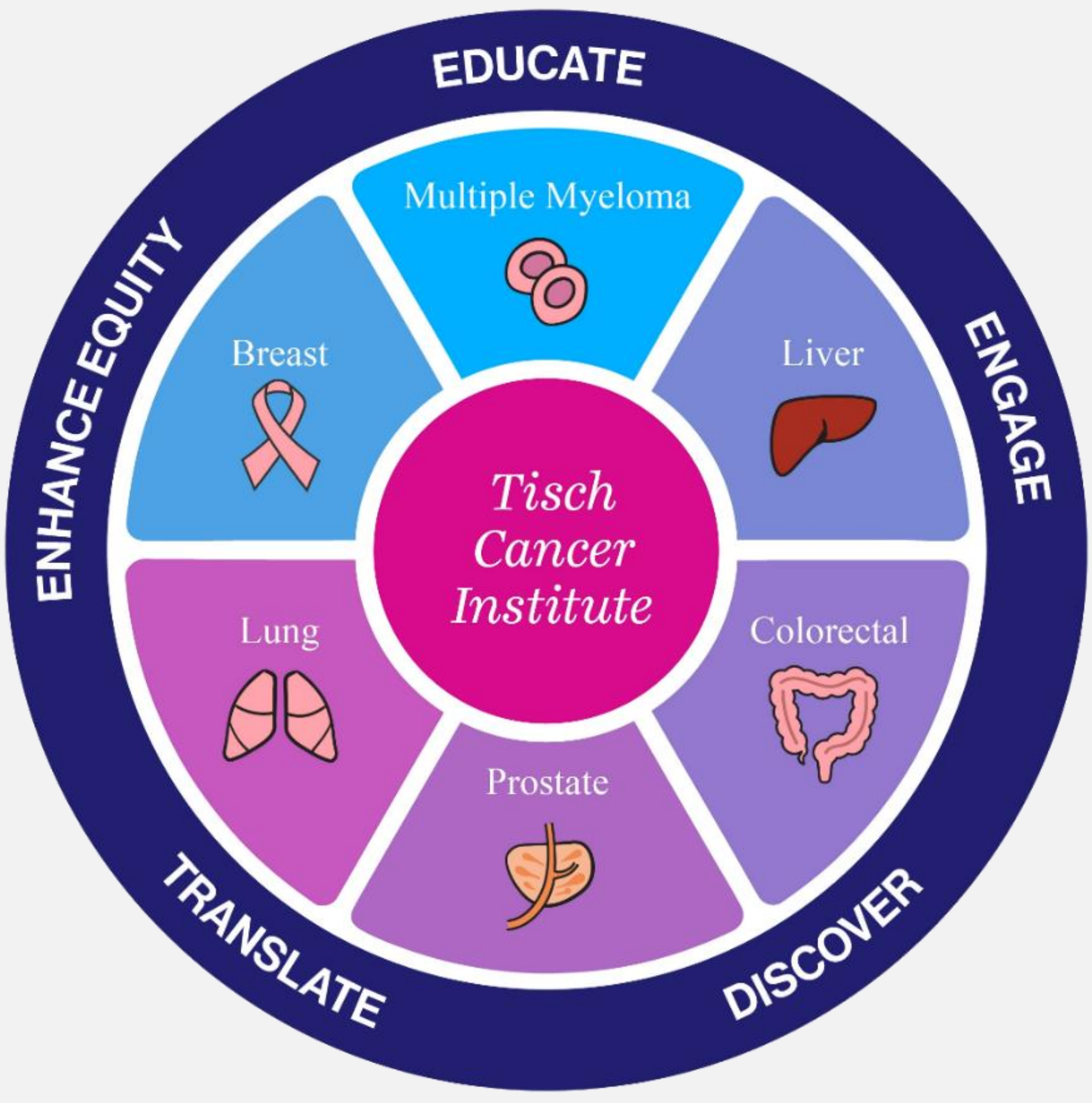
The Tisch Cancer Institute Scientific Retreat

December 6, 2024

8:30am-6:00pm

Celebrating 10 Years of NCI Cancer Designation

New York Academy of Medicine



Mount Sinai *The Tisch Cancer Institute*

The Tisch Cancer Institute Scientific Retreat

December 6, 2024 | 8:30am-6:00pm

Celebrating 10 Years of NCI Cancer Designation

New York Academy of Medicine

AGENDA

TIME	SESSION	PRESENTER(S)	TITLE
8:30 AM	**REGISTRATION AND BREAKFAST**		
9:00 AM	Opening Remarks	Ramon Parsons	Overview and Future
9:25 AM	Session 1: Cancer Prevention and Control	Emanuela Taioli	Cancer Prevention and Control Updates
9:45 AM		Keith Sigel	Anal Cancer Screening in High-Risk Populations
10:00 AM		Deborah Marshall	Improving sexual function in female and LGBTQ+ cancer survivors through the lens of functional anatomy
10:15 AM	Session 2: Community Outreach and Engagement	Melissa Mazor & Sarah Miller	Community Outreach and Engagement
10:35 AM		Karen Hubbard (City College of NY)	DISRUPT's Community Scientist Institute (CSI)
10:50 AM		Colette Smith	Community Scientist
11:05 AM	**BREAK**		
11:20 AM	Session 3: Cancer Mechanisms	Emily Bernstein	Cancer Mechanisms Updates
11:40 AM		Franco Izzo	Mapping genotypes to chromatin accessibility profiles in single cells
11:55 AM		Poulikos Poulikakos	Novel strategies to target oncogenic signaling for cancer treatment
12:10 PM	Session 4: Training and Education	Janice Gabrilove	Exploring the Biology and Clinical Applications of Granulocyte Colony Stimulating Factor: From Hematopoiesis to Therapeutic Innovations
12:30 PM		Camila Vicioso	The role of mannose in MASH-HCC progression
12:35 PM		Erica Camacho & Joshua Dawson	Does Where We Live Impact Our Ability To Complete A Quality of Life Screener?
12:40 PM		Kenneth Li	Endothelial-stellate cell crosstalk underlies fibrosis resolution in liver
12:45 PM		Ji Yoon Yoon	Targeted Approach to Upper Gastrointestinal Cancer Screening
12:50 PM		Julia Blanter	PI3King the Right Partner: Capivasertib and Durvalumab in Hormone Receptor+ Breast Cancer
12:55 PM		Stephanie Tuminello	Immune Genetic Susceptibility and Cancer Risk in a Diverse Population
1:00 PM	**LUNCH**		
2:00 PM	Session 5: Cancer Immunology	Nina Bhardwaj	Cancer Immunology Program Updates
2:20 PM		Alice Kamphorst	Modulating costimulation of PD-1+ CD8 T cells to improve function
2:35 PM		Robert Samstein	Understanding the immunology of pre-cancers towards immune prevention strategies
2:50 PM	Session 6: Cancer Clinical Investigation	Matthew Galsky	Cancer Clinical Investigation Program Updates
3:10 PM		Thomas Marron	Un-hijacking the immune response to cancer
3:25 PM		Ernesto Guccione	Precision medicine in solid tumors
3:40 PM		Stephanie Blank & Elisa Roura	Clinical Trials Patient Experience
3:55 PM	Closing Remarks	Ramon Parsons	
4:00 PM	Poster Session/Cocktail Hour		
6:00 PM	**END**		

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WELCOME

MESSAGE FROM THE DIRECTOR

It is my pleasure to celebrate a remarkable milestone for our Institute: 10 years as an NCI-designated Cancer Center! This achievement reflects the dedication, innovation, and excellence of our entire team—researchers, clinicians, staff, fellows, and students—who have worked tirelessly to advance cancer care, research, and education.

Today's agenda highlights our mission to accelerate the prevention and treatment of cancer, improving the lives of cancer patients and their families in our diverse communities.

I look forward to seeing all of you today at this all-day retreat that is concluding with the poster session and Holiday Reception. Thank you for being a vital part of our journey. Here's to the next decade of breakthroughs and impact!

ABOUT US

The Tisch Cancer Institute was established in 2008 through the generosity of James and Merryl Tisch. It is currently led by Director Ramon Parsons, MD, PhD, and was designated a National Cancer Institute-Designated Cancer Center first in 2015, and again in 2020. With direct cancer-related funding of over $60 million, The Tisch Cancer Institute has fostered four collaborative cancer research programs to advance basic, clinical, and population health cancer research.

- Cancer Clinical Investigation
- Cancer Immunology
- Cancer Mechanisms
- Cancer Prevention and Control

The Institute's cancer research programs are supported by seven shared resources: Bioinformatics for Next Generation Sequencing, Biorepository and Pathology, Biostatistics, Cancer Genomics Technologies, Flow Cytometry, Human Immune Monitoring Center, and Microscopy and Advanced Bioimaging.

The Institute's Clinical Research Support Unit, which includes an Early Phase Trials Unit, provides the infrastructure to conduct novel, investigator-initiated protocols developed by our researchers and supported by our staff members.

https://icahn.mssm.edu/research/tisch

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SPEAKERS

Emily Bernstein, PhD
Professor, Cancer Mechanisms Co-Leader
Department of Oncological Sciences

Emily Bernstein, PhD, Professor of Oncological Sciences and Dermatology, is Co-leader of the Cancer Mechanisms Research Program at The Tisch Cancer Institute. As such, Dr. Bernstein facilitates basic research on genetic, epigenetic, biochemical, and developmental pathways that drive cancer initiation and progression, and fosters intra- and inter-program collaborations that accelerate the development of novel, targeted therapies for cancer.

Dr. Bernstein studies epigenetic regulation of gene expression in cancer and development, with the long-term goal of understanding the chromatin changes that take place at the molecular level during the transformation process of normal cells to cancer cells. Her team studies melanoma, breast cancer, and neuroblastoma.

Dr. Bernstein regularly teaches courses on cancer biology and serves on numerous PhD thesis committees at the Icahn School of Medicine at Mount Sinai. She is a permanent member of the Cancer Genetics Study Section of the NIH Center for Scientific Review and serves as a reviewer for additional grant foundations.

Session 3: Cancer Mechanisms
“Cancer Mechanisms Updates”

https://profiles.icahn.mssm.edu/emily-bernstein

Nina Bhardwaj, MD, PhD
Professor of Medicine, Hematology and Medical Oncology; Urology
Department of Hematology and Oncology
The Tisch Cancer Institute

Nina Bhardwaj, MD, PhD, is a Professor of Medicine (Hematology and Medical Oncology) and Urology. She is the Director of Immunotherapy, Medical Director of the Vaccine and Cell Therapy Laboratory, and Co-Director of the Cancer Immunology Program at The Tisch Cancer Institute. Additionally, she holds the Ward Coleman Chair in Cancer Research.

Dr. Bhardwaj has made seminal contributions to human dendritic cell biology, specifically with respect to their isolation, subset discovery, immunobiology, antigen presenting function, and use of vaccine adjuvants in humans. She developed Toll Like Receptor agonist- and dendritic cell-based vaccines for the treatment of both cancer and infection in several investigator-initiated studies and has pioneered neoantigen vaccine studies at The Tisch Cancer Institute. Dr. Bhardwaj translates basic science advancements into clinically relevant patient trials.

Dr. Bhardwaj’s honors include Scientific American’s Top 50 (2004), the Frederick W. Alt Award (2015), the Jacobi Medallion Award Recipient, Icahn School of Medicine at Mount Sinai (2020), and AAISCR Lifetime Achievement in Cancer Research (2022). She was named ESMO’s Immuno-Oncology Awardee (2022), SITC Fellow (2023), and Mount Sinai Innovation Partner’s Inventor of the Year (2024) and was recently inducted into the National Academy of Medicine.

Beyond her research, she is a senior editor for Cancer Immunology Research and Frontiers in Immunology. She served on the Board of Directors for AACR and is a member of the Scientific Advisory Council of the CRI.

Session 5: Cancer Immunology
“Cancer Immunology Program Updates”

https://profiles.icahn.mssm.edu/nina-bhardwaj

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SPEAKERS

Stephanie Blank, MD
Professor, Obstetrics, Gynecology and Reproductive Science
Director of Gynecologic Oncology, Mount Sinai Health System

Stephanie Blank, MD, is a gynecologic oncologist and serves as the Director of Gynecologic Oncology for the Mount Sinai Health System, Co-Director of the Center of Excellence for Gynecologic Cancer, and Associate Director of The Tisch Cancer Institute for Women's Cancers.

