Tier 1 — Basic Science

PI: Amy Maddox, PhD, Associate Professor, Biology

Project Title: Modeling septins' roles in cancer initiation and progression in a simple animal

Abstract

The cytoskeletons are implicated in many cellular functions essential to avoid cancerous transformation and progression. Septins are conserved cytoskeletal polymers that contribute to cell division and subcellular compartmentalization by scaffolding the cytoskeleton to the plasma membrane. Mutations in septin genes are prevalent in human tumors, and experimental septin overexpression or loss of function is sufficient for dysregulation of cell migration, invasion, and genome stability. It is unknown how septin mutations in cancer contribute to the onset and progression of the disease. An obstacle to defining septins' roles in cancer is the number of septin genes in humans (13 plus splice isoforms) and most animals. Septins are well conserved; in the powerful model animal *Caenorhabditis elegans* as in mammals, septins are implicated in tissue integrity and cell division, but unlike other animals, *C. elegans* has only two septins. The simplicity of *C. elegans* septins, together with their conserved structure and function, makes thorough loss or modulation of septin function or abundance uniquely accessible and straightforward in this animal. We will study septins' roles in the development and progression of cancer by creating a collection of mutant animals bearing patient septin hotspot alleles curated from the Catalogue of Somatic Mutations in Cancer (COSMIC), using CRISPR/Cas9-based genome editing. We will use these animal models to test the effects of cancer-derived septin mutations on whole-animal physiology and tissue integrity. We will incorporate these findings into a proposal for federal funding to study the effects of human cancer hotspot alleles at the cellular and molecular levels.

Tier 1 — Basic Science

PI: Katharina Stapelmann, PhD, Assistant Professor, Nuclear Engineering, North Carolina State University

Project Title: Non-thermal plasma induced immunogenic cell death in pancreatic cancer cells

Abstract

Treatment of cancer with non-thermal plasmas (NTP), a partly ionized gas, has gained interest due to NTP's capability of delivering reactive oxygen and nitrogen species (RONS) in a precise and controllable manner. Similar to the oxidative stress provided by radiotherapy, NTP provides the extra benefit of high precision and localized treatment that generates a strong immunostimulatory effect, suggesting promise for a systemic, immunotherapeutic response. The full mechanism of NTP's anti-cancer effect is still under investigation. NTP treatment enhances immunogenicity of exposed tumors by inducing emission of immunogenic cell death (ICD) markers and release of key pro-inflammatory cytokines that enhance migration and maturation of antigen presenting cells. These in turn stimulate proliferation and activation of tumor-specific T cells. No clear cause-effect relationship between specific RONS and the demonstrated immune-mediated anticancer effect has emerged. Research suggests that either short-lived RONS generated by NTP are responsible for the cellular response or that the total redox stress induced by NTP exposure leads to immunogenic cell death and expression of related markers,

stimulating the immune response. This proposal aims to investigate whether there is a correlation between specific short-lived RONS (·NO, O, and ·OH) and cellular responses related to immunogenic cell death (CRT, ATP, HMGB1, HSP70, and HSP90) *in vitro* in KPC 4662 pancreatic cancer cells. Recent research suggests that immunogenicity of NTP-exposed cells was enhanced without concomitant cytotoxicity. Phagocytosis and migration assays will be performed as an indicator for immunomodulatory changes.

Tier 2 — Basic Science

PI: Gaorav Gupta, MD, PhD, Assistant Professor Radiation Oncology, Biochemistry and Biophysics

Project Title: Targeting DNA Polymerase Theta for Breast Cancer Prevention and Therapy

Abstract

The prognosis for patients with metastatic triple negative breast cancer (TNBC) remains unacceptably poor, largely due to the activation of pathways that allow cancer cells to resist our most advanced therapies. Recent efforts have identified one of these pathways as mediated by an enzyme the is both highly efficient and inaccurate in repairing DNA. This enzyme is call DNA polymerase theta (abbreviated as *POLQ*), and several biotechnology companies are actively developing drugs that can inhibit *POLQ*. However, there are many unknowns with regards to when *POLQ* targeting will be most beneficial to improving cancer treatment. This proposal aims to resolve some of these key unknowns, using sophisticated experimental models that our laboratory has developed over the past few years. Our hope is that by conducting the proposed basic science and clinically oriented research plan, we will be able to bring *POLQ* inhibitors into the clinical for the *right patient* at the *right time* to maximize the possibility of cancer control.

