Tier 2 - Stimulus Awards

Contact PI: Gianpietro Dotti MD

Rank: Professor

Other Investigator: Matthew Foster

Project Title: Exploiting the glucose-regulated protein 94 (GRP94) as immunotherapy target for acute myeloid leukemia

Review Category: clinical-translational

Abstract (for peer review):

In patients with acute myeloid leukemia (AML), leukemia relapse remains a significant cause of failure even after allogeneic hematopoietic stem cell transplantation (HSCT), underlining the need for innovative therapies in these patients. The infusion of T lymphocytes genetically modified with a chimeric antigen receptor (CAR) that targets the CD19 antigen has shown remarkable antitumor effects in acute lymphoid leukemia (ALL), promoting over 75% complete responses in relapsed/refractory patients. In contrast, the development of CAR-T cells faces a major limitation in AML, related to the unique property of the antigen-specific moiety of CARs which is derived from a monoclonal antibody and therefore target molecules only expressed on the cell surface of tumor cells. Indeed, currently known surface antigens expressed by AML blasts, such as CD33 and CD123, are also expressed by normal myeloid precursors. Thus, targeting either CD33 or CD123 by means of specific CAR-T cells causes severe myeloid suppression, precluding the use of these antigens to control leukemia relapse long-term. We here propose to develop an innovative CAR specific for the glucose-regulated protein 94 (GRP94). In normal cells, this chaperon protein is retained in the endoplasmic reticulum (ER) and thus non targetable by GRP94-specific CAR-T cells. In contrast, GRP94 is consistently relocated to the cell surface in tumor cells such as myeloid leukemia blasts rendering them susceptible to killing by GRP94-specific CAR-T cells. This approach has the immediate advantage to target leukemic cells, whilst sparing normal myeloid precursors. Here we propose to assess safety and efficacy of GRP94-specific CAR-T cells both in vitro and in vivo.

Tier 2 - Stimulus Awards

Contact PI: Shelley D Golden PhD, MPH

Rank: Clinical Assistant Professor

Other Investigator: Kurt Ribisl, Thomas Carsey

Project Title: Trends in state tobacco control legislation introduction and enactment

Review Category: population science

Abstract (for peer review):

Public policies implemented at the state level are a primary reason tobacco use rates have dropped, along with associated cancer morbidity and mortality. Despite this progress, tobacco use still remains the leading preventable cause of death, and further improvements in state tobacco control policies are still possible. Although states were very active in this policy arena ten years ago, they are now rarely passing new tobacco control legislation. It is unknown whether this trend reflects waning interest in introducing bills that might have passed, or whether political barriers derail bills after their introduction. To better understand current failures to implement these evidence-based cancer prevention strategies, we propose a Tier 2 study of all tobacco control bills that were introduced in all 50 state legislatures between 2012-2014. After identifying proposed legislation using legal search engines, we will develop a coding scheme to categorize the content of each bill, as well as its progress through the policymaking system. Using this information we will ascertain patterns of bill introduction and enactment, trends in policy content and rationale, and characteristics of bills and state political conditions most associated with ultimate success in the policymaking arena. The current study will illuminate opportunities for improving tobacco-specific policy dissemination, and serve as the template for an R01 proposal to study policy dissemination and implementation related to multiple cancer control policy topics, including human papilloma virus vaccination and tanning bed establishment regulation.

Tier 2 - Stimulus Awards

Contact PI: Adam O Goldstein MD, MPH

Rank: Professor

Other Investigator: Paschal Sheeran

Project Title: Relationships between Little Cigar and Cigarillo Packaging Elements, Perceptions of Characterizing Flavors, and Use among Young Adults

Review Category: population science

Abstract (for peer review):

