NCSU/ECU Applicants-Tier 1

Contact PI: Xiaoxin L Chen

Degree: PhD

Rank: Professor

Department: Cancer Research Program, JLC-BBRI

Email: lchen@nccu.edu

Project Title: Evaluation of NRF2 activity in the esophagus with 18F-FDG/11C-acetate PET/CT

Budget: $50,000

Review Category: Basic Science

Abstract (for peer review):

Esophageal squamous cell carcinoma (ESCC) is a leading cause of cancer deaths in the world. Hyperactive NRF2 due to gene mutations promotes cancer progression, metastasis, chemoradioresistance, and thus is associated with poor prognosis of human ESCC. So far no NRF2 inhibitors have been developed for clinical use. We have been focusing on developing NRF2 inhibitors for NRF2high ESCC using preclinical mouse models. Meanwhile, there is a pressing need of developing a method to elavuate NRF2 activity in the esophagus of live mouse models and human patients. Our previous studies have shown that hyperactive NRF2 upregulated the expression of transporters and metabolic enzymes for 18F-FDG (GLUT1 and HK1/HK2) and 11C-acetate (MCT1, ACSS2) in the esophagus of a transgenic mouse model (Sox2CreER;LSL-Nrf2E79Q/+). Here we hypothesize that the combined 18F-FDG/11C-acetate PET/CT can evaluate NRF2 activity in the esophagus of live mice. We plan to test this hypothesis with two specific aims: (1) To determine whether the combined 18F-FDG/11C-acetate PET imaging can be a surrogate imaging marker for NRF2 activity in the mouse esophagus; (2) To determine whether the combined 18F-FDG/11C-acetate PET imaging can be used for monitoring therapeutic response to an NRF2 inhibitor in the mouse esophagus. In summary, these studies are aimed to explore combined 18F-FDG/11C-acetate PET/CT for the evaluation of NRF2 activity in the mouse esophagus in vivo. If successful, this technology will allow us to diagnose NRF2high ESCC effectively for targeted therapy against NRF2, and to determine the therapeutic efficacy of NRF2 inhibitors for such patients in the future.

Involve faculty at another North Carolina institution: Yes - Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A

Tier 2 - Stimulus Awards

Contact PI: Stephanie M Downs-Canner

Degree: MD

Rank: Assistant Professor

Department: Surgery

Email: stephanie_downs-canner@med.unc.edu

Other Investigator: Jonathan Serody, Benjamin Vincent, Laura Herring

Project Title: Characterizing the Endogenous Antibody Response in Triple Negative Breast Cancer

Budget: $200,000

Review Category: basic science

Abstract (for peer review):

Breast cancer is the leading cause of cancer-related death in women. Triple negative breast cancer (TNBC) has the worst prognosis of all breast cancer subtypes and treatment options are limited to traditional cytotoxic chemotherapy. Unlike other cancers, where T-cells play a critical role, recent data has shown that in TNBC, B-cells in the tumor microenvironment (TME) are predictive of an improved outcome and may play a role in effective immunotherapy for TNBC. Using single-cell RNA sequencing of human breast cancers, we have identified at least 9 distinct clusters of B-cells in the TME as well as clonal restriction of B-cell receptors (suggestive of a tumor-antigen specific immune response). The overall goal of this proposal is to understand the activity of B cells in TNBC and use clonally restricted B-cells to identify novel antigen targets. In Aim 1, we will use single-cell RNA sequencing of tumor-infiltrating immune cells to test our hypothesis that B-cells in TNBC undergo clonal selection and affinity maturation in a germinal center reaction to yield clonally expanded B-cells that are phenotypically distinct from non-clonally expanded B-cells. In Aim 2, we will clone antibodies

from the most abundant B-cell clones to discover antigens and test our hypothesis that B-cells recognize endogenous antigens present in the TME that 1) mediate anti-tumor activity and 2) make antibodies that recognize shared determinants present in different patients. The identification of these antibodies can be used as potential therapeutic or diagnostic approaches for women with TNBC.

