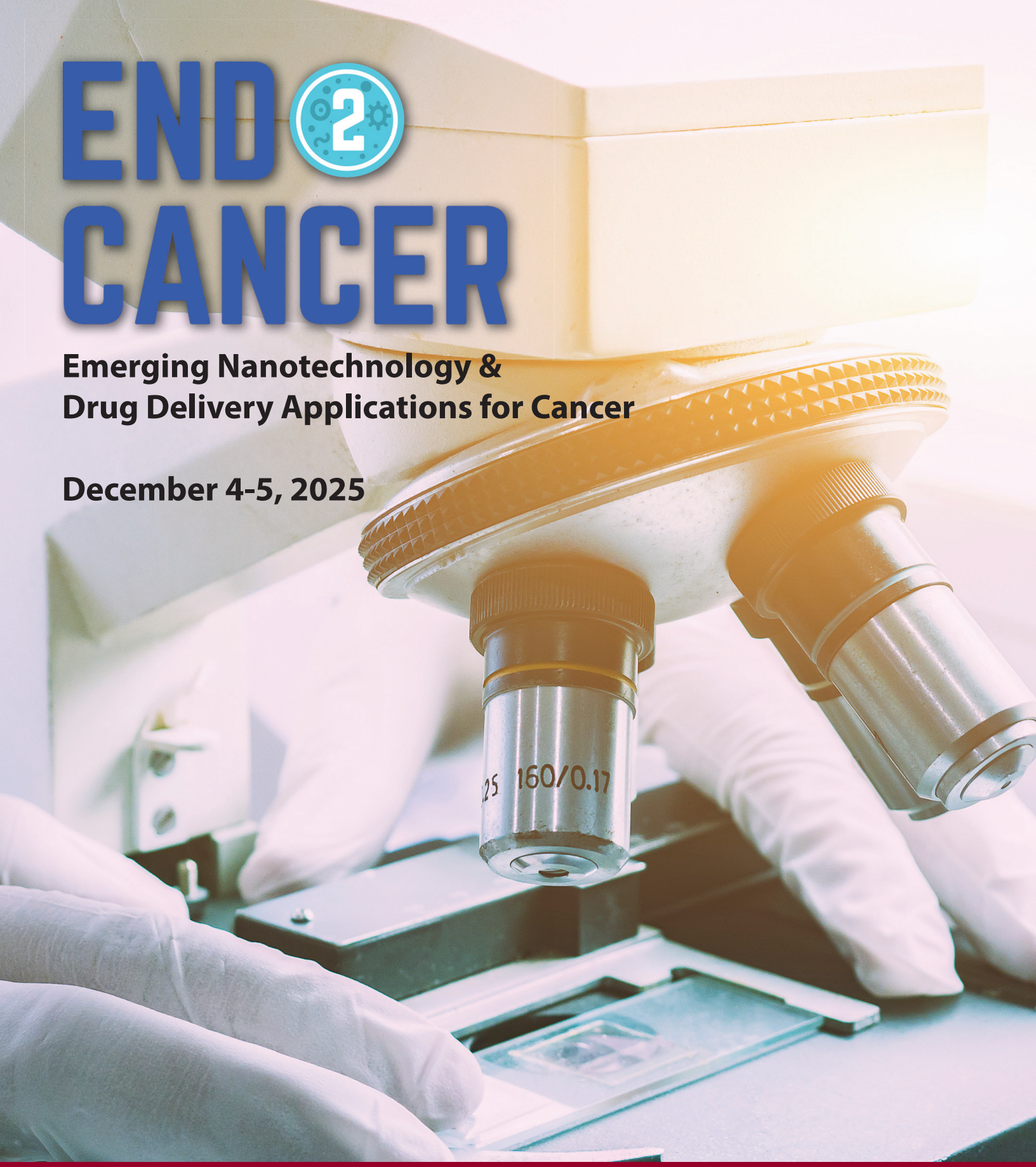
END 2 CANCER

Emerging Nanotechnology & Drug Delivery Applications for Cancer

December 4-5, 2025



OU Health | Stephenson Cancer Center

The UNIVERSITY of OKLAHOMA

WELCOME LETTER

Dear Speakers, Faculties, Scientists, Students, Fellows, Cancer Survivors, Patient Advocates, Educators and Heroes fighting against cancer,

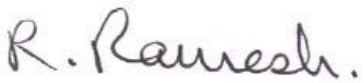
The conference organizing committee on behalf of the OU Health Stephenson Cancer Center is extremely thrilled to welcome you all to the seventh "**END2CANCER**: **E**merging **N**anotechnology and **D**rug **D**elivery Applications for **Cancer**" conference being held at the University of Oklahoma Health Campus, Oklahoma City, OK from December 4th to December 5th, 2025.

This multi-disciplinary two-day conference is carefully planned and will host keynote, plenary and invited lectures by eminent scientists who will discuss under organized thematic sessions new and emerging concepts, and technologies developed for the diagnosis, detection, and treatment of cancer. Additionally, numerous educational and training opportunities for students, fellows and research staff are planned at the meeting.

The conference organizing committee sincerely appreciates and thanks the OU Health Stephenson Cancer Center (SCC), the College of Medicine (COM) and the Jim & Christy Everest Endowed Chair in Cancer Developmental Therapeutics for their support in hosting the conference.