Dr. Blank primarily cares for women with ovarian, uterine, and cervical cancer and for those who are at an increased genetic risk for these types of cancer.

Session 6: Cancer Clinical Investigation
"Clinical Trials Patient Experience"

https://profiles.icahn.mssm.edu/stephanie-v-blank2

Julia Blanter, MD, MSCR
Fellow
Department of Medical Oncology

Dr. Julia Blanter, MD, MSCR, is the current chief fellow in Hematology and Medical Oncology at Mount Sinai. She has spent her training focusing on focusing on breast oncology and early phase clinical trials. She has a particular interest in immunotherapy in hormone-receptor positive breast cancer.

Session 4: Training and Education
" PI3King the Right Partner: Capivasertib and Durvalumabin Hormone Receptor+ Breast Cancer"

SPEAKERS

Erica Camacho, MS
Medical Student
Touro College of Osteopathic Medicine

Erica Camacho, a fourth-year medical student at Touro College of Osteopathic Medicine, is passionate about addressing healthcare disparities. This summer, she conducted research at Mount Sinai's Tisch Cancer Institute, focusing on how a patient's zip code influences disparities in Social Determinants of Health (SDOH) screener completion rates among oncology patients across New York City. With a background in research and community engagement, Ms. Camacho aims to identify barriers to care and implement solutions that promote health equity. She plans to leverage her experiences to advocate for underserved populations as a future community-centered physician.

Session 4: Training and Education
" Does Where We Live Impact Our Ability To Complete A Quality of Life Screener?"

Joshua Dawson, BS
Medical Student
Columbia University

Joshua Dawson, a fourth-year medical student at Columbia University, is dedicated to advancing health equity through research and mentorship. A native of Federal Way, Washington, he earned his B.S. in Cellular Biology from the University of Washington in 2018 before conducting diabetes research at the NIH as a Health Disparities Fellow. At Columbia, Joshua co-founded PUSH (Pick Up Sports and Health), empowering youth in Washington Heights and Harlem to pursue health careers, and served as President of the Black and Latino Student Organization. Currently, he is a WINN CIPP Fellow at Mount Sinai Tisch Cancer Institute in the Mazor Group, pursuing a career in Anesthesiology.

Session 4: Training and Education
" Does Where We Live Impact Our Ability To Complete A Quality of Life Screener?"

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SPEAKERS

Janice Gabrilove, MD
Professor
Department of Medicine

Janice Gabrilove, M.D. is The James F. Holland Professor of Medicine, and the Tisch Cancer Institute Associate Director for Education & Training. The recipient of patents for 2 FDA approved myeloid leukemia drugs and for the discovery of human G-CSF, she was the first to demonstrate the ability of G-CSF to accelerate recovery from myelosuppression and mobilize progenitors into the blood. A member of the American Society of Clinical Investigation, and currently serves aa a member of the LLS National Board of Directors. Dr. Gabrilove graduated from Icahn School of Medicine at Mount Sinai where she held the highest academic standing.

Session 4: Training and Education
“Exploring the Biology and Clinical Applications of Granulocyte Colony Stimulating Factor: From Hematopoiesis to Therapeutic Innovations”

https://profiles.icahn.mssm.edu/janice-l-gabrilove

Matthew Galsky, MD
Professor
Department of Medicine

Dr. Galsky is a medical oncologist focused on the care of patients with bladder cancer. He completed medical oncology fellowship and subsequently joined the faculty. In 2010, he joined the faculty at the Tisch Cancer Institute/Mount Sinai School of Medicine as Director of Genitourinary Medical Oncology. He is currently a Professor of Medicine, Associate Director for Translational Research, and Co-Leader of the Cancer Clinical Investigation Program. Dr. Galsky’s research has focused team science-based approaches dissecting the mechanistic underpinnings of response and resistance to novel bladder cancer therapies as well as on the development of individualized risk-adapted treatment strategies.

Session 6: Cancer Clinical Investigation
“Cancer Clinical Investigation Program Updates”

https://profiles.icahn.mssm.edu/matthew-galsky

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SPEAKERS

Ernesto Guccione, PhD
Professor
Department of Oncological Sciences

Dr. Ernesto Guccione was born in Italy, and graduated from Bologna University, followed by a PhD at ICGEB in Trieste. In 2004, Dr. Guccione joined the Amati Lab for a post doc to study basic mechanisms of transcription and epigenetic regulation in cancer. In 2008, he moved to Singapore to start his lab and since 2019 he is a Professor at Mount Sinai.
He has a long-standing interest in understanding basic mechanisms of transcriptional and post-transcriptional regulation in order to identify therapeutic opportunities in oncology.

Session 6: Cancer Clinical Investigation
“Precision medicine in solid tumors”

https://profiles.icahn.mssm.edu/ernesto-guccione

Karen Hubbard, PhD
Professor
Department of Biology, CCNY

Dr. Hubbard is a Professor in the Biology Department and is the CCNY PI for the U54 CCNYMSK Partnership for Research, Education, and Community Outreach. She has been a PI for the overall U54 program since 2008. She is a co-PI of Advancing Inclusion, Diversity, and Equity in STEM (AIDE-STEM), which promotes advancement of BIPOC and women in STEM and is funded by the National Science Foundation. All these programs have a focus on faculty career development in science and engineering. Recently, she received grant support from Stand Up to Cancer to address barriers for BIPOC patients to enroll in clinical trials. This project has developed a Community Scientist Institute program at CCNY to train community advocates and partners in research approaches for clinical trials.

Session 2: Community Outreach and Engagement
“DISRUPT's Community Scientist Institute (CSI)”

SPEAKERS

Franco Izzo, PhD
Assistant Professor
Department of Oncological Sciences

Dr. Izzo’s research is focused on understanding how somatic mutations are translated into cellular phenotypes in clonal hematopoiesis and hematological malignancies. One of the main challenges of studying the impact of somatic mutations in human blood samples is the presence of an admixture of wild type and mutated cells. To resolve this challenge, Dr. Izzo has developed multi-modal single-cell sequencing technologies that allow for simultaneous capture of genotypes together with transcriptional or chromatin accessibility profiles at single cell resolution. In this manner, analytical identification of wild type and mutated cells allows performing intra-sample comparisons to uncover the effects of somatic mutations, directly in patient samples.

Session 3: Cancer Mechanisms
“Mapping genotypes to chromatin accessibility profiles in single cells”

https://profiles.icahn.mssm.edu/franco-izzo

Alice O. Kamphorst, PhD
Assistant Professor
Department of Immunology and Immunotherapy

Dr. Kamphorst’s research program focuses on T cell biology and aims to determine how costimulation, cell interactions, and other factors in the microenvironment influence T cell function in infection and cancer.

Session 5: Cancer Immunology
“Modulating costimulation of PD-1+ CD8 T cells to improve function”

https://profiles.icahn.mssm.edu/alice-o-kamphorst

SPEAKERS

Kenneth Li, BA
MD/PhD Candidate
Department of Liver Diseases

Kenneth Li is an MD/PhD student at Icahn School of Medicine at Mount Sinai. He is investigating the mechanisms underlying spontaneous regression of liver fibrosis.

Session 4: Training and Education
“ Endothelial-stellate cell crosstalk underlies fibrosis resolution in liver”

Thomas Marron, MD, PhD
Director, Early Phase Trials Unit
Department of Hematology and Oncology

Thomas Marron, MD, PhD is the Director of the Early Phase Trials Unit (EPTU) at the Tisch Cancer Institute, and a Professor of Immunology and Immunotherapy as well as Professor of Medicine, Hematology and Medical Oncology at Icahn School of Medicine at Mount Sinai. He holds a PhD in immunology, and is a practicing thoracic medical oncologist. His research program focuses on development of novel immunotherapies and combinatorial therapeutic approaches for solid tumors. Alongside EPTU he leads a translational oncology bench-to-bedside-to-bench program in partnership with Miriam Merad and her laboratory focused on developing novel therapeutic approaches, and repurposing available biological therapies.

Session 6: Cancer Clinical Investigation
“Un-hijacking the immune response to cancer”

https://profiles.icahn.mssm.edu/thomas-u-marron

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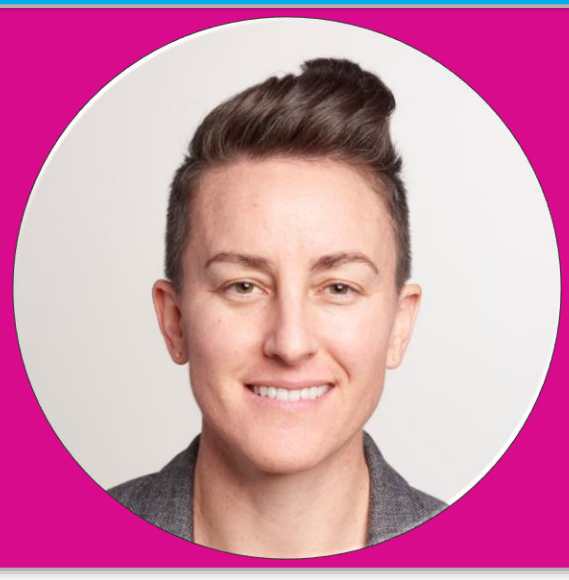
SPEAKERS

Deborah Marshall, MD, MAS
Assistant Professor
Department of Radiation Oncology/
Population Health Science Policy



Deborah Marshall is a Radiation Oncologist and an Assistant Professor in the Departments of Radiation Oncology and Population Health Science and Policy at the Icahn School of Medicine at Mount Sinai. In addition to providing advanced radiotherapy to a diverse population of cancer patients at the New York Proton Center, Dr. Marshall directs a NIH-funded laboratory aiming to advance the understanding of the impacts of radiotherapy on sexual function in female and gender-expansive cancer patients across the lifespan.

Session 1: Cancer Prevention and Control
“Improving sexual function in female and LGBTQ+ cancer survivors through the lens of functional anatomy”

https://profiles.icahn.mssm.edu/deborah-catherine-marshall2

Melissa Mazor, PhD, MS, RN
Assistant Professor
Department of Medicine

Dr. Melissa Mazor is an Assistant Professor in the Department of Medicine, Assistant Director of the Community Outreach and Engagement Program and Co-Director of the Supportive Services Center of Excellence at the Tisch Cancer Institute. Her program of research focuses on advancing equity in supportive and palliative care for underserved individuals with cancer. She is currently funded through National Cancer Institute and American Cancer Society. As Assistant Director of TCI, she co-leads the TCI community scientists’ group, community advisory board, and inaugural TCI Sparked program, a pathway program for high school students underrepresented in science.

Session 2: Community Outreach and Engagement
“Community Outreach and Engagement”

https://profiles.icahn.mssm.edu/melissa-mazor

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SPEAKERS

Sarah Miller, PsyD
Associate Professor
Department of Population Health Science and Policy

Dr. Sarah Miller is a licensed clinical psychologist and health equity research at the Icahn School of Medicine at Mount Sinai. She is a member of the Center for Behavioral Oncology and is the co-Director of the Program for Antiracism and Equity in the Department of Population Health Science and Policy. She is also the Director of Faculty Diversity and Inclusion within the Center for Scientific Diversity. She is actively involved in the Society of Behavioral Medicine's Health Policy Committee and is committed to proposing and supporting policy changes that promote health equity.
Dr. Miller's program of research focuses on identifying system- and patient-level barriers to cancer screening uptake and identifying interventions to overcome those barriers. She is currently spearheading research initiatives that are centered on developing and testing digital health solutions designed to increase cancer screening uptake among medically underserved and socioeconomically disadvantaged patient populations. Her research has been supported by the National Cancer Institute, the National Institute on Aging, and the American Cancer Society.

