Tier 2 – Basic Science

PI: James E Bear PhD, Professor, Cell Biology and Physiology

Co-Investigator: Jenny Ting

Project Title: Intravital imaging of tumor-immune interactions

Abstract

Invasive melanoma is the most deadly form of skin cancer and over 95,000 newly diagnosed cases are estimated to be diagnosed in the United States in 2019. Although there have been great medical advances in the treatment of melanoma with either checkpoint therapy or specific kinase inhibitors, these therapies are only 20-60% effective. One challenge in the treatment of melanoma is overcoming the high level of heterogeneity of both the tumor cells and the immune infiltration within the tumor. This high level of heterogeneity can often lead to tumor reoccurrence or metastasis that cannot be treated with the similar treatment that was previously effective. Tumor cells also find ways to avoid immune recognition, and intratumoral immune cells sometimes provide pro-survival and pro-metastasis signals to the tumor cells. The major focus of immunotherapy has largely been on manipulation of tumor-specific T cells to try to boost anti-tumor immunity. Less work has been done to try to manipulate the myeloid antigen presenting cells (APCs) within tumors that are responsible for both driving the cytokine milieu within the tumors and priming of T cells to recognize tumor cells. Specific activation of pro-inflammatory intratumoral myeloid cells may be the best way to potentiate current immunotherapies by re-polarizing the anti-inflammatory milieu present while generating increased numbers of anti-tumor specific T cell responses. Finally, one of the other limitations in cancer immunotherapy is the scheduling of combinational drug delivery. It has been shown that co-therapy of both aPD1 and aCTLA4 can lead to over-activation of T cell responses and hamper the therapeutic affects of checkpoint inhibition. Studying the temporal changes in the function and interactions of immune cells within the tumor microenvironment (TME) over the development and clearance of tumors during anti-tumor immune cell activation will require new experimental paradigms, but this knowledge will improve the efficacy of current and future immunotherapies.

Tier 2 – Population Science

PI: Keely A Muscatell PhD, Assistant Professor, Psychology & Neuroscience

Co-Investigators: Allison Lazard, Paschal Sheeran

Project Title: Closing the Gap in Socioeconomic Disparities in Cancer: Using Neuroscience and Social Psychology to Improve Cancer Prevention Messaging

Abstract

Socioeconomic status (SES)-related disparities in cancer incidence and mortality rates persist for a variety of cancers, in part due to disparities in cancer-prevention behaviors (sunscreen use, diet and physical activity, screenings). Thus, there is an urgent need to develop cancer-prevention messaging campaigns that motivate behavior change for lower SES individuals, to reduce cancer disparities and promote health equity. The overarching goal of this proposal is to develop these messages, and evaluate their effectiveness in inducing behavior change across the SES spectrum. Our approach is grounded in

recent findings from social psychology, which show that higher SES individuals are more individualistic/self-focused, while lower SES individuals are more interdependent/social-focused. As such, cancer prevention messages focused on the social implications of such behaviors (e.g., the value of behavior change for family), may be more effective for lower SES individuals. Innovative neuroscience techniques will also be used to examine the neural predictors of message-induced behavior change. Specifically, we will identify neural biomarkers of message effectiveness and use them to predict engagement in cancer-prevention behaviors across the SES spectrum. Results from this study will offer a landmark innovation in cancer communication that could be used to help close the current gaps in cancer disparities. Results from the project will also uniquely qualify the team to produce competitive future grant proposals to build on this work, with the ultimate goal of eradicating SES-based cancer disparities and achieving health equity.