We look forward to welcoming you all to the incredible "Sooner" state of Oklahoma and participating in this exciting conference.

Sincerely,



Rajagopal Ramesh, PhD – Chairman
Professor & Jim & Christy Everest Endowed Chair in Cancer Development Therapeutics
Department of Pathology
University of Oklahoma Health Campus

Associate Director for Cancer Research Education, Training and Coordination
Project Co-Leader, Nanomedicine Program
OU Health Stephenson Cancer Center

JOSEPH HARROZ

UNIVERSITY PRESIDENT

Serving the University of Oklahoma for over 28 years in various leadership roles, Joseph Harroz Jr. was named the 15th president of OU on May 9, 2020. Harroz's previous service to the university includes a one-year term as interim president, nine years as dean of the College of Law, 12 years as general counsel, and two years as vice president for executive affair

Under Harroz's leadership, the university has ambitiously pursued the fulfillment of its "Lead On, University" Strategic Plan, sparking a new era of excellence and elevating OU's position as a top-tier public research university with life-changing impact.

More students than ever are choosing OU, with the last four years seeing record-breaking freshman classes. With nearly 5,600 students, the Class of 2028's size represents a 20% increase over the last two years. The class is breaking other university records, with the highest number of first-generation college students and the most Oklahoma residents of any other incoming class.

OU's research momentum continues to accelerate, reaching a record $411 million in externally funded research awarded. The OU research enterprise has achieved an average 12% annual growth rate for awards over the last four years, and OU ranks among the top 8% of research universities nationally.

The historic merger in 2021 to create OU Health has brought immense benefits to the state and its people. As Oklahoma's first comprehensive academic health system, OU Health is delivering world-class health care, training tomorrow's health professionals, and meeting the toughest medical challenges with pioneering research and innovation.

OU Health Stephenson Cancer Center remains Oklahoma's only national cancer institute-designated cancer center, standing at the forefront of cancer research and treatment. In April 2024, OU announced it will bring NCI-level cancer care to thousands more

Oklahomans by expanding the Stephenson Cancer Center to Tulsa. Plans are in motion to build a state-of-the-art facility at OU-Tulsa, with an anticipated opening in June 2027.

Supporting Oklahoma's workforce is another key priority of the Strategic Plan, and OU has significantly expanded enrollment in several key academic areas to support workforce demands. Nursing has seen its annual number of graduates more than double, with over 600 joining the workforce in fall 2024, up from around 300 in 2021. Across all Health Sciences academic programs, fall 2024 new student enrollment is up 18% compared to two years ago. OU has also expanded its top-ranked aviation program to meet growing workforce demands, with enrollment in the School of Aviation more than doubling in just two years. The OU Polytechnic Institute at OU-Tulsa welcomed its inaugural class in fall 2024. OUPI combines cutting-edge curriculum in critical STEM fields with on-site training, equipping graduates to transform Oklahoma industries and fuel economic prosperity.

An abundance of other successes have come to life since the Strategic Plan's introduction – the announcement of a historic $2 billion fundraising campaign, a continued focus on balancing excellence with affordability, the addition of premier freshman housing, entering the SEC, and more. In spring 2024, OU embarked on a Strategic Plan refresh to ensure this living, breathing roadmap continues to evolve to meet the challenges of an ever-changing world while still serving the distinct needs of the OU community. Learn more about the Strategic Plan at **ou.edu/leadon**.

A native Oklahoman, Harroz graduated Phi Beta Kappa from OU in 1989 with a Bachelor of Arts degree in economics and a minor in zoology. He earned his J.D. in 1992 from Georgetown University Law Center. A grandson of Lebanese immigrants to Oklahoma, Harroz is father to Joseph, Zara, and Jude, and is married to Ashley Harroz.

GARY RASKOB

PROVOST

Gary E. Raskob, Ph.D., is Senior Vice President and Provost for the University of Oklahoma Health Campus and its programs across the state. Provost Raskob has overall responsibility for the educational and research programs of its seven colleges, and its Centers of Excellence - the OU Health Stephenson Cancer Center and the OU Health Harold Hamm Diabetes Center. He serves on the Boards of the OU Health System, the University Hospitals Authority and Trust, and the Oklahoma City Chamber of Commerce.

Dr. Raskob holds academic appointments in the College of Public Health and the College of Medicine and is a Regents Professor of Epidemiology and Medicine. He began his career at the University of Oklahoma in 1991. His research and scholarly interests are in the prevention and treatment of deep-vein thrombosis and pulmonary embolism; clinical trials and antithrombotic drug development; evidence-based medicine and public health; and the translation of research evidence into practice.

Dr. Raskob has participated extensively in clinical practice guideline development for several specialty organizations including the American Society of Hematology (ASH), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the American Society of Clinical Oncology (ASCO). He also served as a member of the external advisory panel on thrombosis and hemostasis for the National Heart, Lung and Blood Institute (NHLBI), and as an advisor on blood disorders to the Centers for Disease Control and Prevention (CDC). He was the inaugural Chair of the Steering Committee for the World Thrombosis Day initiative of the International Society in Thrombosis and Haemostasis (ISTH), from 2013 through 2019. He is author or co-author of more than 200 publications on the prevention, diagnosis and treatment of thromboembolic disease, including 21 articles in the New England Journal of Medicine.