Session 2: Community Outreach and Engagement
"Community Outreach and Engagement"

https://profiles.icahn.mssm.edu/sarah-miller

Poulikos Poulikakos, PhD
Professor
Department of Oncological Sciences

Dr. Poulikakos is a Professor in the Department of Oncological Sciences and the Precision Immunology Institute. His group's research is aimed at understanding mechanisms of regulation of oncogenic and immune signaling, with the goal of using this knowledge to develop more effective cancer therapies. Areas of particular focus include RAS/MAPK and CDK-targeted therapeutics. Active projects in the lab include rationally-designed drug combinations for the treatment of lung, colorectal, melanoma, pancreatic, breast, multiple myeloma and other cancer types driven by oncogenic signaling pathways, as well as the development of next generation small-molecule inhibitors, protein degraders (PROTACs) and molecular glues.

Session 3: Cancer Mechanisms
"Novel strategies to target oncogenic signaling for cancer treatment"

https://profiles.icahn.mssm.edu/poulikos-poulikakos

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SPEAKERS

Robert Samstein, MD, PhD
Assistant Professor
Department of Immunology and Immunotherapy

Robert (Robbie) Samstein, MD PhD is a radiation oncologist in the Department of Radiation Oncology at Mount Sinai and a physician scientist with a laboratory in the Precision Immunology Institute at Mount Sinai. He treats a wide variety of cancer, specializing in thoracic malignancies. He graduated summa cum laude from Yale University and completed his combined MD-PhD training in the Tri-Institutional Weill Cornell/ Memorial Sloan Kettering/ Rockefeller MD-PhD Program. He completed his graduate work with Alexander Rudensky studying the development and function of regulatory T cells. He completed his transitional year internship and residency in radiation oncology at Memorial Sloan Kettering Cancer Center in New York, NY. Dr. Samstein's research interests are focused on understanding the interaction between the patient's immune system and cancer cells in the tumor, elucidating the role of the DNA damage repair and response pathway in altering the tumor's ability to be recognized and attacked by the immune system. His laboratory will work to identify new strategies to harness the immune anti-tumor response and expand the therapeutic window of traditional immunotherapies.

Session 5: Cancer Immunology
"Understanding the immunology of pre-cancers towards immune prevention strategies"

https://profiles.icahn.mssm.edu/robert-samstein

Keith Sigel, MD, PhD, MPH
Professor
Department of Medicine

Keith Sigel is a Professor in the Division of General Internal Medicine at the Icahn School of Medicine. Dr. Sigel is a clinical investigator and epidemiologist with a primary research interest in clinical factors related to the abnormal biology of lung cancer and anal cancer in patients with HIV. Dr. Sigel directs the Cancer Core of the Veterans national HIV cohort (the Veterans Aging Cohort Study) and is a member of the executive committee of that cohort. He has served as principal investigator for major NCI funded studies on the screening and treatment of lung cancer in people living with HIV and is currently the principal investigator of an NIH-funded trial studying novel approaches to anal cancer screening in HIV uninfected women with HPV infection.

Session 1: Cancer Prevention and Control
"Anal Cancer Screening in High-Risk Populations"

https://profiles.icahn.mssm.edu/keith-m-sigel

Mount Sinai *The Tisch Cancer Institute*

SPEAKERS

Colette Smith
Community Scientist

Colette Smith, a proud Bronx resident, serves as a Community Scientist on Mount Sinai's Protocol Review and Monitoring Committee and the Community Outreach and Engagement team. As a health advocate with the ambitious goal of impacting lung cancer screening guidelines and educating others about lung cancer, Colette brings a unique perspective and unwavering resilience to her work. With a decade-long journey as a lung cancer survivor, she is dedicated to making a difference in her community. Beyond her professional commitments, Colette is a devoted wife, mother, and grandmother, cherishing her family above all.

Session 2: Community Outreach and Engagement
“Community Scientist”

Emanuela Taioli, MD, PhD
Director, Institute for Translational Epidemiology
Professor, Population Health Science and Policy; Thoracic Surgery

Dr. Emanuela Taioli received her M.D. from University of Milan in 1981. She then attended Columbia University where she received her M.S. and Ph.D. degrees in Epidemiology.
In 2015 Dr. Taioli joined Mount Sinai as Professor of Population Health and Science and of Thoracic Surgery, and the Director of the Institute for Translational Epidemiology. She is also Associate Director for Population Science and a Co-Leader of the Cancer Prevention and Control Program at The Tisch Cancer Institute.
Among her most important contributions are those to the field of cancer prevention, including the study of cancer risk factors in healthy populations, cancer predisposing factors, hormone metabolism and genetic susceptibility to environmental exposure. She is a well-recognized expert in cancer survivorship and the effect of lifestyles changes on the risk for cancer recurrence and the development of new secondary cancers. Moreover, she has worked extensively on health disparities, access to care in minority populations, and chronic diseases prevention in the underserved.
Session 1: Cancer Prevention and Control
“Cancer Prevention and Control Updates”

https://profiles.icahn.mssm.edu/emanuela-taioli

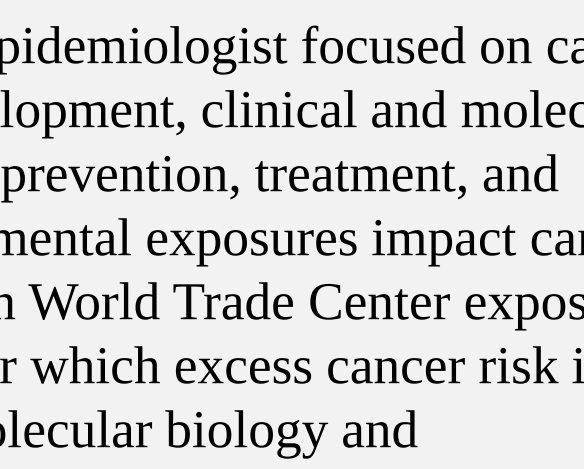
SPEAKERS

Stephanie Tuminello, PhD, MPH
Instructor
Department of Thoracic Surgery
Institute for Translational Epidemiology

Stephanie Tuminello, PhD, MPH is a trained molecular and genetic epidemiologist focused on cancer. Her research interests include immune dysregulation and cancer development, clinical and molecular biomarkers for response to cancer treatment, and inequities in cancer prevention, treatment, and outcomes. Dr. Tuminello's research has also focused on how environmental exposures impact cancer risk. Her PhD dissertation explored an epigenetic mechanism between World Trade Center exposure and cancer development in WTC responders and survivors, groups for which excess cancer risk is well documented. Her overarching goal is to bridge the worlds of molecular biology and epidemiology to conduct research that is translational and impactful for cancer survivors.

Session 4: Training and Education
"Immune Genetic Susceptibility and Cancer Risk in a Diverse Population"

Camila Vicioso, BA
Medical Student
Icahn School of Medicine at Mount Sinai



Camila is a second year medical student at Mount Sinai. She graduated in 2023 from Columbia University with a double major in Biology and Psychology. Camila was a student in the 2024 TCI Summer Scholars Program, where she completed a project considering the role of mannose in MASH-HCC progression. She hopes to pursue a pediatric specialty and continue combining her interests in research and cancer/disease mechanisms. Outside of medical school, Camila enjoys dancing ballet.

Session 4: Training and Education
"The role of mannose in MASH-HCC progression "

Ji Yoon Yoon, MD, MSCR
Instructor
Department of Gastroenterology

Dr. Ji Yoon Yoon is a Gastroenterologist and T32 fellow (Cancer Prevention and Control), interested in decision analytic methods for evaluating cancer screening methods and tackling disparities in cancer care.

Session 4: Training and Education
"Targeted Approach to Upper Gastrointestinal Cancer Screening"

https://profiles.icahn.mssm.edu/ji-yoon-yoon2

POSTERS

Poster Number	Name	Mentor(s)/Program	Poster Title
01	Jeremy Mudd	Juan Wisnivesky/CPC	Longitudinal Quality of Life Following Sub-lobar Resection and Stereotactic Body Radiation Therapy for Early-Stage Non-Small-Cell Lung Cancer
02	Leah Walsh	Allison Applebaum/CPC	Examining differences in quality of life and problems areas of older versus younger caregivers
03	Withdrawn		
04	Beau Baars	Poulikos Poulikakos/CCI	Deciphering SHP2 Regulation in MAPK Signaling to develop more effective therapies
05	Ana Orive-Ramos	Poulikos Poulikakos/CCI	Exploiting conformation selectivity of MAPK inhibitors to design RAS-mutant selective therapy
06	Bijaya Gaire	Poulikos Poulikakos/CCI	Mechanisms determining response to Novel RAS inhibitors in NRAS mutant melanoma
07	Erin Bresnahan	Jose Javier Bravo-Cordero/CM	TGFB1i1 regulates invasive capacities in p95HER2 breast tumors
08	Daniela De Marino	Jose Javier Bravo-Cordero/CM	P4HA2 Regulates Tumor Cell Dormancy by Balancing The Mitochondrial NAD+/NADH Ratio
09	Thirumoorthy Divagar	Hideo Watanabe/CM	The *MYC* family proteins have distinct roles in regulating lineage plasticity of small cell lung cancer
10	Anindita Dutta	Juan Arriaga/CM	Dual role of epigenetic protein ATAD2 in bone metastasis and immune evasion in prostate cancer
11	Ruben Fernandez-Rodriguez	Mihaela Skobe/CM	Vascular Endothelial Growth Factor-C (VEGF-C) enhances anti-tumor effects of oncolytic viral therapy leading to tumor eradication and long-term survival in mouse melanoma
12	Elena Grossi	Emily Bernstein/CM	The SWI/SNF chromatin remodeler PBAF facilitates REST occupancy at inactive chromatin in the melanocytic lineage
13	Bionformatics for Next Generation Sequencing		
14	Biorepository and Pathology		
15	Biostatistics		
16	Cancer Genomics Technologies		
17	Flow Cytometry		
18	Human Immune Monitoring Center		
19	Microscopy and Advanced Bioimaging		
20	Jesminara Khatun	Jerry Chipuk/CM	Metabolic Adaptations To Acute Glucose Uptake Inhibition Converge Upon Mitochondrial Respiration For Leukemia Cell Survival

POSTERS

Poster Number	Name	Mentor(s)/Program	Poster Title
21	Sarah Ann King	Goutam Chakraborty/CM	Examining the impact of male specific histone demethylase KDM5D alteration in prostate cancer
22	Criseyda Martinez	Hanna Irie/CM	Novel PROTAC degrader targets kinas-dependent functions of PTK6 to induce apoptosis of breast cancer cells
23	Cristina Megino-Luque	Jose Javier Bravo-Cordero/CM	Clusterin secretion by dormant DTCs drives the formation of pro-survival brain niches through astrocyte remodeling
24	Prathiksha Prabhakaraalva	Goutam Chakraborty/CM	Targeting the Reprogrammed PIK3R1-Insulin-Glucose Metabolism Pathway: A Novel Therapeutic Strategy for Lethal Prostate Cancer
25	Shamsa Roshan	Tianliang Sun/CM	Single-Cell Analysis of the Biliary Epithelial Cells Reveals Dynamic Heterogeneity and Plasticity During Ductular Reaction
26	Nazifa Salsabeel	Elena Ezhkova/CM	EZH2 degradation as a therapeutic approach for Merkel Cell Carcinoma
27	Swarnima Singh	Igor Bado/CM	Multi-faceted role of CD83+ macrophages in promoting multi-organ metastasis in breast
28	Ke Wang	Elvin Wagenblast/CM	Targeting Quiescent Leukemic Stem Cells through Oxidative Phosphorylation in NUP98-NSD1 Fusion-Positive Acute Myeloid Leukemia
29	Nabila Zaman	Goutam Chakraborty/CM	Molecular insights of low-PSA–expressing high-risk prostate cancer
30	Marina Barcena-Varela	Amaia Lujambio/CI	Gut microbiome affects hepatocellular carcinoma (HCC) progression and response anti-PD1 therapy
31	Matthew Brown	Nina Bhardwaj/CI	Identifying targets of precancerous neoantigen-specific T cell surveillance in patients with Lynch syndrome and immune suppression programs supporting colorectal cancer progression
32	Tanvi Joshi	Dolores Hambardzumyan/CI	Investigating the Role of Aquaporin-4 in Glioblastoma-associated Vasogenic Cerebral Edema
33	Uddipan Kar	Nina Bhardwaj/CI	Investigating changes in cellular metabolism on tumor antigen uptake by conventional dendritic cell 1 (cDC1)
34	Anthony Lozano	Amaia Lujambio/CI	MASH selects against immunogenic hepatocellular carcinoma
35	Guillaume Mestrallet	Nina Bhardwaj	Overcoming immune resistance in MSI-H tumors
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ABSTRACTS

