Tier 1: Translational

PI: Yuri Fedoriw, MD, Associate Professor, Pathology & Lab Medicine

Project Title: Whole Exome Sequencing of HIV-associated Diffuse Large B-cell Lymphomas from Malawi

Abstract
Lymphoma incidence in sub-Saharan Africa is increasing due to epidemic levels of HIV infection, population growth and aging. Yet, robust and comprehensive phenotypic and molecular classification of HIV-associated lymphomas is incomplete. Such characterization may provide unprecedented and generalizable insight into lymphoma biology, and inform prevention and treatment strategies worldwide. Herein, we propose the whole exome sequencing of HIV-associated diffuse large B-cell lymphoma (DLBCL) from the KCH Lymphoma Study in Lilongwe, Malawi. After primary diagnosis at KCH, tissue blocks along with frozen peripheral blood samples are submitted to the UNC for additional assessment and classification. To date, 116 adult cases have been fully characterized in this manner, with approximately half of all lymphomas arising in HIV-positive patients (n=59). DLBCL, the most common lymphoma worldwide, is similarly common within our cohort, representing 49 of the 116 cases. Of the DLBCL samples, 36 have undergone whole transcriptome sequencing with comparison to published expression data and correlation to clinical outcome and pathologic features. While the striking genetic heterogeneity of *de novo* DLBCL is appreciated, similarly thorough studies of HIV-associated DLBCL are lacking. These studies are challenging to conduct, as prospective, single- center cohorts of HIV-associated lymphomas are uncommon in settings where HIV infection is far less frequent. As our program is uniquely poised to overcome these obstacles, we aim to identify gene mutations common in HIV-associated DLBCL and compare mutational status to already generated whole transcriptome data.

Tier 1

PI: Caterina Gallippi, PhD, Associate Professor, Joint UNC & NC State Department of Biomedical Engineering

Co-Investigator: Cherie Kuzmiak, DO

Project Title: ARFI, VisR, and DDAI Ultrasound for Improving Discrimination of Malignant and Unresponsive Breast Cancer

Abstract
The primary objective of breast cancer screening is to identify early stage cancer, or precancerous lesions, at a time before symptoms emerge and when treatment is likely to result in a cure. Screening is beneficial when it averts progression of disease to metastasis and/or death, but adverse effects to patients (and unnecessary medical expense) may result downstream from false positives and indiscrimination of masses that will not re- spond to

chemotherapy treatment. There exists a vital need for a screening technology that exhibits high sensi- tivity and specificity for cancer detection with early identification of unresponsive masses. This urgent need could be met by exploiting ultrasound-based imaging technologies that measure the mechanical properties of breast tissue. As a critical first step, the primary objective of the proposed research is to evaluate *in vivo* the diagnostic relevance of ultrasound-derived metrics for stiffness, elasticity, viscosity, and anisotropy. These bi- omarkers will be measured using novel, noninvasive ultrasound technologies under development in Dr. Gallip-pi's laboratory: 1) Acoustic Radiation Force Impulse (ARFI) imaging for interrogating tissue stiffness, 2) Viscoe- lastic Response (VisR) ultrasound for assessing tissue elasticity and viscosity, and 3) Dynamic Displacement Anisotropy Imaging (DDAI) for measuring tissue anisotropy. These technologies have been demonstrated clin- cally for delineating atherosclerosis, muscular dystrophy, and renal dysfunction, *in vivo*. Their application to breast imaging is a new research focus for the highly qualified research team.

Tier 1: Population Sciences

PI: Jennifer Lund, PhD, Assistant Professor, Epidemiology

Project Title: Generalizing colorectal cancer trial results to real world populations: A pilot study

Abstract
Enrollment onto cancer clinical trials is complex and thus patients that ultimately participate in trials are often not representative of the patients in whom the treatment will be delivered in routine care (i.e., the target population). Underrepresentation of patient subgroups (e.g., older adults) in trials is problematic for healthcare providers because evidence of treatment effect heterogeneity is necessary to guide personalized, patient-level treatment decisions. However, this underrepresentation also presents challenges at the population-level, as generalizability of trial findings to target populations is required to understand the overall impact of a specific intervention for healthcare policymaking. Model-based standardization, a method developed in the field of causal inference, has emerged as a promising approach to assess and generalize findings from trials to target populations. This method essentially estimates subgroup effects using clinical trial data and weights these effects according to their distribution in a target population. Researchers have applied this approach to cardiovascular prevention and HIV trials, but not to cancer treatment trials. This proposed developmental pilot grant will harness clinical trial, population-based cancer registry, and Medicare claims data to assess and apply model-based standardization for generalization of two colorectal cancer trials to target populations of patients treated in routine care. Our work in colorectal cancer will provide a framework for broader application to treatment trials from other cancer sites and generate preliminary data to support a R01-scale application to tailor the model-based standardization approach to enhance its relevance for the cancer trial setting.

