New Jersey Commission on Cancer Research

6th Annual Cancer Research Symposium

November 9, 2022

Program Book

NJ Health
New Jersey Department of Health

NJCCR
NEW JERSEY COMMISSION ON CANCER RESEARCH

New Jersey
Commission on
Cancer Research

6th Annual Cancer Research Symposium

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

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

Agenda at-a-Glance

8:30 am **Registration** (Breakfast Served)

8:45 am **Welcome and Introductions**
Dr. Kenneth Adler, Chair of NJCCR

9:00 am **Keynote Address**
Evolving Impact of Cancer Genetics on Cancer Survivorship
Generosa Grana, M.D. FACP
Director MD Anderson Center at Cooper
Member, NJCCR

9:45 am **Awards Presentation**
Legislative Champion Award
Honorable Daniel R. Benson
Patient Advocate Awards
Aubrey Reichard-Eline
Dorothy Reed
Dr. Jonathan Yavelow Mentor Award
Dr. Katie Devine
Dr. Shridar Ganesan
Dr. Teresa Wood
Dr. Carol Lutz

10:15 am **Scientific Research Presentations by Principal Investigators**
Session 1 *and* **Session 2**

Noon **Lunch**

12:45 pm **"Hot Topics" Panel: Trends in 2022 and Beyond**
Dr. Shawna Hudson, Rutgers RWJ Medical School *(Moderator)*
Dr. Li Li, Novartis Institute For Biomedical Research
Dr. Jane Flint, Princeton University
Dr. Patricia Doykos, Bristol-Myers Squibb
Dr. Peter Cole, Rutgers, CINJ

NJCCR NEW JERSEY COMMISSION ON CANCER RESEARCH

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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Award Presentations

- **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 to advance cancer research, and promoting activities related to the need for innovation in finding a cure for cancer.

- **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

2022
Award
Presentations

Legislative Champion Award: Honorable Dan Benson

Honorable Assemblyman Dan Benson (D-14 Mercer) first joined the Assembly in 2011 and is currently serving his fifth term. A former member of the Environment, Commerce, and Law and Public Safety Committees, the Assemblyman currently serves as the Chair of the Transportation and Independent Authorities Committee and as a member of the Health and Budget Committees, in addition to being Deputy Conference Leader. He represents towns in Mercer and Middlesex Counties including Cranbury, East Windsor, Hamilton, Hightstown, Jamesburg, Monroe, Plainsboro, Robbinsville, and Spotswood.

Assemblyman Benson has a Bachelor of Science in physics and government from Georgetown University and a Master of Public Policy in science and technology policy from Rutgers University. He is an energy and telecommunications policy consultant and resides in Hamilton with his wife Hande and their son Nicholas.

Patient Advocate Award: Dorothy Reed

Dorothy J. Reed is the Co-Founder and President of Sister2Sister, Inc (S2S). She became a breast cancer survivor in 1998. After a mastectomy and treatments, Ms. Reed dedicated herself to spreading the gospel of early detection in the Minority community. In the absence of local support or culturally sensitive resources for Minority women diagnosed with the disease, Ms. Reed formed Sister2Sister (formerly Sisters Network of Central New Jersey) in 2000 with three other breast cancer survivors.

S2S was renamed and rebranded in January 2018. Active in her community, Ms. Reed is a board member of St. Peter's Hospital Cancer Community Public Education, Robert Wood Johnson Univ. Hospital Community Relations Committee, NJ Alliance for Clinical & Translational Science Community Engagement Core Advisory Committee, and the Chair of The Cancer Institute of NJ - Community Cancer Action Board. Mrs. Reed's accomplishments include a recent recognition by the Rutgers Cancer Health Equity Center of Excellence "Excellence in Leadership Award" and a graduate of the Citizen Scientist Program sponsored in conjunction with the Community Outreach and Engagement Department. On a national level, in July 2015 Ms. Reed was selected as a White House Honoree of Precision Medicine "Champions of Change"; She has spent extensive time on Capitol Hill with the National Breast Cancer Coalition. In May 2005, Ms. Reed was selected to participate on the Department of Defense Breast Cancer Research Program committee for the U. S. Army Medical Research Command. Ms. Reed has received numerous honors and awards including an appearance in a 2005 National Television Commercial Campaign by Astra Zeneca "If You Were My Sister" and being selected as one of Lifetime Hero's by Lifetime Television in 2006. Ms. Reed holds a Bachelor of Arts Degree, Cum Laude, from Pillar College.

2022 Award Presentations

Patient Advocate Award: Aubrey Reichard-Eline

Aubrey Reichard-Eline is a high-energy, goal-oriented leader who connects with people on multiple levels through her enthusiasm and "can do" attitude. She came to the world of advocacy from a professional career in merchandising after her daughter was diagnosed with a rare brain tumor in 2018. While working with the American Childhood Cancer Organization she was responsible for securing $44M in new funding at the state level for pediatric cancer research. Aubrey currently holds a development role at Rutgers Cancer Institute of New Jersey. She also sits on the Patient Family Advisory Committee (PFAC) for Newark Beth Israel Medical Center and Rutgers Cancer Institute as well as the Rutgers Cancer Institute Scientific Review Board (SRB) for clinical trial research participation and the NCI Childhood Cancer Data Initiative (CCDI) Cohort working group. Aubrey is Chair of the NJCCR Pediatric Cancer Research Advisory Group and enjoys working with cancer leaders in the state. She co-founded WITH Grace Initiative to make life just a little easier for the kids and families battling cancer.

Dr. Jonathan Yavelow Mentor Award: Dr. Carol Lutz

Dr. Carol Lutz is an Associate Professor, RBHS-New Jersey Medical School and serves as the Associate Dean for Student Affairs, Rutgers School of Graduate Studies. Dr. Lutz earned her BS in Biology with highest honors (1984) from UNC-Chapel Hill and her PhD in Microbiology and Genetics from Duke University (1990). After her postdoc at the University of Pennsylvania, she obtained a faculty position at RBHS-New Jersey Medical School where she teaches at NJMS, RSDM, and SGS. She also serves as an Associate Dean in the Rutgers School of Graduate Studies. She has decades of service on private and federal grant review panels, especially on those related to graduate and post-doctoral fellowships. She has received numerous accolades for teaching, mentoring and service. Her research lab focuses on gene expression regulation in cancer.

Dr. Jonathan Yavelow Mentor Award: Dr. Teresa Wood

Dr. Teresa Wood is a distinguished professor at Rutgers New Jersey Medical School and a Rena Warshow Endowed Chair in MS. She earned her PhD in Molecular Neurobiology from UCLA in 1987 and worked as a postdoctoral fellow at both SUNY and Columbia University. From '92-'03 Dr. Wood was an instructor at RWJ Medical School and from '93 to '05 worked as an associate professor at Penn State University. Dr. Wood is a recipient of the Jacob Javits Neuroscience Investigator Award from the NIH and is an expert in signaling pathway regulation of myelin in oligodendrocytes and IGF and insulin signaling in breast cancer. She has published over 40 peer-reviewed articles on IGF signaling and has pioneered research on the tumor-suppressive functions of IGF1R in breast cancer. Her current work in breast cancer aims to elucidate the tumor-suppressive mechanisms of IGF1R, including in tumor microenvironment regulation and cancer cell adhesion.

2022 Award Presentations

Dr. Jonathan Yavelow Mentor Award: Dr. Katie Devine

Dr. Katie Devine an Associate Professor of Pediatrics and the Section Chief of Pediatric Population Science, Outcomes, and Disparities Research at Rutgers Cancer Institute of New Jersey. Dr. Devine's research focuses on the psychosocial aspects of pediatric, adolescent, and young adult cancer survivorship, including patient and family adaptation to illness, adherence to medical recommendations and survivorship care, and health promotion for survivors. The majority of her work focuses on the unique needs of adolescent and young adult (AYA) patients and survivors who must navigate the challenges of cancer care in the midst of normative developmental transitions (such as graduating high school, pursuing higher education, establishing financial independence, and forming strong peer and intimate relationships).

Dr. Jonathan Yavelow Mentor Award: Dr. Shridar Ganesan

Dr. Shridar Ganesan is the Section Chief of Molecular Oncology, Omar Boraie Chair of Genomic Science, Professor of Medicine and Pharmacology at the Robert Wood Johnson Medical School, Rutgers University. He is also the Associate Director of Translational Research, Co-Leader of Clinical Investigations and Precision Therapeutics Program and last but not least the Director of Comprehensive Genomics Core Facility in Rutgers Cancer Institute of New Jersey. After a Bachelor degree with the highest distinction in Chemistry from Princeton University, he got his dual MD/ PhD degree from Yale University with distinction and PhD thesis prize. He followed his passion by joinging an internal medicine residency program in Brigham and Women's Hospital, Boston, MA. Afterwards, he pursued a medical oncology training and a postdoc appointment in Dana Farber Cancer Institute, Boston, MA, during which he was appointed by the Department of Medicine, Harvard University School of Medicine as an Instructor. In 2005, Dr Ganesan joined the Departments of Medicine and Pharmacology in Robert Wood Johnson Medical School, UMDNJ. Beside his excellent skills as a staff physician, Dr Ganesan has more than 100 peer reviewed articles that were cited more than 30,000 times, enriching the scientific research field with his clinical and research knowledge combined. Throughout his career he received many awards and distinctions including but not limited to R.T. McKay Prize in Chemistry from Princeton University, AFCR Medical Student Award for Excellence and Yale P.A. Program Award for Outstanding Pre-Clinical Lecturer from Yale University, beside many fellowships, investigator, patient care awards and research grants. He also serves in many national grant review panels, major committees and editorial boards. Alongside his teaching responsibilities, Dr. Ganesan was the primary mentor for more than 20 mentees between graduate students, PhD/MD dual degree students, postdocs, and double this number for co-mentorship and undergrad research training mentorship.

Research Presentations

A Novel Strategy for Developing Personalized Cancer Vaccines with Improved Efficiency and Specificity

Liqun Tu
Rutgers Cancer Institute of NJ

The advances in immunotherapies, e.g.immune checkpoint blockade therapies and chimeric antigen receptor (CAR) T-cell therapies, have revolutionized the treatments of certain types of cancer in the last decade. The most of immunotherapies are based on increasing immunities against tumor antigens. The vaccine is one of the most efficient and effective medical procedures to induce antigen-specific immune response. However, therapeutic cancer vaccines have not achieved significant clinical success. Cancer vaccines are usually developed against tumor-associated antigens (TAAs) or single-nucleotide variants-based tumor-specific antigens (SNV-TSAs). These tumor antigens are usually associated with low immunogenicity and/or tumor specificity. New frame-derived antigens (NFDAs) are completely novel protein sequences produced by reading frameshift insertions or deletions (Indels), reading frameshift exon skipping, or intron retentions. Compared to TAAs and SNV-TSAs, NFDAs have the potential to exhibit significantly increased immunogenicity and tumor specificity. NFDAs are usually suppressed by nonsense-mediated mRNA decay (NMD). As such, NFDAs do not express in tumors but can be induced by NMD blockade. Here we propose a novel cancer vaccine strategy: combining NMD blockade and personalized vaccines targeting NFDAs. The **central hypothesis** is that this novel strategy will overcome major challenges in current cancer vaccine strategies and produce improved anti-tumor activities. To prove it, we will perform a **proof-of-concept study** using mouse models. In preliminary studies, we have identified hundreds of NFDAs in eight mouse cancer cell lines. We have validated NMD blockade-induced expression of NFDAs in MB49 and MC38 cells. Specifically, the combination of a vaccine targeting a Dop1b exon skipping variant, which was found in MB49 cells, and NMD inhibition led to the rejection of transplantation of MB49 tumors in immunocompetent mice. In the proposed study, we will validate other NMD-suppressed NFDAs in mouse cancer cell lines. DNA constructs encoding these NFDAs will be prepared as vehicles for vaccinating allograft tumor-carrying, immunocompetent mice. NMD blockade will be induced by dox-inducible shRNA in tumor cells targeting Upf2, a key NMD gene. Antigen-specific immune response and tumor suppression effects will be evaluated. This project will prove the feasibility of a novel vaccine-based immunotherapy strategy. It will nominate NFDAs as a new category of TSAs that have enhanced specificity and immunogenicity for use in cancer vaccines. It will also demonstrate the novel use of NMD as a target for stimulating immunogenicity of tumor cells. By combining NFDA-targeting vaccines and NMD blockade, we will provide novel, personalized, and effective therapeutics to patients that cannot benefit from the treatments currently available.

