

Tier 1: Basic Science

PI: Douglas H. Phanstiel PhD, assistant professor, Department of Cell Biology & Physiology

Project Title: Elucidating the transcriptional drivers of tumor-associated macrophage (TAM) development

Abstract

During breast cancer progression, tumor cells recruit genotypically normal monocytes and drive their differentiation into specialized cells called tumor-associated macrophages (TAMs). TAMs are essential for tumor growth and facilitate multiple tumor-promoting activities including vascularization, tissue invasion, and immune suppression, making them intriguing targets for therapeutic interventions. In contrast to normal macrophages that can assume either pro- (M1) or anti- (M2) inflammatory phenotypes, the unique extracellular signals present in the tumor microenvironment (TME) promote a gene expression pattern that includes genes associated with both pro- and anti- inflammatory functions. However, the regulatory mechanisms that establish this unique transcriptional program in TAMs are currently unclear.

Cell-type-specific gene expression patterns are governed by the complex interplay of transcription factor binding events, enhancer regions, and DNA loops which rewire connections between these elements and the genes they regulate. A functional understanding of these regulatory events requires the coupling of genomic approaches that map these features to precise and high-throughput methods that perturb them. The focus of this proposal is to map and functionally test transcriptional regulatory events that drive TAM formation using integrated genomic technologies and high-throughput CRISPR screens applied to a cell culture model of TAM development.

The experiments proposed here will offer important new insights into the mechanisms of gene regulation and provide a deeper understanding of the nature of human TAMs and the mechanisms driving their development. The results may open new avenues for therapeutic intervention with profound impacts on our ability to diagnose and potentially treat cancer.

Tier 1: Clinical/Translational

PI: Benjamin C Calhoun MD PhD, associate professor, Department of Pathology and Laboratory Medicine

Co-Investigators: Sarah Nyante, PhD, assistant professor, Department of Radiology; Melissa Troester, PhD, professor, Department of Epidemiology, UNC Gillings School of Global Public Health; Katherine Hoadley, PhD, assistant professor, Department of Cancer Genetics

Project Title: Genomic and Morphologic Alterations in Breast Precancer: A Cross-Sectional Comparison Study

Abstract

More than a million women in the United States undergo biopsies with benign or precancer findings annually. Patients whose biopsies show proliferative changes have an increased risk of breast cancer (4-10 fold higher than the general population); however, identification of biomarkers for risk stratification has been impeded by two major challenges. First, there are few benign and precancer breast cohorts with sufficient size and follow-up for breast cancer outcomes. Second, breast precancer lesions are

often small, limiting the amount of genomic material available for biomarker discovery and profiling. Thus, women undergoing biopsy tend to remain in a “high-risk” group for clinical surveillance without precision prevention strategies. Biomarkers that stratify patients according to the risk of developing breast cancer would help avoid overtreatment of low-risk patients and identify those who would benefit most from chemoprevention or prophylactic surgery. This project will ascertain a cohort of women with breast precancer. The goal is to evaluate genomic and morphologic alterations in breast precancer lesions. Cross-sectional comparisons of breast precancer lesions will allow identification of candidate markers associated with risk. We will also evaluate two UNC- identified tumor-specific signatures (PAM50 proliferation score and p53 score) that have shown promise in previous cohorts for predicting risk of invasive breast cancer. Data from this project will support R01 proposals to further develop these biomarkers as breast cancer risk stratification tools for women with breast precancers in large prospective clinical trials of mammographic screening.

Tier 1: Clinical/Translational

PI: William Zamboni PharmD, PhD, associate professor, UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics

Co-Investigator: Elizabeth Claire Dees, MD, professor, Department of Medicine, Division of Hematology/Oncology; Andrew Lucas, MS, PharmD, assistant professor, UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics; Haeseong Park, Allison Deal, MS, Senior Biostatistician, UNC Lineberger

Project Title: Evaluation of biomarkers of the mononuclear phagocyte system as predictors of the pharmacokinetics and pharmacodynamics of glembatumumab vedotin as part clinical studies sponsored by NIH/NCI Experimental Therapeutics-Clinical Trials Network (UM1) Program

