

Fall 2025

Pilot Awards and SPORE Awards

Pilot Award

PI: Caroline Thompson, PhD, MPH, Associate Professor, Epidemiology; and Chris Baggett, PhD, Assistant Professor, Epidemiology

Project Title: Planning CONCERN's Program Project: Emergency Department Care Across the Cancer Continuum

Abstract: Many underserved individuals—including rural residents and those who are uninsured or underinsured—rely on emergency departments (ED) for healthcare access due to limited primary care access. ED encounters represent critical opportunities to address missed cancer screening, accelerate diagnosis, and optimize symptom management, yet ED-based cancer care across the continuum remains poorly characterized and unoptimized. The Comprehensive Oncologic Emergencies Research Network (CONCERN), an NCI-supported collaborative, brings together investigators with active funding/publications in oncologic emergencies. CONCERN is positioned to develop a P01 application addressing this gap, but systematic planning is needed to refine the conceptual framework, generate preliminary data, and coordinate multi-site collaboration. This pilot grant will support three aims: (1) develop a unifying conceptual framework identifying intervention targets across the cancer care continuum; (2) conduct preliminary data analyses using established administrative data resources to characterize ED-based cancer encounters; (3) coordinate team activities and produce a P01 application. LCCC will serve as coordinating center and activities will leverage the Grants Development Office support and build on CONCERN's established infrastructure. Expected outcome: submission of competitive P01 application that integrates 3-4 projects spanning the care continuum, with UNC housing Administrative and Data Management Cores.

Pilot Award

PI: Cyrus Vaziri, PhD, Professor, Pathology & Lab Medicine; Jessica Bowser; Victoria Bae-Jump

Project Title: Defining SGK1-NDRG1 Signaling as a Novel Driver of Metastatic Endometrial Cancer

Abstract: This project will define the molecular mechanisms that govern formation and survival of metastatic cancer ‘spheroids’. Most cancer deaths are caused by the spread of malignant cells. In many metastatic cancers, tumor cells form multi-cellular spheroids in the abdominal cavity, creating a potent metastatic niche. The molecular mechanisms that drive spheroid formation and sustain their metastatic potential are poorly understood. Until we understand the molecular underpinnings of spheroid pathobiology, life-saving therapeutic interventions for many metastatic cancers will not be possible. We have used Endometrial Cancer (EC) cells to establish new patient-relevant model systems for interrogating spheroid pathobiology. Based on exciting pilot work we hypothesize that the spheroid-specific protein kinase SGK1 and its substrate NDRG1 (a DNA repair protein) promote cancer stemness and tumorigenic characteristics in metastatic EC. Our Specific Aims are: (1) Define role of SGK1 protein kinase in mediating tumorigenic phenotypes of EC spheroids. (2) Test role of phospho-NDRG1 in sustaining cancer stemness. We propose an innovative solution to the important problem of how cancer cells metastasize. Our work is significant because we will reveal therapeutically tractable targets that critically drive the deadliest phase of cancer. SGK signaling is hyperactive in individuals with black ancestry, which may help explain racial disparities in EC outcomes between black and Caucasian patients.

Pilot Award

PI: Didong Li, PhD, Assistant Professor, Biostatistics, and Katherine Hoadley, PhD, Associate Professor, Genetics

Project Title: Integrative AI Models for Breast Tumors from Histology and Spatial Transcriptomics

Abstract: Spatial organization in the tumor microenvironment drives breast cancer progression, therapeutic response, and recurrence. Spatial transcriptomics (ST) and digital pathology now allow high-resolution mapping of gene expression and tissue architecture. However, datasets are fragmented across platforms, lack metadata, and are often too small for generalizable models. We propose to develop breast cancer-specific AI models integrating ST, histology, and clinical metadata to identify spatial biomarkers of tumor heterogeneity and outcome. In Aim 1, we will curate a harmonized, multimodal dataset using population and trial data. To enrich metadata, we will develop an AI agent to extract missing clinical information (staging, subtype, recurrence) from publications. Using these curated data, we will build cross-platform representation learning models that align histology, gene expression, and clinical features. In Aim 2, we will use these learned

representations to derive patient-level spatial features that quantify tumor-immune interactions, stromal architecture, and spatial heterogeneity. These features will be tested for association with clinical outcomes using time-to-event models. We will also apply spatial point process models to quantify immune infiltration and tumor-stroma organization. This work will generate robust spatial representations and predictive models tailored to breast cancer, enabling discovery of clinically relevant biomarkers and supporting precision oncology.