Dr. Raskob is a past Chair of the Board of Directors for the Association of Schools and Programs of Public Health, the organization which represents more than 100 universities in

the US and globally with accredited schools and programs in public health, and a past Chair of the Oklahoma City-County Board of Health, which has oversight responsibility for the health department serving the 1.3 million residents of Oklahoma City-County.

Dr. Raskob received his PhD in pharmaceutical sciences from the University of Oklahoma; a Master of Science (MSc) degree in clinical epidemiology and health research methodology from McMaster University in Hamilton, Canada; and a Bachelor of Science degree in pharmacology from the University of Toronto, Canada. He serves as the 9th Senior Vice President and Provost of the OU Health Campus.

ROBERT MANNEL

OU STEPHENSON CANCER CENTER DIRECTOR

Robert Mannel, MD, is the Director of the Stephenson Cancer Center at the University of Oklahoma Health Sciences Center. Since 2010 he has held the Rainbolt Family Endowed Chair in Cancer.

In addition, he serves as the Associate Vice Provost for Cancer Programs at OUHSC, and he is a tenured Professor in the OU Department of Obstetrics and Gynecology.

As the Director of the Stephenson Cancer Center, Dr. Mannel oversees all clinical, research, administrative and educational activities related to oncology medicine and cancer research at OU.

Under his leadership, the Stephenson Cancer Center has grown to become the largest provider of cancer care in Oklahoma. When he was appointed Director in 2007, the Stephenson Cancer Center provided care for 1 out of every 20 cancer patients diagnosed in Oklahoma. Today, it is 1 out of every 6. This year, the Cancer Center will provide care for nearly 3,000 new adult and pediatric cancer patients.

During his time as Director, the amount of cancer research funding to investigators at OU has increased from under $5 million to nearly $50 million. The Stephenson Cancer Center is now the #1 ranked cancer center nationally for the number of patients participating in National Cancer Institute-sponsored clinical trials for promising new cancer therapies.

Dr. Mannel currently serves as the Chair for NRG Oncology, one of four organizations that make up the National Clinical Trials Network. NRG Oncology is the largest group within the Network, placing more cancer patients on NCI clinical trials than any other organization.

Dr. Mannel graduated from the University of Texas – College of Medicine at Galveston and completed his residency in obstetrics and gynecology at Scott and White Hospital in Temple, Texas. After residency, he completed a fellowship in gynecologic oncology at the University of California - Irvine.

In 1989, he joined the faculty at the University of Oklahoma and served as Chair of the OU Department of Obstetrics and Gynecology from 1997 to 2013. He was instrumental in developing the Section of Gynecologic Oncology at the University of Oklahoma into one of the top gynecologic oncology programs in the country.

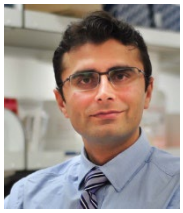
PLANNING COMMITTEE

Dr. Rajagopal Ramesh
Chairman
Professor, Dept of Pathology
University of Oklahoma Health Campus

Dr. C.V. Rao
Professor, Dept of Internal Medicine
University of Oklahoma Health Campus

Dr. Wei Chen
Member
Professor & Chair, Dept of Biomedical Engineering
University of Oklahoma

Dr. Dongin Kim
Member
Assistant Professor
Department of Pharmecutical Sciences
University of Oklahoma Health Campus



Dr. Pankaj K. Singh
Member
Professor and Founding Chairman
Dept of Oncology Science
University of Oklahoma Health Campus

Dr. Marmar Moussa
Member
Assistant Professor
University of Oklahoma

Dr. John R. Clegg
Member
Assistant Professor
Stephenson School of Biomedical Engineering
University of Oklahoma

Dr. Min Li
Member
Professor, Dept of Internal Medicine
University of Oklahoma Health Campus

Dr. Anupama Munshi
Member
Associate Professor
University of Oklahoma Health Campus

Dr. Takemi Tanaka
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Professor Section of Experimental Pathology
University of Oklahoma Health Campus

Dr. Handan Acar
Member
Assistant Professor
University of Oklahoma

Dr. Bulent Ozpolat
Member
Professor, Stephenson Endowed Chair
University of Oklahoma

Dr. Raid Aljumaily
Member
Professor, Dept of Internal Medicine
University of Oklahoma Health Campus

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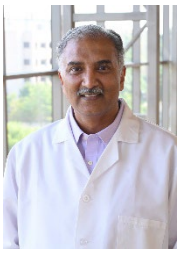
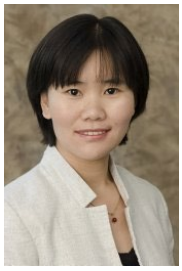
Dr. Maureen Cox
Member
Assistant Professor, Microbiology & Immunology
University of Oklahoma Health Campus

Dr. Surendra Shukla
Member
Assistant Professor
University of Oklahoma Health Campus



Dr. Dinesh Thotala
Member
Associate Professor and Director of Cancer Biology
University of Oklahoma Health Campus

Dr. Kamiya Mehla
Member
Associate Professor
University of Oklahoma Health Campus



Dr. Kai Ping Burrows
Member
Director of Laboratory Services
Laureate Institute for Brain Research

Dr. Murali Ragothaman
Member
Postdoctoral Fellow
University of Oklahoma Health Campus

