Fall 2023
Developmental Awards

Tier 1 – Basic Science

PI: Albert Bowers, PhD, vice chair, Division of Chemical Biology and Medicinal Chemistry, associate professor, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy; Chad Pecot, MD, professor, Medicine

Project Title: Development of B7-H3 Ligands for Cancer-Specific Targeting of Oligonucleotide Therapies

Abstract
KRAS mutations are one the most common causes of cancer and confer high mortality rates in a broad range of cancers including lung, colon, and pancreas. Selectively eliminating mutant forms of the protein while retaining normal nonmalignant KRAS protein is extremely challenging for conventional therapeutic strategies. Pecot and Bowers labs has developed a novel siRNA-based technology capable of suppressing mutant KRAS while sparing wild type transcripts. This proposal will seek to improve the efficiency and potency of this strategy through development of new molecules that can specifically and selectively deliver the siRNAs to cancer cells.

Tier 1 – Clinical/Translational

PI: Jun Lian, PhD, DABR, professor, Radiation Oncology

Project Title: AI-Powered Adaptive Stereotactic Body Radiotherapy for Enhanced Clinical Outcomes

Abstract
Stereotactic body radiotherapy (SBRT) is a powerful tool for achieving local control of tumors, especially when surgical removal might be risky or impractical. Its ability to deliver high doses of radiation with pinpoint accuracy allows for effective tumor treatment while preserving the function and health of surrounding tissues. However, the dynamic nature of internal anatomy, such as organ deformation and volume change, can often complicate this approach, leading to imprecisions in targeting the affected area. Enter Artificial Intelligence (AI): a revolutionary technology known for its advanced computational capabilities. We're harnessing AI to optimize and refine the treatment process in several pivotal ways. 1. Image Enhancement: Leveraging AI, we're transforming the standard, often grainy, medical images into crisp, detailed visuals. This advancement will grant medical practitioners a clearer and more detailed view of the treatment region, ensuring more precise interventions. 2. Adaptive Planning: Our team is developing an AI-driven tool that facilitates real-time adjustments of radiotherapy plans based on the patient's current anatomy. This means instead of relying on potentially outdated images and radiation parameters, we can provide patients with much more accurate treatment using the latest anatomical data and re-optimized radiation therapy plan, akin to navigating with a real-time updating GPS rather than an old static map. 3. Unified Software System: We're constructing a comprehensive software platform integrating all our AI tools, ensuring a streamlined and efficient process for medical professionals. To validate its efficacy, we're initiating retrospective evaluation for two main cancer disease sites. Upon completing our work integrating state-of-the-art technology with clinical insights, we aim to elevate treatment outcomes across radiotherapy centers, regardless of their size or resources. This ensures that a more significant number of patients benefit and experience improved health and recovery outcomes.

Tier 1 – Clinical/Translational

PI: Jeremy Wang, PhD, assistant professor, Genetics

Project Title: Identification of Chromatin Modifiers that Regulate Nuclear Morphology and Genome Stability

Abstract
One of the defining features of a cancer cell is a grossly misshaped nucleus, the region where our genetic material is stored inside the cell. Proteins called "epigenetic modifiers" regulate how the information stored in our DNA is accessed and interpreted. The genes that encode epigenetic modifiers are often mutated in cancer, leading to changes in nuclear morphology and genetic instability—a hallmark of all cancer cells. Yet, how mutations in these epigenetic modifiers causes misshaped nuclei and genetic instability is not well understood. Our recent study on one such epigenetic modifier, called SETD2, has led us to reimagine how the epigenetic modifiers may be functioning to maintain nuclear morphology. We found, an unexpected role for SETD2 during cell division to control the morphology and stability of the nucleus. Perturbing SETD2 leads to grossly misshaped nuclei and genetic instability that we believe is how it contributes to cancer progression. However, we have evidence that SETD2 does not do this alone. Rather, it may be that a number of other epigenetic modifiers, similar to SETD2, also have this role – a result that if true, would shed new light on how epigenetic regulators contribute to cancer. Thus, we seek Tier 1 funding to ask the question: how many other chromatin regulators contribute to the prevention of nuclear abnormalities and genome instability? To answer this question, we will be using cutting-edge CRISPR technology to perform a gene deletion screen of 311 epigenetic modifiers, where we can delete individual epigenetic modifier genes and assess the impact on nuclear morphology and genetic abnormalities through microscopy. This focused study stands to uncover an unappreciated mechanism by which epigenetic modifiers help maintain genetic integrity that would lead to new avenues of research that one day could provide new therapeutic approaches to treating cancer.

