of tumor resection. The hypothesis is that this will eliminate chemotherapy delays and tumor complications, ultimately leading to improved cancer survival.

# 2018 Track 1: Pilot Project Awards

## A Mechanistic Study of Age-Dependent Gender Difference in Melanoma Risk

Investigator

**Feng Liu-Smith, PhD,** *Department of Epidemiology*

The incidence of melanoma continues to increase despite extensive public advocacy for decreasing exposure to harmful ultraviolet (UV) radiation from sunlight. A better understanding of melanoma risks and new prevention methods are therefore needed. Our long-term goal is to develop effective melanoma prevention strategies based on a comprehensive understanding of UV and non-UV melanoma risk factors, and to establish a melanoma center with integrated epidemiological and molecular databases for prevention, treatment and research. In this study, we propose to examine a two-sided mechanism of melanoma development based on better understanding age- and gender-specific melanoma risks at both the population and basic science levels. If our hypothesis and model are proven correct, we should be able to change the current paradigm of melanoma prevention and add new elements based on hormone levels and gender-based genetic variants.

## UHRF1 as a Therapeutic Target for Osteosarcoma

Investigator

**Claudia Benevente, PhD,** *Department of Pharmaceutical Sciences*

Metastasis remains the most significant complication of osteosarcoma, a childhood cancer of the bone. Among the patients who develop metastasis, less than 1 in 5 survive. Thus, there is a pressing clinical need to determine how these tumors metastasize in order to develop new therapeutic strategies. We identified UHRF1 as a protein highly expressed in osteosarcoma and which appears to be critical for osteosarcoma growth and metastasis. This project will further our understanding of UHRF1 in tumor formation and metastasis and will evaluate its potential as therapeutic target for anti-cancer treatment. Given that UHRF1 is highly expressed in multiple cancers, this research proposal has the potential to impact human health beyond osteosarcoma.

## Molecular Mechanism of APOBEC3B-Mediated Mutation Shower in Ovarian Cancer

Investigator

**Rémi Buisson, PhD,** *Department of Biological Chemistry*

In 2018, more than 22,000 women were diagnosed with ovarian cancer in the U.S., and such patients are typically treated with chemotherapy after surgery. However, about half of these patients will develop resistance to the chemotherapy drugs and will ultimately succumb to their disease, motivating the search for alternative treatments. APOBEC3B (A3B) is a major driver of mutations in ovarian cancer that promote cancer progression and drug resistance. By directly attacking DNA and increasing genomic instability, A3B creates a vulnerability that can be exploited to develop new targeted therapies. The goal of this project is to determine how A3B generates mutations in patients with ovarian cancer and to develop novel strategies to specifically target A3B-expressing cancers. Determining the function and regulation of A3B is crucial in resolving the fundamental mechanism through which ovarian cancer cells accumulate mutations, increase genomic instability, and develop resistance to current therapies.

## Control of B-cell Survival & Transformation by the eIF4F Translation Initiation Complex

Investigator

**David Fruman, PhD,** *Department of Molecular Biology & Biochemistry*

Each year, approximately 20,000 people in the U.S. die from B-cell lymphomas and 100, 000 more cases are diagnosed. Progress in treating these patients has been fueled by basic research on the signaling mechanisms of B cells, a type of immune system cell. The goal of this project is to advance the field of B cell tumor biology through increased mechanistic knowledge of the mRNA translation initiation complex known as eIF4F. The project will address an urgent need to develop new mouse models to define the function of eIF4F components in normal B cells and B-cell tumors, an effort that will have substantial positive impact on development of therapeutic approaches targeting mRNA translation.