Longitudinal Quality of Life Following Sub-lobar Resection and Stereotactic Body Radiation Therapy for Early-Stage Non-Small-Cell Lung Cancer

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POSTER 01

Introduction: Many early-stage lung cancer patients are not candidates for lobectomy due to various factors, with treatment options including sub-lobar resection or stereotactic body radiation therapy (SBRT). Limited information exists regarding patient-centered outcomes following these treatments.
Methods: Subjects with stage I-IIA non-small cell lung cancer (NSCLC) at high risk for lobectomy who underwent treatment with sub-lobar resection or SBRT were recruited from five medical centers. We compared quality of life (QOL) using the Short Form-8 (SF-8) for physical and mental health and Functional Assessment of Cancer Therapy-Lung (FACT-L) surveys at baseline (pre-treatment), 7-days, 30-days, 6-months, and 12-months after treatment. Propensity score methods were used to control for confounders.
Results: Of 337 subjects enrolled before treatment, 63% received SBRT. Among patients undergoing resection, 89% underwent minimally-invasive video-assisted thoracic surgery (VATS) or robot-assisted resection. Adjusted analyses showed that SBRT-treated patients had both higher physical health SF-8 scores (difference in differences [DID]: 6.42; p=0.0008) and FACT-L score at 7 days (DID: 2.47; p=0.004) post-treatment. Mental health SF-8 scores were not different at 7 days (p=0.06). There were no significant differences in QOL at other time points and all QOL scores returned to baseline by 12 months for both groups.
Conclusions: SBRT is associated with better QOL immediately post-treatment compared with sub-lobar resection. However, both treatment groups reported similar QOL at later timepoints with return to baseline QOL. These findings suggest that sub-lobar resection and SBRT have similar impact on QOL of early-stage lung cancer patients deemed ineligible for lobectomy.

Examining differences in quality of life and problems areas of older versus younger caregivers

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POSTER 02

Background: The psychosocial and physical challenges of older adult caregivers (OACs) are less often studied compared to younger caregivers. This secondary analysis characterized age-related differences in quality of life (QOL) and self-reported problems in family caregivers to patients with cancer.
Methods: Participants were caregivers of patients receiving predominantly outpatient surgeries recruited between 05/2019-05/2022 as part of a randomized distress screening trial. Caregivers (>18 years, fluent in English) completed baseline measures of QOL (Functional Assessment of Cancer Therapy, General Population) and a list of practical, family, emotional, spiritual, and physical problems. Descriptive statistics and t-tests examined differences in QOL based on age. We used Chi-square tests to compare the percentage of OACS (>65) versus younger caregivers who endorsed at least one problem across each of the five problem areas.
Results: Caregivers (N=136) were primarily female (n=90, 66%), White (n=114, 84%), non-Hispanic (n=122, 91%), and between 21 and 80 years old (M=52). Twenty-nine caregivers were >65 years old (21.3%). OACs reported greater social well-being [t(131)=1.94,p=.045] than younger caregivers, and fewer OACs endorsed at least one concern across practical (37.9% versus 52.9%, p=.15), family (51.7% versus 57.7%, p=.57), emotional (65.4% versus 79.2%, p=.14) spiritual (0.0% versus 9.8%, p=.12), and physical (70.4% versus 75.8%, p=.57) areas, though differences were not statistically significant.
Conclusions: OACs reported greater social QOL, perhaps due to greater available social support than younger adults, a phenomenon amplified by lockdown during the COVID-19 pandemic. Further examination of OACs' experiences may contextualize these findings to identify their unique psychosocial and physical needs.

Deciphering SHP2 Regulation in MAPK Signaling to develop more effective therapies

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POSTER 04

The RAS-RAF-MEK-ERK (MAPK) pathway is frequently deregulated in cancer due to mutations in RAS and BRAF, yet the regulatory mechanisms of RAS are not fully understood. Receptor tyrosine kinases (RTKs) activate various proteins, including SHP2, which plays a critical role in regulating RAS activity and can mediate resistance to MAPK inhibitors. To evaluate the binding potency of small-molecule SHP2 inhibitors (SHP2i) in live cells, we developed an intracellular target-engagement (TE) NanoBRET assay. Our results indicate that SHP2i binding is less effective in mutants favoring an open conformation. Additionally, using small-molecule degraders (PROTACs) targeting SHP2 revealed that ectopic expression of RAS(Q61) reduces degrader effectiveness, which is in line with the resistance observed in RAS(Q61)-mutant cells. This indicates that this mutation induces a conformational shift in SHP2, that impairs both degrader and inhibitor binding. RAS(Q61) also led to paradoxical SHP2 activation which further increases resistance to SHP2i. Similarly, targeting downstream of activated RAS with MEK inhibitor (MEKi) did not effectively suppress activation, as both wild-type and mutant RAS were feedback-activated, contributing to adaptive resistance. Collectively, our data suggest that stabilizing SHP2 in a closed conformation enhances SHP2i efficacy by disrupting the SHP2-GAB1-GRB2-SOS1 complex. The catalytic role of SHP2 remains uncertain, but its phosphatase activity is crucial for organizing the membrane complex and activating RAS. Continued investigation aims to clarify SHP2's regulatory role, which may aid in developing targeted therapies for MAPK-driven cancers.

Exploiting conformation selectivity of MAPK inhibitors to design RAS-mutant selective therapy

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POSTER 05

The therapeutic efficacy of small-molecule inhibitors targeting oncogenic signaling relies on greater pathway inhibition in the tumor than in normal cells. Typically, this is achieved by inhibitors that are selective for a genetically activated oncogenic protein. Deregulation of the RAS/MAPK signaling pathway drives the growth of over 40% of human tumors, frequently due to activating mutations of the components of the pathway RAS or BRAF. Mutated BRAF (BRAF-MUT) signals as monomer, and combination of a RAF monomer-selective inhibitor (mRAFi) that is selective for BRAF-MUT with a MEK inhibitor (MEKi) has shown success for the treatment of BRAF-MUT tumors. Recently, we identified and characterized a novel class of RAF inhibitors that preferentially bind and inhibit dimeric wild-type RAF (i.e. dimer-selective RAFi, dRAFi) and assessed their effectiveness in targeting wild-type RAF downstream of mutant RAS (RAS-MUT). We found that dRAFi potently antagonize MAPK signaling and growth in various RAS-MUT cancer models as compared to normal cells, as RAS activation promotes a drug-sensitive conformation of RAF. In line with these findings, MEK inhibitors (MEKi) are also more potent in suppressing MAPK signaling and growth in RAS-MUT cancer cells compared to normal cells, as they bind better to drug-sensitive conformations of MEK induced by RAS activation. However, the combination of a dRAFi with a MEKi resulted in similar MAPK inhibition in RAS-MUT and normal cells, consistent with the increased toxicities and the modest clinical benefit observed in clinical trials testing these inhibitors. Using in-cell binding assays (NanoBRET technology and targeted degradation – PROTACs), we show that this increased toxicity is due to the relief of negative feedback in normal cells by MEKi treatment, which promotes activated wild-type RAF dimers with increased affinity for dRAFi, resulting in potent MAPK inhibition in normal cells and low therapeutic index. Thus, drug combinations causing similar MAPK inhibition in normal and tumor cells (“adverse synergy”) are unlikely to be clinically successful. After analysis of the binding properties of RAF and MEK inhibitor combinations of various biochemical classes, we identified dRAFi and MEKi combinations that promote greater MAPK and growth suppression in RAS-MUT tumors as compared to normal cells (“therapeutic synergy”) in vitro and in vivo and should be therefore prioritized for clinical testing. Thus, understanding conformational selectivity of MAPK-targeting inhibitor combinations enables the rational design of pharmacological strategies with tumor-selective potency, that are predicted to be more effective and less toxic in patients with RAS-MUT tumors. Increasing tumor selectivity by differentially targeting native conformations of non-genetically altered oncogene effector proteins in tumor and normal cells represents a novel paradigm in targeted cancer therapy.

Mechanisms determining response to Novel RAS inhibitors in NRAS mutant melanoma

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POSTER 06

RAS proteins are mutated in about 30% of human cancers, including 25% of melanomas, however mutated RAS has been historically recalcitrant to direct inhibition. Recently, small molecule direct RAS inhibitors have been developed, including inhibitors selective for KRAS(G12C) and KRAS(G12D), as well as a novel class of pan-RAS inhibitors, targeting the active (ON) state of RAS (RAS-ONi), and are active against multiple RAS-mutant proteins. However, major questions on the mechanisms determining tumor response to these drugs remain open. First, as these compounds target both mutant and wild-type RAS, the mechanistic basis of their selectivity towards RAS-mutant over wild-type cells and consequent Therapeutic Index remains unclear. Second, whether these drugs will show broad and potent activity against RAS-mutant melanomas has not been investigated. To address these questions, we first compared the potency of the RAS-ONi RMC-7977 between mutant and WT RAS cell line models. We found that RAS-ONi inhibited cell growth and MAPK signaling more potently in cell lines with mutant RAS compared to WT RAS. We next assessed the effect of RAS(ON)i on cell growth and MAPK inhibition in a panel of NRAS (Q61X) melanoma lines. We found large variability in their response to RAS(ON)i, with MAPK inhibition correlating well with growth inhibition. Time course experiments showed that unlike the complete and durable RAS/MAPK inhibition by RAS(ON)i in sensitive lines, in resistant lines, RAS/MAPK signaling was incompletely inhibited and recovered in the presence of RAS(ON)I, indicating intrinsic and adaptive resistance mechanisms at play in these cells. Active RAS pull down experiments followed by western blot and mass spectrometry analysis revealed that resistance to RAS-ONi correlates with contribution of wild-type RAS signaling to MAPK. These findings also potentially explain the differential potency of these drugs between mutant and wild-type RAS proteins. We further found that inhibitors of wild-type RAS signaling, such as SHP2 or RTK inhibitors synergize with RAS(ONi) selectively in resistant lines. Thus, concomitant targeting of wild-type RAS is an effective therapeutic strategy for RAS-mutant melanomas resistant to RAS(ON)i. Overall, our data characterize the novel RAS(ON)i as a potent and effective drug for a portion of NRAS (Q61X) melanomas, and identify the contribution of Wild Type RAS signaling in resistance to RAS(ON)i as a targetable node that could potentiate the effectiveness of these drugs.

TGFB1i1 regulates invasive capacities in p95HER2 breast tumors

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POSTER 07

Expression of different HER2 oncogenic isoforms is a source of heterogeneity and therapeutic resistance in HER2+ breast cancer. Using a cancer rainbow mouse expressing three different fluorescently labeled HER2 isoforms in the mammary gland, we show WT HER2, exon-16 null HER2 (d16), and N-terminally truncated HER2 (p95) demonstrate distinct growth and invasiveness dynamics, with significantly increased p95 dissemination to the lung. p95 cells show elevated motility and matrix degradation activity through increased invadopodia formation. Intravital imaging of mammary tumors showed p95 cells displaying frequent amoeboid movement near blood vessels in a rich vascular microenvironment, compared with scarce movement in WT tumors. scRNAseq transcriptomics analysis revealed p95 cells overexpress genes related to actin cytoskeleton dynamics and cell motility, with Tgfb1i1 as one of the most significant differentially expressed genes. Tgfb1i1 knockdown decreased collagen degradation and reduced extravasation rate of p95 cells. Interestingly, p95 cells initially remain as single cells or small clusters at metastatic organs compared with WT cells that undergo massive outgrowth. In accordance with this observation, scRNAseq analysis of p95 cells shows an enrichment in a cancer cell dormancy gene signature. Overall, our data suggests the heightened metastatic ability of p95 HER2+ breast cancer cells is driven by increased motility and TGfb1i1-dependent matrix degradation. An overall shift towards “go” rather than “grow” phenotypes compromised growth at distant sites where p95 cells retain a dormant-like phenotype, revealing a novel functional property of p95HER2 tumor cells and shedding insight on the poor prognosis they convey in patients.