Characterizing flavors, tobacco product additives that alter flavor, appear to increase tobacco use, thus increasing cancer risks. The Family Smoking Prevention and Tobacco Control Act of 2009 banned flavors other than menthol in cigarettes. Flavors are still permitted in other tobacco products like little cigars and cigarillos (LCC). Research on tobacco product packaging demonstrates that packaging design elements (e.g., flavor descriptors, color, shape, branding, and health warnings) influence perceptions about the attractiveness, taste, and health risks of cigarettes. Package design elements that create positive images of LCCs and their users may increase susceptibility to LCC use. This study examines how packaging design elements are associated with risk behavior decision making for LCC use. The proposed study utilizes Amazon's Mechanical Turk (MTurk) survey tool to assess perceptions of characterizing flavors and experimentally examine how LCC packaging design elements relate to use, susceptibility to use, and perceptions of health risk among 6,500 young adult (ages 18-26) LCC users and non-users. The study will assess LCC and tobacco use, knowledge of LCC health risks, and person-level psychosocial factors related to LCC use. Participants will view 10 randomly assigned LCC packages that vary by five separate packaging design elements. After seeing each package, participants will answer questions assessing constructs such as attractiveness, perceived risk, flavor/taste, norms, and prototypes. Data analysis will use linear mixed effects models for continuous outcome variables and logistic mixed effects models for binary outcomes to assess associations between each of the key outcome measures and LCC product pack design elements.

Tier 2 - Stimulus Awards

Contact PI: Lee M Graves PhD

Rank: Professor

Other Investigator: Channing J. Der, PhD

Project Title: Defining the KRAS-dependent kinome in pancreatic cancer

Review Category: basic science

Abstract (for peer review):

Pancreatic cancer is currently the 4th major cause of cancer deaths in the US and it is projected to be the 2nd leading cause by 2020. The 5-year survival rate for this cancer is a dismal 6% and the currently approved therapies are ineffective. To date no effective targeted therapies have been developed for pancreatic cancer.

The near 100% mutation frequency of the KRAS oncogene in pancreatic cancer, coupled with strong experimental evidence that ablation of KRAS function will severely impair pancreatic cancer growth, has make the development of anti-KRAS therapies one of the four major directions identified by the 2013 NCI Pancreatic

Cancer Task Force. While there are now intense efforts to target RAS, each directly faces serious technical limitations such that it is unclear whether any of these current strategies and targets will successfully develop a clinically useful anti-KRAS drug. This concern is reflected in the initiation of the NCI RAS program in 2014, where there is a mandate to pursue novel directions, to identify new targets. Since the ultimate success of currently pursued directions for anti-KRAS drug discovery remains highly uncertain, it is generally agreed that novel directions need to be pursued to identify new targets. The goal of our studies is to identify novel targets for the development of anti-KRAS therapeutic strategies for pancreatic cancer. We hypothesize that a comprehensive profiling of mutant KRAS-dependent protein kinase activities (the “KRAS-ome”) utilizing the innovative multiplexed kinase inhibitor beads and mass spectrometry (MIB/MS) technology will achieve this objective.

Tier 2 - Stimulus Awards

Contact PI: Liza Makowski PhD

Rank: Assistant Professor

Other Investigator: Hursting, Dudley, Troester, Parker

Project Title: Metabolic Immunomodulation Of Obesity-Induced Basal-Like Breast Cancer

Review Category: basic science

Abstract (for peer review):

Obesity is associated with basal-like breast cancer (BBC). Using the BBC C3(1)-Tag mouse, we reported that obese mice demonstrated early latency and elevated progression. The oncogenic HGF/cMet pathway was also increased by obesity in both normal mammary and tumors. Pharmacologic inhibition of cMet signaling reduced obesity-driven tumor burden in C3(1)-Tag mice. Importantly, obesity followed by weight loss resulted in reversal of all obesity-associated effects. We have shown that BBC has unique interactions with stromal cells including macrophages which can be leveraged in approaches to reduce risk. This crosstalk between tumor cells, macrophages and endothelial cells is essential for immunosurveillance, progression, and metastasis. In BBC mice, mammary gland macrophages were increased with obesity and reduced by weight loss. We reported that obese women have greater macrophage infiltration in the mammary gland. A critical question to be addressed is how obesity-induced growth factor signaling and changes in the stroma lead to increased BBC. It is also unclear what subtype of macrophage – pro-tumorigenic or tumoricidal- is regulated by obesity. Aim 1 will test the hypothesis that obesity alters BBC tumorigenesis through changes in stromal cellular components including macrophages and endothelial cells and HGF-dependent neovascularization. Aim 2 will test the hypothesis that manipulating macrophage-specific substrate metabolism alters macrophage subtype and tumor immunosurveillance. Because obesity is increasing worldwide, understanding the role of obesity in BBC and its unique effects on stroma are questions with high public health impact. BBC currently has no targeted therapies, therefore identification of risk factors and novel pathways would be transformative.

