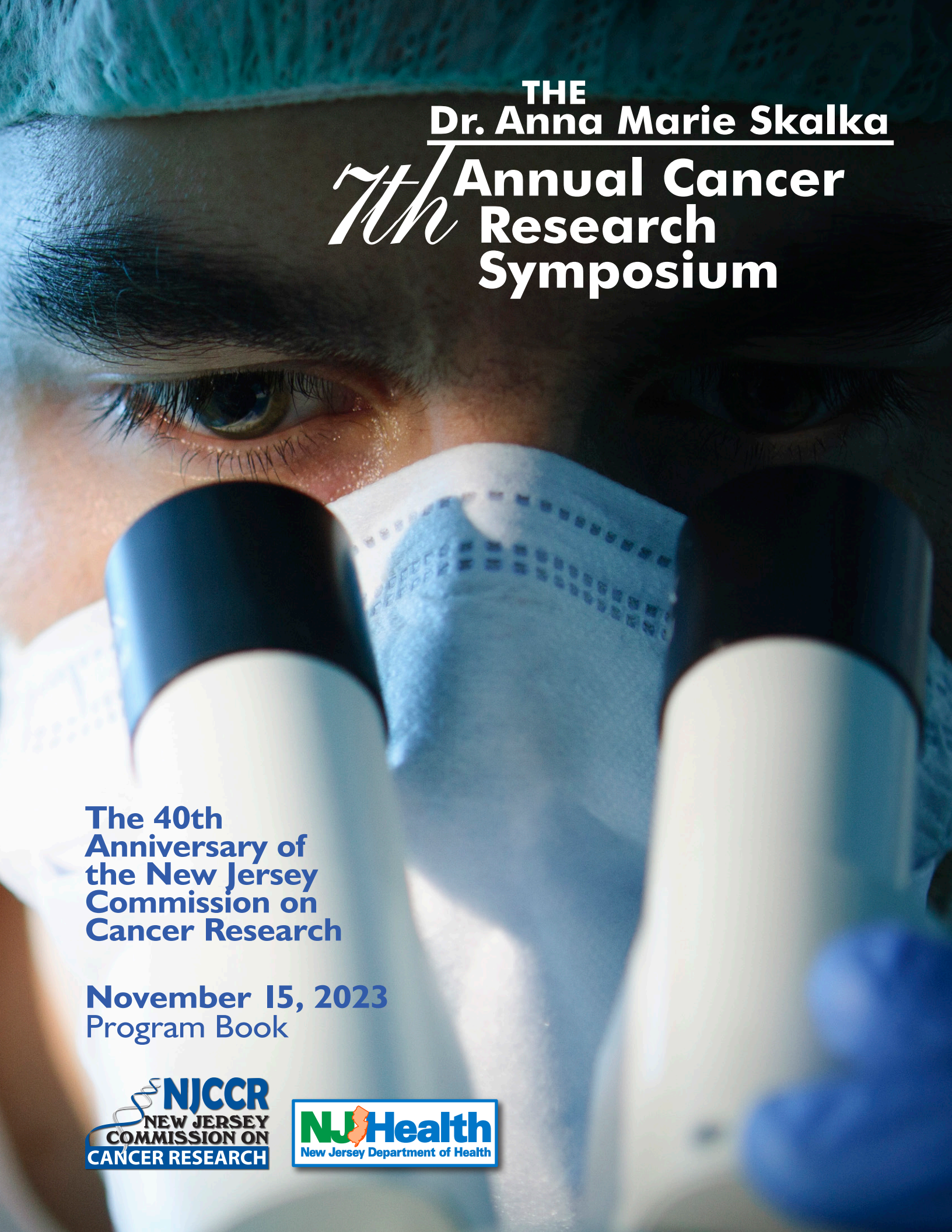

THE Dr. Anna Marie Skalka 7th Annual Cancer Research Symposium

The 40th Anniversary of the New Jersey Commission on Cancer Research

November 15, 2023
Program Book

NJCCR NEW JERSEY COMMISSION ON CANCER RESEARCH

NJ Health New Jersey Department of Health

THE Dr. Anna Marie Skalka 7th Annual Cancer Research Symposium

NJCCR
NEW JERSEY COMMISSION ON CANCER RESEARCH

New Jersey
Department of Health
PO Box 360
Trenton, NJ 08625-0360

609-913-5008
https://www.nj.gov/health/ces/cancer-researchers/njccr/

NJ Health
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Agenda at-a-Glance

8:30 am **Registration,** *Continental Breakfast*

8:45 am **Welcome**
Kenneth Adler, MD, *Chair, NJCCR*

9:00 am **Keynote Address**
Cancer Care and Research: New Opportunities
Steven Libutti, MD, FACS
Distinguished Guest and
Director, Rutgers Cancer Institute of NJ

9:45 am **Awards Presentation**
Legislative Champion Award
NJ State Senator Robert W. Singer
NJ Assemblyman Herb Conaway
Patient Advocate Awards
Grace Eline
Barbara Raphael
Dr. Jonathan Yavelow Mentor Award of Commendation
Dr. Mohamed S. Abou Donia
Dr. Kyle K. Payne

10:15 am **Pre/Post-Doctoral Fellowship Presentations**

12:15 pm **Networking Lunch**

1:00 pm **Panel Discussion:**
Translational Research from Bench to Community
Yibin Kang, PhD
Daniel Notterman, MA, MD
Mark Kaplan, PhD
Anita Kinney, PhD

2:00 pm **Concluding Remarks:**
Kenneth Adler, MD, *Chair, NJCCR*

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The New Jersey Commission on Cancer Research was ushered in by the Cancer Research Act, to support its activities. This Act resulted from the collaborative efforts of people with cancer and their families, clinicians, academicians, scientists, public officials, and representatives of research, pharmaceutical industry, and non-profit organizations.

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Awards

- **Legislative Champion Award:** This Award is given to a state legislator that has championed cancer research on the state level. Past recipients have championed the NJ Commission on Cancer Research's work in funding state cancer research: including support for restoring state funding cuts to cancer research, introducing state legislation creating a dedicated funding source for state cancer research and additional resources for cancer researchers on the state level in New Jersey.

- **Patient Advocate Award:** This Award is dedicated to honoring advocates in the community who work to support cancer patients, whether pushing for early detection of cancer, better treatment options for cancer patients, or support for cancer research. Past recipients include cancer survivors who have used their strength to continue the fight to defeat cancer long after treatment is done.

- **Dr. Jonathan Yavelow Mentor Award:** This Award was created to honor the work of Dr. Yavelow, a longtime member of the NJ Commission on Cancer Research and dedicated mentor to many students over his storied career. Dr. Yavelow was a Professor of Biology at Rider University for 35 years, and a member of the Commission since 1984. He was a dedicated researcher and beloved by his students, many of whom he mentored throughout the years. Mentorship plays a key role in supporting a successful career in cancer research. Therefore, outstanding mentors in cancer research are eligible for this award.

Legislative Champion Award: New Jersey State Senator Robert W. Singer

Senator Robert W. Singer represents the 30th District in the NJ State Legislature—the 30th District is comprised of parts of Ocean and Monmouth counties. The Senator continues to serve as Deputy Minority Leader in the NJ Senate for the 2022-23 legislative session. Prior to this leadership role, he served as Republican Conference Leader.

He is the senior ranking member of the Senate Health, Senior Services and Senior Citizens Committee, and serves on the Senate Commerce and Senate Oversight Committees. In addition to his current legislative responsibilities, commission appointments for Senator Singer include the NJ Commission on Science, Innovation and Technology and he is also a member of the New Jersey-Israel Commission. He served as a member of the Lakewood Township Committee for 30 years, retiring in 2010, and has held many local civic affiliations.

Legislative Champion Award: New Jersey Assemblyman Herb Conaway

The Honorable Herb Conaway, M.D., elected for a 13th term, has been serving New Jersey's 7th Legislative District as its assemblyman for 25 years. In the 220th Legislature, Conaway is a leader in the Democratic majority, Chairman of the Health Committee, member of the Budget Committee and member of the Military and Veterans' Affairs Committee.

Conaway is the only member of the New Jersey State Legislature with both a medical and law degree. He specializes in internal medicine and serves as Director of the Burlington County Health Department. He earned his bachelor's degree in politics from Princeton University, his medical degree at Jefferson Medical College and his law degree from Rutgers Law School, Camden. Conaway also served as a U.S. Air Force Captain in the Medical Corps at McGuire Air Force Base, as a general medical officer and as an assistant director of the primary care clinic for the base.

In addition to playing a leading role in most of the major health legislation signed into law during his 15-year tenure as health chair, Conaway sponsored New Jersey's school funding formula, increased, and modernized nutritional standards in public schools. He has also sponsored successful legislation advancing environmental protection, property tax relief, veterans services and public safety.

2023 Award Presentations

Patient Advocate Award: Grace Eline

The founder of WITH Grace Initiative, Grace Eline, is a childhood brain tumor survivor who uses her experience and voice to make an impact in the childhood cancer community. Grace was giving back to this cause before she was diagnosed herself in 2018. Grace formed her 501c3 non-profit after seeing a need to support other children in treatment while she was in treatment herself. She leads this organization that is focused on three pillars that includes creating care packages for families affected by childhood cancer, raising money for research for less toxic treatments, and building awareness for the unique journey of childhood cancer. Grace also runs a virtual support and connecting group for childhood cancer warriors and survivors to not feel alone, find friendship and gain access to tools that can help those affected by childhood cancer find the tools they need to feel good both mentally and physically. Grace has advocated at the state, federal and international level to build awareness for pediatric cancer, address the need for access to care, demand research dollars specific for childhood cancer as well as communicate the urgency to address survivorship challenges for this community.

Patient Advocate Award: Barbara Raphael

Barbara is a 20-year cancer breast cancer survivor-- she was initially diagnosed with left DCIS in 2003, and in September 2018, she was diagnosed with metastatic breast cancer. In Barbara's own words, "being diagnosed with a terminal disease change everything for anyone", and she has used her diagnosis as a call to action. The highlight of her advocacy pursuits took place in Washington DC in October 2019 – aptly named the "Stampede" – where patients and their families came together from across the country to meet with members of Congress to petition for several bills to be passed that would help their cause of research funding for metastatic breast cancer.

In 2019, she utilized social media to connect with a Delaware Valley-based group, Living with MBC Support Group (Delaware, New Jersey, Pennsylvania). The group would connect virtually on a daily basis, but would also schedule "meet ups", which led to fundraising efforts for research via Metavivor.org, and she has personally raised over $10,000 for the cause. Even while dealing with her own health challenges, she has worked tirelessly to raise money and to ensure that others with the disease have access to activities, mentoring and fellowship with others fighting metastatic breast cancer.

Dr. Jonathan Yavelow Mentor Award: Dr. Mohamed S. Abou Donia

Mohamed S. Abou Donia received his B.Sc. in Pharmacy from Suez Canal University, Egypt in 2004, and his Ph.D. from the School of Pharmacy, University of Utah in 2010. After completing his post-doctoral studies at the University of California, San Francisco, Mohamed started his laboratory in 2014 at the Department of Molecular Biology, Princeton University. There, using a combination of metagenomic, biochemical, and computational approaches, his group investigates the role of the human microbiome in health, disease, and response to therapeutic interventions. Mohamed is a recipient of the NIH Director's New Innovator and Transformative Research Awards, the Kenneth Rainin Foundation Innovation and Breakthrough Awards, the Pershing Square Sohn Prize for Young Investigators in Cancer Research, the Vilcek Prize for Creative Promise in Biomedical Science, and is named a Pew Biomedical Scholar. Thus far, he mentored 13 undergraduate students, six graduate students, and eight postdocs.