Tier 2 – Basic Science

PI: Ling Cai PhD, Assistant Professor, Genetics

Project Title: The role of AR splice variant in development of lethal prostate cancer

Abstract

Standard treatment of prostate cancer with anti-androgen agents fails due to development of therapy resistance and castration-resistant prostate cancer (CRPC), a terminal disease. Therapy resistance and CRPC were linked to an androgen receptor (AR) splice variant-7 (AR-V7), which is a truncated, constitutively active AR. However, mechanisms by which AR-V7 contributes to CRPC and therapy resistance remain unclear. We recently discovered a new, non-canonical gene-expression program controlled by AR-V7, differing from a canonical AR-regulated program: non-canonical signaling of AR-V7 requires ZFX, a new AR-V7-interacting partner we identified, as well as BRD4, an AR-V7-associated epigenetic co-activator. Non-canonical AR-V7 targets sustain CRPC growth, supporting their crucial roles. Integration of our cell model data with TCGA prostate cancer datasets further demonstrated clinical relevance of this new pathway.

We hypothesize that AR-V7 has new, non-canonical oncogenic functions distinct from those of regular AR, thereby producing more aggressive tumor phenotypes and therapy resistance seen in CRPC, and that the two cofactors of AR-V7 (namely, ZFX and BRD4/pTEFb co-activator complex) are essential for AR-V7's transcriptional signaling and represent new drug targets of the terminal CRPC.

Dissecting the molecular events and mechanisms underlying AR-V7-mediated CRPC progression should provide critical insights into new treatment strategies. Because certain AR-V7-associated pathways such as autophagy or WNT signaling and BRD4/CDK9 cofactor complexes are potentially druggable with inhibitors, completion of our proposed research should not only promote a new mechanistic understanding of CRPC but will also yield innovative therapeutics for treatment of affected patients.

Tier 2 – Clinical

PI: Victorial Bae-Jump MD, PhD, Professor, Gynecologic Oncology

Co-Investigator: William Zamboni

Project Title: Pembrolizumab and ONC201 as a Novel Treatment Strategy in Obesity-driven Endometrial Cancer

Abstract

Endometrial cancer (EC) is a growing menace, partly due to a rise in obesity which both increases the risk of developing EC and succumbing to it. Pembrolizumab is a programmed cell death 1 (PD-1) antibody (mAb). PD-1 inhibitors may benefit EC patients based on the following observations: 1) an overwhelming presence of PD-1 expression in ECs; 2) the well-known effect of obesity which activates pro-inflammatory white blood cells and promotes the development of ECs; and 3) the high prevalence of microsatellite instability among ECs that is a marker of sensitivity to this class of drugs. ONC201 is a small molecule selective dopamine receptor 2 antagonist and may increase the efficacy of pembrolizumab in EC via upregulation of TRAIL and activation of T and NK cells. However, the use of pembrolizumab + ONC201 in EC is complicated by obesity. mAbs such as pembrolizumab are cleared via the mononuclear phagocyte system (MPS), and we find that obese patients have higher and more variable MPS mediators, which results in lower exposures of mAbs. Thus, we propose a phase 1 clinical trial of pembrolizumab + ONC201 in parallel cohorts of obese and non-obese metastatic/recurrent EC patients. The primary objective of this study is to evaluate the safety and tolerability of this drug combination. In addition, we will critically assess the impact of obesity on the pharmacokinetics/pharmacodynamics of pembrolizumab + ONC201 as well as comprehensively assess immune-oncology, MPS and inflammatory/metabolic biomarkers as predictors of response to this promising treatment strategy for obesity-driven EC.

Tier 2 – Basic Science

PI: Rihe Liu PhD, Associate Professor, Pharmacy

Project Title: A Constitutively Active STING Mimic for Combination Immunotherapy of TNBC and EOC