Sirtuin 6 Antiviral Function at the Interface Between Gene Expression and Cellular Metabolism

Matthew D. Tyl, Yana V. Miteva, and Ileana M. Cristea
Department of Molecular Biology, Princeton University, Princeton, New Jersey

Beyond being underlying comorbidities for immunosuppressed cancer patients undergoing chemotherapy, virus infections are estimated to cause up to 20% of human cancers worldwide. Although not canonically labeled an oncovirus, the ubiquitous B-herpesvirus human cytomegalovirus (HCMV) has been shown to possess oncomodulatory and potentially oncogenic capabilities. In accordance with these findings, the International Agency for Research on Cancer (IARC) has designated HCMV as a high priority agent for investigation, yet there is currently no available vaccine and there are limited antiviral therapeutics. Since viruses are obligate parasites that rely on cellular processes for their replication, targeting host factors provides a promising therapeutic strategy. Moreover, the understanding of the mechanisms underlying HCMV-driven pathologies remains limited. Our lab has discovered that the human protein sirtuin 6 (SIRT6) exerts an antiviral function against HCMV; however, the mechanism remains unknown. Through a study which bridges mass spectrometry-based proteomics with molecular virology, we (1) identified the important catalytic activity for SIRT6 to restrict HCMV replication, (2) identified the stage of HCMV replication targeted by SIRT6, and (3) determined putative deacetylase substrates for SIRT6 in enacting its antiviral function. We found that SIRT6 utilizes its deacetylase activity to restrict HCMV genome synthesis and suppress virion infectivity. Through integration of SIRT6 protein-protein interaction data with dysregulated acetylation sites after SIRT6 perturbation, we have assembled a first-of-its-kind list of putative SIRT6 substrates during infection which may enable its antiviral function. In sum, our results lead us to a model whereby SIRT6 inhibits the virus-induced shift to a Warburg-like cellular metabolic profile, decreasing production of the nucleotides and lipids which HCMV relies upon for productive infection.

The Role of P53 in Type 2 Innate Immunity and Colon Tumorigenesis

Chun-Yuan Chang
Rutgers Cancer Institute of NJ

The role of p53 in tumor suppression has been extensively studied and well-established. However, the role of p53 in parasitic infections and the intestinal type 2 immunity is unclear. We found that p53 is crucial for intestinal type 2 immunity in response to the infection of parasites, such as Tritrichomonas muris (Tm) and Nippostrongylus brasiliensis (Nb). Mechanistically, we observed that p53 plays a critical role in the activation of the tuft cell-IL-25-type 2 innate lymphoid cell circuit, partially via transcriptional regulation of lymphoid-restricted membrane protein (Lrmp) in tuft cells. Lrmp, a novel p53 target gene, modulates

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Research Presentations

Ca2+ influx and IL-25 release, which are critical triggers of the type 2 innate lymphoid cell response. Our results thus reveal a previously unrecognized function of p53 in regulating intestinal type 2 immunity to protect against parasitic infections, highlighting the role of p53 as a guardian of immune integrity. Moving forward, we are investigating the potential role of Lrmp in colorectal cancer (CRC), especially whether Lrmp regulates immune cells in the tumor microenvironment. Lrmp deficient mice have been employed to test whether Lrmp loss affects colorectal tumorigenesis induced by AOM/DSS treatment. Results from this study have the potential to help us understand the role of Lrmp in CRC as well as the mechanism of colorectal tumorigenesis.

BRCA2 Associates with MCM10 to Suppress PRIMPOL-Mediated Repriming and Single-Stranded Gap Formation After DNA Damage

Zhihua Kang, Bing Xia
Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA

The BRCA2 tumor suppressor protects genome integrity by promoting homologous recombination-based repair of DNA breaks, stability of stalled DNA replication forks and DNA damage-induced cell cycle checkpoints. BRCA2 deficient cells display the radio-resistant DNA synthesis (RDS) phenotype, however the mechanism has remained elusive. Here we show that cells without BRCA2 are unable to sufficiently restrain DNA replication fork progression after DNA damage, and the underrestrained fork progression is due primarily to Primase-Polymerase (PRIMPOL)-mediated repriming of DNA synthesis downstream of lesions, leaving behind single stranded DNA gaps. Moreover, we find that BRCA2 associates with the essential DNA replication factor MCM10 and this association suppresses PRIMPOL-mediated repriming and ssDNA gap formation, while having no impact on the stability of stalled replication forks. Our findings establish an important function for BRCA2, provide insights into replication fork control during the DNA damage response, and may have implications in tumor suppression and therapy response.

Determining the Role of the Lncrna PACER in Gene Expression Regulation in Lung Cancer Cells

Samuel Z. Desind & Carol S. Lutz
Rutgers University

Multiple layers of RNA-mediated gene expression have evolved to regulate the numerous and complex 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, including osteoarthritis, rheumatoid arthritis, and lupus, and in many cancer types,

including breast and lung cancer. We have previously published work on alternative 3' end formation and miRNA-mediated regulation at the 3' end of several genes in the AA pathway.

Long non-coding RNAs (lncRNAs) have been reported to regulate transcription directly through interaction with transcription factors and transcription factors binding sites or indirectly through miRNA sponging and interaction with accessory proteins. However, in many cases, the mechanism of lncRNA regulation is unknown.

We are investigating the relevance of several lncRNAs, including HAND2-AS1, LOX12-AS1, CCEPR, MILIP, and PACER, in AA regulation in the context of lung cancer. Our recent research focuses on the p50-associated COX-2 extragenic lncRNA (PACER) in lung cancer. PACER is directly upstream and antisense to the COX-2 transcript. Our data suggest that the PACER is a key factor regulating the expression of COX-2, a major enzyme in the AA pathway, through an elegant feedback loop. Our experimental results identified previously undescribed transcription factors that may play a role in PACER regulation in lung cancer cells. Using a lung cancer cell model, we are investigating the effects of PACER shRNA knockdown on cell proliferation, migration, and the broader roles in immune regulation.

Disruption of the MTDH-SND1 Complex Enhances Tumor Antigen Presentation and Synergizes with Anti-PD-1 Therapy for Metastatic Breast Cancer

Yong Tang
Princeton University

Breast cancer is one of the leading causes of cancer-related morality among American women. The majority of breast cancer death is resulted from tumor metastases rather than the primary tumor. Metadherin (MTDH) has been identified as a pro-metastasis gene that is associated with poor prognosis breast cancer patients. MTDH promotes tumor progression, metastasis and treatment resistance through its interaction with Staphylococcal nuclease domain-containing 1 (SND1). However, the mechanism underlying these pro-malignant functions of the MTDH-SND1 complex has not been well characterized. We used genetic and pharmacological approaches to reveal a key role of MTDH-SND1 in suppressing anti-tumor T cell responses in breast cancer. The MTDH-SND1 complex reduces tumor antigen presentation and inhibits T cell infiltration and activation by binding to and destabilizing Tap1/2 mRNAs, which encode key components of the antigen presentation machinery. Small molecule compound C26-A6 disrupts the MTDH- SND1 complex, enhances immune surveillance in metastatic breast cancer, and sensitizes the disease to anti-PD-1 therapy. These results indicate MTDH-SND1 targeting as a viable approach to increase immune checkpoint blockade therapy response in metastatic breast cancer.

Research Presentations

Understanding the Multilevel Factors Influencing a Mindfulness-Based Mobile Application Service Implementation for Adolescents and Young Adult Survivors of Childhood Cancer

Gary Kwok
Rutgers Cancer Institute of NJ

Background: Adolescent and Young adult (AYA) survivors of childhood cancer are increasingly recognized as a vulnerable group with unique emotional, social, and practical needs due to the intersection of cancer survivorship and normal developmental processes. AYA survivors are at increased risk for poor mental health; 20-25% of AYA cancer survivors report impaired mental health and many more experience subclinical levels of distress. Mindfulness meditation has shown early efficacy in improving psychological distress among cancer patients. With these benefits, healthcare providers can incorporate mindfulness mobile apps into their practice to support AYA survivors of childhood cancer to manage stress. The goal of this study is to understand factors associated with 1) the engagement of mindfulness mobile apps among AYA and 2) healthcare providers' promotion (e.g., referral) of mindfulness mobile apps to AYA cancer survivors.

Methods: We conducted semi-structured interviews with AYA cancer survivors (n=10) healthcare providers and administrators (n-10) to understand what are some key factors that promote the use and engagement of mindfulness mobile apps.

Conclusion: Findings of the study will inform us of the appropriate strategies to incorporate mindfulness meditation mobile apps into clinical care for AYA survivors of childhood cancer. For example, we can better understand how factors such as organization culture/support and providers' own perception of the mobile app can influence their tendency to refer the app to patients. For AYA survivors, we can learn what makes the mobile app appealing to use. In a border context, this study can inform other mHealth (mobile health) studies; researchers can follow a similar process to understand how to best incorporate other mHealth services into clinical care

Regulatory Mechanism of Oncogenic Chromatin Remodeling

Tinghan Zhao[1], Richard Yang[1] and X.F. Steven Zheng[1,2]
[1]Rutgers Cancer Institute of New Jersey, Rutgers, [2]Department of Pharmacology, The State University of New Jersey

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, partially through ubiquitination and proteasomal degradation, promoting oncogenic chromatin remodeling and 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.

Exploring the Synergy Between Diet and Drugs in Pancreatic Cancer

Asael Roichman
Princeton University

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest forms of cancer. A promising approach to fight this cancer could be affecting its nutrient supply with dietary modifications, and rationally combining these diets with drug-based therapies. A diet that has attracted much attention is ketogenic diet, which was recently shown to enhance the efficacy of phosphatidylinositol-3 kinase (PI3K) inhibitors and cytotoxic chemotherapies in PDAC therapy. However, the underlying mechanisms are not well understood, and the improved efficacy, while encouraging, did not lead to a cure. Here, we investigate how ketogenic diet synergizes with these drugs to suppress PDAC growth. Importantly, we also find new diets that show significant synergistic effects. Our goal is to identify the key dietary factor/s contributing to the synergy, and based on that, design safe and effective diet-drug combination for PDAC patients.