Dr. Jonathan Yavelow Mentor Award: Dr. Kyle K. Payne

Kyle K. Payne, PhD, is an Assistant Professor of Medicine, Section of Cancer Immunotherapy, at the Robert Wood Johnson Medical School and is a Resident Member of the Rutgers Cancer Institute of New Jersey. Dr. Payne earned a bachelor's degree with distinction from Indiana University in 2005 and then went on to complete his PhD in Tumor Immunology at Virginia Commonwealth University in 2015. He then completed his training with an American Cancer Society-sponsored postdoctoral fellowship, first at the University of Pennsylvania/ The Wistar Institute, and subsequently at Moffitt Cancer Center before joining Rutgers University in 2021. He has thus far published over 40 peer-reviewed articles, primarily focused on defining the immunobiology of ovarian cancer and developing novel therapeutic strategies for treating this disease. He was also recently named a recipient of the Pershing Square Sohn Prize for Young Investigators in Cancer Research. Dr. Payne is involved with several national grant review panels and major committees. In addition to the primary mentorship of his trainees, Dr. Payne is actively involved with the Rutgers Youth Enjoy Science Program, which encourages young people from underrepresented groups to pursue cancer research and healthcare careers.

2024 Pre-Doctoral Fellowship Grants

2024 Pre-doctoral Fellowship Grants

Category: Colorectal Cancer
Project Title: *CD74 Receptor Activated Paneth Cells Modulate Intestinal Inflammation and Cancer Progression*

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Colorectal cancer is one of the most commonly diagnosed cancers in the United States contributing to 50,000 deaths annually. Inflammation-associated colon cancer is a subtype of colorectal cancer with a poor prognosis and represents one of the most severe complications associated with chronic intestinal inflammation. Patients with chronic intestinal inflammation observed in both Crohn's Disease and Ulcerativ333e Colitis are at an increased risk of developing colorectal cancer if left untreated or if their treatment fails. The pathways linking inflammation to increased susceptibility of colorectal cancer progression remain incompletely understood. The distal colon of healthy humans do not contain Paneth cells, however, prolonged chronic inflammation in the colon induces the development of metaplastic Paneth cells. These metaplastic Paneth cells are a hallmark of chronic intestinal inflammation. Using single cell RNA sequencing and immunohistochemistry, our preliminary data suggest that a subset of Paneth cells can be activated in response to inflammation to secrete a group of evolutionarily conserved chemokines. We believe this secretion leads to the migration of specific lamina propria immune cells to the inflammatory site, leading to a propagated disease state..

Category: All cancers
Project Title: *Elucidating novel genetic drivers of immune regulation by human dendritic cells*

Ryan McNulty[1], Vanessa Spires[2], Jordan Blum[2], Mark Fereshteh[2], Britt Adamson[1,3]
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The clinical success of immune checkpoint inhibitors in the past decade represents a breakthrough in our ability to fight cancer by tuning the biological signals that control the immune system. Here, we aim to identify additional proteins and gene regulatory pathways that regulate immune response as potential targets for immunotherapies. To achieve this, we focus on dendritic cells (DCs), a type of immune cell which plays a specialized role in activation of the immune system. In this work, we develop a platform to systematically interrogate the genes that participate in immunoregulatory signaling between human dendritic cells and T cells

by pairing an arrayed CRISPR genetic screen with mixed lymphocyte reactions. Pilot experiments implicate LAMP3, a DC-specific lysosomal membrane protein, as exhibiting an inhibitory role in T cell activation. By scaling this platform, we aim to screen 1-2% of the human genome for DC-specific immunoregulatory function to identify novel DC-expressed mediators of T cell function at the immune synapse.

Category: Cancers that are amenable to photodynamic therapy
Project Title: ***Leveraging production of reactive oxygen species in photodynamic therapy for development of a novel drug targeting strategy.***

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The long-term goal of this research is to improve cancer therapy by combining novel targeting strategies with existing therapies to treat drug-resistant cancers. Photodynamic therapy (PDT) is a type of treatment used for cancer that utilizes a photosensitizer to produce reactive oxygen species (ROS) when exposed to a specific wavelength of near-infrared (NIR) light. This production of ROS leads to apoptosis of the cancer cells and cuts off the vasculature to the cells, leading to cell death. We have been developing a drug delivery technology that exploits the overproduction of ROS within tumors as a drug targeting signal. The ROS drive crosslinking of a polymer net that can then specifically capture payloads via click chemistry and use enzymes produced at the tumor site to release the captured drug. Our previous work has shown that: (1) acrylated PEG polymers react with ROS and lead to crosslinking of the terminal acrylate groups; (2) the crosslinking reaction immobilizes the polymer network in tissue mimics and in vivo; (3) a payload can be localized to a polymer network using click chemistry; and (4) MMP degradation can allow for a controlled release on the payload. Our goal is to combine the existing PDT and leverage its effects on the production of ROS to improve the use of our catch-and-release system. The exogenous production of excess ROS via PDT at the tumor will crosslink acrylated polyethylene glycol polymers that include functionalization with one part of a click chemistry pair. As such, the ROS from PDT will primarily damage the tumor and secondarily enable the targeting of therapeutics.

Category: Hematologic
Project Title: ***Investigating genetic susceptibility for chemotherapy-induced cognitive impairment in a juvenile ApoE4 rat model.***

Author(s): Chadni Patel[1, 2], Frank Diglio[2], Jeremy Willekens[2], Derek Adler[3], Yongkyu Park[2], Peter D. Cole[1, 2]

2024 Pre-Doctoral Fellowship Grants

Grant programs are designed to provide scientific opportunities to attract young and seasoned research scientists.

2024 Pre-Doctoral Fellowship Grants

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While most children with cancer can be cured, many survivors experience chemotherapy-induced cognitive impairment (CICI) (or "chemobrain"), leading to difficulty with attention and memory and impacts the quality of life. The interpatient variability in susceptibility to CICI is not well understood. In addition to environmental factors, it is likely that common gene variants explain some of the observed variability. One possible mechanism for CICI is chemotherapy-related changes in blood brain barrier (BBB) integrity, allowing influx of proinflammatory cytokines and oxidative damage within the CNS. Our laboratory focuses on the variant E4 allele of APOE (Apolipoprotein E), which has been linked to decreased BBB integrity and increased permeability compared to the more common E3 allele. Pediatric cancer survivors with the E4 allele of APOE are more likely to display cognitive dysfunction than those without this allele following treatment with identical chemotherapy doses. Juvenile rats homozygous for either the human ApoE3 or ApoE4 gene were exposed to doxorubicin at a clinically relevant dose (2 mg/kg of doxorubicin once weekly for 4 weeks). Behavioral assays of cognition were then used to test whether the rats bearing the ApoE4 allele were more susceptible to doxorubicin-induced memory deficits. Doxorubicin caused spatial memory impairments in both ApoE3 and ApoE4 rats compared to their respective controls. ApoE4 doxorubicin treated rats were more likely to exhibit visual memory impairments than ApoE3 treated doxorubicin rats when compared to their respective controls. No significant changes in BBB integrity within hippocampus and prefrontal cortex were found by contrast-enhanced magnetic resonance imaging. Overall, the experimental outcomes shed light on ApoE4 genetic susceptibility to CICI, setting the stage for further investigation.

Category: **Breast and Melanoma of the Skin**
Project Title: ***Impact of the gut microbiome on tumor progression and cancer immunotherapy***

Salma Youssef, Jeffrey Lee, Moamen Elmassry, Yong Tang, Siddharth Marwaha, Ziqing Chen, Seema Chatterjee, Xiang Hang, Yong Wei, Yibin Kang, Mohamed Abou Donia

Salma Youssef
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Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer immunotherapy by enabling a patient's own immune cells to attack cancer cells. However, widespread application of ICI therapy has been limited due to heterogeneity in patient response. Patients treated with ICI therapy can be classified into responders and non-responders. Previous studies have linked the gut microbiome and ICI therapy efficacy in melanoma patients. These discoveries led to the promisingly successful administration of fecal microbiota transplants as an adjuvant therapy to improve response to ICB therapy in patients. However, molecular mechanisms behind the observed effects on response and immune cell activation are still unknown. Using computational analysis of human fecal metagenome sequencing, we found significant bacteria from the gut microbiome enriched in responders. This allows downstream study of these key bacterial pathways and their products through in vivo and in vitro experiments that explore the mechanism of immunomodulation by the gut microbiome. By utilizing an interdisciplinary approach, we aim to provide novel insights into the crosstalk between the tumor cells, immune cells, and the gut microbiome. Given our lab's expertise on cancer genetics, immunology and discovery of small molecules derived from the gut microbiome, our study will contribute to the advancement and widespread application of ICB therapy in cancer patients.

Category: Liver
Project Title: ***Evaluation of combination mTOR agonist and CD147-IL15-CAR-NK cell therapy in transgenic human CD147 Hepatocellular Carcinoma models***

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Hepatocellular carcinoma (HCC) is one of the most common primary liver cancers, resulting from viral hepatitis, fatty liver disease, and alcohol use. More than half a million patients die from HCC each year. However, HCC treatments remain limited with short overall survival of approximately 13.6 months using multikinase inhibitors such as regorafenib post-diagnosis. Chimeric antigen receptors (CAR)-modified natural killer (NK) cell is a promising approach for malignancies and infection. Taking advantage of the unique feature of CAR-NK cells, including great potential as an 'off-the-shelf' universal CAR product, we recently developed a novel technology for the generation of long-lasting 'memory-like' CAR-NK cells with enhanced lifespan. Based on this platform, we recently devised a novel strategy for targeting HCC, one of the deadliest solid tumor cancers in humans. We report that NK cells transduced with a CAR that targets the HCC surface marker, CD147, also known as Basigin (BSG) or extracellular matrix metalloproteinase inducer (EMMPRIN), can effectively kill malignant HCC cell lines (including SK-Hep1, Huh7, HCO2, Hep3B, and HepG2

cell lines), primary HCC in vitro and tumors in cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) mouse models of liver cancer. However, xenograft models may not fully recapitulate HCC development, considering that the tumor microenvironment (TME) of HCC presents an abundance of immunosuppressive mediators, such as prostaglandin E2 (PGE2), to suppress NK cell proliferation, persistence, and functions. We have designed autocrine interleukin 15 (IL-15) CD147-CAR-NK cells, henceforth CD147-IL15-CAR-NK cells, as IL-15 is frequently supplemented to NK cell culture to enhance NK cell maturation, functions, and persistence. Interestingly, our preliminary data show that IL-15 regulates the mTOR pathway in human primary NK cells. IL-15 alone has been shown to rescue the functions of NK cells in the presence of PGE2 in vitro through the upregulation of phosphorylated S6 kinase (S6K). These data strongly indicate that mTOR complex 1 (mTORC1) plays an important role in positively regulating NK cells, leading to the investigation of a small molecule mTOR agonist named MHY1485 on NK cells in vitro in **Aim 1**. As we are the only group to have human CD147 transgenic mice (hCD147tg) and have also successfully established spontaneous HCC disease in these mice, we will thoroughly evaluate the therapeutic potential of CD147-IL15-CAR-NK cells in combination with MHY1485 in treating HCC in **Aim 2**. Completion of the proposed study will pave the way of using "off-the-shelf" universal CAR-NK cell products in treating solid malignancies.

Category: Lung and Bronchus

Project Title: ***Detailing KRAS/LKB1 (KL) co-mutated non-small cell lung cancer (NSCLC) metastatic dependency on host autophagy***

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Autophagy is a highly regulated process in all living cells, which is performed to break down large molecules into smaller more useful building blocks for intracellular recycle and removal of toxic component. Cells can upregulate or downregulate this process in response to metabolic stress, such as nutrient deprivation to maintain cellular homeostasis. Cancer depends on autophagy to meet the increased metabolic demand resulting from their higher growth rate. Recent studies using preclinical mouse models demonstrated that autophagy supports several types of tumor growth. Lung cancer alone accounts for nearly 25% of all cancer related deaths in the United States, typically with a 5-year survival rate of only 22%. However, once metastasis has begun, these rates plummet to as low as 7%. While the role of autophagy, including host autophagy and cell-intrinsic autophagy, in primary tumor has been intensively

studied, the precise role of autophagy in lung tumor metastasis is still largely elusive. In this project, we propose to explore the role and underlying mechanism of host autophagy in Kras-driven lung cancer metastasis. In particular, we will determine the role and mechanism of metabolic alterations and immune system changes caused by host autophagy ablation in KL NSCLC tumor metastasis. The successful completion of this project can provide insight to a novel therapeutic strategy in the prevention or treatment of lung cancer metastasis by autophagy inhibition.