Tier 2 - Stimulus Awards

Contact PI: Paschal Sheeran PhD

Rank: Full Professor

Other Investigator: Seth Noar, Adam Goldstein

Project Title: How Can Skin Cancer Best Be Prevented? Meta-Analysis of Behavior Change Techniques in Randomized Controlled Trials

Review Category: population science

Abstract (for peer review):

Although reducing sun exposure and indoor tanning would lower rates of skin cancer, it is currently unclear what are the best ways to promote behavior change. This is because (a) a comprehensive meta-analysis of interventions to reduce skin cancer has yet to be conducted, and (b) relevant evidence has not been synthesized in a manner that permits inferences about the effectiveness of strategies deployed in interventions. The proposed research will provide this synthesis. The research aims to (a) quantify the impact of interventions to reduce exposure to ultraviolet radiation (UVR), (b) develop a reliable taxonomy of behavior change techniques used in UVR-protective interventions, and (c) identify the behavior change techniques that are effective in promoting UVR protection. The research comprises a meta-analytic review of behavioral interventions that used a randomized controlled (RCT) design, measured sun protection behavior (e.g., sunscreen use, wearing protective clothing), sunburn, or indoor tanning in the wake of the intervention, and recruited adolescent or adult participants. The research team will draw upon expertise in psychology, health communication, family medicine, and public health in order to develop a bespoke taxonomy of the behavior change techniques used in UVR-protective interventions, and use meta-regression to establish which techniques (or combination of techniques) are effective in changing behavior. The research will not only generate a landmark synthesis of interventions designed to prevent skin cancer, but also uniquely qualify the applicants to produce two competitive NIH grant proposals for new evidence-based interventions.

Tier 2 - Stimulus Awards **Cancer Disparities Targeted RFA**

Contact PI: Stephanie Wheeler PhD

Rank: Assistant Professor

Other Investigator: Alison Tytell Brenner, PhD

Project Title: Mailed reminders plus fecal immunochemical testing (FIT) to increase colorectal cancer screening among Medicaid beneficiaries in Mecklenburg County

Review Category: population science

Abstract (for peer review):

Over one-third of age-eligible US adults are not up to date with colorectal cancer (CRC) screening, despite strong evidence that screening can reduce CRC incidence and mortality. Medicaid-insured populations traditionally have had lower CRC screening rates than other insured populations. Formative work by our team has suggested that mailing screening reminders, with and without fecal immunochemical tests (FIT), to vulnerable patients' homes may remove key access barriers and increase screening rates over traditional, practice-based approaches. Implementing a statewide mailed FIT program for Medicaid beneficiaries could help reduce screening disparities, but pragmatic implementation questions remain, including how to manage the program, whether a mailed FIT program is incrementally more effective and cost-effective than a mailed reminder program alone, and whether clinicians and state Medicaid quality improvement organizations would find such a program acceptable and sustainable. We have previously demonstrated our ability to work with state Medicaid quality improvement organizations to identify unscreened beneficiaries in defined geographic regions of North Carolina using claims databases. Further, we were able to demonstrate the reach and effectiveness of a mailed reminder to encourage beneficiaries to discuss screening with their providers or a centralized patient navigator. We seek to leverage those existing relationships and extend our prior work to demonstrate the comparative effectiveness (Aim1), feasibility and acceptability (Aim2), and cost- effectiveness (Aim3) of a mailed reminder plus FIT screening program in a population of Medicaid enrollees in Mecklenburg County--the most populous county in North Carolina, with some of the lowest CRC screening rates in the state. Idea

Tier 2 - Stimulus Awards

Contact PI: QING ZHANG PH.D

Rank: ASSISTANT PROFESSOR

Project Title: USP15 as a Novel Therapeutic Target in Kidney Cancer by Deubiquitinating HIF2α

Review Category: basic science

Abstract (for peer review):

