Tier 1: Population Sciences

PI: Wendy Brewster, MD, PhD, Professor, Department of Obstetrics & Gynecology

Co-investigators: Lisa Spees, PhD, Post-doctoral Research Fellow; Mahesh Varia, MD, Professor, Department of Radiation Oncology; Stephanie Wheeler, PhD, MPH, Associate Professor, Department of Health Policy and Management; Morris Weinberger, PhD, Vergil N. Slee Distinguished Professor of Healthcare Quality Management

Project Title: Exploring the urban-rural paradox of cancer care in North Carolina

Abstract
Urban-rural disparities in health outcomes are generally attributed to the longer distances rural patients must travel to receive care. Specifically, distance to care has been overwhelmingly associated with worse cancer outcomes in terms of stage of diagnosis, guideline-concordant care, quality of life, and survival. However, recent evidence from North Carolina suggests that, in fact, distance to care has a differential effect on urban and rural patients; among Medicare-insured breast cancer patients in urban areas, those living farther from treatment were less likely to receive radiotherapy. In contrast, in rural areas, those living farther from radiation facilities were *more likely* to receive treatment than those who lived closer. A differential distance to care pattern was also found among rural and urban Medicaid-insured colon cancer patients. We propose to further explore this urban-rural paradox and extend this line of inquiry by including cancer patients of all insurance types. Specifically, we will assess the differential effect of distance to care between urban and rural areas among women diagnosed with cervical cancer from 2003-2015 using data from North Carolina Central Cancer Registry (NCCCR) linked to public and private health insurance claims. If these paradoxical findings continue to be observed, it would require large healthcare systems to reconsider whether current interventions such as teleoncology are the most effective method for addressing treatment disparities among cancer patients. The specific mechanisms that make distance a barrier to care may need to be considered separately when examining cancer patients residing in urban versus rural areas.

Tier 1: Clinical/Translational

PI: Jennifer Brondon MD, MS,Pediatric Hematology Oncology Fellow

Project Title: Mapping Child and Adolescent Self-Reported Symptom Data to Clinician-Reported Adverse Event Grading to Improve Pediatric Oncology Care and Research

Abstract
Adverse Event (AE) reporting is mandatory in treatment trials to ensure patient safety and provide data to sponsors, regulators, patients, and clinicians. In oncology, AEs are graded using the Common Terminology Criteria for Adverse Events (CTCAE). Clinicians grade symptomatic AEs using the CTCAE; however, studies have found that compared to child/adolescent self-

report, clinicians underreport the number and severity of symptoms. Funded by NCI, UNC investigators are leading a study among nine Children Oncology Group (COG) sites to design a system (Pediatric PRO-CTCAE) that allows children/adolescents to self-report symptomatic AEs experienced while undergoing cancer treatment. The proposed study goal is to translate (map) the child/adolescent responses to Pediatric PRO-CTCAE questions to CTCAE grades. Aim 1 will involve 10 senior pediatric oncology physicians (>5 years of practice) to provide initial mapping of Pediatric PRO- CTCAE responses to CTCAE grades. Aim 2 will involve approximately 180 pediatric oncology clinicians (>2 years of practice) from our nine COG sites to select CTCAE grades for Pediatric PRO-CTCAE response patterns where there are differences in opinion from senior physicians. Additionally, we will examine how type of symptom (physical or mental) and patient context (cancer, treatment, age) may differentially influence CTCAE grading. Study results will provide a valuable translation piece for clinicians to interpret the self-report data. This mapping work is necessary to propose a randomized controlled trial examining the feasibility and value of the Pediatric PRO-CTCAE system for improving AE grading/reporting and clinical care.