Category: Hematologic
Project Title: ***Dissecting OTUD5 as a novel therapeutic target in leukemia***

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T-cell acute lymphoblastic leukemia (T-ALL) is a NOTCH1-driven aggressive hematological malignancy that occurs predominantly in pediatric and young adult patients. Despite recent advances in treatments with intensified chemotherapy regimens, 20-50% of patients still relapse, and the prognosis of these refractory/relapsed T-ALLs remains extremely poor. In addition, most T-ALL survivors are at risk for long-term side effects caused by either leukemia itself or by the intensive treatments, highlighting the need to discover novel and safer targeted therapeutic approaches. In this setting, analyses of unbiased genome-wide CRISPR screens in leukemic cells in vitro upon treatment with the IC90 of seven currently used chemotherapeutic drugs in leukemia treatment in the clinic (i.e. L-Asparaginase [L-ASP], vincristine, 6-Mercaptopurine [6-MP], cytarabine [AraC], methotrexate, daunorubicin or maphosphamide) identified the deubiquitinase OTUD5 as the top hit whose loss synergized simultaneously with 6 out of the 7 drugs. However, nothing is known about the role of OTUD5 in T-ALL. To bridge this gap in knowledge, we have generated NOTCH1-induced Otud5 conditional knockout mouse primary leukemias, and we have already shown that isogenic loss of OTUD5 in vitro impairs leukemia progression. Thus, here we will use this unique tool to: (i) test the synergistic role of OTUD5 loss with chemotherapeutic drugs in T-ALL in vitro and in vivo; and (ii) dissect the role and mechanistic effects of OTUD5 loss in T-ALL. Our results might uncover OTUD5 as a very promising target for T-ALL treatment in vivo and, thus, could have broad clinical relevance for the treatment of T-ALL patients in the near future.

2024 Pre-Doctoral Fellowship Grants

The NJCCR offers Pre- and Post-Doctoral Fellowships to trainees at New Jersey non-profit research institutions with formally established and active graduate research programs.

2024 Post-Doctoral Fellowship Grants

2024 Post-doctoral Fellowship Grants

Category: Colon and Rectum
Project Title: *Evaluation The role of Leukemia Inhibitory Factor in colorectal cancer*

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LIF, a multi-functional cytokine, plays pleiotropic roles in a cell- and tissue-dependent manner. Previous reports, including ones from our lab, have shown that LIF is frequently overexpressed in different types of human tumors, including colorectal cancer (CRC), and the overexpression of LIF is often associated with poor prognosis of CRC patients. These observations strongly suggest a potential tumor promoting role of LIF in tumorigenesis. Currently, the role of LIF in colorectal tumorigenesis and its underlying mechanism are not well-understood. It has been suggested that the oncogenic activation in intestinal stem cells, which are ideal candidates to accumulate mutations due to their long-term clonogenic potential to sustain tissue homeostasis, initiates intestinal cancer, supporting the theory of cancer initiating cell (CIC). Our preliminary data strongly demonstrates that LIF, which is often overexpressed in CRC, plays a crucial role in maintaining the number and function of intestinal stem cells, implying a latent role of LIF in promoting CICs. Using genetically engineered mouse intestinal tumor model with different LIF expression levels in intestinal tissues, we will validate our hypothesis that LIF may be essential for CICs, which in turn promotes the development of CRC, and blocking LIF in mice can eliminate CICs and inhibit colorectal tumorigenesis. Mechanically, we will examine whether LIF increases CIC numbers and enhances CIC functions through AKT/GSK3β/β-catenin axis. CRC is the third leading cancer death in the United States. Understanding the features of intestinal CICs would provide novel therapeutic strategies targeting CRC. The goal of this study is to determine the role of LIF in CRC and CIC function to provide effective therapeutic targets/strategies for CRC. The benefit is that we will investigate whether this pathway is amenable for anti-cancer strategies in CRC models where LIF is overexpressed.

2024 Post-Doctoral Fellowship Grants

Category: Liver

Project Title: ***Modeling chronic hepatitis B virus infection and virally-induced hepatocarcinogenesis in a small non-human primate model***

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Liver cancer is one of the most common causes of cancer-related deaths and about 80% of all liver cancers are a result of infections with hepatitis B virus (HBV). Unfortunately, current antiviral therapy can only suppress viremia but rarely leads to a cure. Thus, current antiviral therapy only decreases, but does not eliminate the risk of liver cancer development. A major roadblock for developing more effective therapies and for gaining mechanistic insights into how HBV causes liver cancer is the scarcity of suitable animal models. The reason why HBV cannot infect other monkey species is not understood. HBV hijacks a bile acid transporter called NTCP to enter liver cells. The building blocks and consequently the overall structure of NTCP differ between humans and species that cannot be infected with HBV. We demonstrate that these differences create a barrier for the virus that precludes infection. Notably, when we engineered monkey liver cells to express human NTCP HBV can complete its entire life cycle. This finding demonstrates that viral uptake is the only major barrier that would have to be overcome to establish infection in a small non-human primate model for HBV. We reasoned that it would be easier to adapt the virus to a new host rather than creating a genetically engineered monkey. To adapt HBV, we analyzed whether a virus related to HBV that has been previously identified in wooly monkeys (thus called WMHBV), an endangered species, could possibly infect liver cells from other primates. Interestingly, WMHBV can indeed infect liver cells isolated from marmosets, a small non-human primate species that is commonly used in biomedical research. We went one step further and constructed a chimeric virus that combines a very small piece of WMHBV responsible for mediating viral uptake while keeping 98.5% of the HBV genome intact. This minimally monkey-adapted HBV variant can also infect marmoset cells and has putatively much greater utility for evaluating treatments intended for humans.

2024 Post-Doctoral Fellowship Grants

Category: Breast

Project Title: *Integrated Analysis of Imbalanced Allelic Expression to Infer Gene Regulatory Patterns in Cancer*

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In a diploid genome, the relative abundance of transcripts that express each allele can be dysregulated by germline single nucleotide polymorphisms (SNP) or somatic mutations in regulatory regions such as promoters and enhancers of the genes, resulting in allelic imbalance (AI). Accurate measures of AI, reflected in mutant allele frequency (AF) and relative expression count measurements in RNA, may therefore identify regulatory loci that, when genetically altered, drive transcriptomic changes in cancer. Previous efforts to identify molecular processes and pathways that are altered in tumors have primarily focused on gene-level transcriptomic analyses and do not consider allele-specific expression (ASE). In the context of tumors, ASE/AI assumes immense significance since alterations in the alleles that are preferentially transcribed or induce allele-specific expression are more likely to impact the molecular processes that involve the aberrant expression of corresponding genes.

We tested the hypothesis that altered regulation in cancer is associated with the extent of co-exhibited, imbalanced allelic expression. We developed a quantitative framework for accurately measuring AI reflected in the transcription of alleles, corrected by DNA copy-number and specimen tumor content. We integrated DNA and RNA data to investigate the underlying mechanisms of AI and analyzed allelic expressions from ~900 TCGA breast cancer data and ~300 GTEx samples from normal breast tissue. We showed that bulk sequencing eliminates enrichment of allelic expression across normal tissue and that tumor aberrations are associated with enrichment and co-exhibition of imbalanced allelic expression in genes involved in known and novel oncogenic processes.

Category: Hematologic

Project Title: *A novel biclustering approach for performing single-cell spatial transcriptomic analyses*

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Single-cell transcriptomic studies have enabled the exploration of transcriptional activity in tissues at the level of individual cells, helping uncover both the diversity of cell types as well as the dynamic changes of gene expression between cell states. Recently, rapid advances in experimental techniques and protocols have enabled the information about the spatial locations of the cells in tissues to be retained. Understanding the relationship between cells and their relative locations enables us to form a more holistic understanding of cells in their morphological context. In the context of complex diseases such as cancers, this will significantly aid the identification of novel therapeutic targets and improve treatment modalities. Previously we had developed a novel tunable biclustering algorithm (TuBA) for analyzing large bulk gene expression data sets. TuBA identifies co-regulated genes within subsets of samples in a completely unsupervised manner. In the context of the rapidly growing area of spatial single-cell transcriptomics, biclustering offers a previously unexplored approach to leverage the gene expression data to identify groups of cells located proximally in a given tissue together with the genes they co-express. TuBA has now been adapted for application to single-cell counts data, and we showcase its applications to publicly available data sets obtained from recent spatial transcriptomic studies.

Category: Colon and Rectum
Project Title: ***The regulation of mutant p53 in human cancer***

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Tumor suppressor p53 gene is the most frequently mutated gene in human cancers. Mutant p53 (mutp53) proteins often accumulate to very high levels in human cancers to promote cancer progression through the gain-of-function (GOF) mechanism. Currently, the mechanism underlying mutp53 accumulation and GOF is incompletely understood. Recently, we screened for specific mutp53-interacting proteins and identified TRIM21 as a critical E3 ubiquitin ligase of mutp53. We found that TRIM21 interacted with mutp53, resulting in ubiquitination and degradation of mutp53. TRIM21 deficiency in cancer cells promoted mutp53 accumulation. Currently, we are establishing colorectal tumor models with conditional mutp53 overexpression and/or TRIM21 knockout by crossing conditional APC min/+ mice with conditional p53R172H mutp53 knock-in mice and/or conditional TRIM21 knockout mice. These mice will be used to investigate whether TRIM21 deletion in p53R172H knock-in mice resulted in mutp53 accumulation in colorectal tumors to promote tumor development through the GOF mechanism. These studies will reveal a novel

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and critical mechanism for mutp53 accumulation and GOF in cancer and the tumor-suppressive function of TRIM21 in cancers carrying mutp53, especially in colorectal cancer.

Category: Epithelial carcinomas and solid tumors
Project Title: ***Defining the role of Disheveled in establishing epidermal planar cell polarity.***

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Metastasis, or the ability of cancer cells to invade and spread to healthy tissue, is the leading cause of mortality accounting for about 90% of cancer-related deaths. To invade and spread to distant healthy tissues and organs, cancer cells need to migrate away from the source tumor site. Curiously, signals that instruct cancer cells to migrate away from the tumor and toward healthy tissue are often the same signals that direct cell movements during embryonic development. In the embryo, cell migration is a normal process that shapes our organs and tissues, but cancer cells misuse these embryonic processes to invade and spread during metastasis. One molecular pathway that directs cell movement is the Planar Cell Polarity pathway and evidence suggests that over-activating its components (called planar polarity proteins) enables cancer cells to multiply and migrate in an uncontrolled manner. To prevent such misuse of these proteins by malignant cancer cells, it is vital to understand the behavior of polarity proteins in healthy tissue. In this project, I aim to study how planar polarity is built in healthy skin tissue of a developing mouse embryo. Because this tissue contains both migratory and non-migratory cell types in which planar polarity proteins are present, we can learn what keeps them dormant or active in normal, healthy tissues. This will help devise strategies to prevent planar polarity proteins from promoting aggressive behavior of malignant cancer cells, with profound implications in the development of cancer therapeutics and improving chances of treatment and survival in cancer patients.