Tier 2 — Basic Science

PI: Chad Pecot, MD, Associate Professor, Medicine

Project Title: EGFR-directed Chimeric siRNAs for Dual KRAS+Myc Targeting

Abstract

The KRAS and c-Myc (MYC) proto-oncogenes are two of the most critical genes in cancer, yet they have proven to be amongst the most elusive. We have established a program between the Pecot and Bowers labs to address the growing number of “undruggable” targets in cancer using RNA interference (RNAi)-based therapeutics. RNAi is attractive because it enables silencing of cancer targets that cannot be inhibited using conventional approaches. Recently, we have developed anti-KRAS and anti-MYC fully chemically-modified (FM) siRNAs that resist endonuclease degradation and avoid immune-stimulation. Importantly, the mutant KRAS and MYC pathways are frequently convergent, and at times co-dependent, making dual targeting potentially synergistic. Our preliminary data demonstrates that co-targeting of these oncogenes is highly effective. Using an innovative yet simplistic design, we have created “chimeric siRNAs”, which allow two-in-one molecules to simultaneously silence mutant KRAS and MYC. Additionally, we have developed a ligand-conjugated platform that allows for targeted delivery of these FM siRs into cancer cells, *with pivotal in vivo data showing the feasibility of our platform*. We hypothesize that ligand-directed chimeric siRs will potently co-silence mutant KRAS and MYC in several cancer types; consequently, inhibiting tumor progression with a highly satisfactory

toxicity profile. The objectives of this proposal are: 1) to define how well chimeric KRAS/MYC siRs work compared to their individual KRAS and MYC FM siRNAs, 2) to evaluate the effects of chimeric KRAS/MYC siRs on downstream signaling and 3D cell phenotypes, 3) use in vivo models to determine the therapeutic index and potential dose-limiting toxicities.

Tier 2 — Basic Science

PI: Yuliya Pylayeva-Gupta, PhD, Associate Professor, Genetics

Project Title: Role of plasma cells in eradication of pancreatic cancer.

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is notoriously resistant to therapy and has a dismal 5-year survival rate. We have demonstrated that loss of regulatory cytokine IL35 in B cells is sufficient to invigorate T cell driven anti-tumor immune responses to PDAC. However, complete depletion of B cells in therapeutic setting does not reduce tumor growth, strongly suggesting that non-regulatory B cell functions are required to sustain productive anti-tumor immune responses. We hypothesize that B cells contribute to anti-tumor immune response by producing antibodies. The overarching goals of this proposal are to elucidate B cell-driven mechanisms underlying productive immune responses, and to investigate the translational potential of modulating B cell activity as novel means to augment immunotherapy for PDAC. In Aim 1, we will define how antibody production plays a role in potentiating anti-tumor responses in PDAC using B cell depletion models combined with adoptive transfers of plasma cells and/or sera. In Aim 2, we will assess the translational potential of modulating B cell function to enhance immune rejection of PDAC. Specifically, we will evaluate leading anti-CD40 therapy in combination with disrupting immunosuppressive function of B cells and immune checkpoint blockade as a possible therapeutic strategy in syngeneic murine PDAC models. This project will expand our understanding of how B cell subsets shape the tumor microenvironment and may inform the optimal design of B cell-directed immunotherapy strategies against pancreatic cancer.