Kidney cancer incidence has been increasing steadily for the past several decades, although the reasons for this are unclear. The VHL tumor suppressor gene was identified as a germline mutation in patients at risk for clear cell renal cell carcinoma (ccRCC), which accounts for approximately 85% of all kidney cancers. More importantly, inactivating VHL mutations also play major roles in sporadic renal cell cancer. Work from many laboratories show that the pVHL-associated complex has E3 ubiquitin ligase activity and VHL loss leads to hypoxia inducible factor α (HIF-α, including HIF1α and HIF2α) accumulation. While HIF1α serves mainly as a tumor suppressor in kidney cancer, HIF2α stabilization, as a result of pVHL loss, is sufficient and necessary for promoting kidney tumor growth. Therefore, HIF2α serves as an important therapeutic target in kidney cancer related to VHL loss. While HIF2α can undergo ubiquitination and degradation mediated by pVHL E3 ligase complex, it remains unclear whether HIF2α can also be regulated by deubiquitination pathways. Recently, we performed a deubiquitinase (DUB) siRNA screening (including all of known 96 DUB family members) in kidney cancer cells and identified USP15 as a specific deubiquitinase that regulate HIF2α protein levels in kidney cancer. We hypothesize that USP15 can serve as a novel therapeutic target in kidney cancer by deubiquitinating HIF2α. In specific aim 1, we will determine the mechanism by which USP15 regulates HIF2α protein stability in kidney cancer with VHL loss. In specific aim 2, we will determine the functional role of USP15 in kidney cancer in vitro and in vivo. Successful completion of this proposal will motivate the development of specific USP15 inhibitors that benefit kidney cancer patients.

Tier 1 - Pilot Awards **Chemistry and Cancer Biology Targeted RFA**

Contact PI: Zibo Li PhD

Rank: Associate Professor

Project Title: Development of 18F-PET Probes to Image the IDO Pathway for Immuno-Oncology Clinical Research

Review Category: basic science

Abstract (for peer review):

Several PD-1/PD-L1 pathway inhibitors were recently FDA approved for various solid tumor malignancies. However, not every patient will respond to these expensive, potentially lifelong treatments. In contrast to small molecule inhibitors whose use is contingent upon a companion diagnostic (usually a mutation identified by sequencing of DNA from tumor tissue), there are no reliable biomarkers for these immune-oncology drugs. Clearly, there is an urgent need to identify predictive biomarkers of response to these treatments. Indoleamine2,3-dioxygenase (IDO1) plays a special role in the biology of various cancer types, because it breaks down the essential amino acid tryptophan for immune cell activation. Upregulation of IDO1 significantly correlates with the number of various T cell types in tumor tissues in melanoma and other cancers, suggesting that IDO expression is linked with effective and ineffective ('exhausted') immune response in cancer.

Positron emission tomography (PET) allows us to non-invasively and reliably correlate real-time expression of the marker in all tumor tissues with treatment outcome. Here, we hypothesize that IDO-specific PET probes hold great potential to 'mark' tumors bearing tumor-infiltrating immune cells, an absolute requirement for response to PD-1/PD-L1 pathway inhibitors. Clinically available PET tracers, 18F-fluorodeoxyglucose (FDG), and 18F-fluorothymidine, are nonspecific, whereas clinically available IDO PET tracers are 11C-based, and therefore short-lived and unavailable for widespread clinical use. In this proposal, we aim to synthesize and evaluate novel 18F labeled PET agents with high IDO affinity and specificity, which could be used as a non-invasive predictive method to select patient to anti-PD-1 mAb-based therapies.

Tier 1 - Pilot Awards

Contact PI: Steven I Park MD

Rank: Associate Professor

Project Title: Elucidating the Mechanisms of Resistance to PI3K Inhibition in Lymphoma

Review Category: clinical-translational

Abstract (for peer review):

Despite the promise of novel targeted therapies against signaling pathways in follicular lymphoma (FL), the emergence of resistance presents a major obstacle to the sustained clinical benefit of this approach. Our objective is to further understand the mechanism of resistance in response to targeted therapy in FL. We will characterize the genome, transcriptome, and kinome signatures at baseline and post-therapy to identify compensatory pathways responsible for resistance to targeted inhibition against the PI3K pathway using in vitro and in vivo lymphoma models. We will also characterize the mechanisms of innate as well as acquired drug resistance in tumor samples obtained from patients treated with idelalisib, a PI3Kδ inhibitor. The successful outcome of this research will lead to rational design of highly potent drug combinations in FL to overcome drug resistance.