ABSTRACTS

P4HA2 Regulates Tumor Cell Dormancy by Balancing The Mitochondrial NAD+/NADH Ratio

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POSTER 08

Metastasis is the leading cause of death in cancer patients. Single disseminated tumor cells (DTCs) colonize distant organs where they remain in a deep state of quiescence, called dormancy and reactivate their proliferation years after removal of the primary tumor. Recently, our lab showed that formation of collagen-rich matrix by DTCs is a hallmark of dormancy and contributes to sustaining the quiescent state of DTCs. However, how dormant cells regulate the formation of collagen matrices and the mechanisms mediating collagen homeostasis are not understood. We found that P4HA2, an enzyme responsible for proline hydroxylation and required for the maturation of collagens in vivo, is upregulated upon dormancy onset and its activity is required to sustain the quiescent state of DTCs in lung. Spatial collagen proteomics in tissue revealed that, upon P4HA2 depletion, proline hydroxylation levels on fibrillar collagens significantly decreased. Mechanistically, we found that defects in fibrillar collagen hydroxylation activate autophagy for its degradation, fueling mitochondrial energetics via proline-dependent activity of ALDH4A1. Proline catabolism in P4HA2 deficient cells results in high production of NADH and ATP, powering the awakening of dormant DTCs. Moreover, we observe that in vivo, proline supplement awakens dormant DTCs in the lung of mice, mimicking the phenotype observed upon P4HA2 depletion. Overall, our findings reveal a new function of P4HA2 in limiting proline usage to balance NAD+/NADH ratio and control the quiescent state of dormant tumor cells.

The *MYC* family proteins have distinct roles in regulating lineage plasticity of small cell lung cancer

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POSTER 09

Small cell lung cancer (SCLC), a highly lethal neuroendocrine cancer type, is known to transdifferentiate to lose its neuroendocrine features. We proposed that the MYC family genes, which are commonly amplified in SCLC, play a role in this transdifferentiation. c-Myc amplified SCLC undergoes transdifferentiation, while L-Myc amplified SCLC does not. Hence, while being homologous, they are not functionally redundant in SCLC. Our goal is to determine the molecular mechanism behind this functional difference. We characterized the cistrome and interactome of c-Myc and L-Myc in SCLC using ChIP-seq and rapid immunoprecipitation mass spectrometry (RIME) assays on SCLC cell lines. This was complemented by comparative analysis of c-Myc cistromes in SCLC and c-Myc amplified cell lines from other tissues to identify tissue-specific DNA binding patterns of c-Myc. Second, to identify the protein domains conferring the transdifferentiation function to c-Myc, we plan to combinatorially swap the 8 homologous domains between c-Myc and L-Myc using Gibson assembly and introduce the fusion proteins to SCLC cell lines. Furthermore, given SCLC largely originates from the pulmonary neuroendocrine cell (PNEC), which transit amplifies and reprograms to other non-NE cell types following lung injury, we hypothesize that c-Myc activates similar programs in SCLC. Therefore, we utilized publicly available scRNA-seq data on reprogramming PNEC cells and performed comparative analysis with c-Myc DNA binding targets, to identify candidates for functional validation via knockouts to infer causality. We will present our current progress on this project.

Dual role of epigenetic protein ATAD2 in bone metastasis and immune evasion in prostate cancer

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POSTER 10

Metastatic castration-resistant prostate cancer (mCRPC) is the primary cause of prostate cancer (PCa) related mortality and is resistant to existing treatment modalities, including immunotherapy. The evasion of antitumor immune responses significantly contributes to the growth and metastatic progression of PCa. Increasing evidence indicates multiple aspects of epigenetic regulation in antitumoral immunity. However, the influence of epigenetic factors on tumor advancement and their effect on antitumoral immunity remains inadequately comprehended. Focus on targeting these drivers could yield significant therapeutic benefits by addressing both intrinsic and extrinsic processes of PCa growth and may represent an essential aspect of the immune suppression observed in PCa. By utilizing functional modelling in mouse models, patient gene expression datasets and human xenografts, we have identified ATAD2 as an epigenetic factor, functionally leading to bone metastasis in part by blunting antitumoral immune responses. Indeed, we show that ATAD2 is progressively expressed in metastatic PCa and is negatively associated with metastasis-free survival. Loss of ATAD2 in syngeneic mouse models results in regression of primary tumors and bone metastases. The multimodal impact of ATAD2 encompasses tumor intrinsic antigen presentation via modulation of MHC-I expression, tumor extrinsic macrophage polarization towards a pro-tumorigenic phenotype, and an influence mediated by tumor-infiltrating CD8+ T cells. Thus, our studies help elucidate novel functional and mechanistic dimensions of ATAD2 as a metastatic driver, a prognostic biomarker, and a therapeutic target in the establishment of innovative epi-immune strategies to stimulate immune responses in advanced PCa with heightened ATAD2 levels.

Vascular Endothelial Growth Factor-C (VEGF-C) enhances anti-tumor effects of oncolytic viral therapy leading to tumor eradication and long-term survival in mouse melanoma

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POSTER 11

Tumor-associated lymphatic vessels play multiple roles in cancer that include promoting metastasis and modulating immunity. Vascular Endothelial Growth Factor C (VEGF-C) is the main lymphangiogenic growth factor and it is expressed by many advanced-stage cancers.
Here, we investigated how VEGF-C, expressed by tumor cells, impacts therapeutic effects of oncolytic viruses. We employed two oncolytic avian paramyxoviruses (APMVs): APMV-1 (NDV) and AMPV-4. We generated VEGF-C-expressing B16F10 cells and inoculated them in C57Bl/6J mice. Once the tumors reached ~50 mm3, viruses were injected intratumorally (107 PFU). Expression of VEGF-C in B16F10 melanomas enhanced anti-tumor effects of APMV-4 or NDV, resulting in complete remission in 100% and 86% of mice, respectively. Mice remained tumor-free during the 90-day observation period, and following re-challenge remained tumor-free for more than a year. Additionally, mice did not show any metastasis at the end of the treatment.
Aurora flow cytometry revealed increases in CD8+ and CD4+ T-cell and NK cells relative frequencies and activation, associated with complete remission and unique for VEGF-C tumors treated with NDV. Finally, to simulate a therapeutic approach in humans, we produced lymphangiogenic tumors by inoculating VEGF-C mRNA LNPs in mice bearing B16F10 tumors and treated these with APMV4. VEGF-C mRNA LNPs combined with APMV4 produced a significant tumor growth delay in 50% of the mice and increased mice survival in 50% of the mice compared with APMV4 alone. These studies demonstrate that VEGF-C is a potent enhancer of anti-tumor immunity induced by oncolytic viral immunotherapy.

Mount Sinai *The Tisch Cancer Institute*

The SWI/SNF chromatin remodeler PBAF facilitates REST occupancy at inactive chromatin in the melanocytic lineage

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POSTER 12

Mammalian SWI/SNF complexes are multimeric ATP-dependent chromatin remodelers with a recognized role in controlling chromatin architecture and gene expression. Recently, the development of fast-acting inhibitory compounds has allowed to investigate the dynamics of SWI/SNF chromatin engagement and remodeling at unprecedented resolution. Yet, the individual contribution of each SWI/SNF component remains difficult to dissect, given the modular nature of these assemblies that ubiquitously exist in three distinct conformations: BAF, PBAF and ncBAF complexes. This is particularly relevant in the context of cancer, where genetic alterations in specific SWI/SNF genes are enriched in distinct tumor types. For instance, the PBAF-specific subunit ARID2 is highly mutated in melanoma and recognized as a cancer driver in this malignancy.

We recently demonstrated that ARID2 loss results in impaired PBAF complex assembly, which leads to BAF chromatin redistribution and gain of oncogenic function. However, the unique functions of PBAF-specific regions remain unexplored. To this aim, we conducted comprehensive epigenomic profiling of melanoma cells and primary melanocytes and found that the PBAF complex is enriched at a subset of repressed regions, where it unexpectedly coexists with the Polycomb Repressive Complex 2 (PRC2). Time-resolved approaches revealed that these regions are less sensitive to PBAF ATPase activity, as well as other compensatory remodeling mechanisms. Notably, these PBAF-specific inactive chromatin loci are enriched for REST, a repressive transcription factor that silences neuronal genes in non-neuronal cells. We found that the absence of ARID2 and consequent PBAF loss, reduces REST ability to bind chromatin and repress its target genes, thus leading to upregulation of neuronal and synaptic transcripts in both melanocytes and melanoma cells.

Intriguingly, expression of neuronal signatures is an emerging feature of melanoma brain metastases; we are therefore investigating whether ARID2-mediated control of neuronal genes could favor melanoma adaptation to the brain niche in various in vivo settings. Preliminary results in an orthotopic intracranial mouse model revealed that, when injected into the brain cortex, ARID2 KO melanoma cells upregulate genes involved in axon guidance, a process often co-opted by brain tumors. We are now applying scRNA-seq to test how the brain microenvironment responds to ARID2 KO melanomas.

Bioinformatics for Next Generation Sequencing Shared Resource

Shared Resource Directors: Ernesto Guccione, PhD and Dan Hasson, PhD

POSTER 13

The TCI Bioinformatics for Next Generation Sequencing Shared Resource (BiNGSSR) provides NGS focused computational analyses for cancer investigators and clinicians. The mission is to advise on experimental design and protocols related to NGS technologies, provide a broad range of bioinformatics analyses for multiple applications spanning bulk and single cell epigenomics, transcriptomics and genomics, perform data integration and visualization, and assist in cancer focused data interpretation. BiNGSSR furthers scientific discoveries by establishing robust computational pipelines for analyzing NGS data for TCI members and offers extensive training platforms for the Mount Sinai and global research communities. BiNGSSR is also dedicated to creating opportunities to increase diversity within the STEM pipeline.

Biorepository and Pathology Shared Resource

Shared Resource Director: Rachel Brody, MD, PhD

POSTER 14

The TCI Biorepository and Pathology Shared Resource (BPSR) integrates biorepository, histology, immunostaining, and molecular services in support of basic, clinical, epidemiologic, and translational cancer research throughout the TCI community. Biopsy and surgical specimens are processed, banked, and distributed to investigators as fresh, frozen, fixed, or procured according to investigator specifications. The BPSR hosts a suite of advanced pathology services including diverse staining, imaging, and quantitative digital image analyses; along with macromolecule extraction for subsequent investigations. Liquid biospecimen processing and management support TCI research programs and clinical trials. Finally, the BPSR is a multi-dimensional group providing consultation, education, technical support, and training for basic science, translational, and clinical cancer researchers across the Mount Sinai Health System.

Biostatistics Shared Resource

Shared Resource Directors: Madhu Mazumdar, PhD and Marcio Diniz, PhD

POSTER 15

The TCI Biostatistics Shared Resource (BSR) collaborates with TCI members on designing laboratory experiments, population studies, and clinical trials. The BSR determines optimal experimental group sizes and drafts high-quality statistical analysis plans to ensure rigor and reproducibility. The BSR provides biostatisticians with expertise in comprehensive coverage of analytic methodologies, including software programming, table creation, and data visualization; staff translate these components into language understandable by the scientific community, along with supporting manuscript preparation and grant proposals. The BSR contributes extensive review, monitoring, and oversight for investigator-initiated clinical trials in collaboration with the Clinical Trials Office, Protocol Review and Monitoring Committee, and Data and Safety Monitoring Committees. Training on all quantitative data science disciplines is available through seminars, walk-in clinics, and workshops.

Cancer Genomics Technologies Shared Resource

Shared Resource Director: Robert Sebra, PhD

POSTER 16

The TCI Cancer Genomics Technologies Shared Resource (CGTSR) facilitates scientific, translational, and clinical breakthroughs by harnessing cutting-edge molecular -omics techniques, advanced instrumentation, and computational methods. The CGTSR offers TCI members the latest developments in bulk, single-cell, spatial, and in-situ multi-omics data generation platforms; while also providing expertise to optimize experimental design, data quality, affordability, and access. The team is comprised of 29 staff and faculty harbored in the brand new Mount Sinai Discovery and Innovation Center which includes instrumentation, molecular and cell biology spaces, and BSL2/BSL2+ laboratories. Post-sequencing data analyses are performed using the secured and centralized Mount Sinai High-Performance Computing facility with 1.5 Petabyte storage capacity. The CGTSR maintains a comprehensive suite of genomics services that accelerates cancer discovery, inter- and intra-programmatic collaborations within the TCI community, and benchmarks new technologies to continually match the evolving needs of TCI members.