Category: Drug screening and assay development
Project Title: ***Synthetic discovery of isoform specific TET inhibitors by a novel high-throughput screening assay***

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Triple negative breast cancer (TNBC) is a multifaceted and aggressive disease with a vast molecular diversity. It is known for its high likelihood of relapse and typically has a grim prognosis when it metastasizes. Traditionally, treatments mainly centered

on systemic chemotherapy rather than pinpointed targets and there remains a pressing need to identify new therapeutic targets and discern which populations stand to benefit most from them. TNBC possess a unique DNA methylation signature distinct from hormone receptor-positive breast cancers, ranking them among the most hypomethylated cancers. Epigenetic activity hinges on the balance between methylation and demethylation, with DNA methylase translocase (DNMTs) and Ten-Eleven translocase (TETs) enzymes playing a pivotal role. Our recent findings underscore that TET1 DNA demethylase enzyme expression is heightened in TNBCs relative to hormone receptor-positive samples, a trend not observed with TET2 or TET3. Levels of TET1 expression are associated with hypomethylation across numerous CpG sites, the activation of oncogenic pathways like the PI3K, and a decreased overall survival rate. In TET1-knockout TNBC cell lines, there's an increase in immune response gene activity, a decline in PI3K pathway expression, and diminished cell proliferation.

We aim to explore the mechanism of oncogenic pathway activation due to hypomethylation upon TET1 enzyme inhibition and pinpoint specific therapeutic vulnerabilities in TNBC. By refining a newly developed high-throughput screening assay, we screen for novel TET1 inhibitors in diverse compound libraries. Both TET-C35 and Eltrombopag exhibit potential as specific inhibitors and plan to refine these molecules for enhanced TET1 specificity. By understanding TET1 inhibition in TNBC, we aspire to enhance treatment efficacy and prolong the survival of breast cancer patients.

Category: Liver
Project Title: ***Characterizing the mechanism of the hepatitis B virus (HBV) host range restriction in mice.***

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Hepatitis B virus can infect humans and chimpanzees but not mice due to numerous blocks in the viral life-cycle in mouse cells. The amino acid sequence of the murine orthologue of NTCP differs from the human counterpart in residues that are critical for viral uptake. HBV can enter into mouse cell lines and mice expressing human NTCP but the infection does not proceed. Recent work further revealed that the intranuclear replication stages and subsequent steps in the infectious cycle are supported in murine cells. Collectively, these data suggest that the HBV life cycle is blocked in mouse cells at a late post-entry step but before the conversion of rc- to cccDNA.

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Here, we aimed to systematically analyze this barrier with the long-term goal of establishing a mouse model that is fully permissive to HBV infection. We hypothesized that differences in the abundance and/or species-specific differences in the amino acid sequences of nuclear import related (NI) proteins could conceivably explain the resistance of mouse cells to HBV infection. Proteomic profiling of human and mouse hepatoma cells that were or were not exposed to HBV showed that the localization and abundance of NI proteins is largely similar across all conditions. A systematic loss-of-function analysis of NI proteins in human cells revealed several candidates whose knock-down significantly reduced HBeAg secretion. These candidate proteins were imaged in human and mouse hepatoma cells during infection to characterize HBV influence on localization, whereby certain NI proteins in mouse-infected cells were confined from the nucleus. Notably, overexpressing the human orthologues of some of these NI proteins in mouse cells resulted in increases in HBeAg levels in hNTCP-expressing mouse cells following infection. Taken together, these data are supportive of the notion that incompatibility of a human-specific host dependency factors contributes to the restriction of HBV infection in mice.

Category: Solid tumors

Project Title: ***Subendothelial Fibronectin Disrupts Endothelial Cell Monolayer Integrity and Potentiates Cancer Cell Invasion.***

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Fibronectin (FN) is a large glycoprotein that is polymerized by cells into a 3D extracellular matrix (ECM) and serves as a scaffold for the deposition of other matrix proteins. In normal blood vessels, endothelial cells sit on a thin, laminar basement membrane (BM) that is rich in laminin, collagen IV, nidogen and perlecan, but contains very little FN. The BM is essential for forming cell-cell and cell-substrate contacts and maintaining apical-basal polarity. In the vasculature supplying many solid tumors, FN builds up beneath endothelial cells, and is correlated with vascular leak and new vessel growth. Given FN's role in wound healing and embryonic vasculogenesis, we hypothesized FN is more than a marker of fibrosis in the vessels and is likely playing a role in coordinating vascular dysfunction metastasis. Here we report the effects of FN accumulation on endothelial cell monolayer integrity and provide evidence for an active role of FN in accelerating cancer cell invasion. **Methods**: HUVECs were grown on a Matrigel-coated Transwell membrane for 3 days to establish a uniform monolayer with cell-cell junctions and few Ki-67-positive dividing cells. FN was then added to the basal compartment and allowed to diffuse through the membrane to simulate leak of stromally-produced FN. Cell layers were analyzed at timepoints ranging from 4

– 48 h by immunocytochemistry and immunoblotting for ECM and cell junction proteins. MDA-MB-231 cells were added to treated monolayers to investigate cancer cell attachment and interaction with the endothelial monolayer. **Results**: Subendothelial accumulation of FN was detected as early as 4 h and increased for at least 24 h. Significant increases in Ki67-positive nuclei correlated with the accumulation of FN in the endothelial monolayer and clustered where subendothelial FN staining was brightest. Cells on these FN patches had larger areas and dimmer junctional VE-cadherin staining than surrounding endothelial cells. Quantitative analysis of the relationship between subendothelial FN, Ki67 staining, and cell area suggests that FN accumulation precedes progression through the cell cycle, and that cell size and junctional changes are later events in the phenotypic response to FN. Functionally, exposure to FN affects monolayer permeability as demonstrated by the higher rate of basal to apical transit of albumin compared to cells without basal FN addition. Furthermore, FN accumulation leads to exposed FN patches and increased MDA-MB-231 cell attachment to and spread within the endothelial monolayer. **Conclusion**: Endothelial cell monolayers are affected in numerous ways by exposure to exogenous, basally-localized FN. Alterations in proliferation, cell morphology, and cadherin localization implicate FN as a causative agent in vascular dysfunction in fibrotic disease, and suggest FN as a potential target for modifying vascular dysfunction. Our data suggest that FN's role in the tumor microenvironment includes increasing metastatic potential of cancer cells by increasing vascular invasion

Category: Breast
Project Title: ***Lysine acylation links cellular metabolism to immune signaling during viral infection.***

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Cellular survival relies on phenotypic plasticity in response to changing conditions. Information on cellular state is transmitted through addition or removal of post-translational modifications (PTMs) onto histones to alter gene expression through epigenetic regulation. Further, these same PTMs decorate the entire proteome, serving as a rapid toggle of protein function. Nearly all proteins which add and remove PTMs—as well as the PTMs themselves—depend on crucial cellular metabolites (acyl-CoA's, NAD+, ATP, etc.). The fluctuations of these metabolites indicate the metabolic status of the cell, enabling proper adaptation of the proteome. Here, I focus on how glycolytic output alters the cellular proteome via lactate-derived lysine lactylation. I report the first global analysis of this novel lysine PTM during infection with a pathogen. I uncovered a dynamic upregulation

of lactyllysine on glycolytic and immune signaling proteins during a state of active viral replication. I have been interrogating specific dynamic sites by altering modification state and assaying impacts on viral replication and immune signaling activity. Further, I found an intriguing enrichment for this lactate-derived PTM on intrinsically-disordered regions of proteins, suggesting lysine lactylation specializes in regulating different aspects of protein biochemistry as compared to lysine acetylation. These findings illuminate how changes to glycolytic flux during viral infection induce rapid cellular responses via the dynamic regulation of PTMs, with likely implications to other disease states characterized by dysregulation of cellular metabolism, such as cancer, aging, and autoimmune disorders.

Category: All cancers
Project Title: ***Prognostication of Breast Cancer by Optical Imaging of Immune-Targeted Nanoprobes***

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Advances in the diagnosis and treatment of breast cancer have vastly improved outcomes for the leading cause of cancer in women. Despite these advances, metastatic breast cancer continues to have only a 36% 5-year survival rate and 10-15% of patients will have metastatic spread within 3 years of their initial diagnosis. There is a need to identify patients at risk of metastatic spread to initiate treatment earlier. Direct imaging of the pre-metastatic niche prior to colonization by circulating tumor cells represents a pathway toward earlier prognostication. We propose imaging of the pre-metastatic niche (PMN) through targeting of cells critical to niche development. Myeloid derived suppressor cells (MDSCs) have been identified as critical cells in tumor colonization and are associated with increased tumor burden, metastasis, and immunotherapy resistance due to their immunosuppressive nature. MDSCs are recruited to the niche before circulating tumor cells, preparing an immunosuppressive environment conducive to tumor colonization and growth. Imaging of the MDSCs in situ can provide a reasonable means of detecting metastatic sites early in disease course. Our lab has developed rare earth (Re) metal-based nanoparticles encapsulated in human serum albumin, or rare earth albumin nanocomposites (ReANCs), that emit shortwave infrared (SWIR) light for in vivo optical imaging. In this study, we show the ability of ReANCs functionalized for GR-1 marker binding to target MDSCs in vitro. Our results indicate that our nanoparticles are capable of in situ detection of MDSCs in the pre-metastatic lung niche to differentiate between tumors with distinct metastatic timelines.

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Category: Endometrial
Project Title: ***Ionizable Lipid Nanoparticles for the delivery of therapeutic siRNA to treat endometrial cancer***

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Endometrial cancers are the 5th leading cause of cancer-related deaths in women in the United States, and the annual incidence and mortality associated with this disease are rising globally. Current first-line treatment for endometrial cancer is a total hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. While this is effective in treating early-stage endometrial cancer, it leaves women infertile and in need of lifelong hormonal therapy. Currently, nonsurgical interventions for the treatment of endometrial cancer, such as chemotherapy, hormone therapy, and radiation therapy, are limited in efficacy and often are accompanied by adverse effects that impact treatment tolerance. Therapeutic nucleic acids, such as messenger RNA (mRNA) or small interfering RNA (siRNA), have emerged as alternatives to conventional therapy because they enable modulation of endogenous gene expression in a sequence-specific manner. However, without a drug delivery platform, nucleic acids are quickly degraded in vivo and are not able to enter cells. Here, we developed lipid nanoparticles (LNPs) to deliver siRNA against mouse double minute 2 (MDM2) or programmed death-ligand 1 (PD-L1) as a treatment for endometrial cancer. MDM2 is the prime negative regulator of the tumor suppressor p53. Under normal conditions MDM2 binds to p53 and targets it for ubiquitination, thus decreasing the amount of active p53 present in cells leading to cancer progression. Our data indicates that MDM2-LNPs can effectively knockdown MDM2 levels in two endometrial cancer cell lines (RL95-2 and KLE) in addition to cervical carcinoma cells (HeLa) cells. Additionally, our data suggests that treatment with MDM2-LNPs sensitizes endometrial cancer cells to platinum-based chemotherapies, as pretreatment with LNPs significantly reduces the IC50 over chemotherapy alone. In addition to MDM2 siRNA, we also aim to deliver PD-L1 siRNA in endometrial cancer cells to inhibit the PD-1/PD-L1 checkpoint involved in cancer cell evasion of T cell immunity. Cancer cells upregulate PD-L1 on their surfaces in response to soluble factors released by T cells, leading to T-cell exhaustion and cancer cell proliferation. We are interested in both MDM2 and PD-L1 because clinically, patients with MDM2 amplifications are at increased risk of accelerated cancer progression following treatment with anti-PD-L1 therapy. We have demonstrated that endometrial cancer cells in culture upregulate surface PD-L1 expression in response to type-II interferon signaling, similar to their behavior

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in vivo. We have developed LNPs carrying PD-L1 siRNA and we are currently investigating their ability to silence PD-L1 in vitro. We hypothesize that silencing PD-L1 will enhance T-cell associated cytotoxicity to endometrial cancer cells. These experiments demonstrate the potential for siRNA-loaded LNPs as a therapeutic platform for endometrial cancer. Moving forward, we will use this technology to deliver MDM2 and PD-L1 siRNAs simultaneously and evaluate their ability to halt endometrial cancer progression *in vivo*.