## Advancing Oro-Pharyngeal Cancer Screening and Diagnosis to Overcome Disparities and Improve Control and Outcomes

Investigator

**Petra Wilder-Smith, DDS, PhD,** Beckman Laser Institute

Worldwide, 223,000 deaths occur annually from oral and oropharyngeal cancer (OC). Another 650,000 cases are diagnosed. The mean 5-year survival rate in the U.S. for OC it is approximately 50% and has not improved in decades. The goal of this project is to reduce the pain, suffering and deaths associated with oral and oropharyngeal cancer, which is typically detected only after it has spread. Late diagnosis and treatment are the main cause for the limited treatment options and unusually high mortality of OC. As low-resource and underserved populations have the highest rates of OC in the U.S., our very low cost artificial intelligence-enabled smartphone approach for detecting early and managing OC is specifically designed to be used by community workers or other non-specialist individuals in remote, community or even home settings.

## Macropinocytosis Drives Anabolism and Drug Resistance in Breast Cancer

Investigator

**Aimee Edinger, DVM, PhD,** *Department of Developmental & Cell Biology*

Cancer cells require a steady stream of nutrients to support their unchecked growth. The bloodstream supplies tumor cells with nutrients, but many cancer cells supplement their diet by feeding on the corpses of nearby dead cells using a process called “macropinocytosis.” This pilot project proposal will test whether attacking and disabling these “supply wagons” could be an effective strategy to fight cancer. Preliminary studies suggest that blocking this ghoulish behavior with macropinocytosis inhibitors will shrink tumors by starving cancer cells. Corpse-feeding also makes tumor cells resistant to radiation and chemotherapy; blocking macropinocytosis could make these standard therapies more effective and limit the development of tumor resistance.

## Single-Cell Transcriptome Analysis of Human Merkel Cell Carcinoma Heterogeneity by Single-Cell RNA Sequencing

Investigator

**Ling Gao, MD, PhD,** *Department of Dermatology*

Merkel cell carcinoma is a highly malignant skin cancer with no effective treatment, despite recent advances in immunotherapy. We plan to use novel biotechniques such as droplet-based single cell RNA sequencing to elucidate gene expression patterns in this type of tumor at the level of individual cancer cells. This work will help develop insights into distinctive biological differences found in MCC tumors and develop new drugs to treat this devastating cancer.

## DNA Methylation Markers for Exposures to BPA and Related Compounds and Breast Cancer Risk

Investigator

**Hannah Park, PhD,** *Department of Epidemiology*

Bisphenol A (BPA) and its related compounds, BPF and BPS, are commonly used in plastics and are thought to be potential endocrine disruptors that may play a role in development of breast cancer and other hormone-related cancers. However, the relationship between BPA/BPF/BPS exposure and cancer risk has not been adequately studied. We propose to identify biomarkers that can be used in both previous and future large epidemiologic studies to study the potential link between BPA/BPF/BPS exposure and cancer risk. These markers may improve risk prediction for cancer and other diseases that may have an environmental component.

## True Multi-Modal Image-Guided Intervention System

Investigator

**Farouk Nouizi, PhD,** *Department of Radiology*

Tumor vasculature is a critical component of the tumor microenvironment and is essential for tumor growth and metastasis. Both tumor growth and high dose radiation therapy can decrease tumor blood flow and cause hypoxia, which can affect chemotherapy drug delivery and make the tumors less sensitive to radiation. We have built a first-of-its-kind compact multimodality theranostic instrument by incorporating Fluorescence Molecular Imaging (FMI) into a highly focused radiation system (X-ray SmART, Precision X-ray Inc.) for use in preclinical cancer studies in mouse tumor models. In this project, we will test whether FMI can not only guide the radiation therapy but also provide unique molecular information about the tumor microenvironment and the outcome of radiotherapy.

## Role of Phosphatase Methylation in One-Carbon Metabolism and Cancer

Investigator

**Peter Kaiser, PhD,** *Department of Biological Chemistry*

Numerous studies have shown that most cancer cells and tumors, independent of tissue origin, are highly sensitive to reduced availability of the amino acid methionine. Exploitation of this metabolic Achilles' heel of cancer has been hampered by the lack of molecular understanding of this metabolic dependency of cancer and the lack of biomarkers to monitor efficiency of interventions that lower available methionine. This proposal aims to develop such an understanding and will evaluate potential biomarkers.

