Spring 2024
Developmental Awards

Tier 1 – Basic Science

PI: Dominique Higgins, MD, PhD, assistant professor, Neurosurgery

Project Title: Biomarkers of Ferroptosis in Glioblastoma

Abstract
Glioblastoma (GBM) is an aggressive malignant brain tumor that is ultimately fatal despite standard of care. Ferroptosis is a regulated cell death process that occurs when intrinsic mechanisms do not clear free radicals generated from lipids. We have shown that GBM cells undergo ferroptosis, which allows targeted killing of tumor cells using ferroptosis inducing drugs. We have also shown that dietary depletion of cysteine and methionine, key amino acids needed for ferroptosis, result in GBM cell death and increased sensitivity to ferroptosis inducing drugs. The ability to non-invasively determine when tumor cells have been sensitized to death by ferroptosis is therefore an important next step in translating these findings to patients. Positron emission tomography (PET) imaging is commonly used to cancer tumor cells based on their metabolism of specific molecules or tracers. A glutamate-based PET tracer, FSPG, is taken up by GBM cells via System Xc-, a cysteine-glutamate antiporter, which is critical in ferroptosis. In this proposal, we will investigate using preclinical studies in murine GBM tumors, whether FSPG PET imaging is a valid biomarker of ferroptosis sensitization to cysteine and methionine depletion and System Xc- inhibitor responses; the results from which will be readily translatable to patients.

Tier 1 – Basic Science

PI: Heather McCauley, PhD, assistant professor, Cell Biology and Physiology

Project Title: Enteroendocrine Cells as Tumor Suppressors

Abstract
Colorectal cancer is one of the most common forms of cancer worldwide and its incidence has been increasing, especially in young people. Many lifestyle factors have been associated with increased risk for developing colorectal cancer, but the mechanisms are poorly understood. Here, we propose a novel link between diet and risk for colorectal cancer. Ingested nutrients are sensed by enteroendocrine cells within the intestine, which secrete more than 20 distinct hormones that act locally and throughout the body to coordinate the physiological response to a meal. The abundance and function of these cells is impaired in metabolic diseases like obesity and upon diets high in fat, both of which increase risk for developing colorectal cancer. In an animal model of colorectal cancer, we found that mice with genetic loss of enteroendocrine cells formed more tumors than did mice with the normal population of enteroendocrine cells. Early experiments suggest that the tumors that developed in enteroendocrine-cell deficient mice had increased markers of oxidative stress and DNA damage. Upon DNA damage, repair pathways must be activated, or else cells will acquire additional oncogenic mutations that promote tumor growth and progression. We hypothesize that enteroendocrine cells protect against oxidative damage and promote these DNA damage response pathways, and that upon their loss or impairment, benign polyps are more likely to become cancerous. Enteroendocrine cells and their secreted hormones can be modified by dietary change or by pharmacological intervention, suggesting there may be additional avenues to treat colorectal cancer.

Tier 1 – Clinical/Translational

PI: Christopher Jensen, MD MSCR, assistant professor, Medicine

Project Title: LCCC2406: Pilot Study of a Biometrics-Driven Patient-Reported Symptom Monitoring Program Among Adults with Cancer

Abstract
Managing symptoms effectively is crucial for cancer patients undergoing chemotherapy, as it can significantly improve their quality of life and reduce the need for emergency healthcare visits. This study investigates whether a smartwatch can help patients better manage their symptoms by providing timely updates and feedback. We will enroll 40 patients who are currently receiving chemotherapy and are considered high risk due to their condition but do not qualify for an existing monitoring program. These patients will be divided into two groups. One group will use a Garmin VivoActive 4 smartwatch, which will monitor their health data and send alerts when there might be a need for medical attention. The other group will receive the usual healthcare support without the use of the smartwatch. The main focus is to see if the smartwatch helps improve the patients' overall quality of life. We will also check if the smartwatch helps reduce the number of times patients need urgent healthcare services and how satisfied patients are with this new approach to health monitoring. Our goal is to determine if wearable technology can make a real difference in managing the health of cancer patients by providing timely and accurate health information. This could lead to better health outcomes and less strain on healthcare services. This study aims to show how modern technology, like smartwatches, might be used to improve healthcare for cancer patients by keeping a closer and more continuous check on their health.

