**David Lawrence, PhD**
**Tier 2 Chemistry Proposal**

**Photochemotherapy**

**Abstract:**
The use of light to activate therapeutic agents at diseased sites offers the advantage of aggressive treatment with exquisite spatial and temporal control, hereby reducing potential deleterious side effects at unintended sites. Although photo-activated pro-drugs have been reported, these species require short wavelengths (<450 nm) for activation. However, maximal tissue penetrance by light occurs within the "optical window of tissue" (600 –900 nm),well beyond the wavelength range of existing photo-cleavable functional groups. We've developed (Lawrence Lab) a new technology that can transform virtually any drug into a phototherapeutic while providing the means to assign specific wavelengths for the release of specific drugs from a carrier. Furthermore, we've developed (Dayton Lab) a new technology (Acoustic Angiography)for imaging blood flow, microvasculature, and molecular markers using ultrasound and microbubble contrast agents. The proposed research program seeks to combine these state-of-the-art drug delivery and imaging technologies to reengineer and subsequently image the tumor neovasculature as it is remodeled for therapeutic purposes. Erythrocytes will be used as the carrier for delivering vascular modulating agents, since red blood cells are biocompatible and enjoy a long circulation lifetime (up to four months). The collaborative arrangement between the Lawrence and Dayton labs is new and could potentially prove to be transformative in cancer chemotherapy and photo-surgery. The proposed animal studies are critical for acquiring future financial support for this unfunded research program as well as for generating pre-clinical data for potential commercialization.

**Marcey Waters, PhD**
**Tier 2 Chemistry Proposal**

# Development of Stapled Peptide Inhibitors of the MBD2-NuRD Interaction to Target DNA Methylation Dependent Gene Silencing

## Abstract

The long-term objectives of this research are to characterize the structural details of the MBD2-NuRD complex and develop inhibitors that disrupt complex formation and block methylation dependent gene silencing by MBD2. This complex is involved in the silencing of embryonic/fetal globin genes and is associated with genetic silencing of hypermethylated tumor suppressor genes in cancer. In studying the molecular details of the MBD2-NuRD complex, the structure of the coiled-coil domain from MBD2 in complex with a coiled-coil domain from p66α has been solved by NMR. Based on this work, it has been shown that in vivo expression of the p66α coiled-coil can disrupt the native MBD2-NuRD and reverse MBD2 dependent silencing. This result indicates that specifically targeting the MBD2-p66α coiled-coil can block MBD2 function, making this a potential therapeutic strategy for treating both β-hemoglobinopathies and cancer. Building on this proof-of-principle experiment, we propose to develop stapled, protease resistant, and cell permeable p66α peptides that can inhibit the MBD2-p66α interaction in vitro and intracellularly, as well as the necessary assays to characterize the localization and activity of these peptides in cells. A novel library screening approach is proposed to rapidly identify effective inhibitors. This molecular probe will provide a powerful new tool to investigate the effects of this interaction on complex formation and gene silencing in the chromatin environment of cells, and how this MBD2-p66α sub-complex interacts with other components of the intact NuRD.

**Carey K Anders, MD**
**Tier 2**
**Clinical Translational Science Proposal**

# Dissecting the biology of breast cancer brain metastases

**Abstract:**
Breast cancer brain metastases (BCBMs) are a burgeoning clinical problem associated with poor prognosis and no approved systemic therapy. The current standard of care to treat BCBM is neurosurgical resection and/or radiation therapy; however, intracranial disease recurrence is inevitable, often in the face of progressive extracranial disease. Patients with triple negative breast cancer (TNBC), classified as basal-like by molecular-profiling, and those with HER2-positive breast cancer commonly recur within the brain. Systemic therapies to control both intracranial and extracranial disease are urgently needed. Identifying the underlying biology driving metastasis, and in particular BCBMs, is critical to the development of effective anti-cancer agents to both prevent and treat metastases; such a study has yet to be performed in human tissues with matched primary breast cancers and brain metastases. We propose a genome-wide approach harnessing high-throughput DNA whole exome sequencing to study point mutations and copy number variations in matched primary tumors, brain metastases, and non-brain metastases using surgically-resected human tumor tissues to make the following comparisons: (1) primary breast cancer or non-brain metastases to matched brain metastasis from the same patient to define brain metastasis-specific alterations; (2) primary breast cancers that metastasizes versus those that do not metastasize to the brain, identifying markers for increased risk of brain metastases. This proposal provides a novel direction for our laboratory, and expected results will undoubtedly lead to new hypotheses to foster future extramural funding. Ultimately, we hope to identify novel therapeutic targets to exploit in the prevention and treatment of breast cancer brain metastases.