Tier 1: Population Sciences

PI: Leslie H. Clark MD, Assistant Professor, Gynecologic Oncology (appointment to begin 7/31/17)

Co-Investigators: Victoria L. Bae-Jump, MD, PhD, Division of Gynecologic Oncology; Derek Hales, PhD, Department of Nutrition; Carmina G. Valle, PhD, MPH, Department of Health Behavior; Paola A. Gehrig, MD, Division of Gynecologic Oncology; Wanda Nicholson, MD, Department of Obstetrics and Gynecology; Naim Rashid, PhD Lineberger Biostatistics Core

Project Title: The **MOVES** Trial**: MO**ti**V**ating **E**ndometrial Cancer **S**urvivors with Activity Trackers and Tailored Feedback

Abstract

Women with endometrial cancer (EC) are often overweight/obese and more likely to die from cardiovascular causes than EC. Increased physical activity, even in the absence of weight loss, is associated with improved cardiovascular health and cancer outcomes. Wearable activity tracker based activity interventions have been shown to increase activity in sedentary populations and can be further enhanced through tailored feedback messages. The time of cancer diagnosis represents a “teachable moment” where patients are motivated to make lifestyle changes, yet our data shows that many patients and providers are unable to capitalize on this opportunity. **We propose a pilot study to evaluate the ability of a tailored feedback physical activity intervention using CHART and wearable activity trackers to increase physical activity in EC survivors.** Overweight/obese EC survivors will receive an activity tracker at enrollment. After a baseline week, subjects will be randomized 1:1 to receive or not receive weekly feedback messages for 12 weeks. The change in daily steps from baseline will be compared in the intervention and control arms. We will assess acceptability of the intervention, and the effects of the intervention on BMI, waist-to-hip ratio, quality of life and serum metabolic markers. The data collected in this study will allow us to implement a large-scale randomized controlled trial

of a physical activity intervention in the obese/overweight EC population.

Tier 1: Pilot Award
PI: Jodie M. Fleming, PhD Assistant Professor, North Carolina Central University, Dept. of Biological and Biomedical Sciences

Project Title: Determining the relationship of CRYBB2 and its pseudogene in promoting Breast Cancer Disparities and Patient Outcome

Abstract
African American (AA) women have higher breast cancer (BrCa) mortality rates compared to other races, even within the more favorable outcome Luminal A BrCas. *CRYBB2* is one key gene, differentially expressed by race in healthy and cancerous tissues, and high expression has been linked with poor outcome in breast, colorectal, endometrial, and prostate cancers in AAs. Its function in BrCa is unknown. We propose to conduct functional/biochemical studies to define the consequence of high CRYBB2. Our data show CRYBB2 alters intracellular-Ca2+, IL6, and EGFR/Her2/Her3 levels. Second, we found that expression arrays detect both *CRYBB2* and its pseudogene *CRYBB2P1*, due to sequence similarity. Pseudogenes can regulate their parental genes via generation of antisense regulatory transcripts/non- coding RNAs. We'll investigate whether *CRYBB2P1* functions by these mechanisms to regulate CRYBB2. Our data show distinct regulation of these genes, suggesting additive/synergetic or independent roles. Aim1 proposes RNA *in situ* hybridization in BrCa biopsies, genetic manipulation of BrCa cells, and *in vitro* assays to define the unique roles of CRYBB2/*CRYBB2P1*. We'll then advance these data to understand disparate patient outcomes. Aim2 extends our data to test the effects of CRYBB2-mediated alterations in EGFR/Her2/Her3, Ca2+, and IL6 to identify physiological changes in BrCa cells upon CRYBB2/*CRYBB2P1* deregulation. **Impact:** Survival and gene expression differences exist between AA and CA despite equal treatment or tumor subtype. We identified specific molecules that may underlie biological phenomena responsible for these disparate observations. Our results may provide valuable insight into biological mechanisms that influence cancer risk/progression, therapeutic response, and ultimately patient outcome.