LCCC Membership: Yes.

Involve faculty at another North Carolina institution: No - Not Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A

Tier 1 - Pilot Awards

Contact PI: Shekinah N Elmore

Degree: MD, MPH

Rank: Assistant Professor

Department: Radiation Oncology

Email: shekinah_elmore@med.unc.edu

Other Investigator: Dr. Angela Smith, Dr. Marjory Charlot

Project Title:

Defining the impact of telemedicine on shared decision making surrounding treatment choice for Black patients with prostate cancer

Budget: $50,000

Review Category: clinical-translational

Abstract (for peer review):

The COVID-19 pandemic has precipitated the rapid and likely permanent proliferation of telemedicine in cancer care. Telemedicine visits have become a standard. Maintaining telemedicine may improve value for patients with cancer but could have a differential impact on cancer disparities. Black patients in the United States experience a disproportionate burden of prostate cancer-specific morbidity and mortality. Contributions to this inequity are multiple but include a lack of access to high-quality treatment. Many guideline-concordant, oncologically equivalent therapies for localized prostate cancer exist. Successfully navigating these choices requires shared decision making (SDM), the process by which clinicians and patients partner to make optimal decisions that align with patient values. However, Black patients are less likely to receive guideline-concordant care and more likely to experience treatment decision regret than non-Black patients. This disparity may be due to biases in the construct or application of SDM, as it was not expressly designed for this application. Telemedicine may attenuate or enhance any biases in SDM surrounding treatment choice. Thus, an understanding of telemedicine's impact on SDM for Black patients is essential. We propose a qualitative study to describe the impact of telemedicine on the experience of SDM surrounding treatment choice for Black patients with localized prostate cancer (Aim 1). We will then adapt the SDM model using an iterative, stakeholder-engaged process (Aim 2). This study will provide preliminary data and an adapted SDM model that will be used to test decision-support interventions in future trials to improve SDM and prostate cancer outcomes for Black patients.

LCCC Membership: Yes

Involve faculty at another North Carolina institution: No - Not Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A

Tier 2 - Stimulus Awards

Contact PI: Erin E Kent

Degree: PhD, MS

Rank: Associate Professor

Department: Health Policy and Management

Email: erin.kent@unc.edu

Other Investigator: Dr. Amanda Kong

Project Title: The COVID-19 Cancer Study (CovCS): Exploring disparities and the effects of the pandemic on cancer survivors' health behaviors and outcomes

Budget: $193,650

Review Category: Population science

Abstract (for peer review):

The COVID-19 pandemic is shifting everyday life with profound health and psychological consequences. Cancer survivors experiencing COVID-related stressors may be coping through health behaviors (COVID-preventative behaviors, healthcare seeking, smoking, alcohol use, physical activity). The overall objective of the COVID Cancer Survivor (CovCS) Study is to characterize relationships between COVID-related stressors, health behaviors, and psychosocial well-being among North Carolina cancer survivors and to further investigate racial and socioeconomic disparities in these relationships. We will collect survey data from 500 cancer survivors enrolled in the UNC Heath Register/Cancer Survivorship Cohort (HR/CSC). In Aim 1, we will evaluate whether there are disparities in the prevalence of measures by individual-level race (White vs. Black) and household income. In Aim 2, we will test whether COVID-related stressors are associated with health behaviors, and in turn if stressors are associated with psychosocial well-being. Additionally, we will investigate whether these relationships differ by race and income. In exploratory Aim 3, we will test whether the association between COVID-related stressors and smoking and alcohol use is moderated by neighborhood-level tobacco and alcohol outlet availability. Results may inform the immediate tailoring of clinical interventions to lessen the impact of COVID, especially for cancer survivors experiencing disproportionate burden. Our study may provide evidence that place-based policies, such as reducing the number of tobacco and alcohol outlets could benefit cancer survivors. Finally, results will support an R01 application to design a cohort study using a larger sample to further examine the relationships between multilevel stressors, behaviors, and well-being among cancer survivors.

LCCC Membership: Yes.