Dr. Rafeh Naqash
Member
Assistant Professor, Director Immuno Oncology at Stephenson Cancer Center
University of Oklahoma Health Campus

Dr. Naoko Takebe
Member
Professor Department of Internal Medicine, College of Medicine
University of Oklahoma Health Campus

Dr. Venkateshwar Madka
Member
Assistant Professor, Internal Medicine

University of Oklahoma Health Campus

SCHEDULE AT A GLANCE

DECEMBER 4, 2025

7:00 am – 8:00 am	Breakfast
8:00 am – 8:20 am	Welcome & State of the Cancer Center
8:25 am – 10:20 am	Session I – Gene, mRNA & Drug Delivery
10:20 am – 10:40 am	Break
10:40 am – 12:15 pm	Session II – Cancer Biology and Therapy
12:15 pm – 2:00 pm	Lunch & Poster Session
2:00 pm – 3:55 pm	Session III – Extracellular Vesicles and Cancer
3:55 pm – 4:15 pm	Break
4:15 pm – 5:50 pm	Session IV – Transcriptomics and Data Science

DECEMBER 5, 2025

7:00 am – 8:00 am	Breakfast
8:00 am – 9:55 am	Session I – Drug Discovery, Development and Resistance
9:55 am – 10:10 am	Break
10:10 am – 12:25 pm	Session II – Cancer Metabolism – Biology and Targets
12:30 pm – 2:00 pm	Lunch & Poster Session
2:00 pm – 3:55 pm	Session III – Immuno-oncology
4:15 pm – 4:30 pm	Award Ceremony & Closing Remarks

END2CANCER: EMERGING NANOTECHNOLOGY AND DRUG DELIVERY APPLICATIONS FOR CANCER

DECEMBER 4 & 5, 2025
SAMIS EDUCATION CENTER – OU HEALTH CAMPUS

PRE-CONFERENCE

DECEMBER 3, 2025

DINNER FOR SPEAKERS AND INVITED GUESTS
OU HEALTH STEPHENSON CANCER CENTER 1ST FLOOR LOBBY

6:30 – 9:00 pm Plated Dinner

CONFERENCE

DECEMBER 4, 2025

Poster Display – All day (Level 1)

7:00 am – 8:00 am **Breakfast**
SAMIS AUDITORIUM, LEVEL 2

INAUGURATION AND WELCOME ADDRESS
SAMIS CONFERENCE ROOM (LEVEL 2)

8:00 am – 8:10 am **Introduction –** Dr. Rajagopal Ramesh
Professor, Department of Pathology, University of Oklahoma Health Campus

8:10 am – 8:20 am **State of the Cancer Center Address -** Dr. Robert Mannel
Director, OU Health Stephenson Cancer Center

SESSION I – GENE, mRNA & DRUG DELIVERY
SAMIS CONFERENCE ROOM (LEVEL 2)
Moderators: John Clegg, Bulent Ozpolat, Handan Acar

8:25 am – 8:30 am Session Introduction by Moderators

8:30 am – 9:00 am **Plenary Speaker** – Szu-Wen Wang, Ph.D.
Professor, Department of Chemical and Biomolecular Engineering, University of California, Irvine
"Molecular Engineering of Protein Nanoparticles for Cancer Immunotherapy "

9:00 am – 9:20 am Idris Raji, Ph.D.
Assistant Professor, Department of Chemistry and Biochemistry, University of Oklahoma
"Combinatorial development of lipid nanoparticles for mRNA delivery to the lungs."

9:20 am – 9:40 am Michael J. Mitchell, Ph.D.
Associate Professor, Department of Bioengineering, University of Pennsylvania
"Lipid nanoparticles for overcoming biological barriers to mRNA delivery"

9:40 am – 10:00 am Jyothi Menon, Ph.D.
Associate Professor, Department of Biomedical Engineering, Texas A&M University
"Target, Treat and Prevent: Advanced Drug Delivery Strategies for Cancer and Chronic Inflammation"

10:00 am -10:20 am Chang Wang, Ph.D.
Assistant Professor, School of Biomedical Engineering, OU Norman
"Intravenous administration of blood-brain barrier crossing conjugates facilitate oligonucleotides transport into central nervous system"

COFFEE BREAK
SAMIS AUDITORIUM (LEVEL 1)
10:20 am – 10:40 am

SESSION II – CANCER BIOLOGY AND THERAPY
SAMIS CONFERENCE ROOM (LEVEL 2)
Moderators: Xin Zhang, Anupama Munshi, Geeta Rao

10:40 am – 10:45 am Session Introduction by Moderators

10:45 am – 11:15 am **Plenary Speaker** – Rajgopal Govindarajan, DVM, Ph.D.
Professor and Chair, Department of Pharmaceutical Sciences, Ohio State University
"*Targeting De Novo and Salvage Pyrimidine Synthesis in Pancreatic Cancer*"

11:15 am – 11:35 am Min Yu, Ph.D.
Professor, Department of Pharmacology and Physiology, University of Maryland School of Medicine
"Tumor cell and microenvironmental niche co-regulate brain metastasis dormancy features"

11:35 am – 11:55 am — Devanand Sarkar, MBBS, Ph.D.
Professor, Department of Cellular, Molecular and Genetic Medicine, Virginia Commonwealth University
"Cooperation of co-amplified oncogenes in hepatocellular carcinoma (HCC)"