Evaluation of UHRF1BP1 as a Novel Regulator of Antitumor T Cell Activity in Ovarian Cancer

Rinkee Kumari[1], Kristen E Rigolizzo[1], Elaheh Hosseini[1], Tyler Milonas[1], Steven Wang[1] and Kyle K Payne[1]
[1]Rutgers Cancer Institute of New Jersey

Introduction: Tumor microenvironments (TME) allow tumors to evade immune control. Activation of pathways in response to cellular stress, such as oxygen deprivation (hypoxia) and nutrient deficiencies drive dysregulated antitumor T cell responses in tumor beds. Intriguingly, TME drives mitochondrial stress responses and UHRF1BP1 has recently been demonstrated to function as a response element to mitochondrial stress, however its role in regulating antitumor T cell responses in epithelial ovarian cancer (EOC) is completely uncharacterized.

Hypothesis: Dysregulated mitochondrial stress responses in the absence of UHRF1BP1 improves antitumor efficacy of $CD8^+$ T cell activity in the ovarian

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.

tumor microenvironment through elevated reactive oxygen species (ROS) activity and metabolic reprogramming.

Methods: We have developed a new conditional knockout mouse, in which Uhrf1bp1 is specifically ablated in post-thymic T cells ($CD4^{Cre}$ Uhrf1bp1f/f mice). Utilizing our novel $CD4^{Cre}$ Uhrf1bp1f/f mice the survival upon EOC tumor challenge was studied. To define the immunotherapeutic potential of Uhrf1bp1-ablated T cells, Tumor antigen-primed Uhrf1bp1-ablated T cells were isolated from tumor beds and/or tumor-draining lymph nodes, expanded ex vivo, and infused into syngenic tumor-bearing mice and survival was studied in UHRF1BP1ablated mice relative to littermate control.

Results: We observed that CD4Cre Uhrf1bp1f/f mice implanted with aggressive UPK10 ovarian tumor cells reproducibly experienced significantly enhanced survival compared to littermate controls ($Uhrf1bp1^{wt}$). Interestingly, ex vivo restimulation of $CD8^+$ T cells isolated from tumor beds demonstrated increased frequency of IFN-γ^+ Granzyme B^+ polyfunctional effector phenotype in Uhrf1bp1-ablated T cells compared to littermate controls. Indeed, we found greater production of mitochondrial ROS upon T cell stimulation within Uhrf1bp1-ablated $CD8^+$ T cells and ROS scavenging using N-acetyl-L-cystein (NAC) was associated with a reduction in the effector function of Uhrf1bp1-ablated T cells. Moreover, we observed the potential therapeutic efficacy of artificially antigen-primed adoptively transferred Uhrf1bp1-ablated CD8 T cells in a murine model of EOC. 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 and suggesting potential synergy with checkpoint immunotherapy approaches.

Conclusion: Blocking UHRF1BP1 could be a therapeutic modality in patients with EOC.

Shortwave Infrared-Emitting Nanoprobes for Optical Imaging of Myeloid Derived Suppressor Cells

Siebert JN, Shah JV, Zhao X, He S, Riman RE, Tan MC, Pierce MC, Lattime EC, Ganapathy V, Moghe PV
Rutgers University

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. To improve survival outcomes and treatment decisions, there is a need to identify patients at risk of metastatic spread earlier than is currently possible. One approach to solve this problem is through direct imaging of the pre-metastatic niche prior to colonization by circulating tumor cells. 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. First, we demonstrate conjugation of the GR-1 antibody to the ReANC albumin shell. We then validate ReANC targeting through in vitro binding assays. Preliminary results indicate that our nanoparticles are capable of in situ detection of MDSCs in both the primary tumor and pre-metastatic lung niche. Ongoing studies will seek to image MDSCs within the PMN in proof-of-concept murine breast cancer models for highly metastatic and non-metastatic cancers.

Mutant P53 Signaling in Breast Cancer

Xue Yang
Rutgers Cancer Institute of NJ

Tumor suppressor p53 plays a central role in tumor prevention. p53 is frequently mutated in cancers, including breast cancers. p53 mutations occur in ~30% of all breast cancers and in >80% of triple negative breast cancers (TNBCs). Many mutant p53 (mutp53) proteins not only lose the tumor suppressive function of wild-type p53, but also gain new oncogenic activities to promote tumorigenesis, defined as mutp53 gain-of-function (GOF). Metabolic reprogramming is a hallmark of cancer. Cancer cells often display altered glucose and lipid metabolism, contributing greatly to breast tumorigenesis. Currently, the role and mechanism of mutp53 in metabolic reprogramming and progression of breast cancers are poorly defined. Further, the biological significance of these mutp53-driven metabolic changes in breast cancers carrying mutp53 and their potential applications in breast cancer therapy are not well-understood. To understand the role mutp53 in breast cancer, we established Trp53wm-R172H-MMTV-PyMT mouse model, which were generated by crossing Trp53wm-R172H mice with MMTV-PyMT mice. We have validated the genotype of the mice. The expression of Trp53wm-R172H was induced by injection of Ad5-CMV-Cre virus. We will perform lipidomic analysis to test the lipid changes in Trp53wm-R172H-MMTV-PyMT mice compared to control mice. We further will determine the impact of mutant p53 on FAO, and validate that mutant p53 promotes the growth and metastasis of breast cancers in Trp53wm-R172H-MMTV-PyMT mice. This study will have the direct potential to yield new therapeutic targets and strategies for more effective and personalized breast cancer therapy.

Research Presentations

The Immunosuppressive Role of Leukemia Inhibitory Factor in Tumor Microenvironment

Fan Zhou
Rutgers Cancer Institute of New Jersey

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.

Microbiota-Induced Regulation of γδ Intraepithelial Lymphocyte Immunometabolism and Effector Function

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Intraepithelial lymphocytes expressing the γδ T cell receptor (γδ IEL) are located within the intestinal epithelium and serve as the first line of defense against pathogen invasion, epithelial injury, and tumor surveillance. We recently identified a novel hyperproliferative and hypermotile γδ IEL ($\gamma\delta^{HYP}$) phenotype that can be transferred both horizontally and vertically to wildtype (WT) mice via the gut microbiota. Given the close relationship between metabolism and immune cell function, as well as the influence of commensals on T cell metabolism, we hypothesized that the microbiota associated with the γδHYP phenotype alters γδ IEL metabolism, which in turn, may influence the effector function of these sentinel lymphocytes. Transmission electron microscopy of sorted small intestinal γδ IELs revealed that $\gamma\delta^{HYP}$ IELs exhibit a 70% increase in the number of mitochondria per cell ($p=0.005$) accompanied by a 24% increase in mitochondrial area ($p=0.04$) and a 40% increase in aspect ratio ($p=0.02$) relative to WT. Since elongated mitochondria may be indicative of increased oxidative phosphorylation, we next performed Seahorse mitochondrial stress assays on sorted γδ IELs to assess the bioenergetic capacity of these lymphocytes. We find that $\gamma\delta^{HYP}$ IELs exhibit a 50% increase in spare respiratory capacity compared to WT ($p=0.014$).

Glucose and mitochondrial metabolism were recently shown to influence cytokine production by γδ T cells, thus enhancing or diminishing their cytotoxic capacity. Following stimulation, we observed a 59% reduction in the frequency of IFNγ^{+} γδ IELs and 44% decrease in IFNγ mean fluorescence intensity (MFI) in γδ^{HYP} IELs relative to WT ($p<0.0001$). Inhibition of ATP synthase with oligomycin resulted in an increase in IFNγ production in both WT and γδ^{HYP} IELs by 66% and 44%, respectively ($p<0.0001$). Together, our data demonstrate that γδ^{HYP} IELs have increased mitochondrial mass and oxidative phosphorylation compared to WT, which in turn leads to reduced IFNγ production. Further understanding of the mechanisms regulating γδ IEL homeostasis and effector function may ultimately allow fine tuning of mucosal surveillance to reinforce the epithelial barrier and prevent intestinal tumorigenesis.

Understanding the Mechanism of Hepatitis B Virus Host Range Restrictions

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Hepatitis B virus is a leading cause of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), with more than 250 million people chronically infected worldwide. HCC is one of the most prevalent causes of cancer-related deaths and chronic HBV results in around 887,000 deaths a year with no functional cure. Development of more effective antiviral therapies has been hampered by the scarcity of animal models for HBV infection. Humans and chimpanzees are the only hosts that can be infected with HBV, and while mice pose as the ideal candidate for research, they are resistant to HBV. This apparent resistance is due to numerous blocks in the viral life-cycle in human cells. The amino acid sequence of the mouse orthologue of the HBV receptor, the bile acid transporter NTCP (also known as SLC10A1), differs from the human counterpart in residues that are critical for viral uptake. Our lab has shown that transgenic expression of human NTCP in mice can facilitate HBV entry in mouse hepatocytes but subsequently the virus fails to establish an infection. Recent work from our lab and others further showed that the intranuclear stages of the HBV and subsequent steps in the infectious cycle are supported in mouse cells. Thus, there is considerable evidence that the restriction barrier may be at a step of import of the HBV capsid into the nucleus. Intriguingly, it was previously shown that the HBV capsid interacts with human orthologues of particular isoforms of nuclear import proteins. Thus, I hypothesize that human/primate specific factors are needed for HBV capsid nuclear import/disassembly to break this final species barrier. To test this hypothesis, I am pursing both gain- and loss-of-function approaches. Systematic CRISPRi-directed knockdown of proteins involved in nuclear import human cells will yield candidates that may be important

The purpose of the Pilot Grants is to provide seed funding for fundamentally sound research projects that address current priority areas.

for HBV infection. In turn I can test whether their expression in mouse cells would allow the virus to complete its life-cycle. In an alternative, yet complimentary approach, I am performing an unbiased screen of all the proteins in the human ORFeome, introducing one human protein per mouse cell, infecting these cells with HBV, and analyzing which proteins allow for successful HBV infection. Candidate proteins from this screen will be introduced separately into mouse hepatoma cells and tested for efficacy of HBV infection as well. The overarching goal of my research is to characterize the restriction barrier in mouse hepatoma cells and identify proteins that overcome this block with the aim of pushing the field towards generating a mouse model that is fully permissive to HBV.