Tier 2 — Basic Science

PI: Cyrus Vaziri, PhD, Pathology & Lab Medicine

Project Title: Defining DNA Repair Dependencies and Therapeutic Targets of Endometrial Serous Carcinoma

Abstract

Endometrial serous carcinoma (ESC) incidence is rising and accounts for over half of all uterine cancer patient deaths. DNA-damaging drugs are the only therapeutics that have efficacy in ESC. Unfortunately, intrinsic DNA damage tolerance and acquired resistance (termed ‘chemoresistance’) are major barriers to successful treatment. Current gaps in knowledge of how ESC tolerate and repair DNA damage limit the ability to treat ESC. Our *long-term goal* is to define an integrative network of DNA Damage Response (DDR) and repair in the evolution of ESC from the primary tumor to metastatic and chemoresistant disease. Our *objective* is to identify mechanisms by which ESCs tolerate DNA damage and adapt to DNA-damaging therapy in clinically-relevant models. Our *central hypothesis* is that ESCs deploy unique DDR

mediators to repair DNA damage and tolerate both intrinsic and therapy-induced DNA damage. A *corollary hypothesis* is that the DDR undergoes adaptive reprogramming in response to repeat and long-term DNA-damaging therapies, leading to chemoresistance. The *rationale* is that defining the unique mechanisms by which ESCs resist treatment and adapt to therapeutic agents will reveal dependencies and vulnerabilities that can be exploited to improve the efficacy of existing treatment strategies. The following *Specific Aims* are proposed: Aim 1. Define DDR mediators and other druggable targets that sustain ESC in 3D model systems. Aim 2. Elucidate molecular underpinnings of DDR reprogramming in chemoresistant ESC patients. The proposed work will lead to novel strategies for targeting DNA damage tolerance and chemoresistance in ESC, thereby improving patient outcomes.

Tier 2 — Population Science

PI: Carmina Valle, PhD, MPH, Assistant Professor, Nutrition

Project Title: A pilot randomized trial of a mobile weight loss intervention for adolescent and young adult cancer survivors

Abstract

Survivors of adolescent and young adult cancers (AYAs) are at increased risk for long-term and late effects, including obesity, diabetes, cardiovascular disease, additional cancers, and frailty. Further, unhealthy lifestyle behaviors that contribute to weight gain are common among AYAs and over 50% already have overweight or obesity—a major risk factor for morbidity and mortality. Obesity contributes to cancer progression, influences physical and mental function, and is associated with poorer outcomes in cancer survivors. There is a critical need for weight management interventions for AYAs—*yet few lifestyle interventions have been designed to meet the unique needs of AYAs, and none have targeted weight management.* We previously developed a mobile application for individuals at risk for type 2 diabetes (T2 Connect) that integrates weight and physical activity from digital devices with simplified dietary monitoring to promote daily diet and activity changes for weight control. The proposed study leverages our experiences from trials of physical activity interventions with young adult cancer survivors and mobile weight management interventions with young adults by adapting the T2 Connect intervention for AYAs. We propose the following aims: 1) to adapt the T2 Connect weight loss intervention for AYAs using an iterative process engaging a Community Advisory Board of AYAs and advocates; 2) to conduct a pilot randomized trial with 50 AYAs to determine feasibility and acceptability of the adapted intervention (AYA Connect); and 3) to explore the effects of the intervention compared with a delayed intervention control group on anthropometric, behavioral, clinical, and psychosocial outcomes.

Tier 1 — Clinical/Translational

PI: Christy Inscoe, PhD, Assistant Professor, Physics and Astronomy

Project Title: Contrast-enhanced Stationary Digital Breast Tomosynthesis

Abstract

Breast MRI is often offered for patients at intermediate or high risk of breast cancer. However, patients may have contraindications to MRI related to implants or claustrophobia. Contrast enhanced

mammography has been shown to have near similar sensitivities to breast MRI, but may suffer from lesion localization and biopsy guidance limitations. Conventional digital breast tomosynthesis has significant technical limitations that would prevent its use as a dynamic imaging modality. Our carbon nanotube x-ray based stationary digital tomosynthesis system, however, enables fast imaging without the need of a moving x-ray source, and thus could potentially offer advantages in its use as a 3-D imaging approach for dynamic contrast enhanced breast tomosynthesis. The goal of this study is to perform a contrast enhanced stationary digital breast tomosynthesis (CE-sDBT) pilot study on patients with known breast lesions, and evaluate reader confidence as compared to conventional breast MRI.