# 2018 Track 2: Early-Phase Clinical Trials

## A Phase 1 Study of Pitavastatin in Combination with Venetoclax for Chronic Lymphocytic Leukemia (CLL) or Acute Myeloid Leukemia (AML)

Investigator

**Elizabeth Brém, MD,** *Division of Hematology-Oncology, Department of Medicine*

Venetoclax is the first FDA-approved medication in a class of drugs called BH3 mimetics. It is a once-a-day oral medication that is approved for 2 kinds of leukemia—chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). A class of medicines called statins are used commonly to lower cholesterol, and studies in cell culture and in mice demonstrate that statins improve the ability of venetoclax to kill leukemia cells. In this project, we will launch a first-in-human clinical trial to determine what dose of a statin called pitavastatin to use in combination with venetoclax and make sure the combination is safe, as the basis for launching future clinical trials to determine efficacy.

## A Phase 1b Study of TAS102 in Combination with Irinotecan in Patients with Advanced Gastric and Gastroesophageal Adenocarcinoma

Investigator

**Farshid Dayyani, MD,** *Division of Hematology-Oncology, Department of Medicine*

Cancers of the stomach and lower esophagus are relatively rare in the U.S., but are globally among the top five causes for cancer-related death, and also disproportionately affect the Asian-American and Hispanic residents of Orange County. When the disease has spread to other organs, surgery is no longer possible. Thus, the goal of treatment is not cure, but rather to prolong survival. However, current available treatments result in an estimated survival of only about a year after a patient is diagnosed with advanced stomach cancer. The proposed study will combine two chemotherapy drugs, irinotecan and TAS102, in order to determine whether this combination is active in patients with stage 4 stomach cancer after their cancer has become resistant to standard chemotherapy. The results could establish a new effective treatment option for this highly aggressive disease.

## Experimental Therapeutics for Primary Pediatric Brain Tumors

Investigator

**Ashley Plant, MD,** *Department of Pediatrics*

Pediatric brain tumors are the second most common cancer in children and account for the majority of cancer-related deaths. The outcome for children with malignant brain tumors has changed very little over the past 35 years. Here, we propose to create a translational research platform that allows us to rapidly screen a large number of drug compounds on brain tumor tissue from patients undergoing surgery at Children's Hospital Orange County. We will use cell cultures and animal models to test various novel, targeted therapies on the tumor cells with the goal of moving those drug compounds that are thought to be effective against these tumors into clinical trials for our patients.

## Improving Depression Screening in a Multi-Ethnic Cancer Population

Investigator

**Lari Wenzel, PhD,** *Department of Public Health*

Cancer patients experiencing depression may have worse health outcomes than those who are not experiencing depression. However, screening and referrals for depression in the oncology setting are uneven, and not adequatelyaddressed. The purpose of this pilot project is to assess, via oncology team surveys, the current clinical climate among providers with respect to depression screening and referrals at UCI and UCSF. The results will inform our capacity to develop and test an efficient and novel mechanism to screen for depressive spectrum disorders among cancer patients, thereby ultimately improving cancer-related outcomes.

## The Relationship between the Gut Microbiome and the Efficacy of Immune Checkpoint Inhibitors in Patients with Gynecologic Malignancy

Investigator

**Krishnansu Tewari, MD,** *Division of Gynecologic Oncology*

Immune checkpoint inhibitors (ICI) are a new type of cancer therapy that enhance the ability of the immune system to recognize and attack cancer cells. Despite the recent widespread usage of ICI therapy, a majority of patients still do not respond to this therapy. One reason for poor response may be differences in the gut microbiome, which is the unique set of bacteria and other microorganisms that colonize our intestines. Studies have shown that the gut microbiome is closely related to overall immune system function and that changes in immune system function can impact the effectiveness of ICI. The goal of this study is to study the gut microbiome in patients with gynecologic cancers being treated with ICI to identify which bacteria may be associated with better responses to therapy.