Category: Gastrointestinal

Project Title: *Microbiota-induced expansion of the γδ intraepithelial lymphocyte compartment results in an increased bioenergetic profile and restrains cytokine production.*

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Intestinal γδ intraepithelial lymphocytes (γδ IEL) are a critical component of mucosal host defense in response to intestinal infection or inflammation. We recently identified a hyperproliferative γδ IEL ($\gamma\delta^{HYP}$) phenotype that is transmissible via the gut microbiota and protects against enteric infection. Despite increased IEL number, $\gamma\delta^{HYP}$ mice have no signs of overt intestinal pathology, and thus we hypothesized that additional regulatory mechanisms may be in place to prevent aberrant IEL activation. Given that IELs are intrinsically metabolically constrained, we first performed electron microscopy to assess mitochondrial morphology. We found that $\gamma\delta^{HYP}$ IELs exhibit a 70% increase in mitochondrial number, 24% increase in mitochondrial area and a 22% increase in cristae density relative to WT. Whereas Seahorse mitochondrial stress assays showed similar baseline respiration between WT and $\gamma\delta^{HYP}$ IELs, spare respiratory capacity was increased by 50% in $\gamma\delta^{HYP}$ IELs. We next asked whether increased mitochondrial metabolism influenced γδ IEL cytokine production. Stimulation in the presence of oligomycin increased IFNγ production by both WT and $\gamma\delta^{HYP}$ IELs by 66% and 44%, respectively. Using single-cell metabolic analysis (SCENITH) of γδ IELs isolated from αCD3-treated WT and γδHYP mice, we found no change in the dependency or capacity of individual metabolic pathways between phenotypic and non-phenotypic mice. However, $\gamma\delta^{HYP}$ IELs exhibited a 2.3-fold increase in puromycin incorporation compared to WT after αCD3 stimulation, which was reduced upon treatment with oligomycin or 2-deoxyglucose. These data indicate that $\gamma\delta^{HYP}$ IELs maintain a low baseline respiration under homeostatic conditions yet exhibit increased bioenergetic reserve capacity that enables rapid protein production in response

to stimulation. Bulk RNA-sequencing revealed an upregulation in gene ontogeny pathways associated with Entpd1 (CD39) expression in $\gamma\delta^{HYP}$ IELs relative to WT. Flow cytometric analysis confirmed increased CD39 expression in $\gamma\delta^{HYP}$ IELs, and showed that this CD39hi subset produces less IFNγ compared to CD39neg and CD39int cells following PMA/ionomycin stimulation. Broad-spectrum antibiotic treatment resulted in a 49% reduction in the frequency of CD39hi $\gamma\delta$ IELs in $\gamma\delta^{HYP}$ mice and nearly eliminated this population in WT mice. Taken together, our data demonstrate that a specific microbiota induces expansion of CD39hi $\gamma\delta$ IELs in $\gamma\delta^{HYP}$ mice with reduced cytotoxic potential that may be attributed to a metabolic shift toward oxidative phosphorylation. Further understanding of the mechanisms regulating $\gamma\delta$ IEL homeostasis and effector function may ultimately allow fine tuning of mucosal surveillance to confer protection against intestinal injury or infection while limiting aberrant activation.

Category: Lung

Project Title: ***Understanding the Mechanism and Therapeutic Implications of the PACER lncRNA Expression in Lung Cancer Cell Lines***

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Many layers of RNA-mediated gene expression have evolved to regulate the numerous roles of the arachidonic acid (AA) signaling pathway. Products of the AA signaling pathways have essential roles in maintaining cell homeostasis, cell growth and proliferation, cell death, and regulating immune cell signaling. The AA pathway is also dysregulated in several autoimmune disorders and in many cancer types. We are investigating the relevance of several Long non-coding RNAs (lncRNAs) in AA regulation in the context of lung cancer. Our current focus is the p50-associated COX-2 extragenic lncRNA (PACER) in lung cancer. LncRNAs can regulate transcription directly through interaction with transcription factors or indirectly through miRNA sponging and interaction with accessory proteins. However, in many cases, the mechanism of lncRNA regulation is unknown. Our data suggest that the PACER is a key factor regulating the expression of COX-2, a major enzyme in the AA pathway. We are investigating the mechanisms involved in PACER regulation and the therapeutic potential of PACER modulation using an shRNA knockdown lung cancer cell model. We are studying the effects of PACER knockdown on cell proliferation, migration, and the broader roles in immune regulation. Our shRNA knockdown model significantly shows reduction of both PACER and COX-2 mRNA and COX-2 protein expression in A549 cells.

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We are currently using wound healing assays and Xcelligence migration assays to investigate the role of PACER in cell motility. Our results show a relationship between PACER expression and cell motility; however, further experiments are required to fully understand this relationship.

Category: Breast
Project Title: ***IGF1R and Beta Integrin Crosstalk Mediates IGF1-Dependent Breast Cancer Adhesion***

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Breast cancer is the most common cancer in women, and in the case of triple-negative breast cancer (TNBC), is especially lethal and difficult to treat. TNBCs are characterized by their resistance to multiple therapies such as estrogen or Her2 blockers and present a major challenge when treating patients. One signaling pathway that is implicated in breast cancer aggression is the insulin and insulin-like growth factor (IGF) pathway; however, inhibition of this pathway has not been successful in clinical trials due to either toxicity or lack of efficacy. IGF-1 Receptor (IGF1R) antibodies that selectively block this receptor failed in phase II breast cancer clinical trials largely due to a lack of clinical benefit, suggesting that our understanding of this receptor is lacking. IGF1R is primarily known for signaling through the Erk and Akt transducers, which are prominent oncogenic proteins. However, IGF1R is also known to associate with integrins at the cell membrane and regulate cell adhesion, which likely plays a role in cancer cell invasion and metastasis. The exact role of the relationship between IGF1R and various integrins in cancer metastasis is not well understood, but the delineation of this role may better explain why IGF1R inhibitors failed in clinical trials. Our lab previously showed that inhibition of IGF1R, either through epithelial cell deletion or expression of a dominant-negative IGF1R in a transgenic Wnt1 oncogene-driven mouse mammary tumor model, resulted in increased metastasis. Now, we have shown that inhibition of IGF1R results in decreased cell adhesion in an IGF1-dependent manner. Further, we have shown that IGF1-mediated cell adhesion is integrin-dependent, as either β1 or β3 integrin knockdown abrogates IGF1-dependent increases in cell adhesion. Finally, through immunoprecipitation, our data indicate that IGF1R associates with both β1 and β3 integrins at the cell membrane, but these associations change depending on availability of IGF1. The effect of these associations on a metastatic phenotype remains an open question; however, we hypothesize that reduced cell adhesion through IGF1R inhibition promotes cell invasion and metastasis.

Category: Colorectal

Project Title: ***Reduced γδ intraepithelial lymphocyte number and surveillance precede the onset of Crohn's disease-like ileitis.***

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Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, most commonly affecting the ileum. Recent studies of resected ileal tissue from CD patients reported a loss of intraepithelial lymphocytes expressing the γδ T cell receptor (γδ IEL). γδ IELs provide continuous surveillance of the epithelial barrier and are largely protective in the context of intestinal inflammation and infection. While loss of γδ T cells exacerbates experimental colitis, the role of γδ T cells in the initiation of ileitis remains unclear. We hypothesized that the γδ IEL compartment may be dysregulated prior to disease development. To this end, we used flow cytometry to profile the ileal IEL compartment of $TNF^{\Delta ARE/+}$ mice, which develop spontaneous CD-like ileitis at 8 wks of age, prior to, during, and after ileitis onset (4-16 wks). We observed a 2.5-fold reduction in the frequency of ileal γδ IELs in 5-wk-old $TNF^{\Delta ARE/+}$ mice compared to $TNF^{+/+}$ (WT) littermates ($p<0.001$). Immunostaining of fixed ileal tissue confirmed a 3.2-fold decrease in the total number of γδ IELs at 5 wks of age ($p=0.01$). At 6 wks of age, intravital microscopy revealed a 40% reduction in the average track speed of γδ IELs in $TNF^{\Delta ARE/+}$ mice compared to WT (10.6 vs 6.4 mm/min, $p<0.0001$). To determine whether this impaired motility affects γδ IEL localization along the crypt-villus axis, we assessed the position of individual γδ T cells in cleared ileal tissue. We found that γδ T cells were largely excluded from the lower villus in 6-wk-old $TNF^{\Delta ARE/+}$ mice relative to WT, while the proportion of γδ T cells in the upper villus and crypt regions remained unchanged ($p=0.0003$). Based on previous reports suggesting potential crosstalk between γδ T cells and Paneth cells (PC) located in small intestinal crypts, we next asked if PC number was affected at this early timepoint. While total PC number was similar between the two genotypes, lysozyme staining in PCs was more diffuse in $TNF^{\Delta ARE/+}$ mice ($p=0.06$), and accordingly, ileal *Lyz1* mRNA expression was reduced by 40% ($p=0.02$). Collectively, these studies demonstrate that γδ IELs exhibit impaired surveillance behavior and altered distribution along the crypt/villus axis prior to ileitis onset, which coincides with PC dysfunction in CD-like ileitis.

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Category: Liver and Pancreas

Project Title: ***Elucidating the role of Heat Shock Protein 90 in NK cell immunosurveillance to improve CAR-NK therapies for drug-resistant liver cancer***

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Drug resistance represents a major obstacle for cancer therapy, which makes hepatocellular carcinoma (HCC) difficult to treat. Drug resistance emerges when tumors have genetic changes leading to tumor evolution. The mutations in the genome cause drug-resistant cancers to have "chaotic" proteomes analogous to rock concerts where the chaos is difficult to control. Heat Shock Protein 90 (HSP90) is the security guard that maintains the proteomic chaos allowing cancer cells to survive and evolve. By inhibiting HSP90, we make the tumor cells susceptible to drug therapies. More interestingly, when HSP90 is inhibited, the cancer cells also become susceptible to immune cell-mediated killing. Immune cells, like Natural Killer (NK) cells, are soldiers that survey the body, killing tumor cells, dysfunctional cells, or virally infected cells.

Our lab has recently developed Chimeric Antigen Receptor-Natural Killer (CAR-NK) therapies to target liver cancer. NK cells alone cannot target tumors because tumors can silence immune cells, also known as immune evasion. Therefore, we can engineer NK cells using tools like chimeric antigen receptors (CARs) that detect tumors more precisely. CAR-NK therapies successfully treat blood cancers like lymphomas with minimal side effects to patients. However, major challenges remain in treating liver and pancreatic cancers, leading to poor outcomes.

Nevertheless, the efficacy of CAR-NK cells against drug-resistant liver cancer is not yet known. This study proposes a unique approach to enhance specific CAR-NK immunotherapy with a combination of HSP90 inhibitor chemotherapy to target the drug-resistant HCC. We aim to use a novel "kick and kill" model whereby we "kick" the tumor cells to be sensitive to immune cells and then "kill" the tumor using CAR-NK cell therapy. **I hypothesize that inhibition of HSP90 function will improve precise CAR-NK killing of drug-resistant HCC.** To achieve this, I will use high-throughput assays to evaluate the "kick and kill" model on cells derived from tumors. Then, I will transfer the tumor cells into a mouse to test the efficacy of the combination therapy. The study's long-term goal is to understand a novel role for HSP90 in NK cell killing of tumors and how that could be used to enhance CAR-NK therapy treatment of solid tumors.