Involve faculty at another North Carolina institution: No - Not Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A

Tier 2 - Stimulus Awards

Contact PI: Andrew M Moon

Degree: MD, MPH

Rank: Fellow

Department: Medicine, Gastroenterology and Hepatology

Email: andrew.moon@unchealth.unc.edu

Other Investigator: Stephanie Wheeler, Andrew Olshan, Hanna Sanoff, A. Sidney Barritt

Project Title: Improving hepatocellular carcinoma screening among cirrhosis patients from North Carolina using lab-based risk stratification tools

Budget: $198,666

Review Category: Population science

Abstract (for peer review):

The incidence and mortality rates from hepatocellular carcinoma (HCC) are increasing in North Carolina (NC), where there are large disparities in HCC-related outcomes. These poor HCC outcomes are in part due to low utilization of HCC surveillance with serial ultrasound +/- serum alpha-fetoprotein in patients with cirrhosis, for whom HCC surveillance is recommended. Hepatitis C virus (HCV) is a leading cause of cirrhosis and HCC that is now being easily treated and cured after the introduction of direct acting antivirals (DAAs). Community providers who prescribe DAAs may not evaluate HCV-cured patients for cirrhosis, leading to missed opportunities to provide HCC surveillance. HCC risk stratification models that utilize standard of care HCV lab results should improve the identification of HCV patients at risk of HCC and increase HCC surveillance rates. The long-term goal of this project is to improve HCC screening and improve HCC outcomes in NC, particularly among patients in resource limited settings. The objectives of this application are to improve understanding of current HCC surveillance patterns in NC and understand the feasibility of incorporating risk stratification tools to help community PCPs and gastroenterologists identify high-risk patients for referral to active HCC screening programs. We will accomplish this by assessing current HCC surveillance practices in NC, validating existing lab-based HCC risk stratification tools among NC patients with treated HCV and surveying community providers to assess surveillance attitudes and behaviors and identify interested providers for a subsequent pilot to test the use of point-of-care HCC risk stratification tools.

LCCC Membership: no.

Sponsor: Louise Henderson

Involve faculty at another North Carolina institution: No - Not Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A

Tier 2 - Stimulus Awards

Contact PI: Jennifer/Alison S/T Smith/Brenner

Degree: PhD,MPH/PhD,MPH

Rank: Professor/Assistant Professor

Department: Epidemiology/General Internal Medicine and Clinical Epidemiology

Email: jennifers@unc.edu/alison.brenner@unc.edu

Other Investigator:

Daniel Reuland (Medicine), Stephanie Wheeler (HPM), Noel Brewer (HB), Michael Hudgens (BIOS)

Project Title:

My Body My Test-4 Cervical and Colorectal Cancer Screening Study

Budget: $199,910

Review Category: population science

Abstract (for peer review):

Our overarching goal is to reduce the burden of cervical and colorectal cancers among underserved populations in North Carolina. Both cancers are highly preventable by screening, with higher incidence and mortality in Blacks than Whites. To increase screening uptake, we propose to evaluate an outreach program to deliver cervical and colorectal cancer screening together, based on experience providing mailed self-collection kits for each cancer alone. Aim 1 will demonstrate feasibility of patient identification, mailing self-collection kits, and tracking screening uptake among women not up-to-date for cervical and/or CRC screening. We will develop a query using clinical data to identify women overdue for cervical and/or CRC screening in collaboration with a large federally qualified health center. Aim 2 will determine the effect of mailing self-collection kits for cervical and CRC screening together compared to mailing a single screening option. A total of 1,000 women due for cervical and/or CRC screening will be identified via electronic health record query (n=200 cervical ONLY; n=200 CRC ONLY; n=600 cervical and CRC). Women due for both tests will be randomized to Arm 1: mailed self-collection kit for cervical and CRC simultaneously. Arm 2: mailed cervical self-collection kit alone followed by CRC kit alone. Arm 3: mailed CRC kit alone followed by cervical self-collection kit alone. Women due for only one test will be mailed the appropriate test kit only. We will determine screening uptake by measuring return of the kits. Colposcopy and colonoscopy completion after positive test results will measure follow-up care completion.