Tier 1 - Pilot Awards **Chemistry and Cancer Biology Targeted RFA**

Contact PI: Melanie A Priestman PhD

Rank: Research Assistant Professor

Project Title: Monitoring the Proteasome's Catalytic Signature in Hematological Malignancies

Review Category: basic science

Abstract (for peer review):

It is expected that more than 150,000 people will be diagnosed with a hematological malignancy this year, joining the greater than 1,000,000 people living in the United States with these diseases. Although there has been significant progress in recent years in the treatment of hematological cancers with combination therapies the 5-year survival rates for non-Hodgkin lymphoma, leukemia and myeloma are still unacceptable at 69%, 57%, and 45%, respectively. Within the last 10 years the Food and Drug Administration has approved carfilzomib and bortezomib, both proteasome inhibitors, for treatment of multiple myeloma. In addition, these inhibitors are in clinical trials for treatment of leukemia, B-cell lymphoma, non-Hodgkin lymphoma and mantel cell lymphoma. Given the utility of proteasome inhibitors in the treatment of hematological malignancies but the lack of a diagnostic for which patients will respond versus those that are intrinsically resistant or will acquired resistance during therapy, development of tools that can be used to predict responses to proteasome inhibitors are critical. To this end, I have recently described a set of fluorescent proteasome peptides that allow, for the first time, simultaneous monitoring all three activities of the proteasome. Preliminary studies suggest that the ratios of these activities, defined here as the proteasome's catalytic signature, are specific for each cell type and maybe predictive of sensitivity to proteasome inhibitors. We will explore the feasibility that these sensors can predict which subtypes of hematological malignancies are sensitive to proteasome inhibitors and which patients are resistant or will develop resistance to therapy.

Tier 1 – Pilot Awards

Contact PI – Julian G. Rosenman, MD PhD

Project Title: Reconstruction of a 3D colonic image from colonoscopy video frames

Review category: clinical/translational

Abstract (for peer review):

Screening colonoscopy now has a high enough detection rate of pre-cancerous lesions to have an impact on long term patient survival. Despite this success, colonoscopy video has some significant limitations. For example, video is not good format for review, as this would essentially require viewing most of the video all over again. In addition, colonoscopy video does not permit one to get a global view of the colon; as a result it is almost impossible to determine which colonic surface, if any, was not visualized (missed) during the procedure. Finally, a visual comparison between serial colonoscopies or colonoscopy and CT is not possible because video cannot be directly registered with another video or with a 3D image.

The solution to the above problems is to extract an accurate, fully interactive 3D image of the colon from the thousands of video frames. Such an image would allow the clinician to see the entire colon at-a-glance as well as manipulate it, analyze it, and register it to other 3D images including CT. Our research team has recently succeeded in doing this for endoscopy of the human pharynx, and we now propose to extend and modify our methods for use in colonoscopy. As a start we will train a PhD level graduate student to learn the methodology from the pharynx team, and apply it to colonoscopy videos so as to prove its feasibility before beginning a full-scale project multi-year colonoscopy project.

Tier 1 - Pilot Awards **Cancer Disparities Targeted RFA**

Contact PI: Jennifer S Smith PhD, MPH

Rank: Associate Professor

Project Title: Validation of a novel low-cost colposcope to improve cervical cancer screening

Review Category: population science

Abstract (for peer review):

We propose to collect pilot data on the clinical validity of a newly developed trans-vaginal digital colposcope (TVDC) to improve cervical cancer screening programs in low-resource settings. Invasive cervical cancer affects 500,000 women worldwide each year, resulting in >270,000 deaths, even though it is highly preventable through early detection and treatment of precancerous lesions. Current primary screening methods require confirmation by colposcopic evaluation to avoid overtreatment of clinically insignificant low-grade cervical lesions. Conventional colposcopy relies on the availability of relatively expensive machines and highly trained colposcopists, creating bottlenecks in low-resource and remote regions of the United States and globally. The novel TVDC can be constructed using relatively low-cost materials, and collects high-quality digital images that can be easily transmitted for external colposcopic review.

The proposed Tier 1 pilot project aims to collect preliminary validation data on the TVDC's clinical performance.

Aim 1: To assess concordance of Kenyan colposcopist readings of previously collected paired images obtained by the TVDC and by a conventional colposcope for cases of different known grades of histologically confirmed pathology.