Category: Colorectal
Project Title: *The role of GPR132 in regulating T cell function.*

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T cell-mediated responses are vital for detecting and eliminating malignant cells and represent the basis of current successful cancer immunotherapies. CD8+ T cells undergo robust expansion upon priming and contribute to anti-tumoral responses by producing pro-inflammatory cytokines and releasing cytotoxic granules that can kill cancerous cells. A portion of activated CD8+ T cells survive as long-lived memory T cells that facilitate an accelerated and stronger recall response and protect the body from illness and recurring tumoral events. Tissue-resident memory T cells (Trm) are a subset of memory T cells that are maintained in non-lymphoid tissues and have been shown to be critical for the control of solid tumor growth. Thus far, the signals within the tissue that direct the quantity and quality of CD8+ Trm pools are still unclear. G protein coupled receptors (GPCRs) sense and integrate environmental signals and are essential for regulating T cell function. GPR132 or G2A modulates homeostasis in mature peripheral T cells, and Gpr132-/- mice develop an autoimmune syndrome accompanied by expansion of the T cell compartment. We investigated the function of GPR132 by using a model of intestinal infection by Yersinia pseudotuberculosis. GPR132 expression was elevated on $CD8^+$ T cells early after infection and remained high throughout the memory phase. $Gpr132^{-/-}$ cells displayed enhanced expansion, outnumbering wild-type (WT) cells by 2-4 fold in all tissues. Early differentiation was not impacted by GPR132-deficiency, as there were no differences in circulating and Trm memory precursor subpopulations between WT and $Gpr132^{-/-}$ cells. GPR132-deficient antigen-specific cells persisted after contraction and were able to re-expand in response to secondary challenge. To dissect the mechanism of GPR132 action, we examined the transcriptome of WT and $Gpr132^{-/-}$ naïve T cells during in vitro activation. Minimal differences in gene expression were observed, and both showed comparable proliferation upon TCR-engagement. Comparable proliferative results between WT and $Gpr132^{-/-}$ cells were observed during homeostatic proliferation in vivo. Collectively, these data suggest that the enhanced responsiveness of $Gpr132^{-/-}$ T cells is not programmed at the naïve stage

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but manifests during antigen-specific cell activation. Our results expose a role for GPR132 signaling axis in regulating memory T cell immunity and demonstrate GPCRs can be targeted to modulate T cell responses thus improving $CD8^+$ T cell-based anti-tumoral immunotherapies.

Category: Liver

Project Title: ***Hepatitis B Virus Integrations into KMT2B Drive Hepatocellular Carcinoma***

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Liver Cancer is the second-leading cause of cancer related deaths worldwide. Of all liver cancers, hepatocellular carcinoma (HCC) comprises 80% of all cases. Of these HCC cases hepatitis B virus (HBV) infection is known to be the cause of about half of all the cases, making HBV-induced HCC a necessary field of research. Our lab has previously performed genomic analysis on HBV positive HCC samples, and recurrent HBV integrations were found to localize in two major loci, TERT and KMT2B (MLL4), where in the case of KMT2B all integrations are localized between exon 3 and 6. Though TERT is a well-established oncogene, the oncogenic function of HBV integration into KMT2B remains largely unknown. Our preliminary data suggests that these HBV integrations into KMT2B result in a C-terminal truncated version of KMT2B (KMT2B-T) and that KMT2B-T is oncogenic in vivo. Furthermore, our data also shows that KMT2B-T binds to tumor suppressor MENIN (Men1) and its binding partner LEDGF. The overexpression of KMT2B-T decreases the binding of MENIN to the endogenous KMT2A/B histone methyltransferase complex. Our data shows that the differential length of truncated KMT2B influences tumorigenesis. Therefore, we hypothesize that C-terminal truncated KMT2B produced by HBV integrations between exons 3 and 6 does induces HCC by sequestering MENIN from the endogenous KMT2A/B complex. These studies provide the basis for targeting dysregulated KMT2B as a potential therapeutic approach in HBV caused liver cancer.

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Category: Liver, Hematologic, Lung
Project Title: *Functional analysis of TAD formation and long-range regulatory interactions*

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The human genome is organized into a series of looped domains in three-dimensional (3-D) space, called topologically associated domains (TADs). This 3-D organization is known to play central roles in gene regulation, development, and disease. When this architecture is disrupted, there can be profound effects on gene regulation and such perturbations are often a distinctive landmark of oncogenesis and tumor progression. TADs are delimited at each end by boundaries (BEs). While the general features of chromosome organization have now come into view, little is known about how TADs are formed, or how specific long-distance regulatory interactions take place. In this study, the central hypothesis is that TADs are formed through specific and orientation-dependent pairing between BEs, and that these interactions are mediated by the constellation of proteins associated with each BE. This hypothesis is tested on the model system fruit fly (Drosophila melanogaster) in this study since the general features of TADs and BEs are conserved from fly to human. I focus on the well-characterized Drosophila even-skipped (eve) locus and the two boundaries, nhomie and homie, flanking this locus. I found that homie and nhomie specifically and orientation-dependently pair with each other and such pairing defines the loop topology at eve locus. Together, my research elucidates the fundamental mechanisms of chromatin pairing and the regulation of chromatin architecture and will shed light on the underappreciated causations of altering genome architecture during oncogenesis and tumor progression.

Category: Breast
Project Title: *Co-evolution of tumor-initiating cells and macrophages in breast tumorigenesis and metastatic progression*

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Tumor initiating cells (TICs) are a subset of tumor cells with self-renewal activity and tumorigenic capacity, and are responsible for cancer development, resistance to conventional therapy and distant metastasis. Similar to normal stem cells whose activities are partly regulated by extracellular signals derived from specialized stem cell niche, TICs may co-evolve with the host stroma, generating TIC-niche to

support and accelerate tumor initiation and progression. Ongoing studies in our lab have identified macrophage-mediated CXCR4 chemokine signaling within normal stem cell niche. As tumor microenvironment contains many of the same immune cells that are found in the mammary gland, we hypothesize that breast TICs rely on the interplay with CXCR4-expressing macrophages or its niche to sustain their activities and initiate breast tumorigenesis. Here we showed an increased number of total and CXCR4+ macrophages in preneoplasia glands and early-stage tumors isolated from MMTV-PYMT mice compared to wild type normal mammary glands. To test the role of CXCR4-expressing macrophages in breast cancer development, we generated macrophage-specific CXCR4 knock-out in spontaneous breast tumor mouse model by crossing CXCR4CKO with MMTV-PYMT. Our data showed a delayed tumor onset in PYMT-CXCR4CKO mice compared to PYMT-controls. Suppressed primary tumor growth and lung metastasis were observed in the PYMT;CXCR4-cKO mouse as well. We conducted single cell RNA (scRNA) sequencing of primary tumors isolated from PYMT-Control and CXCR4-cKO mouse to study molecular mechanisms of how CXCR4+ macrophages contribute to TIC activity and tumor progression. We observed that the composition of tumor subtypes and stromal cells, including immune cells differed vastly between the samples. These preliminary findings indicate that CXCR4+ macrophages and its macrophageal niche may involve in breast tumorigenesis and progression.

Category: Liver

Project Title: ***Investigation of molecular mechanisms underlying T-cell dysfunction in acute and chronic hepatitis B virus infection***

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Hepatitis B virus (HBV) is a deadly hepatotropic viral pathogen that affects over 250 million people globally, despite availability of a prophylactic vaccine. HBV can establish itself chronically in the host, causing an infection that is essentially recalcitrant to standard treatments. Chronic HBV infection frequently leads to cirrhosis, end-stage liver disease, hepatic decompensation, and hepatocellular carcinoma (HCC), which annually accounts to over 850,000 deaths. HBV can introduce dysfunction into adaptive immune mechanisms, causing T-cell exhaustion, among other deficiencies. The difficulties encountered in developing better treatments for HBV infection stem from an inadequate understanding of how the component parts of this virus disrupt host immune mechanisms.

The scarcity of immunocompetent small animal models for HBV infection has hampered progress in gaining insights into HBV mediated immune dysfunction. To address this gap, we have created humanized mice dually engrafted with components of a human immune system and a human liver. We demonstrate that such dually humanized mice support HBV infection, which was partially controlled by human immune cells, as evidenced by lower levels of serum viremia and HBV replication intermediates in the liver. HBV infection resulted in priming and expansion of human HLA-restricted CD8+ T cells, which acquired an activated phenotype. Notably, our dually humanized mice also support persistent coinfections with HBV and HIV, which opens opportunities for analyzing immune dysregulation during HBV and HIV coinfection, and preclinical testing of novel immunotherapeutics. With this system in hand, we now continue our efforts to delineate the effects of HBV S-antigen (HBsAg) on the adaptive immune system. More specifically, we aim to quantitatively and qualitatively analyze the role of HBsAg in disrupting the CD8+ T-cell response. Results stemming from our work hold potential for informing new immunotherapeutic approaches aiming at permanently clearing HBV from chronically infected patients.

Category: All cancers

Project Title: ***Investigation the novel role of MTDH in spontaneous tumor regression through its regulation of anti-tumor immunity***

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Early studies showed spontaneous remission, or disappearance of a tumor in the absence of any treatment may happen more commonly than currently appreciated. A better understanding of this natural protective process could potentially provide a better therapeutic strategy to prevent or treat cancers. Here, we found that the rate for major regression (≥50% tumor volume shrinkage compared with the previous tumor measurement) in MTDH whole-body KO mice is nearly three times more frequent than in MTDH WT mice, while complete regression is nearly six times more frequent in MTDH-KO mice than in WT mice (6.6% versus 1.3%). Interestingly, our previous results showed that MTDH expression is up-regulated in macrophage or cytotoxic CD8+ T cells

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upon chronic exposure to LPS. We recently developed the C26A6 series of small molecule inhibitors that disrupt MTDH-SND1 interaction and show potent anti-tumor activities. Taken together, these previous studies support an in-depth study of the role MTDH in early-stage STR through its regulation of anti-tumor immunity. We hope these new findings and the underlying mechanism of STR will help the development of novel therapeutic strategies to prevent cancer incidence in high-risk individuals and improve the treatment outcome of cancer patients.

Category: Colon and Rectum

Project Title: ***Characterizing the bioactivity of the gut microbiome-derived small molecules in colorectal cancer: A cancer hallmarks-guided approach***

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Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths in the US. Every year, ~150,000 new CRC cases are reported. Several factors can increase the risk for CRC, i.e., genetics, lifestyle, and the gut microbiome. While extensive research has been dedicated to study the impact of human genetics and lifestyle on CRC development, the precise influence of the gut microbiome remains enigmatic. Herein, we aimed to interrogate the role of the gut microbiome and its small molecule products in CRC development. Employing a strategy guided by cancer hallmarks, we investigated the bioactivity of small molecules originating from the gut microbiome. As a proof-of-concept, we chose aryl hydrocarbon receptor (AhR) as a potential target because of its role in several cancer hallmarks, e.g., resisting cell death, and activating invasion and metastasis. Furthermore, numerous indole derivatives originating from the gut microbiome have been reported to target AhR, yet no study aimed to comprehensively identify molecules targeting AhR. To this end, first, we generated ~200 chemical extracts (and fractions) originating from 24 bacterial cultures of gut microbiomes associated with CRC. Second, chemical extracts were screened for their ability to activate AhR. We identified a few active fractions of small molecules that exhibited a strong AhR activation. Then, we pursued the isolation and identification of the exact chemical structure of the small molecules responsible for this activity. We successfully isolated and solved the chemical structure of five small molecules by 1D and 2D NMR analyses with mass spectrometric data. Two of them have not been previously identified from the human gut microbiome. These results highlight the potential role of the gut microbiome in CRC development (by targeting important nuclear receptors) and will inform future endeavors to target exact microbiome members for developing new therapies.