Loss of γδ Intraepithelial Lymphocytes and Reduced Immunosurveillance of the Epithelial Barrier Precede the Onset of Crohn's Disease-Like Ileitis

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Inflammatory bowel disease, including Crohn's disease (CD), affects over 3 million Americans and is associated with increased risk of cancer development. A recent single cell sequencing study of CD patients revealed a loss of γδ intraepithelial lymphocytes (IELs) in resected ileal tissue. IELs expressing the γδ T cell receptor (γδ IEL) bridge innate and adaptive immunity and migrate dynamically within the intestinal epithelium as a means of immunosurveillance. However, the contribution of γδ IELs to the maintenance of the intestinal epithelium during the initiation of ileitis remains unknown. We and others have found that the onset of chronic CD-like ileal histopathology occurs at 8 weeks of age in $TNF^{\Delta ARE/+}$ mice; therefore, we profiled the IEL populations prior to and during the initial stages of ileal inflammation (4, 5, 6, 8 and 10 weeks). In agreement with CD patient data, we observed about a 3-fold reduction in the γδ IEL population in ilea of 5-week-old $TNF^{\Delta ARE/+}$ mice compared to $TNF^{+/+}$ (WT) littermates ($p=0.001$). Expression of epithelial butyrophilin-like genes *Btnl1* and *Btnl6* is partially responsible for regulating the seeding of γδ IELs within the epithelial compartment. We find that the expression of both *Btnl1* and *Btnl6* is reduced in 5- and 6-week-old $TNF^{\Delta ARE/+}$ mice ($p=0.001$, $p=0.05$ respectively). Furthermore, the frequency of proliferating γδ IELs is decreased in $TNF^{\Delta ARE/+}$ mice compared to WT littermates at 6 weeks of age ($p=0.05$). γδ IEL motility and function contribute to maintenance of an intact epithelial barrier, as we have recently demonstrated that γδ IELs facilitate shedding of apoptotic epithelial cells. Cleaved caspase 3 staining in fixed ileal tissue revealed increased shedding of apoptotic enterocytes in 6-week-old $TNF^{\Delta ARE/+}$ mice compared to WT littermates ($p=0.05$). Using intravital microscopy, we find that γδ IEL migratory behavior is significantly impaired in $TNF^{\Delta ARE/+}$ mice, as reflected by reduced track speed (7.9 vs

2.8 μm/min, p=0.005) and increased arrest coefficient (p=0.001) relative to WT mice. To determine the contribution of γδ IELs in the development of CD-like ileitis, we inducibly depleted γδ T cells by crossing TNF$^{\Delta ARE/+}$ mice to those expressing diphtheria toxin (DT) receptor driven by a γδ T-cell-specific promoter (TNF$^{\Delta ARE/+}$ TcrdGDL). Our preliminary findings indicate that DT-treated 3-week-old TNF$^{\Delta ARE/+}$ TcrdGDL mice exhibit reduced survival compared to TNF$^{\Delta ARE/+}$ littermates treated with vehicle control (Mantel-Cox log-rank test, p=0.155). In summary, we find that dysregulation of the γδ IEL compartment precedes the onset of ileitis in TNF$^{\Delta ARE/+}$ mice, and further, the reduced survival of TNF$^{\Delta ARE/+}$ mice following γδ T cell depletion indicates that γδ IELs play a critical role in maintaining mucosal tolerance. These studies suggest that restoring γδ IEL number or migratory behavior may be effective therapeutic strategies to maintain remission in CD patients and prevent inflammation-associated tumorigenesis.

Elucidating the Role of Heat Shock Protein 90 In NK Cell Immunosurveillance of Multikinase Inhibitor Resistant Liver Cancer to Improve NK Cell-Based Therapies for Solid Tumors

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Treatments for hepatocellular carcinoma (HCC) are limited because of tumor evolution and reduced drug efficacy. Most CAR-NK therapies show successful results in treatment of refractory hematological malignancies in clinic. More recently, we have shown suppression of HCC growth in a murine model after CD147 CAR-NK treatment. However, major challenges remain for the treatment of solid tumors, which are immune suppressive and evade anti-tumor immunity leading to poor prognosis. Studies show that combination chemotherapy-immunotherapy synergistically lead to enhanced antitumor immunity although limited clinical efficacy in HCC treatment. Heat shock protein 90 (HSP90) is a promising synergistic target because it has essential roles in both cancer cell survival and immune evasion. HSP90 inhibition is shown to 1) improve anti-tumor ligand expression, 2) improve response to immune checkpoint blockade therapies and 3) sensitizes cancers to chemotherapies suggesting a strong role in tumor evolution. The effect of HSP90 dysfunction in the tumor microenvironment on NK immunosurveillance of the tumor is poorly understood. **I hypothesize that disruption of HSP90 function will lead to improved NK cell immune surveillance and CAR-NK killing of MKIR-HCC through upregulation of NK cell ligands.** Preliminary cytotoxicity data suggests a strong HSP90-dependency in multikinase inhibitor-resistant HCC, whereby inhibition enhances killing of the cell lines when combined with regorafenib. Under the same combination therapy conditions, we find both stabilized expression of surface NK-stimulatory ligands and increased expression of surface heat shocks proteins that we could target with a CAR-T therapy. The long-term goal of the study is to understand a novel role

for HSP90 in immunomodulation of NK cells that could be used to enhance CAR-NK therapy treatment of solid tumors. This study proposes a unique approach to enhance precise CAR-NK immunotherapy with combination HSP90 inhibitor chemotherapy and radiation therapy to target the survival of solid tumors.

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 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 the developing $CD8^+$ Trm pools and their activity remain poorly defined. These studies focus on the action of G protein coupled receptors, which sense and integrate environmental signals and have been shown to be essential for lymphocyte function and regulation. Using a murine model of small intestine infection by *Yersinia pseudotuberculosis*, we identified *GPR132* as a potential regulator of Trm cell function and maintenance. *GPR132* ligands include oxidized fatty acids like 9-HODE, which are associated with pro-inflammatory environments. In addition, 9-HODE-synthesizing enzymes are upregulated in a variety of cancers. We have confirmed by flow cytometry that *GPR132* expression is increased after activation of *$CD8^+$* T cells in vitro, and on both circulating and tissue-resident memory T cell subsets in vivo. We further investigated the function of *GPR132* by co-transferring wild type and *$Gpr132^{-/-}$* antigen-specific T cells. During the primary response, GPR132 deficiency did not impact expansion or memory formation of circulating or tissue localizing $CD8^+$ T cells. However, upon reinfection, our data show preferential enlargement of the wild-type cell compartment, as *$Gpr132^{-/-}$* cells displayed limited re-expansion capacity. This cannot be explained by skewing in the formation of memory subsets, as there were no observed differences in the proportions of circulating and tissue-resident memory subpopulations between wild type and *$Gpr132^{-/-}$* cells. Moreover, *ex vivo* peptide stimulation showed that *$Gpr132^{-/-}$* antigen-specific cells are impaired in their production of pro-inflammatory cytokines IFN-γ, TNF-α, and IL-2. Altogether, our results expose a role for *GPR132*-signaling axis in regulating memory T cell immunity, and these data suggest manipulation of *GPR132* signaling in tumor infiltrating lymphocytes could improve $CD8^+$ T cell-based anti-tumoral immunotherapies.

Mechanism-Centric Network-Based Approach Identifies NME2 and MYC Programs as Markers of Resistance to Enzalutamide In CRPC Patients

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Heterogeneous response to Enzalutamide, a second-generation androgen receptor signaling inhibitor, is a central problem in castration-resistant prostate cancer (CRPC) management. Thus, prioritization of patients based on their risk to develop resistance to Enzalutamide is essential as it could potentially improve overall prostate cancer management. Over the years several groups have studied the role of either transcriptional regulatory programs or molecular pathways in prostate cancer however to date no study has evaluated the role of both of these mechanisms together. Hence, in this study, we reconstructed a de novo CRPC-specific mechanism-centric regulatory network that integrates molecular pathways and its upstream transcriptional regulatory programs. Following the reconstruction of the network, we interrogated the network to (i) identify parts of the network (also known as subnetworks) that differentially alter between phenotypes of interest and (ii) prioritize the upstream transcriptional regulatory programs based on their effect on a pathway. Such network interrogation identified the MYC subnetwork as one of the subnetworks that play a role in Enzalutamide response and transcriptional regulatory program, NME2 with the largest effect on the MYC pathway in CRPC Enzalutamide-associated conditions. Further, validation of NME2 and MYC using independent patient cohorts demonstrated NME2 and MYC pathway as predictive markers of Enzalutamide response and could be used to predict patients who are at a higher risk of developing resistance to Enzalutamide. Finally, our experimental investigations demonstrated that targeting MYC and its partner NME2 is beneficial in Enzalutamide-resistant conditions and could provide an effective strategy for patients at risk of Enzalutamide resistance and/or for patients who failed Enzalutamide treatment.

Research Presentations

The purpose of the Bridge Grants is to enhance cancer-related research at New Jersey Institutions by providing funding to promising and productive investigators who anticipate a short-term interruption in funding for research projects focused on cancer prevention, diagnosis, treatment, and survivorship.

Research Presentations

Carnitine Palmitoyltransferase 1A (CPT1A)-Mediated Therapeutic Responses in Estrogen Receptor Positive Breast Cancer

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Breast cancer (BC) is the most commonly diagnosed cancer and second leading cause of cancer-related deaths in women in the United States, with more than 70% of the cases are hormone receptor positive (HR+) disease. Endocrine based therapies (ET) are successfully used, however, 30-50% will acquire ET resistance leading to tumor progression. Since the mechanism of acquired resistance remains unknown for ~60% of patients, identifying novel mechanisms of resistance is essential. We recently reported that carnitine palmitoyltransferase 1A (CPT1A), the rate limiting enzyme in fatty acid oxidation, is overexpressed in aggressive HR+ tumors, including ET resistant patients. We propose that CPT1A level and activity changes the tumor microenvironment to enhance tumorigenesis and contribute to ET resistance. To determine the mechanism by which CPT1A is promoting cell proliferation, tumor microenvironment, cellular signaling and ET resistance, we used a series of in vitro studies incorporating a panel of either endogenously or experimentally derived CPT1A-low and CPT1A-high controls, HR+ breast cancer cell lines as well as their ET resistant counterparts. We determined that CPT1A is upregulated in cell lines that acquire ET resistance. Our analyses demonstrated that levels of CPT1A can affect tumor formation ability in both CPT1A-high and adjacent CPT1A-low tumor cells with concurrent changes in both intra- and inter-cellular signaling which may be essential to promote tumor progression and mediate therapeutic response. Besides, targeting CPT1A sensitized ET resistant cells to endocrine therapy and provided a new strategy to overcome resistance. This represents a promising step in understanding the mechanisms that promote tumorigenesis and ET resistance in HR+ breast cancer.

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Investigation the Novel Role of MTDH in Spontaneous Tumor Regression Through Its Regulation of Anti-Tumor Immunity

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Abstract
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 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.

I hypothesize that MTDH suppress the immunosurveillance-mediated spontaneous tumor regression and inhibition of MTDH can promote STR and inhibit tumor progression. To test my hypothesis, I will pursue the following specific aims: 1) To depict the temporal-spatial landscape of STR in the tetO-PyMT mouse model of breast cancer. 2) To investigate the immunosuppressive role of MTDH in STR. This aim could further divide into: 2a) To identify the target immune population that affected by MTDH during STR; 2b) To investigate how MTDH affects STR by regulating immune response via metabolic reprogramming.

Finally, 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.