**Jeannette Bensen, MS, PhD**
**Tier 2**
**Population Science Proposal**

**Understanding the relationship between environmental inorganic arsenic and prostate cancer**

**Abstract:**
Prostate cancer (CaP) is the most common cancer and the second leading cause of cancer death among US men. There is clear racial disparity, with African Americans (AA) having substantially higher CaP incidence and mortality than European Americans (EA). We hypothesize that environmental exposures to arsenic are linked to CaP, an understudied and likely significant relationship that may underlie racial disparity. Toxic metals such as arsenic typically consumed through drinking water are known carcinogens linked to CaP, yet little is known about the role of arsenic in CaP aggressiveness especially among understudied groups such AA. Men participating in the North Carolina-Louisiana Prostate Cancer Project (NC-LA PCaP), 50% of whom are AA, have clinically and epidemiologically annotated stored urine specimens and are ideally suited to address this question. We will be the first to describe arsenic exposure in men with CaP and to quantitatively assess the association of arsenic and influence of race in men well-characterized for CaP aggressiveness. This research also brings together a strong interdisciplinary team to inform identification of high-risk exposure groups and improve understanding of arsenic dosage and influence on cancer.

**William Kim, MD**
**Tier 2**
**Clinical Translational Science Proposal**

# Combinatorial mTOR / SRC inhibition overcomes acquired everolimus resistance

**Abstract:**
Approximately 65,000 new cases of renal cell carcinoma (RCC) occur annually in the United States, and its incidence is on the rise. Clear cell RCC (ccRCC) is the most common histologic subtype. While ccRCC is notoriously resistant to cytotoxic chemotherapy, a better understanding of the molecular biology underlying RCC has led to the development of targeted therapies for these tumors, which can be broadly grouped into VEGFR and mTOR inhibitors. While mTOR inhibition prolongs survival, the actual tumor response rate is only 5% suggesting robust resistance mechanisms. We have found that mTOR inhibition results in upregulation of cytokines, which we have termed “cytokine reprogramming” and upregulates the TYK2/SRC pathway to promote acquired resistance to mTOR inhibitors. The proposed studies will comprehensively characterize mTOR inhibitor induced cytokine reprogramming as well as the therapeutic value of combinatorial targeting of mTOR and SRC using a novel genetically engineered mouse model of ccRCC. In aggregate, our studies explore the innovative concept of cytokine reprogramming and define a mechanism of resistance to mTOR inhibition, both of which have immediate clinical applicability.

**Chad Pecot, MD**
**Tier 2**
**Basic Science Proposal**

**Fate-Mapping Cancer Cells from Lymph Nodes to Uncover Novel Metastatic Biology**

**Abstract:**
Distant metastases account for 90 percent of cancer-related deaths, yet the fundamental mechanisms governing this process remain poorly understood. As a result, very few therapeutic agents that directly inhibit metastatic biology exist. Although nearly all cancers can spread to lymph nodes, the direct role lymph node metastases have in leading to distant metastases remains a "black box". Current models of the metastatic cascade suggest the most efficient route of progression is through hematogenous spread, and that the lymphatic system is effectively a 'dead-end'. However, the most common site of initial spread is in loco-regional lymph nodes. Also, several large prospective studies found that cancer patients with microscopic lymph node metastases following surgical resection have dramatically worse survival. These studies strongly suggest that spread of cancers to the lymphatic system is by no means a 'dead-end'. Furthermore, mechanisms that promote distant metastases from existing lymph node metastases is largely unexplored. We hypothesize that lymphatic spread is an important process that follows specific molecular pathways in the development of distant metastases. The objective of this proposal is to further develop novel models of lymph node metastasis and to elucidate the key molecular pathways responsible for lymphatic metastasis to develop distant metastasis in cancer. Findings from this proposal may shed light on long-standing unanswered questions in metastatic biology, and may open the door to development of new therapeutic targets that effectively block this lethal process.