Tier 1 – Clinical/Translational

PI: Shivani Sud, MD, assistant professor, Radiation Oncology

Project Title: Circulating Cell-Free DNA for Early Detection of Cancer Therapy-Related Normal Tissue Injury

Abstract
Cancer therapy causes substantial damage to normal tissues. The way we currently monitor for normal tissue injury caused by cancer therapies is by detecting relatively late changes in tissue structure and/or function. For example, in the case of heart damage from cancer therapy we monitor for changes to the thickness of the heart wall or its ability to pump blood. We propose a novel blood test for early detection of normal tissue injury. This test will sample the blood for signal from DNA shed by turnover from injured normal cells (cell free DNA) in a specific tissue (e.g., heart, gastrointestinal tract) by detecting differences in methylation patterns. We will first develop the assay using sequencing data from publicly available databases supplemented with new sequencing data from heart and gastrointestinal cells. We will then test if cell free DNA levels from these tissues are increased in patients receiving radiotherapy to specific parts of the body. If successful, this blood test will potentially be used to guide early interventions to prevent normal tissue toxicity and support normal tissue recovery after injury from cancer therapy. While we will establish this technology for heart and gastrointestinal cells initially, our proposed tissue-specific cell free DNA assay may be adapted for other organs to facilitate novel biomarker-based normal tissue injury research across multiple disciplines at UNC.

Tier 1 – Clinical/Translational

PI: Alexander Villalobos, MD, assistant professor, Radiology

Project Title: Characterization of the Hypoxic Tumor Microenvironment with Blood Oxygen Level-Dependent Magnetic Resonance Imaging for the Prediction of Hepatocellular Carcinoma Response to Yttrium-90 Selective Internal Radiation Therapy

Abstract
Yttrium-90 (Y90) selective-internal-radiation-therapy (SIRT) is a type of radiation-based therapy that is becoming increasingly utilized for liver cancer treatment. Many liver cancers, such as hepatocellularcarcinoma (HCC), are known to thrive in tissue environments with low levels of oxygen (i.e. tissue hypoxia). Because tissue hypoxia has been previously observed to decrease the efficacy of radiation-based therapies, a liver tumor's hypoxic state is suspected to reduce the efficacy of Y90-SIRT on liver cancer. To date, no one has standardized the non-invasive measurement of liver cancer hypoxia nor incorporated tumor tissue hypoxia into the treatment algorithm. This proposal aims to study the impact of liver tumor hypoxia on Y90-SIRT outcomes by leveraging noninvasive MRI sequences already known to be able to assess tissue hypoxia in other non-liver parts of the body. For the first time in human subjects with HCC, this study will develop a non-invasive MRI sequence called blood oxygen level dependent (BOLD) imaging to see how much oxygen is in the liver tumor tissue before Y90-SIRT therapy. Small tissue samples of tumor will also be attained during the Y90-SIRT planning procedure so that a known pathologic maker of tissue hypoxia (hypoxia inducible factor (HIF) 1α) can be measured and subsequently utilized as a 'gold standard' to then correlate the novel BOLD MRI sequence results. Ultimately, this study aims to understand if low-levels of oxygen within a liver tumor will make radiation-based treatments, like Y90-SIRT, less effective – thereby letting doctors better personalize treatment planning, expectations, and follow-up.

Tier 1- Clinical/Translational

PI: Jen Jen Yeh, MD, professor of Surgery and Pharmacology

Project Title: Pilot Evaluation of the Utilization of Multimedia for Enhanced Surgical Consent (SURGIMEDIA)

Abstract
Informed consent for an intervention entails describing the intervention, associated risks, benefits, and alternatives. Unfortunately, the quality of this discussion is not standardized, and the patient experience varies widely depending on both provider and patient. Patients diagnosed with cancer not only need to reconcile a life-changing and life-threatening diagnosis, but also are asked to decide on treatment options. This is especially true for pancreatic cancer patients where the only chance of cure is one of the most complex of cancer operations, the "Whipple". More than half of patients will experience a complication after a Whipple, and two in 100 patients are at risk of death. We aim to improve patient experience in the consent process by creating a multimedia educational video that is informed by stakeholder groups that have had a Whipple. The video will include education on the operation and hospitalization experience. We expect that patients who undergo the video intervention will have a greater understanding of the procedure, feel more informed after the operation, and have higher satisfaction throughout their hospitalization course. Utilizing multimedia as part of informed consent is a novel way to engage patients while providing a high-quality, standardized informed consent discussion. Application of video informed consent creates an opportunity to mitigate healthcare barriers and disparities inherent to the North Carolina population which is ranked 41st in health literacy in the United States. This study is the first to our knowledge to explore the optimal method to obtain informed consent in cancer and vulnerable populations.

Tier 1 – Population Science

PI: Natasha Burse, DrPH, MS, postdoctoral research fellow, UNC School of Nursing

Project Title: Exploring Health Promoting Behaviors and Cultural Identities Influencing Black Women Diagnosed with Breast Cancer

Abstract
Physical activity can improve the health and wellbeing of cancer survivors. However, there are a limited number of physical activity programs to help Black women diagnosed with breast cancer to become physically active. Our goal is to gather insights into the preferences, things that influence physical activity, and survivorship experiences of Black women diagnosed with breast cancer to inform the development of a tailored physical activity program.