Ligand-directed α-galactosyltransferase Gene Therapy Using Hybrid AAV Phage Vector for Antitumor Immune Response

Svetlana Bagdasarov, Ziqiang Yuan, Asha Adem, Daniel Slegowski, Steven K. Libutti

Cancer cells often express a variety of tumor associated antigens that distinguish them from normal cells and can be recognized as foreign by the host immune system. Unfortunately, tumors frequently develop immune resistance mechanisms to evade elimination. The discovery of therapies that can counteract the immunosuppressive environment protecting tumors in vivo has been the aim of the field of cancer immunotherapy. Much of this work has focused on T-cell mediated tumor rejection. An alternative approach is to leverage the power of an acute humoral antitumor response. The α 1,3-galactosyltransferase *(Ggta^1)* gene encodes for the enzyme that synthesizes Gal epitopes on the cell surface of glycolipids and glycoproteins in non-primate mammal tissues. Humans and Old World monkeys lack *Ggta^1* expression and therefore the Gal epitope is absent. In fact, anti-Gal is the most abundant natural antibody in human serum, and its specific binding with Gal epitopes is responsible for rapid hyperacute rejection of porcine xenografts. A strategy to deliver the Gal epitopes selectively into tumor cells will augment an effective antitumor immune response.

Research Presentations

Our lab has previously worked with a hybrid adeno-associated virus phage (AAVP) to safely and specifically deliver therapeutic transgenes. Bacteriophages are viruses that infect and replicate within bacteria and archaea. They lack intrinsic tropism for mammalian cells. AAVP is a bacteriophage-based vector in which incorporation of eukaryotic virus AAV expression cassette and display of ligand peptide motifs allow for receptor-mediated AAVP internalization and superior mammalian cell transduction. This gene therapy system may be a new approach to treat pancreatic neuroendocrine tumors (PNETs) which are increasing in incidence and yet have limited effective therapeutic options. These tumors often overexpress somatostatin receptors (SSTRs) and thereby provide a specific path for ligand-directed targeting. In previous work, AAVP displaying the somatostatin analog octreotide (Oct) enabled targeted delivery of inflammatory cytokine tumor necrosis factor-α (TNF-α) directly to the site of the tumor in a Men1 KO mouse model for PNETs. We developed a *Men1/Ggta1* double KO mouse model that is biologically very similar to humans with loss of *GGTA1* activity in all tissues. Our plan for this project is to use Oct targeted AAVP to elicit a tumor-inhibiting humoral response in *Men1/Ggta1* double KO mice by delivering a *Ggta1* transgene solely to PNETs. Intriguingly, other mutations in Pten cooperate with *MEN1* loss to accelerate tumorigenesis and metastasis in patients who develop PNETs. We developed *Men1/Pten/Ggta1* triple KO mice for in vivo experiments to assess the therapeutic strategy of utilizing *Oct-AAVP-GGTA1* to treat metastatic disease. Based on our strategy and preliminary work, we hypothesize that systemic administration of *Oct-AAVP-GGTA1* vector in these mouse models will induce *GGTA1* expression specifically in tumors and enhance an antitumor immune response.

The Effects of Intratumoral Heterogeneity on Metastasis of Triple-Negative Breast Cancer Cells

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Metastasis is responsible for most cancer-related deaths. Evaluating the risk of metastasis is essential for predicting a patient's prognosis and can be difficult in highly heterogeneous types of cancer, including triple-negative breast cancer (TNBC). Individual cancer cells can undergo changes at the genomic, epigenomic, transcriptomic, and/or proteomic levels that lead to the rise of distinct clonal subpopulations within a tumor. Our lab has derived both invasive, mesenchymal-like and noninvasive, epithelial-like clonal subpopulations from a mouse TNBC cell line. We are investigating the ability of cancer cells within epithelial-like, mesenchymal-like, and heterogeneous tumors to progress through steps of the metastatic cascade. Using an engineered tumor model, we found that cancer cells from heterogeneous and mesenchymal-like tumors invade into the surrounding

matrix and escape into a nearby cavity at a faster rate than cells from epithelial-like tumors. This model has also revealed that the presence of a single mesenchymal-like cell per ninety-nine epithelial-like cells increases the rate of invasion from a tumor and one mesenchymal-like cell per nineteen epithelial-like cells significantly increases the rate of escape. We are also using this model to investigate how selectively targeting mesenchymal-like cells within a heterogeneous tumor affects the rates of invasion and escape. These data are complemented by an in *ovo* model, which we are using to evaluate the ability of homogeneous and heterogeneous populations to form tumors and metastasize. This research will enhance our understanding of the effects of intratumoral heterogeneity on metastatic potential, which is necessary as physicians more towards more personalized medicine.

CDK9 and its Activating Proteins Modulate the Chromatin Landscape of Silenced Genes and Repetitive Elements in Cancer

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Coriell Medical Institute for Medical Research

Epigenetic drug development for cancer has increasingly gained interest in recent times. These drugs target regulation of epigenome to reprogram gene expression, which is reversible and heritable, making them a good candidate for drug development for cancers. These therapies are able to sensitize 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 the 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.

Research Presentations

Transcriptional Silencing of Yeast Heterochromatin by Cohesin

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Cohesin is an architectural protein complex that plays multiple fundamental roles in chromosome biology, including regulation of gene expression. Dysfunction of the complex or its regulators is associated with cancers and developmental diseases. Cohesin loads at specific sites in the genome but then accumulates at distant sites. Processive translocation of the complex along DNA has been proposed as a mechanism to explain redistribution. In one well studied case in yeast, cohesin loads at a tRNA gene but accumulates at the nearby heterochromatic domain known as HMR. Here, I address the following questions: how does cohesin get to HMR and what does it do when it gets there. To test the relevance of processive translocation, I have attempted to block cohesin transit by the imposition of "roadblocks" on DNA. To this end, engineered lac repressors (GFP-lacI chimeras) of increasing size were tethered between the tRNA and HMR. Importantly, a roadblock composed of GFP-lacI fused to four mCherries caused loss of heterochromatic silencing at HMR whereas smaller roadblocks did not. Previous work in the Gartenberg lab showed that the 4x mCherry construct blocks cohesin translocation in vivo. Using a colorimetric transcriptional silencing assay, I found that incorporating 4x mCherry roadblocks caused loss of transcriptional silencing of a reporter gene at HMR. Preliminary ChIP-qPCR data of the locus show that roadblocks decrease the level of cohesin at HMR, albeit slightly. Taken together these data suggest a role for cohesin in transcriptional silencing of heterochromatin in yeast.

Tumor Progression and Cell-Cell Coordination in 3D Breast Cancer Spheroids

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Breast cancer is the most frequent cancer in women and the second-leading cause of cancer -related deaths worldwide. Although our ability to diagnose cancer has improved, it remains challenging to predict whether a specific tumor will evolve to become metastatic, or whether it will remain a benign lesion. Thus, new studies of cancer progression are needed to predict patient-prognosis from the morphology of early-stage tumors and decrease cancer-related deaths.

Here, we take advantage of 3D engineered culture models and computational models of breast tumors, to identify the key parameters of the early tumor that

can be used to predict its dynamics and progression at later stages. We generate 3D breast cancer spheroids consisting of either epithelial-like or mesenchymal-like cells to examine dynamic changes in tumor-like anatomy and behavior. We characterize the individual cell migration within the tumor spheroids and identify both individual cell progression, as well as the cell proliferation and death in the different regions of the tumor. We are developing a 3D agent-based computational model to enable predictions of tumor progression from the morphology at earlier stages. The model consists of an initial, disordered network with embedded cells and accounts for cell migration, proliferation, and death within the tumor. We aim to use this combination of experimental and computational approaches to define the minimal set of parameters that can be used to predict tumor progression.

Reward Processing and Decision Making in Childhood Cancer Survivors: A Pilot Study

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Background: Chemotherapy-induced alterations in dopamine activity have been proposed as one plausible mechanism contributing to long-term cognitive impairment in cancer survivors. However, little is understood about how chemotherapy-induced neurotoxicity altered the neurocognitive functioning of the dopamine system. **Aims**: This study aims to evaluate the effect of chemotherapy on the functions of two dopaminergic neural targets, namely the anterior midcingulate cortex (aMCC) and the striatum, via electrophysiological and behavioral indices of reward processing and valence learning in childhood cancer survivors. **Methods**: We recruited seven childhood cancer survivors aged 6-17-year-olds (M = 12.29 years, SD = 3.73, Males = 3) who were at least one-year post-chemotherapy from the Rutgers Cancer Institute of New Jersey and seven age-and sex-matched controls from the local community of Northern New Jersey. Electroencephalography was recorded as subjects performed a computer-based T-maze task where they navigated a maze to find rewards. **Results**: The preliminary results showed that reward positivity (RewP), an electrophysiological signal reflecting the sensitivity of the aMCC to rewards versus absent of rewards, is reduced in the survivor group (M = -3.34μV, SD = 1.77) compared to the controls (M = -6.72 μV, SD = 3.24; p = 0.03, Cohen's d = -1.30). This finding suggested that the neural processes associated with the aMCC may potentially be affected in childhood cancer survivors. Furthermore, when performing the probabilistic selection task – a task that requires subjects to learn the probability of each stimulus resulting in a reward via trial-and-error, both groups showed comparable performance to learning from

positive feedback [accuracy: Survivor group: M = 74%, SD = 18; Control group: M = 72%, SD = 14; p = 0.81, d = -0.13]. However, the survivor group demonstrated lower accuracies to learning from negative feedback [accuracy: Survivor group: M = 61%, SD = 10; Control group: M = 75%, SD = 14; p = .06, d = 1.13], suggesting that survivors may be less effective in acquiring task-related information based on negative feedback. **Conclusion**: Taken together, this pilot study suggests differential neural and behavioral patterns between survivors and controls, pointing to the potential impacts of chemotherapy-related neurotoxicity on the neurocognitive functioning of the dopamine system in pediatric cancer survivors. The findings will be a first step toward identifying the long-term neurocognitive mechanisms underpinning chemotherapy-induced cognitive impairments. **Future Direction:** Given the limited sample size, increasing the participant survivor group is needed to establish the robustness of these results.

Elucidating the Role of LYN Src Kinase in DNA Repair

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The DNA damage response (DDR) is extremely crucial in maintaining genomic integrity. Failure to repair damaged DNA can result in the propagation of mutations and lesions that can contribute to tumorigenesis. Many key proteins, including kinases, are involved maintaining genomic stability, and their dysregulation leads to the progression and replication of unrepaired DNA, and ultimately, cancer. The poly (ADP-ribose) polymerase (PARP) is a DNA response protein that is transiently recruited to sites of DNA breaks and is also involved in the signaling and recruitment of other DDR proteins. ATM, another DNA damage response protein and serine/threonine kinase, is often responsible for initiating and maintaining the recruitment of other important proteins involved in DNA repair. In the DNA damage response, there is interplay and coordination between proteins that are recruited by both PARP and ATM, but what controls the coordination between these two proteins and their substrates is still to be precisely defined. In our preliminary work, we have found that LYN, a tyrosine kinase and signaling intermediate, may play a role in the coordination of response between PARP and ATM. Our data shows that LYN is recruited to sites of DNA damage in an ATM dependent manner, and that LYN potentially interacts with the tripartite motif-containing 33 (Trim33) during DNA repair. Trim33 is a PARP dependent protein that has been shown to interact with ALC1, a chromatin remodeler. We hypothesize that LYN serves as the signaling intermediate to potentially coordinate the removal of PARP and initiate the recruitment of ATM dependent proteins during DNA damage response. As the hypothesized agent of interaction between PARP and ATM signaling pathways in DNA repair, LYN can serve as a potential therapeutic target for cancer treatment.