Abstract

Compared to small molecule drugs, monoclonal antibodies (mAbs) and antibody-drug conjugates (ADC) are cleared via the mononuclear phagocyte system (MPS) cells (monocytes) and potentially non-MPS cells (neutrophils, T-cells, B-cells). MPS and non-MPS cells serve as a natural mechanism of clearance for immune complexes via their Fc-gamma-receptors (FcGRs) and overall function. These cells express various forms of FcGRs (CD64, CD32, CD16) that will interact with endogenous and therapeutic mAbs. Due to the differences in types and affinity of FcGRs, a variation in receptor expression can lead to significant differences in the ability of MPS and non-MPS cells to clear mAbs and ADCs from the blood. Our results show that the function and expression of FcGRs on MPS and non-MPS cells is highly variable in patients with cancer and that variability in these factors are consistent with differences in the pharmacokinetics (PK) of mAbs and ADCs. Thus, variability in FcGRs and function of these cells may be responsible for the high and clinically relevant variability in the PK and pharmacodynamics (PD) of mAbs and ADCs. We propose to perform the first clinical study evaluating the relationship between biomarkers (FcGRs and function) of MPS and non-MPS cells in blood and the PK and PD of the ADC glembatumumab vedotin alone and in combination with the mAb nivolumab as part of a NCI UM1 sponsored clinical trial. The goals of this proposal are to define novel factors associated with PK and PD variability of these agents and develop methods to optimize their clinical utility.

Tier 1: Clinical/Translational

PI: Jan-Michael Frahm PhD, professor, Department of Computer Science

Co-Investigator: Sarah McGill, MD, MS, assistant professor, Department of Medicine, Division of Gastroenterology and Hepatology

Project Title: Automated Information Extraction and Diagnosis for Endoscopic Video

Abstract

Colonoscopies are important and widespread clinical procedures used for the diagnosis and prevention of colon cancers. While the procedure has been proven to be beneficial, colonoscopists still face the challenging task of detecting polyps and other abnormalities related to cancer. Significant numbers of these malignancies are routinely missed in many procedures. Moreover, the procedure's length makes it inconvenient for later review, and documenting it a tedious endeavor in itself. To boost the procedure's efficiency and reliability, we propose novel video processing techniques to automatically visualize and summarize colonoscopies by applying novel machine learning methods, including the use of deep convolutional neural networks, to medical image processing. The algorithms we research will demonstrate the feasibility of automating three critical tasks to achieve this goal: identifying clinically useful video segments; achieving spatial understanding of the colonoscope's motion to better track the procedure and ensure complete coverage; and identifying and localizing polyps and other abnormalities. We envision our methods to run in-procedure without requiring additional hardware or effort in the existing colonoscopy workflow. This will enable physicians to significantly reduce malignancy miss rates and facilitate a quality-of-service review of the procedure before the patient even leaves the operating table. This in turn will significantly reduce colorectal cancers soon after colonoscopy. We believe the methods developed under this grant will generalize well to a variety of endoscopic procedures and will constitute substantial contributions to the medical vision research communities.

Tier 1: Population Science

PI: Sarah A. Birken PhD, assistant professor, Department of Health Policy and Management

Co-Investigator: Deborah K. Mayer, PhD, RN, AOCN, FAAN, professor, School of Nursing

Project Title: Identifying strategies for comprehensive survivorship care plan implementation

Abstract

Coordination of care to address the risk for late effects of cancer and its treatment is often poor for the 15.5 million cancer survivors in the United States, resulting in the duplication or omission of recommended services, high rates of hospitalization and significant costs to survivors, their caregivers, and the US healthcare system. To improve survivorship care, many cancer care quality improvement organizations recommend the implementation of survivorship care plans (SCPs) i.e., written documents that ideally include information regarding cancer diagnosis, stage, and treatments; plans for follow-up care; and recommended division of responsibilities among follow-up care providers. Despite widespread requirements, SCP implementation is poor. Cancer programs' approaches to implementing SCPs in practice substantially vary, ranging from cursory (i.e., developing SCPs to meet requirements without delivering them to survivors or PCPs) to comprehensive (i.e., promoting adherence to screening and health behavior guidelines and recommended utilization of follow-up care). The objective of this application is to identify strategies for developing comprehensive approaches to implementing SCPs. In Aim 1, we will characterize cancer programs' approaches to implementing SCPs using in-depth semi-

structured interviews with providers and staff in approximately 24 cancer programs. In Aim 2, we will use qualitative comparative analysis to identify organizational-level factors identified in Aim 1 that promote comprehensive approaches to implementing SCPs. We will leverage results from the proposed research in an R01 that will use a rigorous pragmatic trial to test the effect of the strategies identified in this study on processes and outcomes of care for survivors.