Pilot Award

PI: S. Rahima Benhabbour, MSc, PhD, Associate Professor, Joint Department of Biomedical Engineering; Gianpietro Dotti, MD, Professor, Immunology and Immunotherapy Research Program; Barbara Savoldo, MD, PhD, Champion Mitchell Distinguished Professorship, Pediatric Oncology; Shawn Hingtgen, PhD, Professor, Division of Pharmacoengineering and Molecular Pharmaceutics

Project Title: Enhanced Delivery of CAR-T Cells Using an Innovative Thermoresponsive Injectable Hydrogel System for Treatment of Glioblastoma Multiforme (GBM)

Abstract: Glioblastoma multiforme (GBM) is the most aggressive form of brain cancer and ~90% of GBM patients die within 24 months after diagnosis. Treatment options for GBM include surgery and chemoradiation however, recurrence is common, and the disease is universally fatal. Immune checkpoint inhibitors have shown remarkable promise for solid tumors however, they have been markedly ineffective against GBM. This has been largely attributed to the low tumor-specific T-cell infiltration environment of GBM. As such, T cells designed to target tumor-associated antigens, such as chimeric antigen receptor (CAR) T cells, represents a promising strategy in tumors, like GBM, that lack endogenous T cell responses. However, limited delivery of CAR-T cells at the tumor site due to the blood brain barrier (BBB) represents a significant limitation to the clinical utility of CAR-T cell infusions. To address these limitations, we propose to develop a combination therapy that harnesses long-acting delivery (>14 days) of CAR-T cells locally in the tumor resection cavity using a novel injectable and biodegradable biomaterial and co-delivery of cytokines for CAR-T cell proliferation and enhanced efficacy outcomes. This cutting-edge combined approach will be utilized to evaluate the scientific premise of our proposal and advance a unique and highly innovative combinatorial technology to improve treatment of GBM.

Pilot Award

PI: Yinglong Miao, PhD, Associate Professor, Pharmacology, and Henrik Dohlman, PhD, Stanford Steelman Distinguished Professor and Chair, Pharmacology

Project Title: De novo peptide inhibitor design of Gq proteins for treating Uveal Melanoma

Abstract: Heterotrimeric G proteins function as molecular switches for cellular growth and metabolism. G proteins are activated by GDP to GTP nucleotide exchange and then inactivated by GTP hydrolysis. In Gq proteins, mutation of a conserved glutamine residue (Q209) to leucine or proline causes uveal melanoma. Two macrocyclic depsipeptides YM-254890 (YM) and FR900359 have been identified to inhibit Gq proteins with high potency and selectivity. Despite being valuable chemical probes, these natural products have not yet been translated to cancer therapeutics. In recently published studies, the Dohlman lab has determined that the catalytic Q209 modulates critical functions of Gq and the protein signaling emerges from an ensemble of active states, a subset of which are favored in disease and thus druggable for selective cancer treatment. Moreover, the Miao lab has performed accelerated Molecular Dynamics simulations which provide mechanistic insights into binding selectivity of the YM inhibitor in Gq, as well as distinct structural dynamic features in binding pockets of the Gq disease mutants. Based on these findings, we will combine complementary simulations and experiments to design and test novel peptide inhibitors with improved therapeutic properties for Gq disease mutants. Our aims include: (1) Design and test de novo peptide inhibitors against the Q209L/P disease mutants of Gq. (2) Examine selectivity of peptide binding to different G proteins in simulations and cellular assays.