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. 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. Specifically, the S-antigen of HBV (HBsAg) is a critical indicator of the infection status of the host, although little is known about what role it plays in dampening the immune responses that would otherwise effectively clear this virus. This project aims to clarify the effects of S-antigenemia on the adaptive immune system. This will involve examining the impact of HBsAg on CD8+ T-cell function both inside and outside the context of an HBV infection. We will infect humanized mice with adeno-associated viruses (AAV) expressing either an entire HBV virion or HBsAg alone, to determine the effects of HBsAg when it is isolated from other inflammatory components of HBV. By capturing antigen-specific T cells, we will quantitatively and qualitatively analyze the role of HBsAg in disrupting the CD8+ T-cell response. In addition to using flow cytometry to quantify CD8+ T cells and characterize their phenotype, we will use single-cell RNA sequencing (scRNA-seq) to dissect the ways in which T-cell signalling is disrupted by HBsAg by identifying the main signalling pathways disrupted by this antigen. By evaluating this, we will acquire a better understanding of how HBV interferes with the adaptive immune response, which will point us towards effective treatments capable of not just suppressing replication, but achieving permanent clearance of this virus.

Lipid Nanoparticles (Lnps) for the Targeted Delivery of Therapeutic Sirna to Treat Endometrial Cancer

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Endometrial cancers are the 5th leading cause of cancer death 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, decreasing quality of life and

healthcare associated expenses. Currently, nonsurgical interventions for the treatment of endometrial cancer are limited both in availability and in efficacy. 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 will develop lipid nanoparticles (LNPs) to deliver mouse double minute 2 (MDM2) siRNA as a treatment for endometrial cancer. Lipid nanoparticles are comprised of ionizable lipids and excipient ingredients mixed with nucleic acids; the use of LNPs increases cell uptake, circulation time, and stability in vivo. MDM2 is a powerful inhibitor of the p53 tumor suppressor protein that is overexpressed in endometrial cancer tissue. The silencing of MDM2 using siRNA induces apoptosis and suppresses migration of endometrial cancer cells resulting in decreased tumor burden. Towards this goal, we are first developing LNPs that can deliver siRNA to RL95-2 endometrial cancer cells expressing green fluorescent protein (GFP) because they express high levels of MDM2. We created a library of LNPs to discover LNP formulations that yield high GFP siRNA delivery to endometrial cancer cells. Using the high-performing LNPs, we are delivering MDM2 siRNA to evaluate the ability for LNPs to silence MDM2 expression and promote apoptosis. These experiments establish LNPs for siRNA delivery as a treatment for endometrial cancer. Moving forward, we will use these LNPs to deliver multiple siRNAs simultaneously, including siRNA to silence checkpoint inhibitors, as an immunotherapeutic approach to endometrial cancer.

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, suggesting its potential roles during tumor initiation. 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 CXCR4^{CKO} with MMTV-PYMT. Our preliminary data showed a delayed tumor onset in PYMT-CXCR4^{CKO} mice compared to PYMT-controls. These preliminary findings indicate that CXCR4+ macrophages and its macrophageal niche may involve in TIC-mediated tumor initiation.

The Macrophage-Endothelial Interface Regulates CAR T-cell Toxicities *In Vitro*

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Severe and life-threatening hyperinflammatory toxicities following Chimeric Antigen Receptor (CAR) T-cell therapy currently have no effective treatment options, rendering this otherwise life-saving therapeutic as a last-resort option for this critically ill patient population. Reducing the clinical burden of these toxicities may therefore increase accessibility and usage of this highly effective treatment. Preclinical models have identified macrophages as the primary source of the systemic inflammatory toxicity, yet a concurrent neurotoxicity remains refractory to interventions targeting macrophage inflammation. Clinical observations indicate that the vascular endothelium, particularly at the blood-brain-barrier, may drive both the neuroinflammation and systemic inflammation, yet the interplay of the vascular endothelium with inflammatory macrophages and neuronal cell types, its contribution to these inflammatory toxicities, and its potential as a target for risk-mitigating interventions, has yet to be explored.

To understand this multifactorial interaction and identify risk mitigation strategies, we designed and developed a multicellular culture system of macrophages and endothelial cells, stimulated by activated CAR T-cells. The model was designed to incorporate known risk factors for disease development and to recapitulate the pathophysiologic features of this clinical disease as quantitative metrics. We found that the interaction of macrophages and endothelial cells results in distinct pathophysiologic responses unseen in mono-culture conditions. Macrophage inflammation is directly dependent on endothelial activity, and the presence of macrophage inflammation is necessary to facilitate a breakdown in the endothelial barrier, highlighting the importance of this interaction, and the context-dependent manifestations of these cellular responses. Our data demonstrates the endothelium is a central player in this disease pathophysiology and interventions to protect the vasculature, in addition to targeting macrophage inflammation, is a potential risk mitigation strategy to ensure safe and efficacious delivery of CAR T-cell therapies.

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Systematic Examination of The Mechanisms of Cancer Associated Thrombosis
The effect of PAI-1 on Clot Structure and Fibrinolysis

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Pancreatic cancer (PC) has one of the highest mortality rates with a 5-year prognosis of only 5-10% with 12-36% of patients suffering from enhanced blood clotting and development of venous thromboembolisms (VTE). PC patients are proactively given anticoagulants in conjunction with chemotherapy treatments; however, this regiment is underused despite the exacerbated risk of VTE with traditional chemotherapy drugs. There are many unknowns in the mechanisms of what makes PC have this procoagulant effect, but it is thought that there are several factors in the plasma of PC patients that affect the coagulation cascade that causes the excessive clotting as well as reduced ability to break down the clot (fibrinolysis). For example, surplus tissue factor (TF) is secreted from the pancreatic tumor, which is the initiator for the blood clotting process and the formation of a dense fibrin network. This fibrin clot configuration impedes fibrinolysis due to the tightly woven fibrous strands leading to aggregation and lateral transection. There are factors that traditionally stimulate fibrinolysis, notably tissue plasminogen activator (tPA), which is usually found innately in a health body (internal fibrinolysis) or can be delivered as an anticoagulant to resolve a pre-existing blood clot (external fibrinolysis). Tumor necrosis factor alpha (TNF-a) is an additional factor secreted in excess from the pancreatic tumor, which promotes the production of plasminogen activator inhibitor (PAI-1). These latter two factors inhibit fibrinolysis, promoting further blood clotting. Here, we use a turbidimetric assay that allows us to measure internal lysis with increasing concentrations of PAI-1. As expected, we observed a slower rate of lysis (0.01825 vs 0.0007000 fraction of clot degraded per second, $p<0.0001$) and delayed time to 50% lysis (1008 vs 17965 seconds, $p<0.0001$) with increasing PAI-1 concentrations . Surprisingly, we observed a significantly slower rate of clot formation (0.03040 vs 0.009600 fraction of clot formed per second, $p<0.0001$) and increase in maximum optical density (0.1449 vs 0.2483, $p<0.0001$) with increasing PAI-1 concentrations. This led us to believe there was both a biochemical and structural change as a result of exogenously added PAI-1 that had not been observed before. Confocal microscopy identified no change in network density (25.59 vs 26.79 % area fraction, ns) while scanning electron microscopy (SEM) revealed an increase in diameter (82.60 vs 127.3 nm, $p<0.001$) for increasing PAI-1 levels. We propose PAI-1 alters clot dynamics both structurally and enzymatically.These results on the impact of PAI-1 can aid in the development of better clot degradation agents as well as a potential marker for pancreatic cancer to identify clotting.

The Role of IGF1R in Breast Cancer Adhesion and Escape from the Primary Tumor

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Mentored by: Dr. Teresa Wood

Breast cancer is the most common cancer in women after skin cancer, and basal-like breast cancers are particularly aggressive and difficult to treat. Growth factor receptors are known to play a prominent role in cancer progression, and one such receptor, the insulin-like growth factor receptor (IGF1R), has a controversial history in the context of breast cancer treatment. IGF1R overexpression promotes cancer cell proliferation and invasion; however, inhibitors against IGF1R failed clinical trials either due to no effect or at times making patient cases worse. This indicates that IGF1R may have tumor suppressor functions. Published studies from the Wood lab have shown that inhibiting IGF1R signaling is sufficient to convert basal-like mouse mammary tumors from a low to a high metastatic frequency. Although the exact mechanisms that permit metastasis in this model are under investigation, a major, consistent finding has been loss of cell adhesion due to IGF1R inhibition. Interestingly, cells taken from IGF1R-inhibited, highly metastatic tumors and injected into the tail vein seeded lung metastases that proliferated less than the control, wild-type IGF1R cells. These data indicate that IGF1R plays a dual role with opposing effects in the primary tumor and at sites of distant metastases. In in vitro studies with human, triple-negative, basal-like breast cancer cells, IGF1R inhibition causes loss of cell adhesion as measured by a real-time xCELLigence adhesion assay. Thus, we hypothesize that IGF1R, through loss of cell-cell or cell-ECM adhesion, permits escape from the primary tumor site, but inhibits proliferation after metastases are seeded. Determining the mechanisms behind IGF1R regulation of cancer cell release from the primary tumor site will elucidate downstream effectors that are better targets for drug development.

Establishing the Molecular Mechanisms Mediating Chromatin Architecture

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The human genome is organized in three-dimensional (3-D) space into a series of looped domains, 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). In addition to their architectural functions, BEs also have important genetic functions: they can block regulatory interactions between enhancers/silencers

in one TAD and genes in another TAD; they can also mediate long-distance regulatory interactions. 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, I used the fruit fly *Drosophila melanogaster* as a model system to investigate the mechanisms of TADs formation and BEs interaction. Through chromatin conformation capture technique micro-C and transgene assays, I found that BEs pair with each other and exhibit distinct partner preferences and orientation dependence. Such properties define the fundamental mechanisms of TADs formation and chromatin architecture. These findings shed light on the underappreciated causations of altering genome architecture during oncogenesis and tumor progression.

Epigenetic Reprogramming of Breast Cancer Dormancy

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Breast cancer cells (BCCs) can remain undetected in the bone marrow (BM) for extended periods, which correlates with patient relapse and poor prognosis. BC recurrence is attributed to the presence of cancer stem cells (CSCs), which share properties with non-malignant stem cells, have tumor-initiating capacity, and undergo dormancy, a process that conveys resistance to conventional treatments and immune evasion. To complicate the scheme of the disease, progenitor breast cancer cells (BCCs) can transition into dormancy and acquire CSC properties, facilitated by BM-niche cells such as mesenchymal stem cells (MSCs) as well as intrinsic cues. However, the exact mechanisms underlying BC dormancy remain elusive. To understand the processes involved in BC dormancy, we conducted RNA-sequencing studies on MSCs previously exposed to BCCs and their exosomes. Bioinformatic analyses revealed that BCCs dictate the release of the histone 3, lysine 4 (H3K4) methyltransferases (KMT2B and KMT2D) and DNA methyltransferase-1 (DNMT1) from MSCs to allow BC dormancy. Based on these findings we hypothesized that modifications of the DNA and H3K4 methylation landscape in BCCs regulate dormancy acquisition. First, we interrogated the role of H3K4 methylation and DNA methylation in BCC stemness by using the pharmacological inhibitors, MM102 and decitabine, respectively. Our findings indicate that inhibition of H3K4 methylation and DNA methylation decreases the CSC population. Loss-of-function studies targeting KMT2B, KMT2D, and DNMT1 resulted in an expansion of BCC progenitors and diminished the CSC population. Overall, the findings provide crucial insights into the epigenetic regulatory mechanisms underlying BC dormancy and how BCCs leverage BM microenvironmental cells to successfully seek refuge in the BM niche to evade treatment.