Tier 2: Basic Science

PI: C. Ryan Miller MD, PhD, associate professor, Department of Pathology & Laboratory Medicine

Co-Investigators: Ian J. Davis, MD, PhD, associate professor, Department of Pediatrics, Division of Hematology/Oncology; Chuan-Wei Jang, PhD, assistant professor, Department of Genetics

Project Title: Histone H3.3 in neural differentiation and pediatric gliomagenesis

Abstract

Somatic mutations in H3F3A, encoding histone variant H3.3, define the midline childhood brain tumors Pediatric High- Grade Gliomas (pHGG), including Diffuse Intrinsic Pontine Glioma (DIPG). These aggressive tumors have no effective treatments. Understanding mechanisms through which mutant H3.3 induces epigenomic reprogramming in candidate cells-of-origin would facilitate disease modeling and the development of targeted therapies. Because cell identity and differentiation status are largely regulated through epigenomics, we will examine the dynamic consequences during differentiation and transformation of mutant H3.3 in two distinct tumor cells-of-origin - multi-potent neural stem cells (NSC) and terminally-differentiated astrocytes (AC). We hypothesize that mutant H3.3, when combined with co-occurring oncogenic mutations, produce cancer (glioma) stem cells (GSC). We further hypothesize that GSC arise through distinct epigenomic mechanisms based on NSC or AC cell-of-origin. To address these hypotheses, we will generate clinically-relevant non-germline, genetically engineered mouse (nGEM) models using NSC and AC derived from conditional [H3f3a;H3f3b;Trp53]flox/flox mice. Lentiviruses (LV) encoding Cre will be used to induce recombination in vitro. LV encoding mutant H3.3 and PDGF β will be used to investigate whether these mutations transform NSC and AC and maintain a stem-like state by modifying their epigenomic landscapes. We will use developmental neurobiology, epigenomic, and transcriptomic analyses to determine the mechanisms that lead to development of GSC from mutated NSC (GSCNSC) and AC (GSCAC). These nGEM models and preliminary data will be central to future NIH grant proposals focused on comparative studies with human patient-derived tumor cells and preclinical, epigenetic drug development for H3.3-mutant pediatric gliomas.

Tier 2: Basic Science

PI: Michael Emanuele, PhD, assistant professor, Department of Pharmacology

Co-Investigator: Ben Major, PhD, associate professor, Department of Cell and Developmental Biology

Project Title: AKT in breast cancer proliferation and therapeutic resistance

Abstract

The G1/S boundary represents a major barrier to proliferation and is perturbed universally in cancer. The G1/S checkpoint is controlled, in part, by Cyclin Dependent Kinases 4 and 6 (CDK4/6), which inactivate the retinoblastoma (RB) tumor suppressor, initiating S-phase entry. However, after genetic ablation of the CDK4/6-RB pathway, cells proliferate in vivo and in vitro and maintain an intact G1/S

checkpoint. Therefore, other largely unknown pathways can regulate the decision to enter S-phase and are likely to play a role in cancer proliferation. The PI3K-AKT pathway is activated by mutation in approximately 50% of luminal breast cancers and is implicated in tumor metabolism and proliferation. However, its connection to the cell cycle remains poorly defined. We recently described a mechanism by which AKT promotes S-phase entry, through inhibiting a preeminent cell cycle ubiquitin ligase termed the Anaphase Promoting Complex/Cyclosome (APC/C). The APC/C plays a conserved role in restraining S-phase entry, and growing data implicates APC/C in tumor suppression. In this proposal we evaluate the hypothesis that signaling through the AKT- APC/C axis promotes proliferation in luminal breast cancer. This hypothesis implies that AKT promotes proliferation, in part, by dysregulating the protein degradation landscape. However, the contribution of PI3K-AKT to shaping the proteome through global changes in ubiquitination is entirely unknown. We will globally assess these dynamics using an innovative proteomic approach that surveys the ubiquitin landscape at unprecedented depth. This will define features of luminal breast cancer that promote proliferation, and which are invisible to genomic analysis.