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Category: Pancreatic
Project Title: ***The Gut Microbiome Regulates the Anti-Cancer Activity of PI3K Inhibitors***

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The phosphatidylinositol 3-kinase (PI3K) signaling pathway plays a crucial role in cell growth and proliferation and is one of the most frequently activated pathways in human cancer. Drugs have been developed that target PI3K; however, they show limited clinical anticancer activity. Recently, it was discovered that ketogenic diet dramatically enhances the efficacy of PI3K inhibitors in mice, resulting in prolonged survival in one of the hardest to treat cancers, pancreatic cancer. The proposed mechanism involved ketogenic diet blocking "insulin feedback," whereby on standard diet, PI3K inhibition causes hyperglycemia and hyperinsulinemia, which in turn reactivates PI3K. Here we confirm that ketogenic diet dramatically enhances PI3K inhibitor activity in mice, but surprisingly show that this phenomenon is unrelated to dietary starch, glycemia, or insulin, and instead is regulated by the gut microbiome. Specifically, we find that ketogenic diet is one example of a "purified" diet that lacks the normal spectrum of complex carbohydrates, proteins and small molecules found in normal chow and thus generates a limited gut microbiome. High-carbohydrate purified diet also synergizes with PI3K inhibition to treat pancreas cancer in mice, producing multi-month survival gains. Antibiotics that curtail the gut microbiome similarly augment PI3K inhibitor anticancer activity. Mechanistically, the gut microbiota modulates PI3K inhibitor pharmacokinetics, markedly increasing circulating half-life. Resulting enhanced drug exposure produces improved tumor control. These results highlight diet-induced changes in gut microbiome composition as drivers of drug pharmacokinetics and therapeutic efficacy.

Category: All cancers
Project Title: ***CDK9 and its Activating Proteins Modulate the Chromatin Landscape of Silenced Genes and Repetitive Elements in Cancer***

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Epigenetic drug development for cancer has been increasingly gained interests in recent times. As these drugs targets regulation of epigenome to reprogram gene expression which is reversible and heritable. These therapies able to sensitize

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cancer cells to immune therapy by changing the landscape of silenced repetitive elements. Previous studies from our lab have shown that cyclin dependent kinase 9 (CDK9) is a very promising target for epigenetic therapies, as it regulates expression of both genes and repetitive elements. We have also identified cyclin dependent kinase 7 (CDK7) and bromodomain-containing protein 4 (BRD4) as additional molecular targets with similar functions. While these proteins have well-defined functions in the process of transcriptional initiation, the mechanisms by which the inhibition of these proteins upregulate genes and repetitive elements have yet to be elucidated. We propose that CDK7, CDK9, and BRD4 regulate expression of both genes and repetitive elements through the modulation of the chromatin landscape during transcription and replication. We will use strand-specific RNA-seq, Repli-seq, and the YB5 system to determine the contribution of transcription and replication to the upregulation of gene and repetitive element expression. Additionally, we will use MNase-seq, ChIP-seq, and siRNA knockdowns in the YB5 cell line to elucidate how CDK7, CDK9, and BRD4 each affect the chromatin landscape.

Category: Ovarian

Project Title: *Tumor-induced stress response pathway: A regulator of T cell activity in ovarian cancer by modulation of lipid-raft-associated T cell receptor signaling*

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Background: Epithelial ovarian cancer (EOC) remains the deadliest gynecological malignancy in the world. Despite significant progress in immunotherapy, like PD-1 inhibitors, these treatments are effective for only a small proportion of EOC patients. While the presence of T cells is associated with better clinical outcomes, tumor microenvironment (TME)-induced immunosuppressive mechanisms promote T cell dysfunction in EOC beds. Here, I investigated how tumor-infiltrating T cells are impacted by the integrated stress response, which more broadly senses TME-induced stress through phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2α by the stress sensing kinases PERK, PKR, HRI, and GCN2).

Methods: Utilizing our novel CD4Cre Uhrf1bp1f/f mice the survival upon tumor challenge was studied. To mimic TME, CD8+ T cells were exposed to ascites from EOC-bearing mice, and lipid rafts were quantified. To define the immunotherapeutic potential of uhrf1bp1 -ablated T cells, tumor antigen-primed

Uhrf1bp1-ablated T cells were isolated from tumor beds expanded ex vivo and infused into syngenic tumor-bearing mice.
Results: I found that polymorphism (M1098T) in the UHRF1BP1 gene is associated with better survival outcomes for EOC patients. Interestingly, CD4Cre Uhrf1bp1f/f mice demonstrated superior survival upon EOC challenge. *Ex vivo* restimulation of Uhrf1bp1-ablated $CD8^+$ T cells isolated from tumor beds showed an increased frequency of $IFN\gamma^+$ Granzyme B^+ polyfunctional T cells compared to littermate controls suggesting the absence of Uhrf1bp1 elevates T cell effector function and antitumor activity. Importantly, ascites from EOC mice cause disassembly of lipid rafts and reduced T cell receptor signaling. Critically, UHRF1BP1 KO T cells are resistant to lipid raft loss in TME suggesting blocking UHRF1BP1 could rescue protective activity of $CD8^+$ T cells in the tumor beds. Mechanistically, UHRF1BP1 is transcriptionally driven by the integrated stress response pathway (ISRP) and involved in lipid turnover under the TME-driven ISR pathway. Interestingly, the adoptive transfer of antigen-primed Uhrf1bp1KO $CD8^+$ T cells into tumor-bearing syngeneic mice significantly enhanced survival in the UPK10 model suggesting its potential clinical applicability. The enhanced efficacy of these T cells was observed in association with elevated PD-1 expression, potentially demonstrating denser infiltration of antigen-specific T cells.
Conclusion: UHRF1BP1 restrains the protective $CD8^+$ T cell activity in EOC and targeting UHRF1BP1 could serve as a potential therapeutic approach in patients with EOC.

Category: Lung
Project Title: ***Modulation of cytosolic NADPH generation/level to suppress Kras-driven lung tumorigenesis***

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Lung cancer is the leading cause of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) accounting for more than 85% of these cases. Oncogenic KRAS mutations (either $KRAS^{G12D}$ or $KRAS^{G12C}$) are present in approximately 15-25 % of patients with NSCLC and confers a poor prognosis in the metastatic setting, and a high risk of cancer recurrence. With the recent exception of $KRAS^{G12C}$, targeting oncogenic RAS directly has not been effective, and inhibiting downstream effectors of RAS signaling such as the MAP kinase pathway has not produced durable responses. Thus, new treatments are still urgently needed for KRAS mutant NSCLC. RAS activation causes cancer cells to alter their metabolism to

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meet metabolic demands for high proliferation, including upregulation of *de novo* lipogenesis. Targeting cancer metabolism is already a successful approach to cancer treatment and recent advances in our understanding of tumor metabolism are revealing new targets. Many efforts have been put in targeting de novo lipogenesis as potential cancer therapy. However, we recently found that that glucose-6-phosphate dehydrogenase (G6PD), the first enzyme in oxPPP, is not essential for Kras-driven tumor growth. Therefore, elucidating the metabolic pathways involved in cytosolic NADPH production will provide us with meaningful information for targeting tumor redox homeostasis. As one of the universal electron carriers, NADPH is also involved in protecting against the toxicity of reactive oxygen species (ROS) and provides the reducing equivalents for biosynthetic reactions. Therefore, we propose central hypothesis: dissection of cytosolic NADPH production routes in Kras-driven lung tumors and NADPH-mediated metabolic pathways will provide novel metabolic vulnerabilities that can be used for therapeutic target in the treatment of KRAS-driven lung cancer.

Category: Breast

Project Title: *The association of Covid-19 pandemic restrictions with patient-reported outcomes and lifestyle behaviors among breast cancer survivors: Evidence from a cohort of Black and Hispanic women in New Jersey*

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The impact of the COVID-19 pandemic restrictions in the US since March 2020 on cancer survivorship among Black and Hispanic breast cancer (BC) survivors remains largely unknown. We aimed to evaluate the association of the pandemic with patient-reported outcomes (PROs), and lifestyle behaviors among Black and Hispanic BC survivors in the Women's Circle of Health Follow-Up study and the

New Jersey BC Survivors Study. We included 447 Black and 182 Hispanic BC survivors who completed a home interview ~24 months post-diagnosis between 2017 to 2023. The pandemic era was defined as pre- (prior March 2020) and post- (after March 2020). The association of the pandemic with binary outcomes were estimated using robust Poisson regression models. Hispanic and Black BC survivors in the post-pandemic group reported higher socioeconomic status and less comorbidities. Adjusted robust Poisson models indicated that compared to the pre-pandemic group, Hispanic women in the post-pandemic group were less likely to report low health-related quality of life, compared to the pre-pandemic group. While Black women in the post-pandemic group reported a higher prevalence of clinically significant sleep disturbance and efficiency, and functional well-being. This study highlights the importance of considering the impact of the pandemic in all aspects of research, including in the interpretation of findings. Ongoing research is crucial to untangle the factors behind racial and ethnic disparities in cancer survivors' characteristics, PROs, and lifestyle behaviors post-pandemic.

Category: All cancers

Project Title: ***The immunosuppressive role of leukemia inhibitory factor in tumor microenvironment***

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LIF, a multi-functional cytokine, plays a critical role in a variety of biological processes. LIF is frequently overexpressed in many solid tumors and correlated with poor survival in cancer patients. Recent studies revealed some mechanisms of LIF in tumorigenesis which are mainly through regulating the biological functions of cancer cells. However, there are very limited studies on the role of LIF in tumor microenvironment, especially its effect on tumor-infiltrating immune cells. My preliminary data revealed that LIF deficiency in host inhibited the growth of syngeneic xenograft tumors with much increased amount of tumor-infiltrating immune cells, indicating the immune suppressive role of LIF. Further, LIF largely impaired PD-1 immune checkpoint efficiency. Based on the results from my preliminary studies, I hypothesize that LIF is an important negative regulator for anti-tumor immunity in solid tumors, which in turn promotes tumor growth and resistance towards immune checkpoint inhibitor (ICI) therapy. The goal of this proposed study is to establish the role of LIF in suppressing anti-tumor immune function and reveal its underlying mechanism, which can deepen our understanding on how cancers escape immune surveillance and are resistant to immune checkpoint therapy.

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Category: All cancers
Project Title: *Regulatory Mechanism of Oncogenic Chromatin Remodeling in Liver Cancer*

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AT-rich interactive domain-containing protein 1A (ARID1A) is a key component of the SWI/SNF chromatin remodeling complex and a major tumor suppressor. ARID1A is genetically inactivated through frequent mutations in cancer, promoting tumorigenesis and causing chemoresistance. Despite the apparent importance of ARID1A in cancer, its regulation by growth and oncogenic signals is not well understood. Mechanistic target of rapamycin (mTOR), a conserved protein kinase, is a central controller of growth and metabolism, and an oncogenic driver. Herein we show that mTOR interacts with the ARID1A-SWI/SNF complex genetically and biochemically. Oncogenic activation of mTOR regulates the stability and activity of ARID1A protein through ubiquitination and proteasomal degradation, impacting the integrity and function of BAF SWI/SNF complex and further promoting downstream proliferation pathways. Moreover, ARID1A mediates the anticancer action of the mTOR inhibitor rapamycin. On the other hand, lost function mutations in SWI/SNF complexes render rapamycin resistance. Because mTOR pathway is commonly activated in cancer, our study uncovered a general mechanism by which ARID1A is inactivated through a post-translational mechanism, which has important implications in tumorigenesis and mTOR-targeted therapies.

Category: All cancers
Project Title: *Combining NMD blockade and personalized vaccines to target new frame-derived tumor antigens*

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Indels that cause reading frameshifts, and splice site mutations that cause intron retentions or frameshift exon skipping provide novel reading frames. These new frames produce completely novel protein sequences that are appended to the carboxyl-terminus of truncated proteins. We define these novel sequences as new frame-derived antigens (NFDAs). These antigens have been included in some cancer vaccine studies. However, most of these NFDAs usually do not express because of nonsense-mediated mRNA decay (NMD), an mRNA quality

control process. Thus, NMD-suppressed NFDAs can be potential Tumor Specific antigens that do not exist in tumors normally but are inducible by NMD blockade. We hypothesize that combining NMD blockade and NFDA-targeting is an ideal strategy for developing personalized cancer vaccines. We have identified NMD-suppressed NFDAs in mouse cancer cell lines. Specifically, the combination of a vaccine targeting a Dop1b exon-skipping variant (Dop1b-NFDA, found in MB49 mouse bladder carcinoma cells) and NMD inhibition led to the rejection of transplantation of MB49 tumors in immunocompetent mice.