Tier 1: Basic

PI: Jesse Raab, PhD, Assistant Professor, Genetics

Project Title: SWI/SNF mediated genome regulation in SChLAP1-dependent prostate cancer

Abstract
Understanding the mechanism by which localized prostate cancer progresses to metastatic disease is neces- sary to develop efficacious prostate cancer therapies. The long noncoding RNA SChLAP1 (Second Chromosome Locus Associated with Prostate cancer 1) is a highly prognostic indicator of aggressive prostate cancer. It inter- acts directly with the SWI/SNF complex core subunit SNF5 (INI1/SMARCB1/BAF47) and depletes it from many of the SNF5 binding sites genome-wide. The expression of SChLAP1 can transform benign prostate cells into invasive cells, and is required for tumor formation in xenograft models. This led to the hypothesis that SNF5, and the SWI/SNF complex more generally, function as a tumor suppressor in prostate cancer. However, SWI/SNF subunits are not mutated in prostate cancer, highlighting the possibility of an alternate model. Additionally, the SWI/SNF complex is not a single entity and instead can be combinatorially assembled based on subunit inclusion to create hundreds or thousands of biochemically distinct complexes. It remains unknown how the functional interplay of these many other forms of SWI/SNF function in prostate cancer progression. Here, we propose to define the precise mechanism by which SChLAP1 expression alters chromatin state and drives prostate cancer. We hypothesize that distinct forms of SWI/SNF are required to alter chromatin in SChLAP1 expressing tumors. Completion of this proposal will definitively determine how SWI/SNF functions in prostate cancer, identify the molecular basis of SChLAP1 function, and will provide the foundation for future studies to identify novel therapeutic targets and epigenetic regulators of prostate cancer.

Tier I: Clinical/Translational

PI: Andrew Smitherman, MD, Fellow, Pediatric Hematology/Oncology (sponsored by Bill Wood),

Project Title: Patterns of cancer care and clinical trial enrollment among adolescents and young adults (AYAs) in North Carolina

Improvements in treatment have led to increased survival for many patients with cancer; however, adolescents and young adults (AYAs, 15-39 years-old) have experienced less survival improvement than children and older adults. Evidence suggests that lower rates of participation in research studies among AYAs contribute to worse outcomes. The UNC Lineberger Integrated Cancer Information and Surveillance System (ICISS) provides a unique tool for understanding the patterns of AYA cancer care and the factors associated with research study participation. By combining information from the North Carolina Central Cancer Registry (NCCCR) with health insurance claims data, ICISS provides a reliable way to identify AYA patients in North Carolina and to obtain information regarding their treatment. By combining data from ICISS with research study enrollment data from the National Cancer Institute (NCI), a very accurate estimate of AYA research study enrollment will be obtained. Our objectives for this study are to describe the patterns of cancer care for AYAs in North Carolina and to determine if the likelihood of research study participation is affected by the type of medical center at which

cancer treatment is received. We will be able to identify the location of cancer diagnosis and to track patients through treatment while exploring the factors that influence this process. With a better understanding of the relationship between AYA cancer care and research study participation, we will identify barriers that currently prevent access to studies and optimal patient care.

Tier 1: Imaging and Medical Oncology

PI: Hong Yuan, PhD, Associate Professor, Radiology

Project Title: Imaging tumor hypoxia in brain metastasis: a step closer towards personalized therapy

Abstract
Brain metastases (BM) represent a serious clinical problem with high morbidity and mortality. Innovative multi-disciplinary approaches are needed for more effective diagnosis and treatment. Hypoxia in tumor has a significant impact on the effectiveness of radio/chemo therapy due to the hypoxia-induced treatment resistance. The long term goal of this study is to target tumor hypoxia in BM and utilize hypoxia imaging to guide the radiosurgery on BM and achieve personalized therapy for better patient outcomes. The immediate goal of the proposed pilot study is to establish the PET imaging with effective hypoxia probe on animal models of BM and characterize its hypoxia features on various BM models. Two specific aims are proposed: 1) To evaluate the newly developed hypoxia PET imaging marker ^{18}F-HX4 on mouse model of breast cancer BM; 2) To characterize the hypoxia and vascular features in breast and lung cancer BM using hypoxia PET/MR imaging. The study will systemically characterize the ^{18}F-HX4 probe, and compare side-by-side with ^{18}FMISO, which is the mostly studied probe but with known limitations. Based on the results from Aim-1 study, the effective hypoxia probe will be selected for the study in Aim-2, where PET imaging in combination with MRI will be used to characterize hypoxia and vascular features in various brain metastases, including lung cancer BM, Her2 positive and negative breast cancer BM. The project is the first to study the hypoxia in BM using imaging technique. It will help to pave the way towards personalized image-guided therapy on patients with BM.