# 2017 Track 1: Pilot Project Awards

## Glutamine Supplementation Deters Melanoma Tumor Growth Via Epigenetic Reprogramming

Investigator

**Mei Kong, PhD,** *Department of Molecular Biology and Biochemistry*

Recent studies indicate that in some tumors, including melanoma skin cancers, levels of the amino acid glutamine are abnormally low, leading to changes in gene methylation and expression and resulting in resistance to therapy with inhibitors targeting the kinase BRAF. Dr. Kong will determine whether dietary glutamine supplementation will inhibit the growth of patient-derived melanoma tumors in mice, and investigate the molecular mechanisms involved.

## Repurposing Statins to Enhance Efficacy of BH3 Mimetics in Multiple Myeloma

Investigators

**David Fruman, PhD,** *Department of Molecular Biology & Biochemistry*

**Elizabeth Brem, MD,** *Department of Medicine, Division of Hematology Oncology*

Venetoclax (Venclexta®) is a member of new class of drugs known as BH3 mimetics that induce cell death in tumor cells, particularly cancers of B-lymphoid cells. Work in Dr. Fruman's laboratory has shown that the lipid-lowering statin medications increase the ability of BH3 mimetic drugs to kill cancer cells from patients with chronic lymphocytic leukemia and non-Hodgkin B-cell lymphoma. Dr. Fruman will collaborate with hematologist/oncologist Dr. Brem to extend these studies to multiple myeloma, a currently incurable cancer of antibody-producing mature B cells.

## Circadian Metabolic Deregulation of Colorectal Cancer

Investigator

**Selma Masri, PhD,** *Department of Biological Chemistry*

Our biological clock (circadian rhythm) controls many physiological processes in our bodies and has also been linked to cancer development and growth, but the mechanisms are poorly understood. Dr. Masri's laboratory has generated a novel mouse model to elucidate the effects of circadian clock disruption on intestinal cell proliferation and colorectal cancer. Her preliminary analysis identified a central role of metabolism as a key feature of cellular proliferative control. The focus of this research will be to define the contribution of deregulated circadian metabolism that is responsible for influencing growth and survival pathways in the intestine.

## Immunotherapeutics Targeting Altered N-glycosylation in Cancer

Investigator

**Michael Demetriou, MD, PhD, FRCP,** Department of Neurology and Microbiology and Molecular Genetics

T-lymphocytes from patients with cancer that are engineered to identify and kill tumor cells (so-called CAR-T cells) are a promising new approach to cancer therapy, but the technology has been difficult to apply to common cancers like breast, colon, and lung cancer. Dr. Demetriou's laboratory has developed a chimeric protein that recognizes abnormal carbohydrate antigens expressed exclusively on a diverse array of cancer cells. This proposal will optimize the design and test this approach in a mouse cancer model, with the potential of developing an entirely new class of immunotherapeutic agents for cancer.

## Identifying the Anti-neoplastic Targets of SH-BC-893

Investigator

**Aimee Edinger, PhD,** Department of Developmental & Cell Biology

Dr. Edinger's laboratory has developed a novel set of drugs that have broad anti-cancer properties by affecting nutrient pathways and the trafficking of certain growth-modulatory proteins through the cell nucleus. This proposal will investigate potential molecular targets of this class of drugs and determine the mechanism of the anti-cancer effects. These results will be important in the effort to move these agents into human clinical trials.

## Analysis of Hippo Signaling in Breast Cancer Development

Investigator

**Wenqi Wang, PhD,** Department of Developmental & Cell Biology

Dysregulation of the Hippo signaling pathway and overexpression of its downstream effector YAP are associated with a broad spectrum of cancers. Previous studies from Dr. Wang's laboratory have demonstrated a crucial role of YAP in breast cancer development through its ability to transform normal mammary epithelial cells, accelerate breast cancer cell proliferation and survival, maintain breast cancer stem cells, and promote breast cancer metastasis. This proposal will determine if breast cancer cells are "addicated" to YAP, and develop approaches to target activated YAP for breast cancer therapy.