Tier 1 — Clinical/Translational

PI: Xianlu Peng, PhD, Assistant Professor, Pharmacology

Project Title: Interrogation of epigenetic disparities in minority population for precision medicine in gastric cancer

Abstract

Gastric cancer (GC) is known to show considerable heterogeneity among patients and races, which presents as a barrier to precision medicine. Current large-scale genomic studies in GC have provided unprecedented opportunities in understanding the molecular heterogeneity and stratifications in patients. By re-analyzing the TCGA stomach adenocarcinoma dataset, we found significant disparities in more advanced stage disease at presentation between Black or African American and other races, which are not explained by molecular subtypes. To better understand the underpinning molecular characteristics, we used our newly developed computational tool, DECODER for the deconvolution of biological compartments. We found strong evidences pointing to the methylation differences in Black or AA, which may have implications on their worse prognosis and higher mortality rate. Although we saw promising results for delineating the race disparities by molecular profile deconvolution, the limitation on race diversity in the large-scale genomic studies is of concern. The under-representation of minorities may bias the conclusions in these studies. Therefore, we propose to evaluate GC samples from the UNC LCCC Tissue Procurement Facility, where approximately 1 in 3 patients are either Black or AA. We will perform RNA-seq and bisulfite-seq (BS-seq) on this cohort for the compartment deconvolution and associate the molecular disparities seen to clinical and pathological manifestations. These results will provide foundation for a future R01, that will propose to investigate the molecular disparities in Black or AA GC patients using multiple layers of omics data, including DNA-seq, RNA-seq, BS-seq, ATAC-seq and mass spectrometry. Our study may provide the knowledge needed to tailor therapy regimens and achieve better patient outcomes in the minorities.

Tier 2 — Clinical/Translational

PI: Yuri Fedoriw, MD, Professor, Pathology and Lab Medicine

Project Title: HIV-Associated DLBCL as a Spontaneous Model System to Investigate Tumor-T cell Interactions

Abstract

Diffuse Large B Cell Lymphoma (DLBCL) is the most common lymphoma worldwide, but outcomes remain sub-optimal with multiagent chemotherapy. Promising immunotherapies are available, but the tumor-host interactions in DLBCL are poorly understood. Addressing this gap in knowledge is necessary for patient selection, biomarker discovery, and for development of new treatment strategies. However, human studies to date have been limited by the lack available advanced technologies applied to appropriate patient cohorts. Our *long-term goal* is to improve outcomes for DLBCL by deciphering the diversity, functional heterogeneity, and spatial distribution of effector T-cells within the tumor microenvironment (TME). In this proposal, we utilize DLBCL spontaneously arising in HIV-negative HIV-positive/antiretroviral therapy (ART)-naïve, and HIV positive/ART-experienced patients as a comparative model system to investigate the anti-tumor T-cell response on lymphomagenesis. With a collaboration between UNC and Cedars-Sinai Medical Center, our access to clinically annotated DLBCL samples from HIV- and ART treated and un-treated HIV+ patients, and advanced technologies, we are in a unique position to fully characterize TME and establish cause and effect of intrinsic TME architecture with patient outcome. To address our goal, we will use highly-multiplexed imaging mass cytometry to characterize the topology of functional T-cell subsets within the TME of DLBCL and perform immune sequencing to study the T-cell receptor (TCR) repertoire characteristics in the TME and peripheral blood. Finally, we propose the development of a new method that combines imaging mass cytometry and immuno sequencing to study TCR diversity within microcompartments of the DLBCL TME.