Pilot Award

PI: Deepika Sharma, PhD, Assistant Professor, Microbiology and Immunology, and Ankit Malik, PhD, Assistant Professor, Microbiology and Immunology

Project Title: Stress disrupts immunosurveillance in colorectal cancer through adrenergic signaling

Abstract: Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer mortality worldwide. CRC incidence in adults under 50 continues to rise, and effective treatment options for advanced disease remain elusive. Immune dysfunction plays a critical role in CRC progression, and although sympathetic neurons innervate tumors, their contribution is poorly understood. Stress promotes sympathetic activation and is associated with worse outcomes in CRC. However, the underlying

mechanism remains unknown. We hypothesized that stress-mediated activation of sympathetic neurons contributes to immune dysfunction and colorectal cancer progression. Using a murine CRC model, our preliminary data indicate that sympathetic neurons promote immune dysfunction and drive tumor progression via alpha2A-adrenergic signaling. Similarly, stress impairs anti-tumor immune response and increases tumor burden in CRC. In this proposal, we will identify the cellular and molecular mechanisms of sympathetic-immune interactions and assess their contribution to the impact of physiological stress on CRC. Using interdisciplinary approaches from immunology and neurobiology, we will elucidate mechanisms underlying sympathetic control of antitumor immunity in CRC. Given that stress and sympathetic modulators are widely encountered in human populations, understanding how these factors alter immune responses has significant implications for human health and CRC treatment strategies.

Pilot Award

PI: Jillian Perry, PhD, Assistant Professor, Eshelman School of Pharmacy; Chad Pecot, MD, Professor, Division of Oncology; Sacha Tuchman, MD, MHS, Professor of Medicine, Clinic Medical Director for Malignant Hematology

Project Title: Development of CD38-directed IRF4-targeting siRNA to treat multiple myeloma

Abstract: Multiple myeloma (MM) is the second most common hematologic malignancy and remains largely incurable due to relapse and the emergence of drug resistance. A key vulnerability in MM is its dependence on the transcription factor IRF4, a master regulator of survival, proliferation, and metabolism. Targeting IRF4 offers a compelling strategy to overcome resistance, yet no small-molecule inhibitors exist because IRF4 is an intrinsically disordered protein that lacks a defined binding pocket. To address this, we developed a novel antibody-oligonucleotide conjugate (AOC) combining a potent IRF4-targeting siRNA with the anti-CD38 monoclonal antibody Daratumumab (Dara) for selective MM delivery. Preliminary data show efficient synthesis, uptake, and silencing activity in MM cell lines, supporting the feasibility of this targeted RNA therapeutic. Leveraging expertise in MM biology, RNA therapeutics, and targeted drug delivery, we will (1) characterize Dara-IRF4 siRNA conjugates in vitro for uptake, receptor specificity, and IRF4 pathway inhibition in vitro, and (2) evaluate in vivo pharmacokinetics, tumor accumulation, and therapeutic efficacy in MM xenograft models. Successful completion of this project will validate a first-in-class therapeutic strategy that directly disrupts a non-druggable transcriptional

dependency in MM and may be adaptable to other malignancies expressing targetable surface antigens.

Cancer Health Disparities SPORE in Endometrial Cancer Developmental Research Program

PI: Benjamin Albright, MD, MS, Assistant Professor, Gynecology Oncology

Abstract: In the US, endometrial cancer is the 4th most common cancer of women. Incidence and mortality risk is increasing across groups, with disparities by age, race, geography, body mass index, and comorbidity. Over 90% of endometrial cancers present with abnormal bleeding. Yet, a patient's course from symptom onset to diagnosis can be complex and variable, and delays can impact outcomes. Symptom recognition and access to care impact timing and location of initial presentation. Diagnostic testing with ultrasound and/or endometrial biopsy may vary depending on the setting and evaluating provider specialty/training. Earlier identification of disease during pathogenesis is essential to efforts to reduce the incidence and mortality burden of endometrial cancer, particularly given it is highly curable at early-stage. The objective of this study is to describe patterns in care seeking behavior (patient interval) and evaluation for bleeding symptoms (diagnostic interval), aiming to identify pitfalls, barriers, and disparities in the course to diagnosis of endometrial cancer and precancer. For Aim 1, we will collect primary patient data on bleeding patterns and perceived barriers to care via directed questionnaire and clinical data extraction for new diagnoses at UNC. For Aim 2, we will utilize a unique population-based data resource that links the North Carolina cancer registry with multi-payer claims data to study diagnostic care patterns at the population-level for endometrial cancer.