Flow Cytometry Shared Resource

Shared Resource Director: Jordi Ochando, PhD

POSTER 17

The TCI Flow Cytometry Shared Resource (FCSR) provides access to modern technologies, services, and expertise in flow cytometry to enhance scientific discovery and collaboration within the TCI community. The FCSR proactively monitors and introduces new flow cytometry equipment, methods, and data analyses approaches to promote impactful studies and align with the cancer center’s expanding needs. The FCSR maintains cancer-focused personnel and contributes to the TCI’s research mission by providing consultation, priority access with TCI dedicated equipment, education, and cost-effectiveness with center pricing and subsidies.

Human Immune Monitoring Center Shared Resource

Shared Resource Directors: Miriam Merad, MD, PhD and Sacha Gnjatic, PhD

POSTER 18

The TCI Human Immune Monitoring Center Shared Resource (HIMCSR) is a collaborative consortium of technologists, immunologists, clinicians, and computational biologists with the coordinated goal of generating unprecedented immune profiling datasets to interrogate the etiology of cancer, novel biomarkers of disease course, and response to immunotherapy trials in cancer patients. The HIMCSR includes a range of cutting-edge high-throughput technology platforms to define circulating immune factors in blood and body fluids; characterize immune cells in blood, bone marrow and tissue samples; interrogate specific cellular, molecular immune pathways that may be dysregulated in disease; and characterize changes upon therapy or treatment. These complementary technology platforms are fully integrated with automated laboratory, biospecimen, and data management systems to facilitate detailed immune characterization of diverse patient samples at exceptional scale with uncompromising data quality and scientific rigor. These data may be linked with cutting-edge computational, bioinformatics, and machine learning pipelines to extract meaningful and actionable therapeutic insights. The HIMCSR contributes to the TCI's mission by providing state-of-the-art technologies, project development, consistency, interpretations, and cost-effectiveness to all TCI programs.

Microscopy and Advanced Bioimaging Shared Resource

Shared Resource Director: Deanna Benson, PhD

POSTER 19

The TCI Microscopy and Advanced Bioimaging Shared Resource (MABSR) manages cutting-edge instrumentation and imaging strategies for the cancer community. The MABSR provides access, expertise, and consulting services for state-of-the-art super-resolution, light-sheet microscopy, and electron microscopy; in addition to confocal, multi-photon, and widefield microscopes. With TCI-focused staff, the MABSR collaborates with TCI members to develop advanced image analyses strategies and pipelines along with integrating new equipment and technologies based on TCI needs. A strong commitment to education is supported by participation in numerous campus-based and national initiatives, along with co-directing an annual graduate-level microscopy course. As such, the MABSR offers complete imaging support from consultation, sample preparation, microscopes training, staff-assisted data capture, and high-performance computing workstations for image analysis.

Metabolic Adaptations To Acute Glucose Uptake Inhibition Converge Upon Mitochondrial Respiration For Leukemia Cell Survival

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POSTER 20

One hallmark of cancer is the upregulation and dependency on glucose metabolism to fuel macromolecule biosynthesis and rapid proliferation. Despite significant pre-clinical effort to exploit this pathway, additional mechanistic insights are necessary to prioritize the diversity of metabolic adaptations upon acute loss of glucose metabolism. Here, we investigated a potent small molecule inhibitor to Class I glucose transporters, KL-11743, using glycolytic leukemia cell lines and patient-based model systems. Our results reveal that while several metabolic adaptations occur in response to acute glucose uptake inhibition, the most critical is increased mitochondrial oxidative phosphorylation. KL- 11743 treatment efficiently blocks the majority of glucose uptake and glycolysis, yet markedly increases mitochondrial respiration via enhanced Complex I function. Compared to partial glucose uptake inhibition, dependency on mitochondrial respiration is less apparent suggesting robust blockage of glucose uptake is essential to create a metabolic vulnerability. When wild-type and oncogenic RAS patient-derived induced pluripotent stem cell acute myeloid leukemia (AML) models were examined, KL-11743 mediated induction of mitochondrial respiration and dependency for survival associated with oncogenic RAS. Furthermore, we examined the therapeutic potential of these observations by treating a cohort of primary AML patient samples with KL-11743 and witnessed similar dependency on mitochondrial respiration for sustained cellular survival. Together, these data highlight conserved adaptations to acute glucose uptake inhibition in diverse leukemic models and AML patient samples, and position mitochondrial respiration as a key determinant of treatment success.

Examining the impact of male specific histone demethylase KDM5D alteration in prostate cancer

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POSTER 21

Prostate cancer (PC) is the most common urological malignancy and the second leading cause of male cancer-related fatality. In the United States, over 90% of patients present with localized or locally advanced disease at the time of discovery, with morbidity or mortality often resulting. While the loss of the Y chromosome (ChrY) in men has been associated with an increased disease risk, the role of ChrY genes in PC progression remains poorly understood; previous studies have shown that ChrY mutation influences tumor growth and therapy resistance. ChrY genes have been largely overlooked in next-generation sequencing datasets primarily due to challenges posed by highly repetitive DNA sequences within human ChrY, combined with low ChrY expression in adults. The functions of many ChrY genes remain largely unknown, although recent reports highlight the importance of multiple ChrY genes, namely DDX3Y and KDM5D. Our study aims to explore the impact of ChrY alterations on the development of castration-resistant, metastatic prostate cancer. Pursuant to this goal, we have isolated single-cell-derived clones from human prostate cancer cell line LNCaP, with ChrY alterations enabling the study of the molecular phenotype associated with chromosomal aberration. Additionally, we have now developed several stable KDM5D CRISPR knockout and DDX3Y shRNA knockdown lines in each 22RV1 and LNCaP cells. Our novel study aims to demonstrate the vital significance of ChrY alterations in prostate cancer biology. This study has the potential to help establish ChrY alteration as a driver in the transformation of indolent, localized prostate cancer to lethal mCRPC.

Novel PROTAC degrader targets kinase-independent functions of PTK6 to induce apoptosis of breast cancer cells

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POSTER 22

PTK6, a non-receptor tyrosine kinase, is an oncogenic driver in many tumor types. However, agents that therapeutically target PTK6 are lacking. Although several PTK6 kinase inhibitors have been developed, none have been clinically translated, which may be due to kinase-independent functions that compromise their efficacy. PTK6 kinase inhibitor treatment phenocopies some, but not all effects of PTK6 downregulation. PTK6 downregulation inhibits growth of breast cancer cells, but treatment with PTK6 kinase inhibitor does not. To chemically downregulate PTK6, we designed a PROTAC, MS105, which potently and specifically degrades PTK6. Treatment with MS105, but not PTK6 kinase inhibitor, inhibits growth and induces apoptosis of breast cancer cells, phenocopying the effects of PTK6 shRNA/CRISPR. In contrast, both MS105 and PTK6 kinase inhibitor effectively inhibit breast cancer cell migration, supporting the differing kinase dependencies of PTK6's oncogenic functions. Our studies support PTK6 degraders as a preferred approach to targeting PTK6 in cancer.

Clusterin secretion by dormant DTCs drives the formation of pro-survival brain niches through astrocyte remodeling

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POSTER 23

Brain metastasis develop in 10-30% of women with metastatic breast cancer (BC) and is one of the major causes of their mortality. Autopsy studies support the idea that BC disseminated tumor cells (DTC) are able to remain in a dormant state in the brain and survive until optimal conditions restart their growth forming metastasis. However, the mechanisms by which brain DTCs can survive in this hostile microenvironment remain largely unknown. High-resolution light-sheet microscopy revealed that dormant DTCs reside in discrete niches in several anatomical regions of the brain, including the cortex, midbrain, hypothalamus, and basal forebrain. Multiplex immunofluorescence of brain niches revealed that dormant DTCs promote neuroprotective microenvironments characterized by increased BDNF and TGFb1 levels as well as suppression of proinflammatory markers such as IL1b, 4-HNE or iNOS. Consistently, multiome single-cell ATAC-seq and RNA-seq analysis revealed that dormant DTCs induce astrocyte and neuron plasticity. Dormant DTCs impose a neuroprotective state in astrocytes characterized by high levels of S100A10 and increased expression of transcription factors that promote neuronal survival and development, like Npas3 or Nrxn3. Proteomics analysis of dormant DTCs secretome identified Clusterin (CLU) as a major regulator of astrocyte plasticity. CLU induces a neuroprotective microenvironment that counteract the stress microenvironment induced by DTC seeding through lipid clearance. Finally, we discovered that CLU depletion in dormant DTC prevents astrocyte remodeling and compromises dormant DTCs survival in the brain. Our findings revealed a new mechanism by which dormant DTCs instruct brain astrocytes to promote their survival through the formation of neuroprotective microenvironments.

Targeting the Reprogrammed PIK3R1-Insulin-Glucose Metabolism Pathway: A Novel Therapeutic Strategy for Lethal Prostate Cancer

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POSTER 24

Background: Prostate cancer is projected to cause 35,250 deaths in the U.S. in 2024, highlighting the urgent need to understand the genomic alterations driving its progression to castration-resistant metastatic prostate cancer (mCRPC), which is incurable. This study focuses on PIK3R1, a regulatory subunit of the PI3K signaling pathway, frequently mutated in aggressive prostate tumors. PIK3R1 alterations are more common in mCRPC and linked to worse clinical outcomes.
Study design & Results: We generated 22 patient-derived PIK3R1 mutations and analyzed their effects on protein expression in 293T cells, finding that some mutations activate AKT phosphorylation while others inhibit it. We also employed CRISPR/Cas9 to create PIK3R1 knockout 22RV1 cells. Insulin treatment of PIK3R1 KO (Clone B5) cells increased levels of AR downstream targets, suggesting a link between PIK3R1 loss and altered AR signaling. Additionally, increased mTOR signaling in PIK3R1 KO (Clone E1) cells indicates potential for metastasis and therapy resistance. PIK3R1 CRISPRed 22RV1 clones (B5 and E1) developed large prostatospheres compared to control cells. Indicating the loss of PIK3R1 may increase tumorigenic potential in vitro.
Conclusion: Our findings demonstrate that loss of PIK3R1 enhances tumorigenic potential and sensitivity to pharmacological AKT inhibitors in prostate cancer models. Given the aggressive nature of PIK3R1-altered tumors, this research provides insights into the molecular mechanisms underlying lethal prostate cancer progression and suggests that targeting the PI3K/AKT pathway alongside insulin blockers could benefit patients with mCRPC harboring PIK3R1 alterations. This study lays the groundwork for future therapeutic strategies in this challenging cancer subtype.

Single-Cell Analysis of the Biliary Epithelial Cells Reveals Dynamic Heterogeneity and Plasticity During Ductular Reaction

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POSTER 25

Cholangiocarcinoma (CCA) is a highly lethal malignancy and the second most prevalent primary liver cancer, predominantly arising from biliary epithelial cells (BECs). Currently, there are no effective treatments for this disease. Notably, there is an increased incidence of CCA among patients with primary sclerosing cholangitis (PSC) and metabolic dysfunction-associated steatohepatitis (MASH). However, the mechanisms by which cell-autonomous and non-cell-autonomous signaling influence BEC plasticity during the pathogenesis of CCA remain largely uncharacterized.

The ductular reaction, a prominent feature in various chronic liver diseases including MASH and PSC, exhibits both pro-regenerative and pro-disease characteristics. This phenomenon holds significant potential for elucidating the interactions between BECs and their microenvironment.

Utilizing single-cell profiling in both mouse and human models, we identified a specific subpopulation of BECs that is markedly enriched in the context of PSC and MASH. This proliferative BEC subpopulation arises from naive BECs following injury. Notably, we observed the upregulation of several genes in this disease-specific BEC population, including S100A6 and ANXA3, which have been validated in mouse models of MASH and in cases of DDC-induced liver injury. These genes are implicated in inflammatory processes and epithelial-to-mesenchymal transition (EMT), suggesting enhanced communication between BECs and endothelial cells (ECs).