11:55 am – 12:15 pm — Ralf Janknecht, M.S., Ph.D.
Professor, Department of Cell Biology, University of Oklahoma Health Campus
"Oncogenic Enigma and Potential Drug Target: The Nucleotide Hydrolase DNPH1"

LUNCH & POSTER SESSION COMPETITION FOR HIGH SCHOOL, UNDERGRADUATE, POST-BACCALAUREATE STUDENTS, AND POST-DOCTORAL FELLOWS

SAMIS AUDITORIUM (LEVEL 1)
12:15 pm – 2:00 pm

SESSION III – EXTRACELLULAR VESICLES AND CANCER

SAMIS CONFERENCE ROOM (LEVEL 2)
Moderators: Kaiping Burrows, Murali Ragothaman, Rajagopal Ramesh

2:00 pm – 2:05 pm — Session Introduction by Moderators

2:05 pm – 2:35 pm — **Plenary Speaker** – Raghu Kalluri, M.D., Ph.D.
Professor, Department of Cancer Biology, MD Anderson Cancer Center
"Cancer without disease: Combining the concept of healthy living and aging with strategies to prevent malignant disease of cancer"

2:35 pm – 2:55 pm — Devika Soundara Manickam, Ph.D.
Associate Professor, Department of Neurology, UT Health, Houston
"Delivery of mitochondria using large extracellular vesicles"

2:55 pm – 3:15 pm — Aijun Wang, Ph.D.
Professor, Department of Biomedical Engineering and Surgery, University of California Davis
"Engineering stem cell derived extracellular vesicles for targeted delivery"

3:15 pm – 3:35 pm — Sunila Pradeep, Ph.D.
Associate Professor, Department of Obstetrics and Gynecology, Medical College of Wisconsin
"Extracellular Vesicles Steer Immune Responses in the Tumor Microenvironment"

3:35 pm – 3:55 pm — Shailendra Dwivedi, Ph.D.
Assistant Professor, Department of Obstetrics and Gynecology, University of Oklahoma Health Campus
"EV-Mediated Sarcoma-Carcinoma Crosstalk in Uterine Carcinosarcoma"

COFFEE BREAK

SAMIS AUDITORIUM (LEVEL 1)

3:55 pm – 4:15 pm

SESSION IV – TRANSCRIPTOMICS AND DATA SCIENCE

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Pankaj Singh, Takemi Tanaka, Marmar Moussa

4:15 pm – 4:20 pm	Session Introduction by Moderators
4:20 pm – 4:50 pm	**Plenary Speaker** – Denis Wirtz, Ph.D. Professor, Department of Chemical and Biomolecular Engineering, Johns Hopkins University

"3D multi-omic mapping of precancerous lesions and tumors"

4:50 pm – 5:10 pm	Jun Li, Ph.D. Professor and Chairman, Department of Molecular Genetics and Genome Sciences, University of Oklahoma Health Campus

"Mechanism or Prediction - have we delivered?"

5:10 pm – 5:30 pm	Sooryanarayana Varambally, Ph.D., MBA Professor, Department of Pathology, University of Alabama Birmingham

"From Big Data to Discoveries: Comprehensive Cancer Proteogenomic Platforms for Data Analysis and Target Discovery"

5:30 pm – 5:50 pm	Tae Gyu Oh, Ph.D. Assistant Professor, Department of Oncology Science, University of Oklahoma Health Campus

"Uncovering the Molecular Landscape of Rare Diseases through Spatial Technologies"

DINNER

OKLAHOMA CONTEMPORARY ARTS CENTER

6:30 pm – 10:00 pm

6:30 pm – 7:30 pm	Networking and Passed Hors d'oeuvres
7:30 pm – 10:00 pm	Dinner

DECEMBER 5, 2025

Poster Display – All day (Level 1)

7:00 am – 8:00 am **Breakfast**

SAMIS AUDITORIUM, LEVEL 2

SESSION I – DRUG DISCOVERY, DEVELOPMENT AND RESISTANCE

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: C.V. Rao, Dongin Kim, Raid Aljumaily

8:00 am – 8:05 am Session Introduction by Moderators

8:05 am – 8:35 am **Plenary Speaker** – Trever Bivona, M.D., Ph.D.
Professor, Department of Medicine, University of California San Francisco

"New insights into lung cancer pathogenesis and therapy resistance"

8:35 am – 8:55 am Naoko Takebe, M.D., Ph.D.
Professor, Department of Medicine, University of Oklahoma Health Campus

"Evolutionary-Revolutionary: Berathomics for Early Cancer Detection"

8:55 am – 9:15 am Shwetal Mehta, Ph.D.
Professor; Department of Translational Neuroscience; Barrow Neurological Institute

"Breaking the Barrier: PK/PD anchored Hybrid Early Phase Clinical Trials for CNS Cancers"

9:15 am – 9:35 am Abdul Rafeh Naqash, M.D.
Associate Professor, Department of Medicine, OU Health Stephenson Cancer Center

"Integrated molecular and clinical characterization of pulmonary large cell neuroendocrine carcinoma"

9:35 am – 9:55 am Jie Wu, Ph.D.
Professor, Department of Pathology, University of Oklahoma Health Campus