Cancer Health Disparities SPORE in Endometrial Cancer Developmental Research Program

PI: Sarah Van Alsten, PhD

Project Title: Data Integration to Understand the Role of Adiposity and Sociodemographic Features on Endometrial Cancer Immune Profiles

Abstract: Better characterization of the endometrial cancer (EC) immune microenvironment and determinants thereof may aid in identifying the patients most likely to respond to immunotherapy. Given that the cancer immune microenvironment is shaped by both patient-level factors such as obesity, and intrinsic tumor biologic features such as genomic instability and molecular subtype, comprehensive understanding requires

integration of multiple features assessed at different scales. Moreover, as both endometrial cancer incidence and mortality are rising, with Black patients having the poorest outcomes, it is critical to address potential tumor immune differences by race and social context. Our proposed research will use the Carolina Endometrial Cancer Study, a diverse cohort of endometrial cancers oversampled for Black women, to investigate patient, social, and tumor features that impact the EC immune microenvironment. We will employ bulk RNA-sequencing to deconvolve immune cell populations and estimate genomic instability in EC tissue, validating results with confirmatory immunofluorescence for a subset of key immune populations (e.g. CD8+ T-cells). We will also leverage a novel statistical method (Data Integration Via Analysis of Subspaces [DIVAS]) to disentangle interrelations amongst immune and tumor biologic features, obesity, and patient-level sociodemographics, thereby uncovering interactions that drive anti-tumor immunity.

Cancer Health Disparities SPORE in Endometrial Cancer Career Enhancement Program

PI: Kari Hacker, MD, PhD, Associate Professor, OBGYN-GYN Oncology

Abstract: CCNE1 amplification occurs in a subset of endometrial cancers (EC), is associated with poor survival, and disproportionately affects racially diverse women. Despite its clinical significance, the mechanisms underlying adverse outcomes in CCNE1-amplified EC remain poorly understood. Emerging evidence suggests that CCNE1 amplification influences the tumor immune microenvironment (TME), promoting immune evasion and therapy resistance. This project will test the hypothesis that CCNE1-amplified EC exhibits a more immunosuppressed TME than CCNE1-wildtype tumors, contributing to poor clinical outcomes. I propose two complementary aims. Aim 1 will define the immune landscape of CCNE1-amplified versus wildtype EC using immunofluorescence and transcriptomic profiling of existing tumor specimens, focusing on immune cell composition, checkpoint expression, and inflammatory signaling. Aim 2 will characterize tumor and stromal features associated with CCNE1 amplification by analyzing transcriptomic datasets to identify pathway alterations linked to aggressive behavior. Findings from this study will provide mechanistic insight into how CCNE1 amplification shapes the immune and molecular environment of EC, generating hypotheses for future therapeutic interventions. Participation in the Career Enhancement Program will provide mentorship and resources to establish this research focus, laying the foundation for a career dedicated to improving outcomes in high-risk EC patients.