Project Title: *Dynamics of cellular heterogeneity in urothelial bladder carcinoma*

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Intra-tumor heterogeneity contributes to treatment failure and poor survival in urothelial bladder carcinoma (UBC). Analyzing single cell transcriptome from a cohort of UBC tumors, we report that intra-tumor transcriptomic heterogeneity indicates co-existence of tumor cells in epithelial and mesenchymal-like transcriptional states. These transcriptional states correlate with other cancer hallmarks, and bi-directional transition between them occurs within and between tumor subclones, adding a layer of phenotypic plasticity and dynamic heterogeneity. We model spontaneous and reversible transition between partially heritable epithelial- and mesenchymal-like transcriptional states in UBC cell lines and characterize their population dynamics during in vitro evolution. SMAD3, KLF4 and PPARG emerge as key regulatory markers of the transcriptional state dynamics. Dominance of transcriptional states with low PPARG expression indicates an aggressive tumor phenotype and predicts survival in UBC patients. We propose that transcriptional state dynamics contribute towards phenotypic plasticity and dynamic, non-genetic intra-tumor heterogeneity, modulating both the trajectory of disease progression and adaptive treatment response in UBC.

Translational Research from Bench to Community Panel

Yibin Kang, PhD

Dr. Kang is a Warner-Lambert/Parke-Davis Professor of Molecular Biology at Princeton University, a founding member of the Ludwig Institute for Cancer Research Princeton Branch and an Associate Director of Rutgers Cancer Institute of New Jersey. Dr. Kang has served as the President of the Metastasis Research Society (2016-2018), the Chair of the American Association for Cancer Research (AACR) Tumor Microenvironment Working Group (2018-2019), and President of the Chinese Biological Investigator Society (2018-2022). Dr. Kang's research focuses on the molecular mechanisms of breast cancer metastasis. His work discovered new genes that promote progression, metastasis, immune evasion and treatment resistance of breast cancer, delineated tumor-stromal interactions that are essential for metastatic growth, identified novel regulators of normal and cancerous stem cells, and developed new cancer therapeutic agents. Dr. Kang has published over 200 original articles in leading journals including *Science, Cancer Cell, Nature Cell Biology, Nature Cancer and Nature Medicine*.

Daniel Notterman, MA, MD

Dr. Notterman Is a pediatric intensive care physician and molecular biologist who is a professor and senior advisor to the provost at Princeton University. He is also an attending physician and clinical professor at Robert Wood Johnson Medical School and former chair of the Department of Pediatrics and Physician-in-Chief of the Bristol-Myers Squibb Children's Hospital in New Brunswick. He trained in pediatrics at New York University--Bellevue Hospital and in molecular and tumor biology at Princeton University. His laboratory studies genetic and epigenetic effects in child development.

Translational Research from Bench to Community Panel

Mark Kaplan, PhD
Dr. Kaplan is the Director of Translational Medicine at Bristol Myers Squibb in Summit, NJ. Mark's primary role is to serve as the Translational Lead for lymphoma programs in late-stage clinical trials, particularly golcadomide (CC-99282). Prior to joining BMS in August 2020, Mark was at a variety of small, medium, and large biopharma companies, including Pfizer and Roche, first as a discovery scientist before transitioning to translational science. He received his PhD in Biophysics from UCSF and was a Leukemia and Lymphoma postdoctoral fellow at the University of Wisconsin, Madison. Mark's main areas of interest include clinical biomarkers, personalized medicine and struggling with the NY Times crossword puzzle.

Anita Kinney, PhD
Dr. Kinney joined Rutgers University School of Public Health in 2018 as professor of Biostatistics and Epidemiology, and inaugural Director of the Cancer Health Equity Center of Excellence and Director of ScreenNJ, a statewide cancer prevention and screening program. Dr. Kinney also serves as the Associate Director for Population Science and Community Outreach for the Rutgers Cancer Institute of New Jersey. Her research has been funded by the National Institutes of Health for over 25 years. Dr. Kinney's research brings a combination of behavioral science, clinical, and epidemiologic perspectives to address unsolved cancer prevention and control problems in diverse populations and settings. She is internationally regarded for her translational cancer disparities practice and policy changing research. In her roles at the Rutgers Cancer Institute and School of Public Health, and ScreenNJ, Dr. Kinney seeks to advance cancer health equity in prevention and care delivery through community partnerships and engagement, outreach, and a team science approach. She is highly prolific, co-authoring over 175 peer-reviewed publications.

Meet the Commission Members

Kenneth Adler, MD

Chair

Dr. Adler specializes in Hematology/Oncology, with a special interest in benign and malignant hematology and in geriatric oncology. He is an attending physician at Morristown Medical center. He serves as Co-chair of the American Society of Hematology Practice Partnership and is a fellow of the American College of Physicians, a member of the American Society of Clinical Oncology and the American Society of Hematology. Dr. Adler has been awarded several outstanding honors throughout his career. In 2014 he received the prestigious Augustus Stone Award for his voluntary service to the Morristown Medical Center, and in 2017 he was the Medical Honoree of the American Cancer Society for the Northwest New Jersey. Most recently in 2019 he was honored by the Summit Medical Group at their Annual Gala for his community service.

Dr. Kathleen Scotto, PhD

Vice-Chair

Dr. Scotto is currently Vice-Chancellor for Research and Research Training, Rutgers Biomedical and Health Sciences, and Dean for the School of Graduate Studies, Rutgers, The State University of New Jersey. She received her Ph.D. from the Cornell Graduate School of Medical Sciences. Prior to joining Rutgers, she served as an Associate Professor of Molecular Pharmacology and Experimental Therapeutics at Memorial Sloan Kettering Cancer Center and a Professor with tenure at the Fox Chase Cancer Center. In addition to her administrative roles Dr. Scotto maintains an active laboratory at Rutgers studying the Role of ABC Transporters in Tumor Survival and Treatment Response.

Wendy Budin, PhD, RN-BC, FAAN

Dr. Wendy Budin is Professor and Associate Dean for the Entry to Baccalaureate Practice at Rutgers School of Nursing. Previously, she was the Director of Nursing Research at NYU Langone Medical Center and faculty at NYU College of Nursing. Dr. Budin is involved in an ongoing program of research on psychosocial adjustment to breast cancer. In 2019, she co-authored a book chapter entitled “Theoretical Frameworks and Philosophies of Care,” in Current Trends in Oncology Nursing— Second Edition. Dr. Budin is a Fellow in the American Academy of Nursing and the New York Academy of Medicine (NYAM) for her achievements. She received the NJ Governor’s Award for Nursing Research and Distinguished Alumnae Awards from the NYU College of Nursing and Seton Hall University, and in 2018 she received the March of Dimes, Nurse of the Year Award for Research.

Generosa Grana, MD, FACP

Dr. Grana is the Director of the MD Anderson Cancer Center at Cooper. She is also a Professor of Medicine at Cooper Medical School of Rowan University and an adjunct professor of cancer Medicine at the University of Texas MD Anderson Cancer Center. Dr. Grana completed her fellowship in Hematology and Oncology at Fox Chase Cancer Center and Temple University in Philadelphia where she also completed a Postdoctoral Fellowship in Preventive Oncology. Dr. Grana's clinical and research endeavors at Cooper have focused on breast cancer, cancer genetics, and community outreach interventions aimed at underserved populations. She has received numerous awards including the American Cancer Society Silver Chalice Award and the Susan G. Komen for the cure "Light of Life" Award.

Shawna Hudson, PhD

Dr. Hudson is Vice Chancellor of Dissemination and Implementation Science at Rutgers Health and the Senior Associate Dean for Population Health Research at Rutgers Robert Wood Johnson Medical School. She also is the Founding Director of the Center Advancing Research and Evaluation for Patient-Centered Care at the Rutgers Robert Wood Johnson Medical School. A Medical Sociologist, she is a full research member of the Rutgers Cancer Institute of New Jersey in the Cancer Prevention and Control Program, and also has a secondary faculty appointment in the Rutgers School of Public Health in the Department of Social and Behavioral Health Sciences. She serves as Director of the Community Engagement Core of the NJ Alliance for Clinical and Translation Science (NJACTS) which is a Clinical and Translation Science Award (CTSA) Consortium between Rutgers University, Princeton University, and the New Jersey Institute of Technology. Dr. Hudson is internationally known for the NIH-funded research that examines long-term follow-up care for cancer survivors and their transition from specialist to primary care and has authored and co-authored numerous research papers and book chapters.

Li Li, PhD

Dr. Li is currently Executive Director at the Novartis Institute for Biomedical Research, where he has worked for over 17 years. He received his Ph.D., in Toxicology from the University of Texas-Houston School of Public Health. He is a member of the Society of Toxicology and a Board-certified Toxicologist. He is a recipient of numerous awards, most recently the Team Innovation Award for Novartis. In addition, he has co-authored many articles on toxicology innovation in research journals.

Meet the Commission Members

The NJCCR consists of dedicated volunteer members that are involved, both statewide and nationally, in the field of cancer.

Meet the Commission Members

Jane Flint, PhD

Dr. Flint is a Professor Emerita of Molecular Biology at Princeton University. Dr. Flint's research focused on investigation of the molecular mechanism by which viral gene products modulate host cell pathways and antiviral defenses to allow efficient reproduction in normal human cells of adenoviruses, viruses that are widely used in such therapeutic applications as gene transfer and cancer treatment. Her service to the scientific community includes membership on various editorial boards, several NIH study sections and the NIH Recombinant DNA Advisory Committee. She also is a founding author of the acclaimed textbook "Principles of Virology", now in its 5th edition.

Loletha C. Johnson, RN, MSN

NJDOH Commissioner's Designee

Loletha Johnson is a public health practitioner with the New Jersey Department of Health, Division of Community Health Services, and oversees the NJ Cancer Education and Early Detection (NJCEED) Program and Office of Cancer Control and Prevention (OCCP). She has an eclectic array of experience working with priority populations to address the most salient health outcomes and health disparities across the life course. Her forward thinking has led to innovative interventions to reduce mortality and morbidity in at-risk populations across multiple disease states. She has been instrumental in data-driven environmental, systems, and policy initiatives that impact access to health services through addressing social determinants of health barriers to care with multisectoral collaboration, as both a collaborator and program administrator.

Christine Schell, MPA

Christine Schell is currently the Manager of the New Jersey Department of Environmental Protection's Environmental and Public Health Analysis Program (EHPA). A 30-year veteran of the NJDEP, Ms. Schell has managed EPHA for over a year during which time she has facilitated the development and release of the interim NJ Environmental Justice Mapping, Assessment and Protection (NJ EJMAP) Tool and the launch of Healthy Community Planning NJ (HCP-NJ), a joint initiative with the NJ Department of Health to provide municipal level environmental and public health data to communities to guide and direct local planning and positively impact public health outcomes. Currently, she leads NJDOH's Healthy NJ 2030's Environmental Health Workgroup in developing meaningful and measurable strategies to address the state's largest environmental public health issues.

Anna Marie Skalka, PhD
Chair Emerita
Dr. Anna Marie (Ann) Skalka is Professor Emerita and former W.W. Smith Chair in Cancer Research at the Institute for cancer research at the Fox Chase Cancer Center in Philadelphia, where she served as Senior Vice President for basic science from 1987 until 2008. She received a Ph.D. degree in Microbiology from New Jersey University Medical School. Dr. Skalka has also been deeply involved in State, National and International advisory groups concerned with broader, societal implications of scientific research, including the NJCCR which she chaired from 2008-2013. In recognition of her many research accomplishments; she has been honored by election to the American Academy of Arts and Sciences, the American Association for the Advancement of Science, the New York Academy of Science, and the Board of Governors of the American Academy of Microbiology.

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NJCCR NEW JERSEY COMMISSION ON CANCER RESEARCH

"There's always hope beyond what you see."

Cora Connor
Caregiver

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