Aim 2: To assess TVDC clinical performance (sensitivity, specificity, positive predictive value, and negative predictive value) compared to conventional colposcopy for the detection of high-grade precancerous lesions (CIN2+) in a population of 200 high-risk women in Mombasa, Kenya.

The proposed pilot study will produce preliminary data for use in the development of an R01 proposal for a large validation study of the TVDC.

Tier 1 - Pilot Awards

Contact PI: Timothy J Stuhlmiller Ph.D.

Rank: Postdoctoral Research Associate

Other Investigator: Gary Johnson (sponsor)

Project Title: High-throughput interrogation of the kinome and epigenome for adaptive bypass targeting and the discovery of synergistic combination therapies

Review Category: basic science

Abstract (for peer review):

The identification of oncogenic drivers across cancer types has led to the development and clinical application of a vast array of small molecule inhibitors. Targeted therapies only benefit a subset of patients, however, and adaptive resistance limits the durability of clinical responses. Tumors rewire their signaling networks to upregulate alternative, compensatory kinase signaling to bypass the effects of the drug. Targeting these adaptive kinases can have synergistic effects on tumor cell growth, but selecting appropriate combination therapies is a significant clinical challenge. In my recent work, I discovered that targeting the epigenetic machinery involved in the upregulation of adaptive kinases could suppress multiple compensatory pathways at a transcriptional level, generating a stable inhibition of growth. Here, I propose to establish a high-throughput cell viability screening platform of clinically-relevant kinase inhibitors and epigenetic enzyme-targeting small molecules for the discovery of synergistic combination therapies for cancer. This unique library of 160 compounds will thus interrogate both compensatory kinase signaling and epigenetic regulatory networks. To optimize this screen, I will use CRISPR/Cas9-generated PIK3CA-mutant and –wild type HER2+ cell lines as my model system. Screening these isogenic lines in parallel in the presence or absence of PI3K inhibitor will provide a comprehensive analysis of differential drug sensitivity imparted by this common genetic alteration. Establishing this platform will create a unique resource for therapeutic discovery at UNC, applicable to virtually any cancer type. Identifying synergistic combination therapies provides a clear direction for extramural funding applications and presents preclinical rationale for clinical trial design.

Tier 1 - Pilot Awards

Contact PI: Jing Zhang Ph.D.

Rank: Postdoctoral Research Associate

Other Investigator: Qing Zhang (sponsor)

Project Title: Identification of ZHX2 as a VHL Substrate in ccRCC to Promote Tumorigenesis through Regulation of NF-kB

Review Category: basic science

Abstract (for peer review):

Clear cell renal cell carcinoma (ccRCC) is resistant to a variety of cancer therapies and is highly lethal. A hallmark of ccRCC is the inactivation of the von Hippel Lindau (VHL) tumor suppressor gene. pVHL functions as an E3 ubiquitin ligase that promotes the degradation of HIFα, however, evidences indicate that additional pVHL substrates exist and their roles in renal cancer remain unknown. Here we identify zinc-finger/homeodomain protein ZHX2 as a novel pVHL substrate by a newly developed genome-wide in vitro expression strategy coupled with GST-binding screening. Our preliminary data indicates that ZHX2 promotes renal cancer cell oncogenic phenotypes in VHL-deficient renal cancer by regulation of oncogenic NF-kB target genes potentially via interaction with RelA/p65. We hypothesize that ZHX2-NF-kB interdependent signaling axis is critical in driving VHL-deficient renal cell oncogenesis. In specific aim 1, we identify ZHX2 as a novel pVHL substrate. We will characterize regulation of ZHX2 by pVHL and determine the oncogenic significance of ZHX2 upregulation in VHL-deficient renal cancer with cancer cell lines, tumor xenograft and patient tissues. In specific aim 2, we find the functional significance of ZHX2-RelA/p65 signaling axis. We will implement integrated analyses of ChIP-Seq and gene expression to determine ZHX2-RelA/p65 genomic overlap and their potential inter-dependence. Successful completion of this proposal would establish a critical mechanistic missing link between pVHL loss and hyperactivation of NF-kB in renal cancer, and would provide significant new molecular insight into oncogenic mechanisms associated with ccRCC as well as the potential targets for new therapies of this disease.