Our objective is to investigate the functional roles of these candidate genes in biliary epithelial cell proliferation and morphological alterations, as well as their interactions with endothelial cells, utilizing BEC-derived liver organoids and EC co-cultures. Through this research, we aim to provide novel mechanistic insights into the ductular reaction.

EZH2 degradation as a therapeutic approach for Merkel Cell Carcinoma

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POSTER 26

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer with poor prognosis due to resistance to chemotherapy and immunotherapy. Novel therapeutic approaches are required to tackle this disease. Overexpression of Enhancer of zeste homolog 2 (EZH2) is found in >50% of MCCs and correlates with metastasis and decreased 5-year survival. EZH2 is a catalytic subunit of Polycomb Repressor Complex 2 that deposits methyl groups on histone H3 lysine 27 (H3K27me3) to repress gene expression. We hypothesized that EZH2 is crucial for MCC growth and targeting EZH2 would be an effective treatment strategy against MCC. Two pharmacological strategies are available to target EZH2: small-molecule inhibitors of EZH2 methyltransferase (MT) activity (EZH2MTi) and EZH2 proteolysis targeting chimera (PROTAC) that cause degradation of EZH2 protein (EZH2DEG). We observed that nanomolar doses of EZH2DEG reduced MCC growth, whereas EZH2MTi treatment did not meaningfully impede MCC growth even at high doses. We conclude that MCC requires the total functions of EZH2 protein, including MT-independent activities not yet described in MCC, and that EZH2DEG has strong potential as an MCC treatment. We discovered that EZH2DEG treatment of NU/J mouse xenografts of MCC cell lines decelerated MCC tumor growth in vivo as well. Our findings illustrate that EZH2 is critical to MCC growth and that abrogation of EZH2 impedes MCC growth. Our studies build a foundation for innovative MCC treatments by improving our understanding of the biology of EZH2 in MCC.

Multi-faceted role of CD83+ macrophages in promoting multi-organ metastasis in breast

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POSTER 27

Metastasis is responsible for 97-99% of breast cancer-related deaths in the United States. Metastatic triple-negative breast cancer (TNBC) disproportionately affects young women, especially those of African ancestry and is highly aggressive. There is a great need for more effective targeted immunotherapies beyond immune checkpoint inhibitors that can treat mTNBC while reducing drug toxicity. Tumor associated macrophages(TAMs) can contribute to tumor growth and metastatic progression. In developing rational macrophage-targeting therapies, it is essential to understand the extent of TAM heterogeneity and identify actionable markers in an organ-specific manner. We observed an increased infiltration of Cd83+ metastatic TAMs in BC-induced bone metastases compared to lung metastases in murine models and in chemotherapy resistant primary tumors. Treating E0771-derived lung metastases with an anti-CD83 ab resulted in dramatic tumor regression despite the relative paucity of Cd83+ mTAMs in lung metastases. Single cell RNA sequencing revealed that while the percentage Krt8+ tumor cells decreased after CD83 treatment, the number of total Cd68+ mTAMs actually increased along with Cd82+ Cd62l+Cd44+ T effector memory cells. KEGG analysis of differentially expressed genes in Cd68+ Cd83+ mTAMs in CD83ab treated lung mets revealed the expression of genes associated with bone marrow lineage myeloid cells and an up regulation of pathways related to antigen processing/presentation & T cell activation. E0771 bone metastases had opposite trends, where, CD83ab treatment resulted in a worsening of bone metastases and the accumulation of ascite fluid as well as muscle invasion of the metastatic tumor. Flow analysis revealed a decreased in Cd8+ T cells as well as mTAMs accompanied by an accumulation of Ly6g+ neutrophils. I hypothesize that CD83 plays a multi-faceted cell/organ type specific role in mTNBC. Targeting CD83 in certain contects can deplete CD83+ mTAM subsets, differentiate Cd8+ T cells into an effector-memory phenotype, and can directly target tumor cells leading to tumor regression. This warrants further investigation into the organ/cell-specific role of Cd83 targeting in mTNBC.

Targeting Quiescent Leukemic Stem Cells through Oxidative Phosphorylation in NUP98-NSD1 Fusion-Positive Acute Myeloid Leukemia

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POSTER 28

NUP98-NSD1 fusion-positive acute myeloid leukemia (AML) is a subtype associated with poor prognosis in children. This fusion involves the nuclear pore complex member NUP98 on chromosome 11 and the histone methyltransferase NSD1 on chromosome 5. Individuals with concurrent NUP98-NSD1 and transcription factor WT1 mutations exhibit chemotherapy resistance and poor outcomes. However, the molecular characteristics and developmental dependencies for NUP98-NSD1-driven AML remain unclear.

To address these gaps, we established a humanized AML model by using CRISPR/Cas9 to induce endogenous NUP98-NSD1 fusion and WT1 knockout in primary hematopoietic stem cells (HSCs) from human fetal liver, postnatal umbilical cord blood, pediatric, and adult bone marrow. Notably, NUP98-NSD1 displayed a developmental dependency, where its expression transformed fetal liver HSCs, to a lesser extent cord blood, but, remarkably, not pediatric and adult bone marrow HSCs. In vitro, endogenous NUP98-NSD1 oncoprotein conferred clonal selection and proliferation advantages in HSCs. In vivo, xenotransplantation into mice recapitulated myeloid bias and leukemogenesis. ScRNA-seq and scATAC-seq revealed that NUP98-NSD1 maintains a self-renewal program characterized by aberrant expression of HOX genes, heightened inflammatory pathways, and enhanced epigenetic activity of EGR1, MYC, and AP-1 complex. Importantly, WT1 loss-of-function mutations exacerbated these effects, leading to a more primitive hierarchy enriched with quiescent leukemic stem cells (LSCs) that were resistant to chemotherapy.

This study elucidates the developmental specificity of NUP98-NSD1 fusion-positive AML, particularly the role of WT1 mutations in therapy resistance. PRDM16, a regulator of stem cell self-renewal and oxidative metabolism, is crucial for leukemia progression and a potential therapeutic target in NUP98-NSD1 AML.

Molecular insights of low-PSA–expressing high-risk prostate cancer

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POSTER 29

Background: Despite advances in molecular genetics and genome sequencing, identifying lethal and non-lethal forms of prostate cancer in the early stages of the disease remains challenging. A significant number of prostate cancer patients have high-risk tumors that produce low levels of prostate-specific antigen (PSA) at the time of diagnosis. There is an indication that the therapeutic outcome of these patients, may be considered unfavorable as they may not respond as well to ADT or androgen receptor pathway inhibitors (ARPI). Consequently, this type of high-risk prostate cancer with low PSA secretion may be associated with a unique subtype of the disease that has not been fully characterized.
Methods: From 2013 to 2023, 3,619 patients diagnosed with prostate cancer underwent robotic-assisted radical prostatectomy (RARP) performed by a single experienced surgeon (AKT). The patients were classified into four groups based on their PSA levels: very low (< 2.5 ng/ml), low (2.6-5.0 ng/ml), medium (5.1-8.0 ng/ml), and high (> 8.0 ng/ml). We conducted an ANOVA analysis to compare various clinical characteristics across these groups. Additionally, we explored the gene expression profiles from the Cancer Genome Atlas (TCGA) prostate cancer cohort, specifically examining differential PSA/KLK3 mRNA expression within cancer cells. Furthermore, we selected and expanded single-cell clones from the LNCaP parental population to investigate the molecular landscape of low PSA expressing prostate tumor cells.
Results: We observed that patients with high-risk prostate cancer and a very low PSA level (< 2.5 ng/ml) had higher rates of biochemical recurrence compared to those with high-grade cancer but PSA levels (> 2.5 ng/ml). Additionally, we noticed a significantly high presence of seminal vesicle (p = 1.058e-05) and neurovascular invasion (p = 0.0047) in both the very low and high PSA groups compared to the other two groups. Importantly, the very low PSA group exhibited a higher rate of lymph node invasion (p = 0.00095) compared to the other three groups. Our transcriptomic analysis in the TCGA cohort revealed that genes which are upregulated in the very low PSA group compared to the high PSA group are significantly (p < 0.001) enriched in metastatic castration-resistant prostate cancer (mCRPC). Furthermore, our study on LNCaP-derived clones revealed an increased migration potential and elevated expression of mesenchymal markers in LNCaP-PSALow clones compared to the clones expressing high PSA
Conclusions: Our research identifies a distinct subtype of localized prostate cancer, demonstrating that low-PSA, high-risk prostate cancer is significantly invasive and leads to potentially lethal disease. This highlights the need for further investigation to better understand the biology of this poorly defined but aggressive subtype of localized prostate cancer.

Gut microbiome affects hepatocellular carcinoma (HCC) progression and response anti-PD1 therapy

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POSTER 30

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths. Although the advent of immune-checkpoint blockade (ICB) in the treatment of HCC has improved the therapeutic options, patient selection strategies, and discovery of predictive biomarkers are imperative. Different ICB responses have been correlated with gut microbiome signatures across different cancer types. We aim to address the crosstalk between patient's gut microbiota composition and clinical response to ICB in HCC patients. We performed deep shotgun metagenomic sequencing of stools from HCC patients on R2810-ONC-1866 clinical trial of Cemiplimab (anti-PD1). We identified a gut microbial abundance of Bacteroides as a signature of non-response to Cemiplimab. To address the direct impact of gut microbiome composition in tumor progression we generated an immunocompetent mouse model of HCC that overexpresses c-Myc and b-Catenin, two common mutations in liver cancer patients. These tumors have previously been shown to be resistant to anti-PD1 monotherapy, while responsive to the combination anti-PD1 + anti-VEGF, demonstrating certain plasticity on their resistance to anti-PD1. We demonstrated the pro-tumoral effect of Bacteroides enrichment in this model of HCC by dysregulating the gut microbiome composition with specific antibiotics. We finally demonstrate the utility of our model to address the human gut microbiome effects in HCC development by performing fecal transplants with patient's stools that present Bacteroides-high vs Bacteroides-low, validating the significant correlation between HCC progression and Bacteroides enrichment in vivo.

ABSTRACTS

Identifying targets of precancerous neoantigen-specific T cell surveillance in patients with Lynch syndrome and immune suppression programs supporting colorectal cancer progression

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POSTER 31

Background: Patients with pathogenic germline variants in the mismatch repair (MMR) genes, or Lynch syndrome (LS), are at increased risk of developing colorectal cancer (CRC). These MMR protein deficient (MMRd) tumors are characterized by a high microsatellite instability (MSI-H) phenotype. We and others have identified shared, immunogenic frameshift (fs)-neoantigen peptides in MMRd cancers and fs-specific T cell receptors (TCRs) in primary and metastatic tumors. Additionally, elevated T cell infiltrates in normal colon mucosa are associated with later CRC onset. Therefore, we hypothesized that fs-neoantigen-specific T cell surveillance may be observed early in MMRd tumor development, but in advanced stages of disease, fs-specific T cell activity may be abrogated by immune regulatory programs in the tumor microenvironment (TME).
Methods: PBMCs and LS normal, precancerous (adenoma) and malignant colon tissues were analyzed from a cohort of 92 patients. Immune landscape was assessed with single-cell and spatial transcriptomics. Whole-exome and bulk RNA sequencing were performed to assess fs-neoantigen expression. Functional T cell phenotypes and specificity were analyzed with in vitro T cell expansion and stimulation assays(4), ex vivo flow cytometry and single-cell RNA/TCR sequencing of PBMCs and tissue-infiltrating T cells in MMRd lesions.
Results: Shared frameshift mutations encoding highly immunogenic peptides were expressed in MMRd normal mucosa, precancerous adenomas, and tumor lesions of LS patients. T cells capable of recognizing these peptides were identified in peripheral blood, precancerous tissue, and the TME of LS patients. Immune editing of neoantigens early in tumor development is evidenced by i) distinct neoantigen repertoires in precancerous tissues compared to MMRd tumors cross-sectionally and ii) exposure to MMRd lesions earlier in life precludes recurrence of high affinity (but not low affinity antigens) in subsequent lesions later in life in the same LS patients. Transcriptomic and ex vivo functional analysis also revealed that T cells in tumors relative to normal/precancerous tissue show reduced functional capacity associated with an infiltration of immunosuppressive myeloid cell subsets (primarily tumor-associated neutrophils and TREM1+ macrophages).
Summary: Overall, we present a map of the fs-neoantigen landscape in MMRd tumor development in patients with LS to serve as high quality and off-the-shelf vaccine targets for cancer immunoprevention in LS . We also identify specific immune regulatory programs supporting neoplastic progression.