"Progress and challenge in RET-targeted cancer therapy"

COFFEE BREAK

SAMIS AUDITORIUM (LEVEL 1)

9:55 am – 10:10 am

SESSION II_– CANCER METABOLISM – BIOLOGY AND TARGETS

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Kamiya Mehla, Surendra Shukla, Min Li

10:10 am – 10:15 am	Session Introduction by Moderators
10:15 am – 10:45 am	**Plenary Speaker** – John Blenis, Ph.D. Professor, Department of Pharmacology, Weill Cornell Medical College

"Mechanisms linking diet and metabolism to cancer development & progression"

10:45 am – 11:05 am	Ramandeep Rattan, Ph.D. Professor, Division of Gynecologic Oncology, HFH-MSU Health Sciences, Henry Ford Health, Detroit, MI

"Feeding the Fight: Reprogramming Macrophages Through Diet in Ovarian Cancer"

11:05 am – 11:25 am	Todd W. Miller, Ph.D. Professor, Department of Pharmacology and Toxicology, Medical College of Wisconsin

"Leveraging metabolic vulnerabilities in ER+ breast cancer."

11:25 am – 11:45 am	Amber Vu, Ph.D. Staff Scientist, Department of Radiation Oncology, University of Oklahoma Health Campus

"CMLD-2-mediated inhibition of HuR induces mitochondrial dysfunction and autophagy in cancer cells"

11:45 am – 12:05 pm	Srinivas Malladi, Ph.D. Associate Professor, Department of Pathology, UT Southwestern Medical Center

"Targetable Metabolic Dependencies of Brain Metastatic Cells"

12:05 pm – 12:25 pm	Simon Grelet, Ph.D. Assistant Professor, Department of Biochemistry and Molecular Biology, University of South Alabama

"Lineage Tracing and Fate Mapping of Nerve-to-Cancer Cell Transfer of Mitochondria During Metastasis"

LUNCH & POSTER SESSION COMPETITION FOR GRADUATE STUDENTS

SAMIS AUDITORIUM (LEVEL 1)

12:30 pm – 2:00 pm

SESSION III_– IMMUNO-ONCOLOGY

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Maureen Cox, Dinesh Thotala, Venkateshwar Madka

2:00 pm – 2:05pm	Session Introduction by Moderators

2:05 pm – 2:35 pm	**Plenary Speaker** – David A. Barbie, M.D. Professor, Dana Farber Cancer Institute

"Unleashing cGAS-STING signaling to promote cancer immunogenicity"

2:35 pm – 2:55 pm	Sean Lawler, Ph.D. Associate Professor, Department of Pathology and Laboratory Medicine, Brown University

"Designing new approaches for glioblastoma: from drug delivery to antiviral therapies"

2:55 pm – 3:15 pm	Chih-Chi Andrew Hu, Ph.D. Professor, Houston Methodist Neal Cancer Center

"Secretory IgM drives malignant progression of B cell leukemia"

3:15 pm – 3:35 pm	Rajagopal Ramesh, Ph.D Professor, Department of Pathology, University of Oklahoma Health Campus

"Rekindling the Innate Immunity Signaling Through HuR-Targeted Therapy in Medulloblastoma"

3:35 pm – 3:55 pm	Wei Chen, Ph.D. Professor and Director, School of Biomedical Engineering, University of Oklahoma

"Local Ablative Immunotherapy for Cancer"

AWARD CEREMONY & CLOSING REMARKS

SAMIS CONFERENCE ROOM (LEVEL 2)

4:15 pm – 4:30 pm

GENE, mRNA & DRUG DELIVERY

SESSION I – GENE, mRNA & DRUG DELIVERY

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: John Clegg, Bulent Ozpolat, Handan Acar

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"Target, Treat and Prevent: Advanced Drug Delivery Strategies for Cancer and Chronic Inflammation"

10:00 am -10:20 am	Chang Wang, Ph.D. Assistant Professor, School of Biomedical Engineering, OU Norman

"Intravenous administration of blood-brain barrier crossing conjugates facilitate oligonucleotides transport into central nervous system"

Szu-Wen Wang, Ph.D.

Plenary Speaker

Professor, Department of Chemical and Biomolecular Engineering

University of California, Irvine

Szu Wang is a Professor of Chemical and Biomolecular Engineering at the University of California, Irvine. She received her B.S. in Chemical Engineering at the University of Illinois, Urbana-Champaign, and her M.S. and Ph.D. in Chemical Engineering at Stanford University. Dr. Wang has held research scientist positions at The Liposome Company and TransForm Pharmaceuticals, biotechnology companies that specialized in aspects of drug delivery and formulations. Currently, her research group at UC Irvine uses engineering approaches to design biomimetic materials, with an emphasis in immunomodulation and molecular delivery of therapeutics. Applications of these investigations are in biomedical areas such as cancer immunotherapy, vaccines, and drug delivery, which have led to stimulating collaborations with the UC Irvine School of Medicine. This interdisciplinary research has been supported by the National Science Foundation, National Institutes of Health, and the Department of Defense.