Tier 1: Clinical/Translational

PI: Katherine A. Hoadley, PhD, Assistant Professor, Department of Genetics

Project Title: Development of an Intrinsic Classification Signature Specific to Basal-like Breast Cancer

Abstract
Basal-like breast cancer is an aggressive subset of breast cancers. In the clinic, the term triple negative breast cancer (TNBC) is often used as a surrogate since most basal-like breast cancers typically lack expression of ER, PR, and do not have amplified HER2; but this classification is not identical and not always overlapping. Analysis with 11 other tumor types from TCGA showed that the basal-like breast cancer and not necessarily the triple negative breast cancers are

distinct from other breast cancers in the pan-cancer analysis suggesting they represent a separate disease within the breast. Attempts to develop a basal-like specific subtype classification have used variably expressed genes and often led to subtypes that are based on non-tumor features such as the stroma or immune cells. While these features play important roles in the tumor pathogenesis, they may be masking important tumor-intrinsic features that could help to further classify basal- like breast cancer and potentially identify new therapeutic targets. Here, I propose to use multiple samplings of basal-like breast cancers to identify genes that are "intrinsic" to the tumor. These genes have low variance between repeated measurements of the same tumor and high variance across tumors from different patients. This approach was highly successful in identifying the robust classifications of the PAM50 and now within the context of basal-like subset will help to further classify this subset in a robust manner.

Tier 1: Pilot Award Intervention Research to Optimize the Carolina Health Assessment & Resource Tool (CHART)

PI: Allison J. Lazard, PhD, Assistant Professor, School of Media and Journalism, UNC at Chapel Hill

Co-Investigators: Heidi Hennink-Kaminski, PhD Associate Professor, School of Media and Journalism; Brad Love, PhD Associate Professor, Stan Richards School of Advertising and Public Relations Associate Director, Center for Health Communication,the University of Texas at Austin; Laura Ruel, MA Professor, School of Media and Journalism, University of North Carolina at Chapel Hill

Project Title: Designing effective interactive applications for cancer-prevention interventions

Abstract
Despite repeated efforts of behavioral scientists to communicate up-to-date, evidence-based prevention information with online tools, there is very little guidance for how to design interactive applications to ensure adoption. Visual and interactive design is the critical link to application use and user engagement. First impressions are made within the first 50 milliseconds and have a lasting impact for willingness to engage with online health information. Ignoring design can detrimentally impact the communication of evidence-based science to patients or health consumers who need this information the most. This study aims to address this gap through optimization of the Carolina Health Assessment & Resource Tool (CHART). Using a two-phase approach, this study will 1) develop interactive application formats through an iterative design approach that incorporates researchers' and potential users' feedback and 2) test the relative effectiveness of the developed application formats for technology adoption. In phase one, application formats will be developed that include theory-based design features of design complexity, prototypicality, social presence, and affordances. In phase two, Amazon's Mechanical Turk will be used to conduct a series of experiments to assess how these design features influence user's (*n*=2000) intentions to use CHART, along with perceptions of the

interactive intervention's usefulness and usability. With a need to connect at-risk populations with evidence-based prevention tools, the proposed project will provide guidance for how to effectively design interactive cancer- prevention interventions. Additionally, this project will produce preliminary data necessary for a competitive NIH grant proposal regarding dissemination and implementation of research-tested health behavior change interventions.

Tier 1 Pilot: Population Sciences

PI: Jennifer S. Smith, PhD, MPH, Professor, Epidemiology, UNC Gillings School of Global Public Health

Other Investigators: Satish Gopal MD, MPH. Assistant Professor, Department of Medicine; Irving Hoffman, PA, MPH, Professor, Department of Medicine, Division of Infectious Diseases; Chifundo Zimba, PhD, GCGH, RN, RM, Behavioral Scientist/Post-doctoral Fellow, UNC Project Malawi; Quefeng Li, PhD, Assistant Professor, Department of Biostatistics, UNC Gillings School of Global Public Health; Jacob Hill, ND, MS, Postdoctoral Research Fellow, Department of Physical Medicine and Rehabilitation