## Feasibility of a Family Focused Intergenerational Social Media Intervention for Orange County Vietnamese Families to Increase Preventive Cancer Screenings

Investigator

**Suellen Hopfer, PhD,** Program in Public Health

Orange County's large Vietnamese community has historically lower rates of screening for cancer. Effective intergenerational communication with an upstream and interactive flow of preventive cancer information in the context of group family chats has been shown to be effective in improving cervical cancer screening in such communities. This study will identify effective intergenerational messaging for online, family focused social media platforms that are designed to increase breast, cervical, colorectal, and liver cancer screening behaviors among first and 1.5 generation Vietnamese community members.

## RhoJ Inhibitors — A Novel Treatment for Early Stage Melanoma

Investigator

**Anand K. Ganesan, MD, PhD,** Department of Dermatology and Biological Chemistry

While kinase inhibitors and immunotherapies are effective at treating metastatic melanoma, their use in tumors that have not yet disseminated systemically is limited by their side effects. The Ganesan laboratory previously determined that RhoJ, a gene highly expressed in BRAF mutant melanomas that metastasize to lymph node, promotes both the growth and metastasis of melanoma tumors in a mouse model. Here, they will test the efficacy of novel compounds that inhibit RhoJ function as anti-cancer agents against melanoma and other RhoJ-expressing cancers.

## Modulation of the Immune Response Against Metastatic Melanoma Using CD47 Blocking Antibodies

Investigator

**Alexander Boiko, PhD,** Department of Molecular Biology and Biochemistry

Studies in the Boiko laboratory have shown that metastatic melanomas frequently express CD47, a cell surface protein that sends a "don't eat me" signal to macrophages, protecting the tumor from the immune response. This project will test characterize the therapeutic potential of CD47–blocking antibodies in a novel immune-competent mouse model bearing human melanoma tumors.

# 2017 Track 2: Early-Phase Clinical Trials

## Pilot Study of Mirtazapine for the Dual Treatment of Depression and Temozolomide-induced Nausea and Vomiting in Newly-diagnosed Glioma Patients

Investigators

**Daniela Bota, MD, PhD,** Department of Neurology
**Thomas Taylor, PhD,** Department of Epidemiology
**Charles Nguyen, MD,** Department of Psychiatry
**Robert Bota, MD,** Department of Psychiatry

Patients with brain cancer (glioblastoma) suffer frequently from depression, as well as nausea and vomiting induced by their chemotherapy. Mirtazapine is a antidepressant drug with anti-nausea properties, but its safety and efficacy in brain cancer has not been studied. This project is a single institution clinical study of the efficacy and tolerability of mirtazapine when administered to depressed glioma patients, aimed at reducing depression and nausea, and maintaining patient weight.

## Pilot Study of the Safety and Feasibility of Immediate Adjuvant Chemotherapy in Patients with Invasive Colonic Adenocarcinoma

Investigator

**Alessio Pigazzi, MD, PhD,** Department of Surgery

Patients with stage III colon cancer (with lymph node involvement) should receive adjuvant chemotherapy after surgical resection of the primary tumor, but delays in delivering chemotherapy may lead to the development of distant metastases. This proposal will determine the feasibility, safety and tolerability of chemotherapy that is started in the immediate preoperative period, and study effects on circulating tumor cells, which may mediate spread of the cancer.

## Feasibility Study of a Mediterranean Diet Intervention to Reduce Inflammatory Cytokines in Patients with Myeloproliferative Neoplasms

Investigators

**Angela Fleischman, MD, PhD,** Department of Medicine, Division of Hematology Oncology
**Andrew Odegaard, PhD, MPH,** Department of Epidemiology
**Lari Wenzel, PhD,** Department of Medicine and Program in Public Health

Patients with myeloproliferative neoplasms (MPNs) such as polycythemia vera and myelofibrosis have symptoms (weight loss, fatigue) due to increased inflammation and circulating inflammatory cytokines. Dr. Fleischman and her colleagues in UCI Department of Epidemiology and Program in Public Health will test whether a reduction in inflammatory cytokines brought about by adherence to a Mediterranean diet will alleviate disease-related symptoms and also delay disease progression in MPN patients.