Tier Two: Population Sciences

PI: Antonia Bennett, PhD, Assistant Professor, Health Policy & Management

Project Title: Pedometry as a Reflection of Symptoms and Function in Advanced Cancer
Symptom severity and function are key endpoints in cancer outcomes research, and can indicate the need for dose-reductions and symptom management in advanced cancer. The fields of patient-generated health data and mobile health are rapidly developing with the advent of new activity trackers and data processing systems. Although patient-reported

outcome (PRO) measures are the standard approach for assessing symptoms, function, and quality of life (QOL), PRO assessment is not feasible for some older adult patients, and as a result they are excluded from research. This mixed-methods study will provide an evidence base for the feasibility and value of using steps data (pedometry) in cancer outcomes research and clinical care as an indicator of symptom burden and function. We plan to conduct a prospective study among older adults with advanced cancer and diverse demographic characteristics, receiving treatment at the North Carolina Cancer Hospital, with the following aims: Aim 1: Examine the value of pedometry as an indicator of symptoms, function and QOL in older adults with advanced cancer through its association with patient-reported symptoms, functional status, physical activity, and global measures of health status and QOL, by analyzing cross-sectional and longitudinal data from pedometry and PRO assessments among a racially, ethnically, and educationally diverse sample of participants. Aim 2: Evaluate the patient-centeredness of pedometry assessment, including the meaning and relevance of this construct and the ease of participating in pedometry assessment, by conducting in-depth interviews among a racially, ethnically, and educationally diverse sample of patients who participated in Aim 1.

Tier 2: Clinical /Translational

PI: Laura Hanson, MD, MPH, Professor, Geriatric Medicine

Project Title: Palliative and Oncology Collaborative Care for Advanced Cancer

Abstract
The Institute of Medicine and American Society of Clinical Oncology endorse early Palliative Care for patients with Stage IV cancer, to improve communication of goals of care and quality of life, while reducing intensity of treatment, hospital re-admissions, and cost. However, widespread use of concurrent Oncology and Palliative Care is rare, due to very limited personnel and delays in referral. Research is needed to determine if more pragmatic and sustainable models can improve late-stage cancer outcomes. In collaborative care, outpatient care is made more effective by systematically tracking high-risk patients and facilitating collaborative care between primary physicians and specialists. Collaborative care is effective for psychiatric illness and chronic disease, but is untested in palliative care. Our research objective is to generate preliminary evidence that collaborative care can improve palliative care outcomes for Stage IV cancer. We propose a clinical trial with historical controls: Aim 1. To develop a Collaborative Palliative Care model for patients with Stage IV cancer, with input from specialty Palliative Care, Medical Oncology, and Primary Care providers. Aim 2. To conduct a preliminary clinical trial of Collaborative Palliative Care, to assess feasibility and to generate initial evidence of effect on goals of care communication (primary outcome), written advance care planning, quality of care for symptom distress, access to specialty Palliative Care and Hospice, 30 and 60 day hospital and emergency department use. During Year 2, investigators will write NIH and ACS grants to conduct a randomized controlled trial of Collaborative Palliative Care for advanced stage cancer.

Tier 2: Basic Science
PI: Lindsey James, PhD, Assistant Professor, Eshelman School of Pharmacy

Project Title: Discovery of Novel Chemical Probes for Polycomb Complexes for Cancer Therapy