Tier 1 – Population Science

PI: Jennifer Lund, PhD, associate professor, Epidemiology

Project Title: Evaluation of the Impacts of Hurricane-Related Flooding on Delays in Initial Cancer-Directed Care and Mortality in North Carolina

Abstract
Medical breakthroughs have led to improvements in the fight against cancer. However, these improvements are threatened by the effects of climate change. With rising temperatures around the globe, we are seeing more extreme weather events, such as hurricanes, that can impact our ability to get to a doctor and get medical care when needed. Cancer patients, who face several medical challenges, are among the most vulnerable groups when disaster strikes. These events can disrupt patients' ability to get to their oncologist or surgeon, creating significant challenges for healthcare facilities responsible for delivering these services. NC, like other regions, has experienced several hurricane disasters; however, there is not a lot of information on how these disasters affect cancer care for patients in NC. Our goal is to study how exposure to hurricanes and flooding affects the care received by individuals who have recently been diagnosed with cancer. To do this, we will first identify and compare different measures of hurricane impact, including flooding, power outages, and federal disaster declarations. Then, we will link this hurricane data with the NC Central Cancer Registry, a database of individuals newly diagnosed with cancer, including details of each individual's type of cancer and their treatment. Our goal is to measure the effects of hurricanes on treatment delays and mortality for cancer patients in NC. The results of our study will help healthcare systems and state and local government agencies to develop effective plans that will ensure all cancer patients receive the care they need.

Tier 1 – Population Science

PI: Klarissa Jackson, PhD, assistant professor, Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy

Project Title: Exposome Analysis of Black Women in North Carolina to Elucidate Underlying Mechanisms of Breast Cancer Disparities

Abstract
The goal of this research is to better understand why Black women experience worse forms of breast cancer (more aggressive subtypes) compared to White women. This study will use new research techniques to measure environmental chemicals, dietary markers, and metabolites in the plasma of Black and White women with and without breast cancer to identify whether differences in the plasma markers can be used in the future to predict if a woman may develop aggressive breast cancer. The long-term goal of this research is to reduce racial disparities through prevention and early intervention.

Tier 2 – Basic Science

PI: David Williams, MD, PhD, professor, Pathology and Lab Medicine; Albert Bowers, PhD, vice chair, Division of Chemical Biology and Medicinal Chemistry, associate professor, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy

Project Title: Developing a Selective Inhibitor of the ETO Protein as a Novel Therapeutic Strategy for Acute Myeloid Leukemia

Abstract
Acute myeloid leukemia is an aggressive and lethal blood cancer affecting an estimated 20,000 adults and children with over 11,000 deaths in 2023. Current treatments involve chemotherapy that has serious side effects and often does not lead to a cure. While the genetic abnormalities and proteins that cause this cancer have been known and studied for a long time, we have yet to develop targeted therapies for most patients. The Williams laboratory has recently shown that an inhibitor of the ETO proteins could be a new and powerful treatment for most forms of this disease. They have teamed up with the Bowers laboratory who are expert at identifying protein inhibitors. Together, they plan to further our understanding of the structure and function of ETO proteins and to develop novel inhibitors of their function. Ultimately, this research could lead to a new therapy with limited side effects that works for many patients with this deadly disease.