ABSTRACT

New biomaterials that can be programmed to elicit immunological responses have enormous potential in therapeutic applications. Our research group uses a biomimetic approach to design such materials, and we apply tools of recombinant engineering to produce nanostructured protein-based entities. One aspect of our research has focused on engineering highly-stable, 30-nm protein nanoparticles as delivery systems for antigens and other immune-activating molecules. These particles can overcome the low immunogenicity of tumor microenvironments and educate the immune system to recognize tumor-associated antigens and neoantigens. Their efficacy has been demonstrated by activating antigen-specific CD8 T cell responses and increasing *in vivo* survival in different tumor models. Our studies have also examined several design strategies that can be incorporated into these nanoparticle delivery systems to synergistically enhance anti-tumor potency.

Idris Raji, Ph.D.

Speaker

Assistant Professor, Department of Chemistry and Biochemistry

University of Oklahoma

Dr. Idris Raji did his PhD in organic chemistry at Georgia Tech, during which he developed small molecules that modulate the functions of epigenetic regulating proteins. Following postdoctoral training at the center for drug discovery at Baylor College of Medicine, he joined the Langer-Anderson lab at MIT and Harvard Medical School, where he helped develop lipid nanoparticles for vaccine and non-vaccine applications. Subsequently, Dr. Raji joined the non-viral delivery group at CRISPR Therapeutics as a senior scientist, where he continued working on developing lipid nanoparticles for CRISPR-Cas9 mRNA delivery to extrahepatic tissues. He recently joined the Department of Chemistry and Biochemistry at the University of Oklahoma, Norman as an Assistant Professor.

Dr Raji's research group at OU is developing small molecules for cancer immunotherapy and lipid nanoparticles for *in-vivo* delivery of nucleic acids as therapeutic interventions in monogenic diseases that can benefit from gene therapy.

ABSTRACT

Since the clinical approval of two lipid nanoparticle (LNP)-based mRNA vaccines for COVID-19, there has been growing interest in leveraging LNPs for non-vaccine applications. However, a one-size-fits-all approach is inadequate, implying that LNPs must be custom-made for specific therapeutic contexts. Current efforts to develop novel LNPs for nucleic acid delivery mostly focus on discovering new ionizable lipids—key components of LNPs—and optimizing their composition for targeted applications.

This presentation highlights our recent work on developing LNPs for efficient mRNA delivery to the lungs. By synthesizing libraries of ionizable lipids with novel chemical structures and optimizing formulation parameters, we created LNPs that outperform benchmark formulations in pulmonary mRNA delivery.

Michael Mitchell, Ph.D.

Speaker

Associate Professor, Department of Bioengineering

University of Pennsylvania

Michael J. Mitchell is an Associate Professor of Bioengineering at the University of Pennsylvania, and the Lipid Nanoparticle Delivery Systems Group Leader at the Penn Institute for RNA Innovation. He received a BE in Biomedical Engineering from Stevens Institute of Technology in 2009, a PhD in Biomedical Engineering with Prof. Michael King from Cornell University in 2014. He was a Postdoctoral Fellow in Chemical Engineering with Prof. Robert Langer at MIT from 2014-2017, prior to pursuing his independent career at University of Pennsylvania in 2018. The Mitchell lab's research broadly lies at the interface of biomaterials science, drug delivery, and cellular and molecular bioengineering to fundamentally understand and therapeutically target biological barriers. Specifically, his lab engineers new lipid and polymeric nanoparticle platforms for the delivery of different nucleic acid modalities to target cells and tissues across the body. His lab applies their research findings and the technologies developed to a range of human health applications, including the engineering of CAR T cells for cancer immunotherapy, mRNA vaccines, genome editing, cardiovascular disease, and in utero therapeutics to treat disease before birth.

Mitchell has received numerous awards as an independent investigator, including the National Institutes of Health Director's New Innovator Award, the Rising Star Award from the Biomedical Engineering Society, the Career Award at the Scientific Interface from the Burroughs Wellcome Fund, and the Research Scholar Award from the American Cancer Society. In 2022 Mitchell was named "Emerging Inventor for the Year" by Penn's for Innovation in recognition for his lipid nanoparticle technologies and received the Young Investigator Award from the Society for Biomaterials, the T. Nagai Award from the Controlled Release Society, and the National Science Foundation CAREER Award. In 2023 he was named a Young Innovator in Cellular and Molecular Bioengineering, and in 2024 he received the Controlled Release Society Young Investigator Award. He was named a Top 1% Highly Cited Researcher by Clarivate Analytics, and received the Kabiller Rising Star Award from Northwestern University in 2025. He is a co-founder and serves on Scientific Advisory Board of numerous biotechnology companies focused on developing non-viral delivery technologies for genetic medicines, including Liberate Bio and Capstan Therapeutics.

ABSTRACT

Recent years have witnessed tremendous developments and breakthroughs in the field of RNA-based therapeutics and vaccines. The distinct mechanisms of exogenous RNAs and analogs, including messenger RNAs, small interfering RNAs, microRNAs, and antisense oligonucleotides, have brought them unprecedented potential to treat a variety of pathological conditions. However, the widespread application of RNA therapeutics and vaccines is hampered by their intrinsic features (e.g., instability, large size, and dense negative charge) and formidable host barriers. Development of safe and efficient vectors is key for successful delivery and translation of RNA therapeutics and vaccines. In this talk, I will discuss our efforts towards the development of new lipid nanoparticles (LNPs) that enable the delivery of RNA therapeutics and vaccines to target cells and tissues *in vivo*. Furthermore, I will describe new therapeutic strategies utilizing these LNPs for (i) mRNA delivery to solid tumors for cancer immunotherapy, (ii) in vivo reprogramming of immune cells for in situ CAR T cell engineering, (iii) targeting the placenta to treat deadly pregnancy disorders.