Tier 1 – Population Science

PI: Andrew Smitherman, MD, MSc, associate professor, Pediatrics

Project Title: Predictive Model for Acute Care Encounters Among Adolescents and Young Adults (AYAs) in the Early Survivorship

Abstract
Most adolescents and young adults (AYAs, ages 15-39) diagnosed with cancer will be long-term survivors of their cancer. Because of this, there is a growing population of AYA cancer survivors in the United States with health needs that are distinct from other AYAs without a history of cancer. These health needs may result in emergency department visits and/or unplanned hospitalizations, collectively called acute care events (ACEs), even after cancer treatment is finished. ACEs are disruptive for AYAs, negatively impact their quality of life, and are financially costly – both for patients and the health system. We want to better understand the patient, cancer-, and treatment-related factors that are more commonly associated with ACEs in AYAs who are within five years of cancer diagnosis. Using the factors that are commonly associated with ACEs, we can identify AYAs who are more likely to have an ACE and develop tools to help support these AYAs to prevent them from needing an ED visit or hospitalization.

Tier 1 – Population Science

PI: Andrew Moon, MD, MPH, assistant professor, Medicine

Project Title: Risk Evaluation And cancer Detection in Younger Adult Liver Disease Patients (READY)

Abstract
Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition in which fat accumulates in the liver leading to inflammation and scarring. Significant scarring of the liver from MASLD can progress to cirrhosis, liver failure, and liver cancer. Up to 1 out of 3 Americans have MASLD. The increase in MASLD is a major contributor to the rising number of deaths from liver cancer in the US. For unclear reasons, an increasing number of younger people (aged <40 years old) are developing MASLD. Accelerated biological aging, due to economic and social stressors, may be a risk factor for MASLD in younger individuals. In this project, we aim to enroll younger individuals (age 18-39) with liver disease. We will combine information from these participants with information from an ongoing research project that is examining environmental risk factors for liver disease in older individuals (age 40-75 years old). Using this combined group, we will compare the characteristics and risk factors for MASLD among younger (<40 years old) and older (40+ years old) individuals. We will also use blood testing to estimate participants' biological ages and determine if social and economic stressors predict weathering (estimated biological age versus chronological age). The long term goal of this project is to identify risk factors for younger onset MASLD that we can address to prevent cases of cirrhosis and liver cancer.

Tier 2 – Basic Science

PI: Sharon Campbell, PhD, MS, Gary F. Liebscher Distinguished Professor of Biochemistry and Biophysics

Project Title: Targeting an NRAS Melanomagenic Mutant-Specific Druggable Pocket

Abstract
RAS proteins (KRAS, NRAS and HRAS) are found in every human cell and are crucial on/off switches that regulate cells to grow properly. Mutations found in ~25% of cancers prevent the switch to turn 'off' so that RAS proteins are chronically 'on' or activated, resulting in deregulated growth. While RAS proteins were once considered undruggable, exciting recent advances have approved 2 FDA RAS drugs. Sadly, these drugs are only approved for 1 mutation out of 100+ identified, leaving cancer patients in dire need for additional RAS mutant-specific drugs. The 30+ years from RAS's cancer-causing discovery to the approval of RAS drugs highlights the difficulty in targeting cancer causing RAS mutants without affecting healthy RAS-regulated cells. One of the three RAS proteins, NRAS, is highly mutated in thyroid cancers and leukemia and is the 2nd most common driver of skin cancer (cutaneous melanoma). Currently, there are limited options to treat highly aggressive skin cancers driven by NRAS mutations. We are excited to share our discovery of a novel druggable pocket selectively present in two of most prevalent mutations occurring in ~80% of melanoma patients. Notably, this pocket appears specific to NRAS but not other RAS (K- and HRAS) proteins. We have also identified molecules, including an FDA-compound, that bind to the pocket selectively present in the 'on' state of prevalent NRAS melanoma mutants. We propose using synthetic chemistry to optimize selective binding of compounds to melanoma-driving NRAS mutants in an effort to shut 'off' the switch, while doing no harm to normal RAS functioning cells. Ultimately, this could provide the highly needed therapy for NRAS driven melanoma patients.