Abstract

Triple-negative breast cancer (TNBC) and epithelial ovarian cancer (EOC) are two most common cancer types among women that have very low survival rates. How to inflame the immunologically “cold” TNBC and EOC into ICI responsive “hot” one and make more patients benefit from immunotherapy is an urgent unmet need. This project aims at developing a constitutively active, Universal STING Mimic (USM) that potently activates the STING downstream signaling totally independent of cGAMP, cGAS or the expression of STING, and use it to sensitize the ICI immunotherapy with synergistic anti-cancer efficacy against TNBC and EOC. The proprietary universal STING mimic, invented in the Liu lab at UNC, is fundamentally different from all the known STING agonists at both structural and mechanistic levels. Structurally, the USM is a unique, constitutively active form of STING (tetrameric STING) that is efficiently formed by self-assembly of an engineered STING fusion protein. Mechanistically, it can potently activate STING signaling totally independent of cGAMP, cGAS or the expression of STING that are frequently downregulated or lost in many human malignancies, making it possible to be applied to numerous solids tumors. We use a clinically validated mRNA/LNP system that allows for highly efficient local delivery of mRNA of USM in the TME, effectively restricting the activation of the immune system within TME and therefore significantly reduced systemic diffusion and irAEs. The proposed intratumoral immunotherapy is clinically amenable to both TNBC and EOC, providing realistic strategies for combination immunotherapy and future clinical treatment of TNBC and EOC.

Tier 1 – Population Science

PI: Jessica R Cohen PhD, Assistant Professor, Department of Psychology and Neuroscience

Co-Investigators: Keely A. Muscatell, E. Claire Dees, Martin Styner, Tobias Egner

Project Title: A Transdisciplinary Approach to Improving Assessment of Chemotherapy-Induced Cognitive Decline in Breast Cancer: Specificity, Risk Factors, and Multimodal Brain Network-Based Predictors

Abstract

Increasing survival rates after breast cancer diagnosis have raised awareness of the long-term negative effects of chemotherapy (CT) treatment, most notably cognitive impairment in domains such as attention, executive function, and memory that may persist for years following treatment completion. Yet our knowledge of the specific cognitive domains disrupted by CT, as well as our ability to identify individuals who are at particular risk for experiencing CT-related cognitive decline, is lacking. This proposal will leverage advances from the field of cognitive neuroscience to improve assessment of cognitive decline and vulnerability to future cognitive decline in order to propel forward our evaluation and identification of CT-induced cognitive decline. This pilot study, designed to generate preliminary findings for a future R01 application, includes comprehensive assessment of pre-CT clinical, demographic, psychosocial, cognitive and neural characteristics in breast cancer patients scheduled to receive CT, followed by a second cognitive assessment after CT termination. Our goals are to: 1) assess cognitive domains impacted by CT using innovative tasks developed to identify precise and subtle changes in specific sub-components of cognition; and 2) identify pre-CT individual differences that contribute to cognitive function and decline. We will implement brain network analyses, which have a unique ability to quantify and summarize complex patterns in distributed large-scale brain organization, and thus are promising biomarkers for predicting future cognitive decline. This line of research will revolutionize how cognitive difficulties that arise from CT are identified, evaluated and treated, leading to improved cognition and quality of life for breast cancer survivors.

Tier 1 – Basic Science

PI: Lori O'Brien PhD, Assistant Professor Cell Biology and Physiology

Project Title: Towards a mechanistic understanding of Wilms' tumor development utilizing a kidney organoid model

Abstract

Wilms' tumor is the most common pediatric renal cancer. Overall survival rates are ~90%, however, this is dependent on stage and histological classification. Stromal and epithelial subtypes are intermediate risk while blastemal subtypes are high-risk, resulting in increased relapse and reduced survival rates. Tumor misclassification due to the lack of strict histological criteria and accurate biomarkers also contributes to reduced survival. This represents a critical deficiency in the diagnosis and treatment of Wilms' tumor. To this end, we have developed a novel kidney organoid model to study blastemal subtypes. Our goal is to attain mechanistic insights into Wilms' tumor formation, aiding the identification of new biomarkers and therapeutic targets. The tumor blastema is phenotypically