Novel Insights into the Interplay Between Viral Rta and Host Notch to Regulate Lytic Reactivation in Kaposi's Sarcoma-Associated Herpesvirus

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Kaposi's sarcoma (KS) is the most common cancer in HIV-infected individuals and its tumor progression is dependent on the lytic reactivation of its etiologic agent – Kaposi's sarcoma-associated herpesvirus (KSHV). KSHV also causes Primary Effusion Lymphoma (PEL), the lymphoproliferative disease Multicentric Castleman's Disease (MCD), and the newly discovered KSHV Inflammatory Cytokine Syndrome. Reactivation of KSHV from latency requires the viral protein, ***Replication and transcriptional activator (Rta)***, to form a complex with the host cell protein ***Recombination signal-Binding Protein for Jκ (RBPJ*κ). RBPJκ is the DNA binding component and primary target of the host oncogenic Notch signaling pathway, which is constitutively active in KS and PEL cells as well as in other cancers. The Rta/RBPJκ complex then binds and transactivates viral promoters to initiate a cascade of viral gene expression that leads to virus production and propagation. We have demonstrated that Rta is the only viral component necessary to drive this lytic switch – and while Notch activation seems to play an important role in optimal latent escape, Notch alone cannot reactivate KSHV. Still, Notch is necessary for KSHV pathogenesis and *in vitro* knockdown studies reveal severe abrogation of reactivation. Notably, although Rta and Notch have clearly distinguished functions, they both utilize sequence-specific RBPJκ binding to the KSHV genome. While there is very limited viral gene expression during latency, most KSHV oncogenes are expressed during reactivation when Rta and Notch function together. However, the mechanisms underlying how Rta and Notch specify transcriptional targets during reactivation remain unclear. *We believe that Rta and Notch intricately and cooperatively interplay to control KSHV reactivation via their mutual interaction with RBPJκ and other host cellular components to regulate promoter specific transactivation.*

In virus-negative cancers, activated Notch is known to stimulate DNA binding of RBPJκ to cellular genes; however, our data indicates that Rta, but not Notch, stimulates DNA binding of RBPϑκ to viral promoters. This dynamic binding of RBPJκ suggests Rta-Notch interactions may be critical in determining the viral latent-lytic switch. To this end, we performed a preliminary ChIP-seq screen of the KSHV-genome to identify set of host cellular proteins, or Motif Binding Proteins (MBPs), that are candidates to associate preferentially with RBPJκ binding during latency and reactivation. We plan to use our well-developed in vitro and in vivo promoter and virus reporter assays to characterize MBP participation in mediating interactions of Rta, NICD1, and RBPJk with DNA to specify transcriptional targets during lytic reactivation.

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Furthermore, while the isoform 1 of RBPJκ is required for reactivation, our preliminary studies reveal that alternatively spliced RBPJκ variants are abundantly expressed in KSHV-infected B cells. Two of these variants are completely novel and have not been previously indexed in gene expression repositories. While our original ChIP-seq studies could not distinguish the in vivo DNA binding capacities of these RBPJκ variants, our newer preliminary experiments suggest that they have functionally active binding sites on the viral genome. We successfully cloned cDNAs encoding these isoforms to examine their participation in Rta and NICD1 promoter transactivation and viral reactivation. We believe that these *non-canonical RBPJκ isoforms variably capacitate the Rta -mediated lytic switch via their differential binding to Rta and viral promoters.* Their characterization may reveal additional degrees of complexity in the Rta-Notch interaction to specify transcriptional targets and may help clarify inconsistencies in RBPJκ-dependent transcriptional specification studies reported in the literature. Thus, *by understanding how Rta and Notch function with RBPJκ in KSHV reactivation, we can learn more of the non-canonical Notch mechanisms underlying pathogenesis in various cancers, while potentially identifying participation of other novel host components.*

Structure-Activity Relationship Study of Tetrahydroisoquinoline-3-Carboxylic Acid Derivatives as Inhibitors of the Pd-1/Pd-L1 Immune Checkpoint Pathway

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Cancer immunotherapies, specifically immune checkpoint inhibitors (ICIs), have revolutionized cancer care and demonstrated durable survival benefits in patients across a wide range of solid and hematologic malignancies. While antibodies targeting PD-1 and PD-L1 are widely used in clinical practice, there are currently no FDA-approved small molecule ICIs. Small molecules offer an alternative therapeutic modality to the antibodies with potential for oral administration. Given that ICI monotherapy elicits responses in only 10-59% of patients in clinical trials, there is a strong impetus for the development of highly potent, orally bioavailable, small molecule ICIs suitable for use in combination with other oral anticancer agents. Here, we present our design, synthesis, and structure-activity relationship study of a series of 1,2,3,4-tetrahydroisoquinoline (THIQ)-3-carboxylic acid derivatives. The new inhibitors were generated by cyclizing the benzylamine to the ether linker of the (5-cyanopyridin-3-yl)methoxy moiety of our previously reported inhibitor **LH1305**. We found that inhibitors with appendages off the 1-position of the THIQ (e.g., **LH1388**, IC50 = 21.4 nM) resulted in greater inhibitory potency as compared to those with attachment on the nitrogen atom (e.g., **LH1352**, IC50

= 329 nM). **LH1388** is a promising compound for further optimization into potent inhibitors against the PD-1/PD-L1 immune checkpoint pathway.

Association Between Air Pollution and Mortality Among Older Women with Breast Cancer in the United States

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Background: The World Health Organization has described climate change as the "single biggest health threat facing humanity." Factors associated with climate change, such as air pollution levels, have been associated with increased risk for hospitalizations and death. Cancer survivors, especially when receiving active cancer treatment, are at higher risk for both acute and chronic health complications and, therefore, may be more vulnerable to the health impacts of climate change. This specific research evaluated the association between local air pollution levels and mortality among women with breast cancer. Air pollution was defined as particulate matter (PM) 2.5 and used the Environmental Protection Agency national annual PM2.5 standards (12μg/m3) to represent high PM2.5 exposure. **Methods:** Using SEER-Medicare data linked with a high-resolution predictive PM2.5 model by residence zip code (2007-2016) across the US, we designed a cohort of women ≥66 years with incident stage I-IV BC and assessed PM2.5 exposure, categorized as <8 (low), 8-12 (moderate) and >12 (high), during the year prior to the BC diagnosis. We assessed all-cause mortality within 5 years of BC diagnosis (ending at Dec 31, 2018). We fit multivariable Cox proportional hazard models to assess effects of PM2.5 exposure, adjusting for individual-level characteristics (demographics, tumor characteristics, comorbidities), neighborhood features, and state. **Results:** Among 86,139 women (mean age 75 years, 82% white, 52% stage I, 31% stage II, 9.9% stage III, 6.6% stage IV), the mean PM2.5 exposure was 9.2μg/m3, with 31%, 55%, and 14% exposed to low, moderate, and high PM2.5, respectively. We observed 19,979 deaths during follow-up of 336,440 person-years. Mortality incidence rates (per 1,000 py) were 53, 61, and 65. The mortality adjusted HRs for moderate and high PM2.5 were 1.02 (1.00-1.04) and 1.06 (1.04-1.08), respectively. **Conclusion and Next Steps:** Modern-day PM2.5 levels were associated with all-cause mortality among older women with BC, even at levels below US national standards. Further research is needed to evaluate the impact of climate change on the health of patients with cancer and approaches to mitigate adverse health outcomes. This research was supported by the NJCCR Postdoctoral Cancer Research Fellowship.

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Shortwave Infrared-Emitting, Albumin-Coated Nanoprobes for T Cell Targeting and Imaging

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Immune checkpoint inhibitors (ICIs) have revolutionized the field of oncology by utilizing a patient's own immune system to combat cancer. However, many patients do not respond well to the treatment. To minimize the physical and economic impact to the patient, there is a need to identify biomarkers that can inform on the response to ICIs. The presence of tumor infiltrating lymphocytes (TILs) has demonstrated good prognostic value in determining if a patient should receive ICIs. Current clinical methods to assess TILs, and more specifically the CD8+ cytotoxic T cells (CTLs) responsible for mounting an attack against cancer cells, involve invasive biopsies and immunohistochemistry, which suffer from a lack of real-time feedback. Here, we utilize rare earth (Re) metal-based nanoparticles encapsulated in human serum albumin, termed rare earth albumin nanocomposites (ReANCs), that emit shortwave infrared (SWIR) light, allowing for non-invasive, deep-tissue imaging and high signal-to-noise ratios compared to visible or near infrared fluorescence probes. In this study, we report on the ability to conjugate antibodies to the albumin shell of ReANCs to target mouse CTLs in vitro. Conjugation of the anti-CD8 antibody (clone 53-6.7) or an isotype control (clone 2A3) was performed using maleimide chemistry. Target specific binding was validated by flow cytometry as a measure of increased uptake of particles by CTLs. Our results demonstrate that anti-CD8-conjugated particles effectively bind to T cells without affecting effector function in vitro. Next, we explored the ability of ReANCs to non-invasively image the immune burden around a mammary fat pad murine tumor in vivo. SWIR imaging revealed distinct signal profiles depending on the antibody ligand conjugated to the ReANCs administered to the mice. Future studies will explore the use of CTL-targeted SWIR-emitting ReANCs to stratify populations that would or would not respond to ICIs based on real-time imaging of the tumor-immune burden.

Significance of Transcriptional State Dynamics in Urothelial Bladder Carcinoma

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Intra-tumor heterogeneity contributes towards treatment failure and poor survival in urothelial bladder carcinoma (UBC) patients, but underlying drivers are poorly understood. Analysis of single cell transcriptomic data from UBC patients suggests that intra-tumor transcriptomic heterogeneity is, partly due to, admixtures of tumor cells in epithelial and mesenchymal-like transcriptional states, which covary with other cancer hallmarks. Transition between these cell states likely occurs within and between tumor subclones, adding a layer of phenotypic plasticity and dynamic heterogeneity beyond genetic variations. 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. Nutrient limitation, as in large tumors, and radiation treatment perturb the cell-state dynamics, initially selecting for a transiently resistant phenotype and then reconstituting heterogeneity and growth potential, facilitating adaptive evolution. Our data suggests that transcriptional state dynamics contributes towards phenotypic plasticity and non-genetic intra-tumor heterogeneity, modulating the trajectory of disease progression and adaptive treatment response in UBC.

Manipulating Fibronectin Extracellular Matrix to Understand Vascular Fibrosis

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The recruitment of a vascular supply has long been hailed as a crucial step in cancer progression, establishing a blood supply to support metabolic demand and providing a potential route of metastasis. Solid tumor vessels are leaky and fibrotic, features that likely promote metastasis and interfere with drug delivery. Tumor vasculature is highly reactive for fibronectin (FN), an extracellular matrix (ECM) protein that increases tumor cell migration and invasion and is the primary structural component of de novo matrix assembly. FN binds endothelial cell receptors that can modulate cell behavior, raising the possibility that FN accumulation around endothelial cells in tumor vasculature could be hindering endothelial cell barrier function and promoting leakiness. To investigate endothelial cell matrix accumulation, we have established a co-culture setup to study ECM contributions by multiple cell types.