Cancer Health Disparities SPORE in Endometrial Cancer Career Enhancement Program

PI: Jillian Perry, PhD, Assistant Professor, Eshelman School of Pharmacy

Abstract: Endometrial cancer disproportionately affects Black, obese, and socioeconomically disadvantaged women, who experience 40–90% higher mortality rates than their White counterparts, despite similar incidence. These disparities arise from limited access to surgical care, higher comorbidities, delayed diagnosis, and reduced treatment tolerance, leaving many women without safe or effective options. To address these inequities, we developed OncoWave, a customizable, chemotherapeutic-eluting intrauterine device (IUD) for localized, non-surgical treatment. Using a low-cost, additive manufacturing platform, OncoWave enables rapid prototyping and scalable production to be deployed in outpatient or resource-limited settings. Our interdisciplinary team of clinicians, additive manufacturing specialists, and translational scientists will fabricate and characterize OncoWave IUDs with varied drug loadings and compositions to optimize local drug release and anti-tumor efficacy. Using established human EC cell lines and orthotopic mouse models, we will define how each design feature influences drug release kinetics, tumor penetration, and therapeutic response both in vitro and in vivo. These studies aim to yield a locally administered therapy that achieves potent tumor regression, reduces systemic toxicity, and overcomes barriers to care. OncoWave has the potential to close gaps in EC treatment and provide effective therapy to women currently excluded from surgical interventions.

Breast SPORE Developmental Research Program

PI: Nick Brown, PhD, Associate Professor, Pharmacology

Project Title: Mechanistic Studies of Metabolic Regulation of TET DNA Demethylases in Triple-Negative Breast Cancer

Abstract: Patient responses to immune checkpoint inhibitor (ICI) therapy in triple-negative breast cancer (TNBC) are inconsistent, related to poor T cell recruitment and activity. Data from our group has shown that the DNA dioxygenase TET2 is important for tumor immunity by controlling the expression of key antigen presentation machinery (APM) genes. Consistently, knockout of TET2 in the B16 melanoma model significantly blocked anti-PD-L1 efficacy. TET proteins are -ketoglutarate(-KG)-dependent enzymes that demethylate DNA to control gene expression. Both published and unpublished data from our group

indicate that TET activity is lost in a portion of tumors, including some TNBC, without loss of expression of TET2. Using a cell-free, NMRbased activity assay, we uncovered that the metabolite oxaloacetate (OAA) potentially blocks TET2 function. Based on new data using TNBC cell lines, organoids, and tumors, we hypothesize that OAA-mediated inhibition of TET activity occurs in a portion of TNBC, resulting in lower expression of APM genes, reduced tumor immunity and poor ICI response. Here, we will utilize TNBC organoid models and generate metabolomics data from TNBC tumors to characterize TET expression/activity along with APM genes expression, potentially revealing an explanation for reduced tumor immunity in some TNBCs. If successful, these data will bolster our R01 resubmission that received a 16th percentile score on the first submission.

Breast SPORE Developmental Research Program

PI: Justin Milner, PhD, Assistant Professor, Microbiology and Immunology

Abstract: Adoptive Cell Therapy (ACT) is a transformative immunotherapy approach with curative potential in hematologic malignancies. However, ACT efficacy in solid tumor settings, such as in breast cancer, remains limited due to the immunosuppressive tumor microenvironment (TME), which restricts T cell activity, accumulation, and persistence. A tactical advantage of ACT is that T cells can also be genetically engineered to endow functional attributes that augment their function. However, our understanding of the genetic programs that control T cell responses in cancer are primarily derived from loss-of-function approaches. In contrast, gain-of-function (GOF) perturbations—where genes are overexpressed or artificially activated—represent a powerful but underexplored means to reprogram T cells. To profile GOF perturbations and the formation of new T cell states, we have recently developed a single-cell GOF screening platform that enables high-throughput profiling of GOF perturbations in T cells at single-cell resolution. Aim1 of this proposal will investigate key GOF perturbations predicted to enhance T cell activity in the tumor microenvironment in preclinical breast cancer models. Aim2 will build on our novel genetic screening approach to define new regulators of T cell activity and accumulation in breast cancer. In summary, this Breast Cancer Spore CEP proposal unites cutting-edge genetic screening with synthetic immunology to overcome the barriers to effective ACT in breast cancer.