Tier 2 – Basic Science

PI: Albert Baldwin, PhD, William R. Kenan, Jr. Distinguished Professor, Cell Biology and Physiology

Project Title: Control of Canonical and Non-Canonical EZH2 Functions in Triple-Negative Breast Cancer

Abstract
The most successful COVID vaccines use a new a technology called, mRNA lipid nanoparticle vaccines. Among the different intrinsic subtypes of breast cancer, triple-negative breast cancer (TNBC) is considered the most aggressive and most deadly. Additionally, African American and Hispanic women have an increased burden from TNBC. In contrast with estrogen-receptor positive and Her2-positive tumors which express specific targets for therapy, TNBC does not have an established therapeutic target. In addition, TNBC is often poorly responsive to immunotherapy. Therefore, understanding molecular changes that make TNBC such an aggressive and difficult to treat cancer will provide the potential for new TNBC therapeutic options. Here we propose that EZH2, a well-established epigenetic regulator, is an essential driver of TNBC. EZH2 is an enzyme that modifies (methylates) histone H3, one the building blocks of nucleosomes that organize and regulate DNA and gene expression. In this setting,

EZH2 functions to repress gene expression through a larger complex known as PRC2. Evidence has accumulated that EZH2 is pro-oncogenic, and inhibitors of its catalytic activity have been developed which lead to therapeutic responses against some cancers. In TNBC, EZH2 is over-expressed but other components in the PRC2 repressive complex are not, suggesting a distinct function for EZH2 separate from its normal activity. In this regard, work from others and our own work indicate that in TNBC (and in other cancers) EZH2 can activate gene expression in addition to its gene repressive roles. This function of EZH2 appears not to involve its catalytic activity, and is called non-canonical EZH2 activity. One of the hallmarks of TNBC is the dysregulated activation of certain transcription factors such as c-Myc and NF-kappaB, both of which contribute to classic oncogenic mechanisms such as cell proliferation and cancer immunity defects. Both NF-kappaB and c-Myc are known to be active in TNBC. We have shown that EZH2 and NF-kappaB interact in TNBC, and that EZH2 promotes NF-kappaB activity to promote the expression of genes known to promote TNBC. Additionally, our preliminary data suggest that EZH2 promotes the activity of c-Myc in TNBC. Our data indicate that both canonical (enzymatic) and non-canonical (non-catalytic) properties of EZH2 drive TNBC oncogenic properties. This strongly suggests that EZH2 inhibitors of catalytic activity alone will not be fully effective for TNBC treatment. In this proposal we address two key questions: (i) (ii) How is EZH2 directed into the non-catalytic mode in TNBC? How does EZH2 promote TNBC through its catalytic mode of action? Our team brings together significant experience in epigenetics (Strahl), cancer signaling (Baldwin) and breast cancer clinical practice and kinase signaling (Spanheimer). If successful, our study will identify a signaling pathway (or pathways) that promote non-canonical EZH2 in TNBC and novel downstream targets of EZH2 methylase activity that promote TNBC. This would identify EZH2 as a critical regulator of TNBC oncogenic phenotypes and identify therapeutic strategies for blocking this pathway and improving outcomes in this difficult to treat disease.

Tier 2 – Clinical/Translational

PI: William Kim, MD, Rush S. Dickson Distinguished Professor of Medicine, Professor, Genetics and Pharmacology

Project Title: Harnessing Aberrant RNA Processing for Immunotherapy in Renal Cancer

Abstract

We have found a subset of clear cell renal cell carcinomas (ccRCC) with global loss of a core RNA quality control pathway—nonsense mediated decay (NMD)—that is associated with loss of mTOR activity and increased immune cell infiltration. We hypothesize that loss of NMD leads to increased expression of tumor neoantigens and subsequent immune cell recruitment. Using mouse models, this proposal will investigate the mechanisms by which NMD is suppressed in ccRCC and determine if NMD suppression, or mTOR inhibition, can be utilized to promote enhanced response to immune checkpoint inhibition.