reminiscent of a condensed, mesenchymal nephron progenitor pool present only in the developing fetal kidney. This suggests Wilms' tumors arise from a malignant transformation of nephron progenitors during development. A recurring glutamine-to-arginine mutation in the DNA-binding domain (Q177R) of the related master regulators of nephron progenitor self-renewal, SIX1 and SIX2, has been identified in high-risk and relapsed cases of Wilms' tumor. We hypothesize the Q177R mutation in SIX1/2 alters downstream regulatory targets, promoting persistent nephron progenitor proliferation and antagonizing their differentiation potential. To this end, we will utilize genetically engineered iPSCs which carry the Q177R mutation at the SIX1 locus to produce kidney organoids which model Wilms' tumor in vitro. We will perform ChIP-seq and RNA-seq analyses to gain mechanistic insights into the networks which drive tumor development and identify novel candidates for therapeutic targeting.

Tier 1 – Population Science

PI: Kimberly Kasow DO, Professor Pediatrics Hematology Oncology

Co-Investigator: Stephanie Wheeler; Kristin Page; Matthew Kelly

Project Title: Evaluating the financial impact of hematopoietic stem cell transplantation on pediatric patients and their families

Abstract

Financial toxicity, a concept characterizing the major financial burden healthcare places on patients and their families, is a significant yet under-studied hardship associated with cancer treatment. In particular, intensive treatments such as hematopoietic stem cell transplantation (HSCT) may impose an even greater financial toxicity on cancer patients and their families; among patients with hematological malignancies, the healthcare costs of those who received an HSCT were on average $146,000 to $373,000 higher in the 12 months post-diagnosis compared to those who did not receive an HSCT. Consequently, social workers and insurance coordinators are integrated into HSCT recipients' care during treatment. However, for pediatric HSCT patients, the financial consequences often continue for several years post-HSCT. In part, this is due to the occurrence of late complications and chronic medical conditions these patients will have to manage for the rest of their lives. If pediatric HSCT patients and their families experience significant financial hardship despite access to substantial resources, this has significant implications for how interventions, such as financial navigation, will need to be adapted to be effective among HSCT patients who continue to experience financial toxicity beyond treatment. Using mixed methods, we propose to develop a more nuanced understanding of the prevalence of financial toxicity among pediatric HSCT patients and identify specific opportunities for improved financial support resources. This project will serve as the preliminary study for adapting a financial navigation intervention among pediatric HSCT recipients.

Tier 1 – Population Science

PI: Erin Kent PhD, Associate Professor, Health Policy and Management

Co-Investigator: Eliza Park

Project Title: Family cancer caregiving in rural North Carolina: A multi-stakeholder study to inform the development and adaptation of cancer caregiving interventions

Abstract

Approximately six million individuals currently provide unpaid care to cancer patient in the U.S. Family caregivers are invaluable to both cancer patients and the healthcare delivery system, valued on average at $4800/month. Approximately 21% of cancer caregivers reside in rural areas, yet little is known about their unique unmet needs. Interventions to support rural cancer caregivers are needed because rural cancer patients experience poorer health outcomes than their urban counterparts, including later stage at diagnosis, and poorer health status. Understanding rural cancer caregivers' unmet needs -and the barriers to addressing these needs- is critically important for improving both patient and caregiver outcomes. The objective of the proposed study is to develop a deeper understanding of the experiences and needs of rural cancer caregiver by conducting a multi-stakeholder inquiry to inform intervention development, adaptation, evaluation, and implementation.

Specific Research Aims are to characterize unmet needs of family caregivers of rural adult cancer patients (1) who travel for cancer care and (2) whose patients receive care in rural community settings; and (3) identify the barriers and facilitators of strategies for meeting unmet caregiver needs from the perspectives of clinicians and healthcare administrators. The proposed study will use semi-structured interviews of family caregivers of adult rural cancer patients, clinicians, and healthcare administrators. Qualitative data analytic methods will be applied to identify key themes for future use in a caregiver research prioritization survey and creation of a tool to identify, adapt, and evaluate interventions for rural cancer caregivers and barriers and facilitators to implementation.