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Confocal microscopy examination of endothelial cell matrix demonstrates that endothelial cells secrete and deposit FN matrix basally when cultured on laminin, suggesting that increased FN deposition will separate endothelial cells from the laminin substrate, increasing the FN:laminin ratio available for receptor binding and thus impacting matrix-derived signaling cues. To manipulate FN matrix deposition, we have generated peptides through phage display that bind the assembly domain of FN. We have discovered peptides that can be used to label FN matrix in vitro, increase FN matrix, or decrease FN matrix assembly. These novel reagents and co-culture techniques will be crucial to understanding how endothelial cell matrix accumulates and impacts endothelium barrier function.

Neighborhood Archetypes and Cardiovascular Health Among Black Breast Cancer Survivors in the Women's Circle of Health Follow-Up Study

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Background: As a record high number of breast cancer (BrCa) survivors live in the United States, understanding multilevel factors affecting survivorship including cardiovascular health (CVH) becomes a public health priority. Prior studies tend to assess single neighborhood measure without considering their complex interacting impact on CVH and cancer outcomes. **Objective**: We used Latent Class Analysis (LCA) to characterize neighborhood social and built environment archetypes where BrCa survivors reside in the Women's Circle of Health Follow-Up Study (WCHFS), a population-based prospective study of Black BrCa survivors in New Jersey. **Methods**: The current study included 713 participants diagnosed between 2012-2017 who completed a home interview ~24 months post diagnosis. The CVH score (range: 0-14) was summed across the seven individual components (BMI, smoking, physical activity, diet, blood pressure, glucose level and cholesterol); higher score indicates better CVH. Residential addresses of participants were linked to tract-level social and built environment features. We used LCA to generate neighborhood archetypes based on 16 tract-level indicators on: % race/ethnicity (Black, Hispanic, White, Asian), proportion foreign born, density of supermarkets, food stores other than supermarkets, fast food restaurants, restaurants other than fast-foods, physical activity facilities, walkable destinations, green space, religious institutions, and health care facilities. **Results**: The LCA model with four archetypes had the lowest AIC and highest entropy and provided archetype interpretations that were the most meaningful. Archetypes were named based on their most relevant characteristics as: 1) Urban/Multi race&ethnicity/High SES; 2) Urban/High %Black/Low SES; 3) Suburban/Low Resources/High %Black and 4) Suburban/Low Resources/

Multi race&ethnicity/High SES. The majority of the Black BrCa survivors in our sample reside in the Urban/High %Black/Low SES archetype (42%). Further, participants living in the Urban/High %Black/Low SES archetype had the lowest mean CVH score whereas women in the Urban/Multi race&ethnicity/High SES showed the highest CVH score (7.19±2.0 and 7.96±2.2, respectively). **Conclusion**: Women in the Urban/High %Black/Low SES archetype had worse CVH compared to women in the other urban and suburban archetypes. Improved understanding of neighborhood context in where Black BrCa survivors reside is critical to guide public health policy for cancer health equity.

Hepatitis B Virus Integrations into KMT2B Drive Hepatocellular Carcinoma

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Rutgers University

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.

"Hot Topics" Panel: Trends in 2022 and Beyond

Shawna Hudson, Ph.D.
(Moderator)
Shawna Hudson, Ph.D. is Professor and Research Division Chief in the Department of Family Medicine and Community Health and founding director of the Center Advancing Research and Evaluation for Patient-Centered Care (CARE-PC) 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 for the Community Engagement Core of the NJ Alliance for Clinical and Translational Science (NJ ACTS) which is a Clinical and Translational Science Award (CTSA) consortium between Rutgers University, Princeton University and the New Jersey Institute of Technology. Dr. Hudson is internationally known for her NIH funded research that examines long-term follow-up care for cancer survivors and their transitions from specialist to primary care, and has authored and co¬authored numerous research papers and book chapters.

Patricia Doykos, Ph.D
Patricia Doykos, Ph.D. serves as Director of the Bristol-Myers Squibb Foundation whose mission is to promote health equity and improve the health outcomes of populations disproportionately affected by serious diseases and conditions. Patricia works on health strategy and evaluation for the Foundation overall and currently leads two national grant programs, *Specialty Care for Vulnerable Populations*® and *Together on Diabetes*®*: Communities Uniting to Meet America's Diabetes Challenge*. She has also developed and led U.S. and international grant making and public-private partnership programs for women's health, cancer, serious mental illness and global HIV/AIDS. Currently, she serves on the board of Grantmakers in Health, the Health Working Group of the Social Impact Exchange, the Steering Committee of PolicyLink's Institute for Health Equity and chairs the Board of the new Center for Health Equity at Dartmouth-Geisel Medical School.

"Hot Topics" Panel: Trends in 2022 and Beyond

Jane Flint, Ph.D.
Jane Flint, Ph.D. is a Professor Emerita of Molecular Biology at Princeton University. Dr. Flint's research focuses on investigation of the molecular mechanisms 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.

Li Li, Ph.D.
Dr. Lis 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 from Novartis. In addition, he has co-authored may articles on toxicology innovation in research journals.

Peter Cole, M.D.
Peter Cole, MD is the Embrace Kids Foundation Endowed Chair in Pediatric Hematology/Oncology, Chief of the Pediatric Hematology/Oncology Service Line for the Rutgers Barnabas Health System, a tenured Professor of Pediatrics at Rutgers Robert Wood Johnson Medical School, and Director of the New Jersey Center for Pediatric Cancer and Blood Disorders Research. His research focuses on improving therapy for children, adolescents, and young adults with cancer and blood disorders. He has led international clinical trials testing novel chemotherapy and immunotherapy regimens in collaboration with the Children's Oncology Group. His NIH-funded translational research focuses on better understanding, and preventing, the toxicity caused by chemotherapy, with an emphasis on chemotherapy-induced cognitive impairment. Dr. Cole is fully committed the academic development of the next generation of innovative clinicians and scientists, with a track record of mentoring students, trainees, and junior faculty who have gone on to successful academic careers.

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 is the 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 volunteer service to the Morristown Medical Center, and in 2017 he was the Medical Honoree of the American Cancer Society for northwest New Jersey. Most recently in 2019 he was honored by The Summit Medical Group at their annual gala for his community volunteerism.

Dr. Kathleen Scotto

Vice-Chair

Dr. Scotto is currently Vice-Chancellor for Research and Research Training, Rutgers Biomedical and Health Sciences, and Vice 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.

Dr. Wendy Budin

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.

Dr. Generosa Grana

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.

Dr. Shawna Hudson

Dr. Hudson is professor and research division chief in the Department of Family Medicine and Community Health and founding director of the Center Advancing Research and Evaluation for Patient-Centered Care (CARE-PC) 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 Healh 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 Translational Science (NJACTS) which is a Clinical and Translational 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 transitions from specialist to primary care and has authored and coauthored numerous research papers and book chapters.

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

Loletha C. Johnson, MSN, RN
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.

Dr. Li Li
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 from Novartis. In addition, he has co-authored many articles on toxicology innovation in research journals

Christine Schell
Christine Schell is currently the manager of the NJ 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.

Dr. Anna Marie Skalka
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 sr. vice president for basic science from 1987 until 2008. She received a PH.D. degree in microbiology from New York University Medical School. Dr. Skalka has also been deeply involved in state, national, and international advisory groups concerned with the 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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"There's always hope beyond what you see."

Cora Connor
Caregiver

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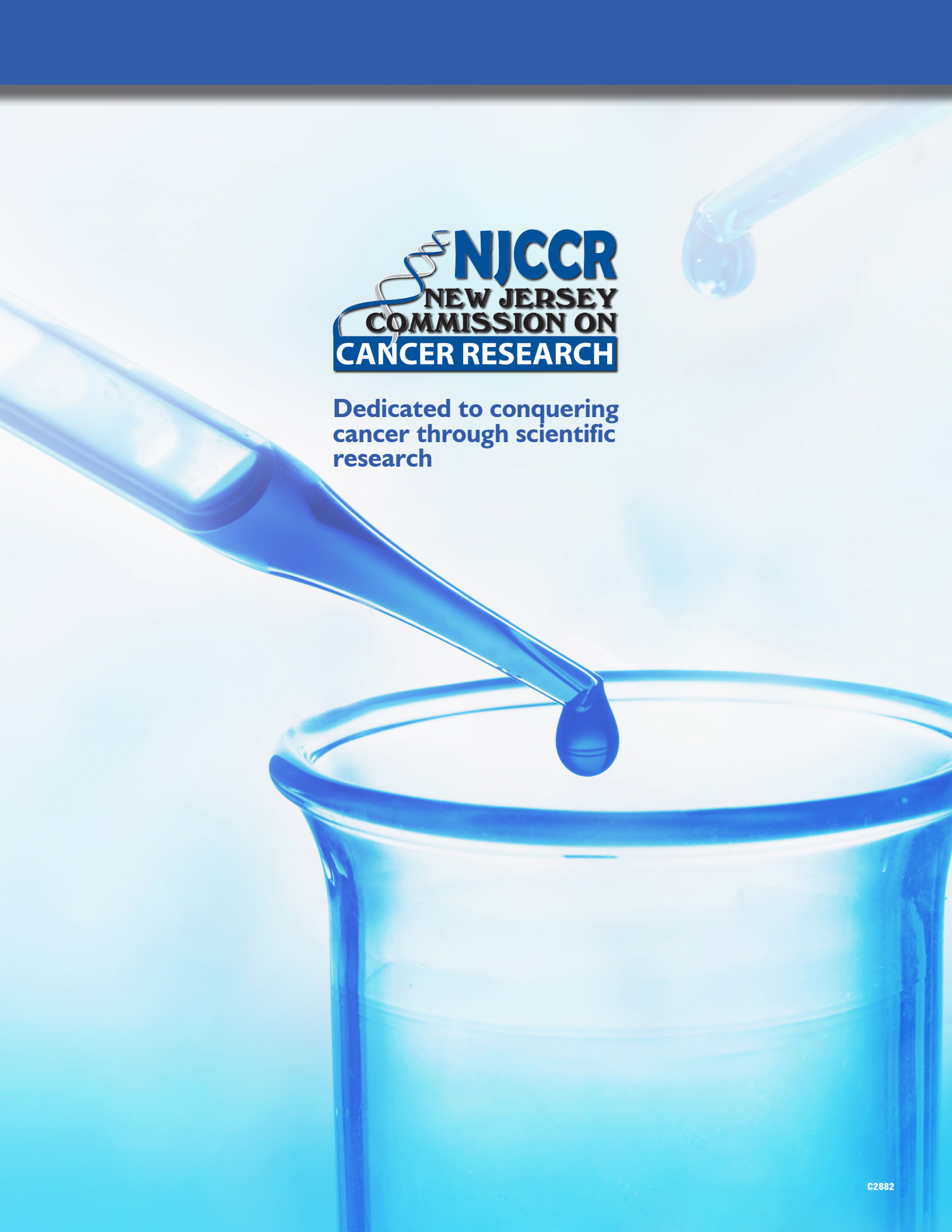
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