Breast SPORE Developmental Research Program

PI: Didong Li, PhD, Assistant Professor, Biostatistics

Project Title: Integrative AI Models for Breast Tumors from Histology and Spatial Transcriptomics

Abstract: Spatial organization in the tumor microenvironment drives breast cancer progression, therapeutic response, and recurrence. Spatial transcriptomics (ST) and digital pathology now allow high-resolution mapping of gene expression and tissue architecture. However, datasets are fragmented across platforms, lack metadata, and are often too small for generalizable models. We propose to develop breast cancer-specific AI models integrating ST, histology, and clinical metadata to identify spatial biomarkers of tumor heterogeneity and outcome. In Aim 1, we will curate a harmonized, multimodal dataset using population and trial data. To enrich metadata, we will develop an AI agent to extract missing clinical information (staging, subtype, recurrence) from publications. Using these curated data, we will build cross-platform representation learning models that align histology, gene expression, and clinical features. In Aim 2, we will use these learned representations to derive patient-level spatial features that quantify tumor-immune interactions, stromal architecture, and spatial heterogeneity. These features will be tested for association with clinical outcomes using time-to-event models. We will also apply spatial point process models to quantify immune infiltration and tumor-stroma organization. This work will generate robust spatial representations and predictive models tailored to breast cancer, enabling discovery of clinically relevant biomarkers and supporting precision oncology.

Breast SPORE Career Enhancement Program

PI: Yash Agrawal, MD, Assistant Professor, Division of Oncology

Abstract: Aging is associated with higher breast cancer incidence and mortality and is reflected in changes in tumor subtype distribution and the immune microenvironment. Aging is also linked to systemic immune dysregulation, which may correlate with chemotherapy response. We hypothesize that age-related peripheral immune alterations are reflected in the breast cancer microenvironment, and that these features, along with plasma proteomic “aging clocks,” can predict neoadjuvant chemotherapy response. Our goals are: 1) To analyze how circulating immune cell gene expression features correspond with matched breast cancer immune-related gene expression signatures across intrinsic subtypes and with age. We will apply bulk RNA sequencing (RNAseq), deconvolution, and hierarchical clustering to assess correlation between tumor features and peripheral blood

lymphocyte (PBL) profiles across 10-year age groups from an institutional biorepository. 2) To investigate how plasma proteomic markers of biological and organ aging and matched PBL profiles of senescence correlate with neoadjuvant chemotherapy response. From the same biorepository, we will quantify >1000 plasma proteins with liquid chromatography coupled with mass spectrometry, compute protein signatures of aging along with matched PBL RNAseq signatures that correlate with age, and apply differential expression analysis, hierarchical clustering, and logistic regression to identify which features are associated with treatment response.

Breast SPORE Career Enhancement Program

PI: Tigist Tamir, PhD, Assistant Professor, Biochemistry and Biophysics

Abstract: Despite advances in targeted therapies, a subset of breast cancer patients develop resistance to therapy, leading to relapse and poor outcomes. A major barrier to overcoming resistance is our limited understanding of adaptive regulatory mechanisms at the interface of signaling and metabolism. Metabolic reprogramming is a hallmark of therapy resistance and incorporates the oxidative stress response (OSR), which maintains redox homeostasis in hypoxic, nutrient-limited environments by dynamically regulating redox metabolism. Phosphorylation critically modulates metabolic enzyme activity, stability, and interactions, yet its role in therapy-resistant breast cancer remains unclear. This project will define phosphorylation-dependent redox rewiring that drives therapy resistance. I hypothesize that phosphorylation generates emergent, systems level properties not evident from individual enzymes or gene expression, enabling tumor plasticity and survival. Using an integrative multi-omics strategy, CRISPRi screening, and computational modeling, I will: (1) map OSR pathway reprogramming in patient tumors and preclinical models, (2) evaluate the therapeutic impact of targeting redox metabolism. My vision is to identify redox-dependent mechanisms that drive resistance and use patient samples, including FFPE tissue, to predict vulnerabilities and guide treatment. This work aligns with Breast SPORE goals to apply combinatorial, systems-level approaches to advance breast cancer research.