Tier 2: Basic Science

PI: Scott E Williams, PhD, assistant professor, Department of Pathology & Laboratory Medicine

Co-Investigator: Xiaoxin "Luke" Chen, MD, PhD, professor, Cancer Research Program, NCCU

Project Title: Role of hotspot p53 mutations and "reverse" sexual dimorphism in oral and esophageal squamous cell carcinoma

Abstract

Squamous cell carcinomas of the upper GI tract, which include Oral Squamous Cell Carcinomas (OSCCs) and Esophageal Squamous Cell Carcinomas (ESCCs), almost always harbor mutations in p53 - the "guardian of the genome." While p53 is mutated rather than lost in most cancers, occurring primarily at four "hotspots" (R175/R248/R273/R282), most pre-clinical studies rely on loss-of-function (p53-/-) models. Moreover, few animal models of OSCC or ESCC induce tumors in the native sites, instead relying on the skin as a surrogate. To better model OSCC initiation and progression, we have developed orthotopic mouse models utilizing two of the most frequent hotspot mutations occurring in OSCC (p53R172H and p53R270H, the murine equivalent of the human R175 and R273). In our model, both R172H and R270H mutations half the latency period before tumors develop in the oral cavity, mirroring the poorer outcomes of human patients with hotspot mutations. Surprisingly, we have also identified an unprecedented "reverse sexual dimorphism" in both mice and humans with p53 mutations in OSCC, where females display poorer survival compared to males, in opposition to virtually every other non-reproductive cancer. Our central hypothesis is that mutant p53 induces distinct patterns of gene expression in male and female oral cancers, distinct from changes that occur upon p53 loss. Our dual objectives here are to 1) directly compare p53 mutation and loss in OSCC/ESCC at a cellular and transcriptional level, and 2) utilize our mouse models and TCGA patient RNAseq data to uncover p53-dependent gene expression differences between sexes which may explain dimorphic patient outcomes in OSCC. Our long-term goal will be to uncover targetable pathways specifically upregulated by mutant p53 which can be utilized for therapeutic benefit.

Tier 2: Clinical/Translational

PI: Lameck Chinula MD, assistant professor, Department of Obstetrics and Gynecology

Co-Investigators: Satish Gopal, MD, MPH, associate professor, Department of Medicine; Jennifer Smith, PhD, MPH, associate professor, Department of Epidemiology, UNC Gillings School of Global Public Health; Jennifer Tang, MD, MSCR, assistant professor, Department of Obstetrics & Gynecology

Project Title: A novel cervical cancer screen-and-treat demonstration project with HPV self-testing and thermocoagulation for HIV-infected women in Malawi

Abstract

Invasive cervical cancer (ICC) is preventable with human papillomavirus (HPV) vaccination and screening and treatment of cervical dysplasia. However, the burden of ICC remains unacceptably high in low-and-middle income countries (LMICs) such as Malawi, due to low population coverage of vaccination and screening and high population HIV prevalence. WHO recommends HPV testing, visual inspection with acetic acid (VIA), and cryotherapy as the preferred approach to prevent ICC in LMICs. Malawi has attempted to implement VIA and cryotherapy since 2004, but screening coverage remains abysmal, as do completion rates for treatment among women with screening abnormalities. As a result, current approaches based on VIA and cryotherapy are unlikely to avert the ICC epidemic in Malawi. Innovative, scalable, public health solutions are urgently needed. We propose a demonstration project for a novel ICC screen-and-treat strategy among HIV-infected women receiving antiretroviral therapy in Lilongwe: self-collected vaginal swabs for HPV testing, followed by VIA and cervical thermocoagulation for those who are VIA positive. This strategy has not been robustly evaluated, utilizes new technologies developed specifically for low-resource settings (Xpert HPV assay, thermocoagulation), and can be completed in a single day. These attributes are likely to address the coverage and attrition problems that have limited current approaches. We will assess uptake and feasibility, estimate under- and overtreatment rates, and evaluate efficacy of thermocoagulation for high-grade dysplasia treatment. This study will provide essential preliminary data to inform the Malawi Cervical Cancer Program and applications for future R01 and/or cooperative clinical trials groups in global oncology.