ABSTRACT
Suppression of differentiation and senescence in cancer cells is largely tied to the H3K27me3 epigenetic mark, which is installed and recognized by the polycomb repressive complexes, PRC1 and PRC2. Oncogenic mutations are already known to exist in the PRC2 methyltransferase, EZH2, and the PRC1 component, BMI1, and current literature implicates additional PRC components in numerous cancers. For example, CBX7 (a methyl-lysine reader) regulates cellular life span and is upregulated in follicular lymphoma, leukemia, and prostate cancers, although its downregulation in other carcinomas suggests a context dependent function. The centrality of PRC activity in cancer establishes a pressing need for chemical probes that target the PRC components. Selectively disrupting PRC activity in oncogenesis has yet to be broadly achieved with small molecules, as only EZH2 probes are currently available. This proposal aims to discover novel chemical probes for the components of PRC1 and PRC2 which recognize the H3K27me3 mark and help to recruit PRC complexes to chromatin: the CBX orthologs and EED. High-quality, first-in- class probes will be developed and characterized in vitro and in cells, and eventually, in vivo. Such probes have the potential to inform target selection and establish a new class of cancer therapeutics. The demonstration that our first- generation PRC1 CBX chemical probe, UNC3866, has cellular activity is promising and highlights the feasibility of the work proposed herein, but probes for EED and ortholog selective CBX probes require further investigation. The establishment of transdisciplinary collaborations with members of LCCC will break new ground in this area of cancer research.

Tier 2: Clinical/Translational

PIs: Yueh Z. Lee, MD, PhD, Assistant Professor, Radiology, and James Coghill, MD, Assistant Professor, Medicine

Project Title: 18-FLT PET/MR Imaging to Predict Graft Failure and Graft Versus Host Disease in Bone Marrow Transplant Patients

Abstract
Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is curative for numerous chemotherapy resistant hematologic malignancies. Nevertheless its success is limited by graft rejection and graft- versus-host disease (GVHD), a process in which donor T cells mount inflammatory responses against normal host tissues. Currently there is no established method for radiographically predicting the development of either of these complications in the early post-transplant setting. The current proposal describes the use of a novel imaging modality, 18F-3′-deoxy-3′ -fluorothymidine (FLT) PET/MRI to evaluate for graft failure, GVHD, and disease relapse in human patients undergoing HSCT. FLT is a thymidine analog and a known marker of DNA replication. As a result, FLT imaging has the potential to serve as a non-invasive marker of

cellular proliferation within the host bone marrow and secondary lymphoid tissue after transplant. Our research group has already evaluated the feasibility of FLT imaging in mouse models of allogeneic transplant and GVHD. In mice a FLT signal was noted within the recipient bone marrow approximately one full week before count recovery. Furthermore, in those mice destined to develop GVHD, an intense FLT signal was noted initially in recipient secondary lymphoid tissue which preceded a subsequent proliferative response within so-called GVHD target organs themselves (colon and liver). If we are successful in identifying FLT and/or MRI imaging criteria that can successfully predict for the development of graft failure and/or GVHD in their earliest stages this could allow for preemptive changes to a given patient's immunosuppressive regimen in order to hopefully prevent both complications.

Tier 2: Basic Application

PIs: Matthew Parrott, PhD, Assistant Professor, Radiology, and Benjamin Vincent, MD, Assistant Professor, Medicine

Project Title: TIL-PET - Positron Emission Tomography of Tumor Infiltrating Lymphocytes

Abstract
The tumor immune microenvironment is recognized as a key component of tumor biology. Density of T-cell infiltration and a high ratio of cytotoxic to regulatory T-cells have been associated with prolonged survival and response to immune checkpoint inhibition in multiple tumor models. Thus quantitation of tumor-infiltrating T- cells can give potentially important prognostic and predictive information. Current methods for interrogating the tumor immune microenvironment depend on invasive tissue biopsies, which limits clinical application due to procedural risk. We have developed a novel approach named Tumor-Infiltrating Lymphocyte Positron Emission Tomography (TIL-PET), in which we use PET imaging to track lymphocyte trafficking *in vivo*. Our preliminary data using ^{89}Zr-DFO-anti-CD3 to track pan-T-cell accumulation shows precise murine lymphatic mapping with increased induced frequencies of activated and memory cytotoxic T-cells. We propose here to map dynamic changes in T-cell accumulation in differentially immune-infiltrated murine models of bladder cancer using TIL-PET. We will test whether treatment with the TIL-PET radiotracer changes the numbers and/or frequencies of leukocyte subsets in the tumor immune microenvironment. Finally we will develop an anti-CD19 B-cell TIL-PET method to complement T-cell TIL-PET. We hypothesize that T-cell accumulation will be seen in both murine models tested, that DFO-anti-CD3 treatment will yield increased frequencies of tumor- infiltrating memory cytotoxic T-cell populations, and that B-cell TIL-PET will be effective for imaging B-cell trafficking in the lymphatics and in tumors. We expect data generated here to support development of an R01 proposal and clinical trial to test TIL-PET safety and imaging efficacy.