Project Title: Concomitant Conventional Treatment and Traditional, Complementary, and Alternative Medicine (TCAM) Use by Cancer Patients in Malawi

Abstract
Less developed countries (LDCs) experience the majority of the worldwide burden of cancer. Conventional cancer treatment (surgery, chemotherapy, radiation) is expanding in resource poor locations to address this oncology disease burden. LDCs also have a high prevalence of the use of traditional, complementary, and alternative medical practices (TCAM). Combination of conventional treatment and TCAM use creates the potential for TCAM to cause a delay in seeking a clinical cancer diagnosis, and possible safety concerns due to herb/drug interactions. There are limited published data on TCAM use among cancer patients in sub-Saharan Africa, and no such data from Malawi. We propose to implement an interviewer-administered quantitative survey of conventional treatment and TCAM use in adult cancer patients presenting to the Kamuzu Central Hospital in Lilongwe, Malawi, and to conduct qualitative focus groups of cancer patients. The primary outcome measure will be the frequency of concomitant TCAM use among adult cancer patients undergoing conventional cancer treatment. The secondary outcome measure will be the frequency of delayed clinical cancer diagnosis due to seeking alternative TCAM treatment for symptoms. Data obtained will inform clinicians and researchers about the extent of TCAM use among patients receiving conventional treatment, and the proportion of patients delaying seeking cancer diagnosis due to utilizing TCAM treatment. This study does not promote the alternative treatment of cancer, and supports current conventional care by assessing whether TCAM may present barriers to clinical diagnosis and treatment.

Tier 2: Stimulus Awards; Population Science

PI: Hazel Nichols, PhD Assistant Professor, Department of Epidemiology

Co-Investigator: Jennifer Mersereau, MD Associate Professor, Department of Obstetrics & Gynecology

Project Title: Reproductive Outcomes among Adolescent and Young Adult Cancer Survivors

Abstract
In the U.S., >45,000 women are diagnosed with cancer during adolescence and young adulthood (AYA, ages 15-39) each year. Reproductive issues are critically important to AYA survivors, but insufficient information on future pregnancy outcomes is available to address their concerns. In this project, we will develop and conduct an online survey of >5,000 women diagnosed with AYA lymphoma, breast, melanoma, thyroid, or gynecologic cancer (the 5 most common cancer types among women in this age group). The survey will leverage the UNC Odum Institute's expertise in survey research to query 1.) reproductive intentions and receipt of fertility counseling; 2.) attempts to conceive and pregnancy loss history; and 3.) self-reported cancer recurrence. These characteristics are not available in existing U.S. cancer registry and health databases and complement our ongoing project to assess the risk of adverse birth outcomes among AYA cancer survivors in North Carolina. Further, this research is responsive to one of few reviewer-identified weaknesses of our multi-site NIH R01 application, "Clinical pregnancy outcomes among adolescent and young female cancer survivors." Lastly, we will work with investigators across UNC to identify additional questions for survey inclusion that would provide preliminary data for other AYA-focused R01 applications (e.g. regarding clinical trial participation, advanced care planning, etc.). In this way, our findings will provide urgently needed answers that can be directly applied to fertility and reproductive counseling within the 2-year grant period, and expand the LCCC's capacity for investigator-initiated research to address the needs of AYAs with cancer in the future.

Tier 2: Stimulus Awards, Clinical/Translation

PI: Marc Niethammer, PhD, Associate Professor, Department of Computer Science Biomedical Research Imaging Center

Co-PI: Steve Marron, PhD, Amos Hawley Distinguished Professor, Department of Statistics and Operations Research

Co-Investigators: Charles M. Perou, PhD, The May Goldman Shaw Distinguished Professor of Molecular Oncology Department of Genetics; Carey Anders, MD, Associate Professor, Department of Medicine

Project title: Joint Image and Genomic Analysis for Breast Cancer: Prediction, Data Fusion, and Assessment of Heterogeneity