**Barbara Savoldo MD, PhD**
**Tier 2**
**Clinical/Translational Science Proposal**

**Exploiting the iC9 safety switch to pharmacologically modulate CD19.CAR-T cell function**

**Abstract:**
The introduction of chimeric antigen receptors (CARs) into T cells allows the rapid generation of effector cells specific for virtually any surface molecule. In particular, CAR-T cells targeting the CD19 antigen have shown remarkable antitumor effects in phase I clinical trials in patients with B-cell lymphoid malignancies. However, in its current form, major caveats remain to be addressed to make this approach safely and reproducibly applicable, including the occurrence of: (1) a life-threatening systemic inflammatory response syndrome (SIRS), (2) long-term and likely unnecessary B cell aplasia and (3) graft versus host disease (GvHD), similarly to the conventional donor lymphocyte infusion (DLI), when used in patients relapsed after allogeneic stem cell transplant (SCT). Our central hypothesis is that by incorporating the inducible caspase9 (iC9) safety switch and the selectable marker ΔNGFR within the CD19.CAR retroviral vector (iC9/ΔNGR/CD19.CAR), it should be possible to pharmacologically modulate CAR-T cells infused in patients, either to control side effects without entirely abolishing CAR-T cell activity, or to completely eliminate CAR-T cells "on demand", to allow reconstitution of normal B lymphocytes. We propose to test this hypothesis by preclinical validating our approach ex vivo and in vivo in a humanized leukemia mouse model, and then by manufacturing the clinical grade packaging cell line that produces viral particles to bridge for NIH funding and translate the proposed strategy in a phase I clinical trial of T cells transduced with the iC9/ΔNGR/CD19.CAR, infused into patients with B-cell malignancies either in the autologous or allogeneic setting.

**Janelle Arthur, PhD**
**Tier 1**
**Basic Science Proposal**

**High-throughput in vivo approach to identify and quantify tumor-associated resident microbes**

A high risk of colorectal cancer (CRC) is experienced by inflammatory bowel disease (IBD) patients. IBD and CRC patients harbor an altered intestinal microbiota, including increased mucosally-adherent bacteria. Microbial functional capabilities that permit tumor colonization and augment tumorigenesis in the setting of inflammation remain incompletely understood. Our overarching hypothesis is that inflammation promotes CRC by augmenting mucosal colonization with resident pro-carcinogenic bacteria. A specific functionally-defined subset of Escherichia coli termed "adherent-invasive E. coli (AIEC)" are abundant in IBD and CRC patients, linked to inflammation and cancer in mouse models, and often produce virulence factors that impact tumor development. It has been impossible to distinguish AIEC in vivo without labor-intensive ex vivo culturing, because in vitro functional attributes rather than molecular signatures define AIEC. Therefore, it is unknown if in vitro-defined AIEC colonize tumors better than non-AIEC strains. To address this, we have developed a novel high-throughput in vivo approach coupling genomics and gnotobiotics. We hypothesize that human IBD-associated AIEC strains better colonize colonic tumors than non-AIEC strains. Our aim is to determine the extent to which in vitro-characterized clinical IBD-associated AIEC differ from non-AIEC in colonizing inflamed, non-inflamed, tumor and non-tumor mucosa using Il10-/-, WT, and azoxymethane/Il10-/-germ-free mice. This will lead to independent funding to validate the tumor-promoting ability of robust colonizers in gnotobiotic models and comparative genomics to molecularly define the AIEC phenotype. This will inform novel microbiota-based diagnostic and therapeutic approaches for IBD patients at risk for CRC.