Tier 2: Clinical/Translational

PI: Jonathan S. Serody MD, professor, Department of Medicine, Division of Hematology/Oncology

Co-Investigators: Charles Perou, PhD, professor, Department of Genetics and of Pathology & Laboratory Medicine; Benjamin Vincent, MD, assistant professor, Department of Medicine, Division of Hematology/Oncology

Project Title: Characterizing the Function of B cells in Triple Negative Breast Cancer

Abstract

Triple negative breast cancer (BrCA) (TNBC) represents approximately 20% of BrCA cases. While TNBC is responsive to chemotherapy, disease recurrence is common leading to an inferior survival for patients with this subtype of BrCA. Recently, our group demonstrated that TNBC is highly infiltrated with immune cells that are made up of both B and T lymphocytes. Our most recent evaluations have suggested a strong correlation between the presence of B cell metagenes in the tumor microenvironment (TME) and clinical survival for patients with TNBC.

B cells have multiple functions including the generation of antibody and the presentation of antigen. We have found that B cells in the TME of mice and patients are clonally restricted suggesting that they respond to an endogenous tumor antigen. This had led to the hypothesis that B cells may generate antibodies specific to endogenous antigens in the TME, which may be critical to anti-tumor activity. Here, we use a novel single cell method to clone antibodies from B cells and plasmablasts present in the TME in women with BrCA. We will characterize the tumor antigens recognized by these B cells, which can be used as a therapeutic and a biomarker. Using pre-clinical murine models, we will evaluate the hypothesis that B cells are critical to the function of dual checkpoint inhibitor therapy targeting PD-1 and CTLA-4 and that B cells must generate antibody for this activity. Completion of this proposal will change our understanding of CPI therapy and offer new avenues for antibody therapy.

Tier 2: Population Science

PI: Louise Henderson PhD, associate professor, Department of Radiology

Co-Investigators: M Patricia Rivera, professor, Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine; Jared Weiss, MD, associate professor, Department of Medicine, Division of Hematology and Oncology; Jason Akulian, MD, MPH, assistant professor, Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine; William Funkhouser, MD, professor, Department of Pathology & Laboratory Medicine

Project Title: A Multidisciplinary Collaboration to Assess Use of Guideline Recommended Molecular Biomarker Testing in Rural Versus Urban Lung Cancer Patients

Abstract

In the U.S., lung cancer is the leading cause of cancer death with lung cancer incidence and mortality rates higher in rural versus urban areas. Most lung cancers are diagnosed at advanced stages when prognosis is poor, resulting in a metastatic 5-year survival rate of only 4%. To our knowledge, there is no difference in lung cancer survival by rurality for patients diagnosed at advanced stages, likely due to a lack of effective treatment options. However, this may change as molecular biomarker testing of advanced stage non-small cell lung cancer (NSCLC) tumors allow for the identification of actionable genomic abnormalities. Treating NSCLC patients with specific targeted therapies may significantly improve survival outcomes. The long-term goal of this research is to improve the use of biomarker testing for all patients with advanced NSCLC. The objective of this pilot application is to explore rural/urban disparities associated with biomarker testing. We will accomplish this by linking lung cancer pathology reports from the UNC LCCC RCA Program with access and contextual factors from U.S. Census data to evaluate the impact of recent molecular advances in lung cancer treatment on health disparities. Our results will fill a knowledge gap in understanding how molecular biomarker testing is being used in a population setting and if these advancements in care are potentially widening rural/urban disparities. The key to realizing the benefits of precision oncologic therapy is dependent on the patient receiving biomarker testing and their health care providers using the results to inform initial treatment decisions.