Abstract

Current clinical practice for the diagnosis of cancer is through biopsies with pathology reviews. More recently genomic signatures have been used for a refined diagnosis and in particular for tumor classification to enable patient-specific treatment and improved long-term disease prognosis. Recently, such methods have been approved for clinical use, but a major premise of this proposal is that improved prognosis should be available from combining both pathological image and genomic information. Hence, we propose to develop newly integrated image analysis and statistical methods that will exploit the combined information from these two distinct data-types. We will quantify the relation between genomic and imaging data for outcome prediction in the context of breast cancer, and will carefully investigate the value added of this approach over standard prognostic indicators, including tumor grade, hormonal status and genomic class, using conditional statistical analyses that enable the distinguishing of joint and individual modes of variation. This will allow us to assess how similar (respectively complementary) the information captured through genomic and imaging data is. Furthermore, we hypothesize that image information alone allows for the prediction of prognostic indicators, thereby allowing for cost-effective patient stratification and patient assessment in the absence of sufficient tissue sample quantity to perform genomic testing. Lastly, we hypothesize that such image-based predictors can be used to assess tumor heterogeneity as they allow for spatially-localized prediction of prognostic indicators. The computational and statistical methodology we will develop will directly benefit breast cancer research, but will be generally applicable and therefore relevant and useful in parallel studies of other cancer types and beyond.

Tier 2: Basic science

PI: Dale Ramsden, PhD, Professor, Biochemistry and Biophysics

Co PI: Gaorav P. Gupta, MD PhD, Assistant Professor, Radiation Oncology

Project Title: Essential functions of Pol q in cells with homologous recombination defects.

Abstract

The efficient repair of DNA double strand breaks (DSBs) is necessary for survival of normal and cancer cells alike. However, some cancers develop with defects in the homologous recombination (HR) machinery, suggesting that they might be more reliant on alternative pathways for DSB repair. We helped describe a novel alternative pathway in mammalian cells, dependent on the repair polymerase Pol q. Additionally, our unpublished work indicates that a wide range of HR defective cancer cells require Pol q for viability whereas HR proficient cells do not. Pol q is thus an ideal therapeutic target. Despite these provocative initial findings, many questions remain unanswered regarding Pol q functions in both HR proficient and HR deficient cellular contexts. We propose to use innovative DSB repair assays and genetically engineered cells to identify essential functions of Pol q in cells with or without an intact HR pathway. Ultimately, we assert that understanding the essential functions of Pol q in various HR deficient contexts will facilitate the optimal clinical application of Pol q inhibitors for cancer therapy.

Tier 2 Stimulus Award Basic Research

PI: Bryan L. Roth, MD, PhD, Professor

Other Investigator: Channing J. Der, PhD, Professor

Project Title: Evolving new solutions for targeted cancer therapy

Abstract

Targeted cancer therapies leverage patient genetic information to treat disease. Rather than wholesale targeting of cell proliferation, targeted therapies endeavor to precisely inhibit the oncogenic context of a tumor. Targeted therapies now effectively treat what were previously dire cancer diagnoses. The RAS family of oncogenes, the first mutated genes identified in human cancer, recur in the most lethal cancers in the United States. After 30 years of effort a clinically effective anti-RAS therapy remains elusive. Here we propose to generate viable targeted therapies for RAS oncogenes using a novel method of directed evolution recently developed in our laboratory; **V**iral **E**volution of **G**enetically **A**ctuating **S**equences (**VEGAS**). VEGAS uses Sindbis, a highly mutagenic RNA virus, to continuously evolve transgenes in mammalian cells – the first system of its kind. Using VEGAS, we have engineered transcription factors, nanobodies, receptors, and kinases – in under a week – to augment *in vivo* signal transduction. Using VEGAS, we aim to address the unmet needs of targeted cancer therapeutic design. Specifically, in this proposal, ***we will generate oncogenic KRAS inhibiting nanobodies*** to suppress mutant RAS signaling *in vivo*.