Investigating the Role of Aquaporin-4 in Glioblastoma-associated Vasogenic Cerebral Edema

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POSTER 32

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults, with a dismal 5-year survival rate of ~6.5%. Vasogenic cerebral edema is a severe complication that occurs in majority of GBM patients, leading to a significant increase in intracranial pressure, neurological deficits, and increased mortality rates. GBM-associated edema is almost exclusively managed by the corticosteroid dexamethasone, the use of which is associated with immunosuppression and interference with radiation therapy. While there is considerable research on edema formation, virtually no research exists on how edema resolution occurs. This highlights a need to better understand the mechanisms of edema resolution to identify alternative treatment strategies. The water channel aquaporin-4 (AQP4) is a critical player in the brain's water homeostasis, with increased levels in GBM compared to the normal brain. To gain more insight into the role of AQP4 in GBM-associated edema, we used the RCAS/tv-a system to generate de novo GBM with different driver mutations in Aqp4 knockout (KO) and wild-type (WT) mice. Our results indicated that Aqp4 KO tumor-bearing mice had decreased survival, increased edema, and smaller endpoint tumor burden on MRI. Aqp4 loss significantly decreased astrocyte coverage in the tumor core but not the tumor periphery. Our scRNA-seq data suggests that Aqp4 loss results in an astrocytic shift towards a less reactive, progenitor-like state and affects the macrophage and T-cell populations in the microenvironment. Ongoing studies focus on further characterization of the impact of Aqp4 loss on astrocytes, tumor cells, and their interactions with the microenvironment.

ABSTRACTS

Investigating changes in cellular metabolism on tumor antigen uptake by conventional dendritic cell 1 (cDC1)

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POSTER 33

Dendritic cells, or primary antigen-presenting cells, are critical immune sentinels essential in bridging the body's adaptive and innate immune responses. Among DC subsets, conventional dendritic cell subset 1 (cDC1) stands out for its unique ability to cross-present antigens, which is crucial for initiating effective cytotoxic T-cell responses against tumors. Unlike normal cells, abnormal lipid accumulation (leading to lipid droplet formation) is observed in several cancers, which is considered one of the major reasons for DC dysfunction. However, very few reports are available on the impact of lipid metabolism on dendritic cells' antigen cross-presentation ability.

To achieve this, in-vitro generated cDC1s were cocultured with heat-killed dying tumor cells and subsequently subjected to bulk RNA sequencing. Transcriptomic profiling was performed on cDC1s in the presence or absence of dead cells. Our analysis revealed distinct transcriptome profiles highlighting differential gene expression patterns linked to lipid metabolism, cholesterol regulation, and lipid droplet formation. Furthermore, we carried out various in-vitro metabolic functional assays and observed increased lipid drop formation on antigen uptake. We validated this observation using confocal microscopy and lipidomic study. In the future, we will reprogram lipid metabolism (using pathway inhibitors and gene knockdowns) and test dendritic cell-based antigen cross-presentation.

Our findings suggest a crucial role for lipid metabolism in modulating the cross-presentation machinery of cDC1s within the tumor microenvironment. Understanding the mechanisms underlying this interplay between lipid metabolism and. DC cross-presentation may offer novel insights into the design of immunotherapeutic strategies aimed at harnessing DC-mediated immune responses against cancer.

MASH selects against immunogenic hepatocellular carcinoma

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POSTER 34

Metabolic Dysfunction-Associated Steatohepatitis (MASH) is the fastest-growing cause of Hepatocellular Carcinoma (HCC) in the US. MASH- HCC is associated with particularly poor prognosis, which might be partly due to its late and difficult diagnosis. Previous studies suggested that MASH alters liver immunity by activating dendritic cells and PD1+ CXCR6+ CD8 T cells that attack hepatocytes independently of antigen expression. This T-cell activity exacerbates liver damage and inflammation, promoting the progression from MASH to HCC. These findings support the hypothesis that MASH behaves like an auto-aggressive disorder, inducing a shift in T-cell function from protective to harmful. Interestingly, it was suggested that MASH-HCC might be associated with resistance to aPD1 therapy. However, the roles of immune cells during the development of early MASH-HCC lesions and how they fail to mount an effective anti-tumor response remain poorly understood. To investigate these mechanisms, we developed an immuno-genetic MASH model in mice that combines diet-induced MASH with hydrodynamic gene delivery. This approach enables stable expression of oncogenes, deletion of tumor suppressor genes, and antigen expression within MASH-damaged livers. Unexpectedly, in the MASH model, hepatocyte overexpression of immunogenic MYC (MYC-lucOS) enhanced immunosurveillance and failed to generate tumors. Immunophenotyping revealed increased dendritic cell populations and heightened infiltration of antigen-specific CD8+ T cells in the livers of mice fed a Western diet. In addition, we found that MASH-HCC patients tend to have a lower mutational burden compared to HCC from other etiologies. These results indicate that MASH-affected livers are highly effective at initiating anti-tumor immune responses against antigen-expressing cancer cells. We hypothesize that in advanced MASH, continuous immune pressure drives immune editing, selecting for tumor cells with low mutational and neoantigen burdens, impaired antigen presentation or mutations promoting immune escape and exhaustion. Understanding the mechanisms of immune activation in MASH and the strategies used by cancer cells to evade immune clearance could lead to the development of new therapies and reveal biomarkers for predicting responses to immunotherapy.

Overcoming immune resistance in MSI-H tumors

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Patients with mismatch repair deficiency (MMRd) are highly susceptible to several cancers, but while anti-PD-1 therapy has shown promise, many MMRd and mismatch repair proficient (MMRp) colorectal cancers (CRC) do not respond. We discovered that collaborations between immune cells like MHC+ C1Q+ CXCL9+ macrophages and TCF+ BHLHE40+ PRF1+ T cell subsets play a crucial role in controlling MMRd tumor growth, especially after anti-PD-1 treatment. However, immune evasion and resistance are associated with high levels of TIM3, LAG3, TIGIT, and PD-1 on T cells, along with immunosuppressive TREM2 macrophages and monocytes. Combining anti-PD-1 with anti-LA3, anti-CTLA4, and anti-TREM2 resulted in up to 100% tumor eradication in MMRd CRC and 73% in MMRp CRC, compared with less than 10% with anti-PD-1 only, by leveraging macrophage, CD4+ and CD8+ T cell interactions. This study highlights the efficacy of multi-checkpoint and myeloid blockade in achieving complete tumor elimination in both MMRd and MMRp settings.

Epigenetic Therapy Boosts mRNA LNP Cancer Vaccine Efficacy Through Viral Mimicry Signaling

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POSTER 36

Epigenetic therapies can enhance cancer cell immunogenicity by activating transposable elements (TEs) and inducing type I interferon (IFN-I) responses, but they have largely failed as monotherapies in solid tumors. mRNA-based vaccines have renewed interest in cancer vaccination for melanoma; however, exploration of vaccination combination with epigenetic therapy remains limited and the role of TEs in such combinations is not well understood.

In this study, we identify the epigenetic therapies azacytidine (aza) and entinostat (ent) as agents that activate a cancer cell-intrinsic IFN-I response dependent on reverse transcriptase activity and the MAVS and STING nucleic acid sensing pathways, indicative of a TE-mediated viral mimicry response. We demonstrate that aza and ent transform the antigen repertoire of melanoma cells and activate expression of treatment-inducible antigens (TIAs) across different antigen classes. Specifically, we confirm that aza enriches the expression of cancer-testis antigens (CTAs) and show that it preferentially upregulates TEs with coding potential. Using an ovalbumin model system, we show that T cells exposed to TIAs maintain superior functionality compared to those exposed to stably expressed antigens and that vaccination targeting treatment-induced ovalbumin can effectively limit tumor growth. Finally, combining aza with a tumor-associated antigen and neoantigen-targeting mRNA vaccine significantly enhances therapeutic efficacy in a preclinical melanoma model, an effect that is dependent on cancer cell-intrinsic MAVS and STING signaling.

Our findings robustly characterize the impact of epigenetic therapy-induced TE responses on the efficacy of translationally relevant mRNA vaccination, highlighting a strategy to improve mRNA vaccines with similar antigen targets currently in clinical trials for melanoma.

Co-opting Viral Mimicry to Combat Chemoresistance

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POSTER 37

Chemotherapy targets rapidly dividing cells, which can include immune cells. While this suggests chemotherapy may counteract immunotherapy, paradoxically, many chemotherapies enhance immune checkpoint blockade, leading to widespread use of chemoimmunotherapy regimens. Understanding how chemotherapies engage the immune system is crucial for designing effective drug combinations that prevent resistance. Chemotherapies that induce double-strand breaks (DSBs) can engage the immune system through cancer cell production of type-I IFN (IFN-I). Moreover, DSB therapies, like topoisomerase inhibitors (TOPis), can disrupt chromatin in cancer cells, resulting in loss of epigenetic control over repressed loci, including transposable elements (TEs). In a process known as viral mimicry, TE transcription spurs formation of immunogenic RNA species, prompting antiviral sensors to trigger an innate signaling cascade culminating in IFN-I. Although TOPis were previously reported to activate a subset of TEs in vitro, their ability to initiate viral mimicry responses in cancer cells is unknown. The work presented here characterizes viral mimicry induced by TOPis in cancer and investigates how this response augments tumor surveillance. Through transcriptomics, immunofluorescence, and flow-cytometry, we demonstrate TOPis induce epigenetic dysregulation and TE de-repression in cancer, prompting generation of RNA species that trigger cancer autonomous IFN-I through RIG-I and cGAS pathways. Using in vivo studies of mice harboring tumors with CRISPR/Cas9 knockouts of innate signaling mediators, we further show viral mimicry mediates TOPi efficacy in tumors lacking intact STING signaling. Together, this work uncovers a previously undescribed mechanism of TOPi activity, offering new context for the mechanisms driving antitumor efficacy and immune engagement following chemotherapy.

Leveraging cDC1 populations for enhanced RNA cancer vaccination

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RNA vaccines have revolutionized the efficiency of vaccine development against infectious diseases. Despite these advances, there is a clear lack of consensus on the optimal RNA cancer vaccine strategy, with RNA vaccines trialed clinically exhibiting different designs in terms of the RNA base modifications and lipid-based delivery platforms utilized, warranting further study. An ideal cancer vaccine should elicit robust anti-tumor cytotoxic CD8+ T and CD4+ Th1 cell responses, orchestrated by specialized antigen presenting cell populations such as conventional type-1 dendritic cells (cDC1). cDC1 frequency, activity and function is often impaired in the tumor microenvironment and reduced cDC1 intratumoral infiltration correlates with poor prognosis and disease progression. Therefore, determining how RNA vaccine formulations and strategies can be engineered to enhance cDC1 activation and expansion, for more effective induction of anti-tumor immunity is essential. We have generated a sequence-to-RNA vaccine pipeline, allowing the design and production of tumor antigen targeted RNA vaccines. Preliminary data generated using this RNA vaccine pipeline and Batf3-/- mice suggests a key role for cDC1s in RNA vaccine efficacy, and additionally demonstrate that RNA base modification, incorporating N1-Methylpseudouridine (m1Ψ), promote more efficient induction of tumor antigen-specific T cells following vaccination. Additionally, we demonstrate a vaccination strategy utilizing delivery of adjuvant RNAs encoding FLT3L to promote the activation and expansion of intratumoral cDC1s, with therapeutic efficacy evaluated in our neoantigen characterized orthotopic tumor models. Ultimately this project aims to harness cDC1s to develop an optimal RNA vaccine formulation and strategy for use in the prevention and treatment of cancer.