LCCC Membership: Yes.

Involve faculty at another North Carolina institution: No - Not Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A.

Tier 1 - Pilot Awards

Contact PI: Daniel I Dominguez

Degree: PhD

Rank: Assistant Professor

Department: Pharmacology

Email: didoming@email.unc.edu

Project Title: mTOR as a master regulator of RNA quality control in cancer

Budget: $50,000

Review Category: basic science

Abstract (for peer review):

Clear cell renal cell carcinoma (ccRCC), as the most common form of kidney cancer, is responsible for the most kidney cancer-associated deaths. Inhibitors of the mTOR pathway, among others, have been approved for the treatment of ccRCC, however, overall treatment success varies and suggests we need a better understanding of cellular dysfunction that promotes tumorigenesis in ccRCC. Because RNA processing is an important regulatory phase of gene expression that is often mis-regulated in cancer, we evaluated the transcriptomes of ccRCC tumors and matched normal kidney tissue. We found high expression of aberrant RNAs that would normally be degraded by an RNA quality control pathway, nonsense-mediated decay (NMD), in a subset of ccRCC tumors. Compared to other ccRCC cases, this subset of cases had differential rates of mutations in the PI3K/mTOR pathway and significantly reduced overall survival. We hypothesize that the presence of aberrant RNAs in this subset indicates a global loss of NMD activity may be caused by reduced mTOR activity. Here we propose key pilot studies to establish that NMD is regulated by mTOR in ccRCC and that mTOR pathway mutations decrease NMD activity. This work will delineate a new tumorigenic mechanism, NMD mis-regulation, that has been understudied in cancer and may uncover new druggable targets for the benefit of ccRCC patients.

LCCC Membership: yes.

Involve faculty at another North Carolina institution: No - Not Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A

Tier 1 - Pilot Awards

Contact PI: Timothy Gershon

Degree: MD, PhD

Rank: Professor

Department: Neurology

Email: gershont@neurology.unc.edu

Other Investigator: Gianpietro Dotti

Project Title: Developing CAR-T cell therapy for medulloblastoma using endogenous mouse tumor models and single-cell transcriptomic analysis

Budget: $50,000

Review Category: clinical-translational

Abstract (for peer review):

We will develop chimeric antigen receptor T-Cell (CAR-T) therapy for medulloblastoma, using primary mouse medulloblastoma models and analysis by sc-RNA-seq. Immunotherapy is needed for

medulloblastoma because conventional radiation and chemotherapy cause long-term brain injury and fail too many patients. CAR-T cell therapy has been found effective for refractory cancers such as relapsed ALL with brain infiltration. However, clinical trials of CAR-T cell therapy for solid tumors have not been as successful, and animal models are needed to optimize implementation. At present, all preclinical studies of CAR-T cell therapy for brain tumors have used exogenous cells xenografted into immunocompromised mice. Primary mouse brain tumors do not express antigens that match brain tumor-specific antigens in humans. Studies of CAR-T cell therapy in immunocompetent mice with endogenous brain tumors are needed, and these studies require new models.

To meet this need, we genetically engineered mice that develop endogenous, medulloblastomas expressing the mouse homolog of B7-H3, a cell-surface antigen specifically expressed on pediatric brain tumors, including medulloblastoma. We now propose to treat these mice with B7-H3+ medulloblastomas with B7-H3-directed CAR-T cells, that we have already tested in mouse xenografts and to follow mouse survival and tumor growth. We will also analyze tumors under treatment using single-cell RNA-seq to define gene expression changes in CAR-T cells, other immune cells, and tumors cells, as each of these cell types interact. These studies will bring new insight into the mechanisms of CAR-T cell therapy and resistance and provide a new platform for optimizing CAR-T cell treatment.

LCCC Membership: yes.

Involve faculty at another North Carolina institution: No - Not Collaborate with another NC institution

Proposal also submitted to elsewhere: N/A