**Leah Frerichs, PhD**
**Tier 1 – DISPARITIES RFA**
**Population Science Proposal**

# Development of a Decision Aid and Patient Navigation Intervention to Address American Indian Colorectal Cancer Screening Disparities

**Abstract:**

**Background:**

Colorectal cancer (CRC) is a leading cause of death among American Indians (AI), and AI CRC screening rates remain lower than other races/ethnicities. AI CRC screening barriers include low knowledge, low perceived susceptibility, and poor provider communication. AI also indicate cultural beliefs, mistrust of healthcare providers, and navigating CRC screening processes (e.g., returning FIT/FOBT kits, completing colonoscopy preparation) are specific challenges. Combining decision aids and patient navigation interventions have been effective in increasing CRC-related knowledge, intent, and test ordering and completion among underserved populations. However, a culturally-adapted CRC decision aid and navigation intervention has not been rigorously developed for AI.

**Objective:** To develop a culturally-appropriate CRC screening decision aid and patient navigation intervention for AI by adapting general population versions to address relevant AI barriers.

**Study Design:** We will conduct focus groups and semi-structured interviews with AI patients and healthcare providers to examine barriers and facilitators, and elicit specific input regarding an AI-focused CRC screening decision aid and patient navigation intervention. Based on these findings, we will create a decision aid prototype, which we will pilot test for feasibility, usability, and impact on AI CRC screening knowledge, self-efficacy, and intent.

**Significance:** This study will provide insights into overcoming CRC screening barriers for AI, and yield a practical tool (the decision aid) and feasibility and efficacy data. This will provide a foundation and preliminary data for a future, multi-site randomized control trial testing the effectiveness of this decision aid and navigation intervention in increasing CRC screening in AI populations.

**Yanzhe Gao, Ph.D.**
**Tier 1**
**Basic Science Proposal**

**Validating Hormad1 as a Novel Therapeutic Target in Radio-resistant Cancer Cells**

**Abstract:**
Resistance to radio-chemo therapy is a major cause of mortality in many cancer patients. Therefore there is an urgent need to devise novel strategies to treat radio-chemo resistant cancers. Radiotherapy and many chemotherapies kill cancer cells and normal cells by inducing irreparable DNA Double Stranded breaks (DSB). However, because pre-neoplastic cells experience considerable oncogenic stress and DNA damage during tumorigenesis, cancer cells often acquire resistance to DSB. Mechanisms by which neoplastic cells tolerate intrinsic and therapy-induced DSB are not fully understood. The gaps in our knowledge of DNA damage tolerance limit our understanding of tumorigenesis and preclude effective prevention and treatment of cancer. The broad long-term goal is to solve the problem of how cancer cells acquire resistance to DSB-inducing therapies. Based on preliminary work we hypothesize that Hormad1, a 'Cancer/Testes Antigen' (CTA), that is normally germ cell-restricted yet aberrantly up-regulated in many cancers promotes DSB repair via 'Homologous Recombination (HR). HR allows proliferation of cells harboring spontaneously-occurring or therapy-induced DNA DSB. The Specific Aims (SAs) are: (1) To define the mechanism of Hormad1-mediated HR. (2) To determine the effects of Hormad1 expression on tolerance of therapeutic DNA damage. The proposed research is innovative because there is no paradigm for how CTAs affect genome maintenance, tumorigenesis or cancer therapy. The work is significant because our results will lead to novel strategies that target DNA repair and combating chemo/radio-resistant cancers but are innocuous to normal cells.

**Yang C Yang, PhD**
**Tier 1**
**Population Science Proposal DISPARITIES RFA**

**Social Relationships and Cancer Mortality: The Role of Inflammation**

**Abstract:**
Recent research in the social epidemiology of chronic disease has increasingly linked social stressors such as social relationship deficits to cancer outcomes. However, critical gaps exist in our understanding of the nature and strength of such links or underlying biological mechanisms. This interdisciplinary biosocial study expands previous research to assess the process by which social relationship stressors increase the risk of cancer mortality through inflammatory mechanisms. Drawing on both questionnaire and biospecimen data from the ongoing UNC Health Registry/Cancer Survivorship Cohort (HR/CSC) study, it aims to examine the effects of social relationship quality (social support and satisfaction with support) on risk of mortality from overall cancer as well as breast, colorectal, and other cancers; obtain five biomarkers of inflammation using blood serum samples from enrolled patients; estimate associations between social relationship quality and inflammation; and test for the mediating role of inflammation in the social relationship-cancer mortality links. The results may provide new mechanistic knowledge about how specific social conditions “get under the skin” to affect cancer survival.