Tier 2 – Basic Science

PI: Jean Cook, PhD, chair & professor, Biochemistry and Biophysics, professor, Pharmacology

Project Title: Molecular Mechanisms of Escape from Drug-Induced Arrest

Abstract
Many new cancer drugs are called targeted therapies. They target unique cancer cell weaknesses and usually have fewer side effects than traditional non-targeted drugs. One example is a breast cancer drug called Palbociclib. Palbociclib stops, or "arrests," cancer cell division. Palbociclib and similar drugs benefit many breast cancer patients, but a key challenge is drug resistance. Drug resistance is when the cancer cells stop responding to the drug. Our goal is to understand how resistance develops. If successful, we could design ways to block resistance or target resistant cancer cells. Typical drug resistance studies compare groups of sensitive cells (that respond to drug) to resistant cells. Resistant cells already have many changes, and it is not obvious which of those sparked the new cell division. Instead, with time-lapse video microscopy we observe individual cells being treated with Palbociclib. Although all cells arrest, a few resume growth after a few days. What makes one cell escape arrest to grow again and not its neighbor? To define the differences that cause escape from drug-induced arrest, we developed innovative laboratory tools that predict escape before it occurs. With these tools, we can now isolate escapers from arrested cells. We will generate complete profiles of molecular changes in the cells destined to escape. We will then examine patient tumor data for patterns similar to the escaping cells. We propose that escaping cells rely on altered signaling pathway dynamics. These pathways may be sensitive to additional inhibitors that prevent escape or kill escapers.

Tier 2 – Clinical/Translational

PI: Carla Chibwesha, MD, MSc, associate professor, Obstetrics & Gynecology

Project Title: Correlative Studies for the Phase 2b Trial Acceptability and Feasibility of Combination Treatment for Cervical Precancer Among South African Women Living with HIV (ACT 2)

Abstract
Cervical cancer is the second most common cancer among women worldwide. Nine of every ten cervical cancer cases occur in low-and middle-income countries (LMICs). New treatment approaches are urgently needed to decrease the burden of cervical precancer (CIN2/3) and cancer in HIV-infected women, particularly in LMICs. Our team is currently conducting a clinical trial to evaluate a new combination treatment approach for cervical precancer among HIV-infected women in South Africa. The combination treatment approach involves using an anti-cancer cream (5-fluorouracil) after surgical removal of the precancerous tissue. In this application, we propose additional laboratory studies to improve our understanding of how the combination treatment approach works.

Tier 2 – Clinical/Translational

PI: Hyman Muss, MD, Mary Jones Hudson Distinguished Professor of Geriatric Oncology

Project Title: Investigating Cellular Senescence And Organ Aging In Breast Cancer Patients Undergoing Adjuvant Chemotherapy: A Novel Approach Utilizing Organ Specific Age Proteomics

Abstract
Chemotherapy has revolutionized cancer treatment, but these advances come with a downside – accelerated aging. p16INK4a, a gene in all human cells, codes for a protein that dramatically increases as humans age. This protein causes "cell senescence," a condition where cells stop dividing but do not die. Senescent cells are present in all organs and secrete chemicals that cause inflammation and other organ damage, accelerating aging. We measure p16INK4a in blood from immune cells. Our research team has demonstrated that p16INK4a rises rapidly, dramatically, and likely irreversibly after adjuvant chemotherapy for breast cancer. For some chemotherapy regimens, the change in p16INK4a expression from before to several months after chemotherapy treatment suggests 10 to 20 years of accelerated aging. In mouse experiments, changes in p16INK4A are seen in all organs as mice age, but not all organs age at the same rate. Likewise, chemotherapy organ aging may not be the same in all organs. Recent research has suggested that measuring proteins in human plasma (proteomics") can accurately determine organ age in humans. The innovative project we propose will compare changes in p16INK4a expression and plasma protein signatures of organ age pre and post adjuvant chemotherapy. Our primary goal is to correlate pre-and post-chemotherapy organ aging trajectories with p16INK4a changes. For example, can we detect changes in protein expression reflecting brain, nervous system, and cardiac aging? If so, we could identify patients, early after completion of chemotherapy, who are at highest risk for severe toxicities and develop early interventions.

Tier 2 – Population Science

PI: Sarah Nyante, PhD, associate professor, Radiology

Project Title: Characterizing the Breast Microbiota in Women with Benign Breast Disease: Implications for Breast Cancer Risk?

Abstract
Bacteria, fungi, and viruses, also known as “microbes,” are found in many body parts, including the breast. Studies have shown that microbes in healthy tissue are different from microbes in cancers, including breast cancer, but there are questions about whether microbes are related to the chance of getting breast cancer. We will test if microbes are related to the chance of getting breast cancer by measuring microbes in breast tissue removed from women who had a high chance of getting breast cancer. Comparing the types of microbes found in women who went on to get breast cancer later in life

to the microbes in women who did not get breast cancer will tell us which microbes may be involved in breast cancer and should be studied more closely. The microbes will be measured using a new lab method that has been shown to work well with tissue samples that have been kept in storage, like the ones we will use in this study. Half of the women in this study will be Black and half will be White, so that we can see how our results apply to women with different backgrounds. This study will be the first to show if there is a connection between microbes and breast cancer using tissue that was collected before cancer developed. Knowing more about the connection between microbes and chance of getting breast cancer will help researchers find new ways of identifying women who are more likely to get breast cancer.