Jyothi Menon, Ph.D.

Speaker

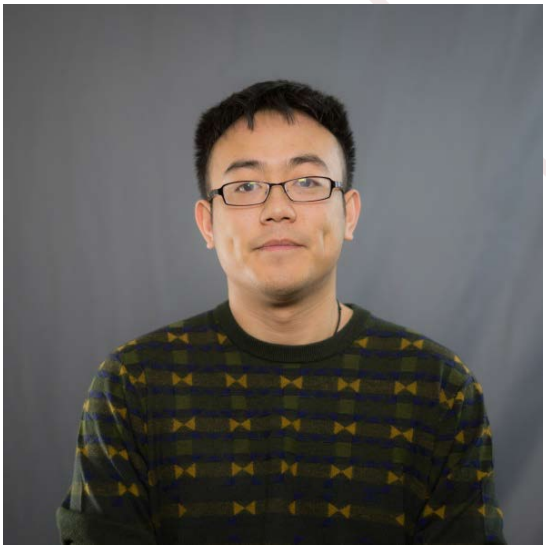
Associate Professor, Department of Biomedical Engineering

Texas A&M University

Dr. Jyothi Menon is an Associate Professor of Biomedical Engineering at Texas A&M University. Her research focuses on developing targeted drug delivery systems and tissue engineering strategies to treat chronic lung and liver diseases and prevent their progression to cancer. Her research has been supported by the National Cancer Institute through the Cancer Moonshot Scholars initiative, and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Dr. Menon has authored over 40 peer-reviewed publications, three book chapters, and holds two patents in the fields of nanomedicine and tissue engineering. Prior to joining Texas A&M in 2025, she was an Associate Professor of Biomedical and Pharmaceutical Sciences at the University of Rhode Island. She received her Ph.D. in Biomedical Engineering from the University of Texas (UT) at Arlington - UT Southwestern Medical Center joint program and then completed her postdoctoral training at the University of Oxford, UK.

ABSTRACT

Persistent, chronic inflammation is closely linked with the onset and progression of several cancers. In the liver, alcohol-associated inflammation poses a significant oncogenic risk. Although promising progress has been made in the treatment of chronic inflammatory disorders, challenges such as systemic drug toxicity and off-target side effects remain. Nanoparticle-based drug delivery formulations can potentially improve the delivery of anti-inflammatory and anti-cancer compounds to the site of action for treatment and to prevent disease progression. We have developed polymeric nanoparticle-based drug delivery systems that are engineered to target specific cells (e.g. Kupffer cells) in the liver and simultaneously deliver anti-inflammatory therapies for site-specific and effective treatment of chronic alcohol-associated liver inflammation. In mouse models of alcohol-associated liver disease (ALD), our developed nanoparticle system showed excellent cytocompatibility, targeted liver accumulation, and marked reduction in pro-inflammatory cytokine production, lipid droplet formation and serum aspartate aminotransferase and alanine aminotransferase levels. Taken together, our data demonstrates the potential of our nanoparticle-based targeted therapies to modulate inflammatory microenvironments, offering a novel strategy for cancer prevention. Ongoing studies are assessing this versatile nanoparticle system for the treatment of late-stage liver disease and liver cancer.



Chang Wang, Ph.D.

Speaker

Assistant Professor, School of Biomedical Engineering

University of Oklahoma

Dr. Chang Wang joined the School of Biomedical Engineering at the University of Oklahoma as a tenure-track assistant professor in August 2025. He completed his postdoctoral research at the Icahn School of Medicine at Mount Sinai and Mount Sinai Hospital. Dr. Wang earned his Ph.D. from Lehigh University and his B.Sc. from Tianjin University.

ABSTRACT

Delivery of oligonucleotides to the central nervous system (CNS) remains challenging because of the restrictive nature of the blood-brain barrier (BBB). We developed a BBB-crossing conjugate (BCC) system that facilitates delivery into the CNS through γ-secretase-mediated transcytosis. Intravenous administration of a BCC10-oligonucleotide conjugate demonstrated effective transportation of the oligonucleotides across the BBB and gene silencing in animal models and human brain tissues.

CANCER BIOLOGY AND THERAPY

SESSION II – CANCER BIOLOGY AND THERAPY

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Xin Zhang, Anupama Munshi, Geeta Rao

10:40 am – 10:45 am	Session Introduction by Moderators
10:45 am – 11:15 am	**Plenary Speaker** – Rajgopal Govindarajan, DVM, Ph.D. Professor and Chair, Department of Pharmaceutical Sciences, Ohio State University

"*Targeting De Novo and Salvage Pyrimidine Synthesis in Pancreatic Cancer*"

11:15 am – 11:35 am	Min Yu, Ph.D. Professor, Department of Pharmacology and Physiology, University of Maryland School of Medicine

"Tumor cell and microenvironmental niche co-regulate brain metastasis dormancy features"

11:35 am – 11:55 am	Devanand Sarkar, MBBS, Ph.D. Professor, Department of Cellular, Molecular and Genetic Medicine, Virginia Commonwealth University

"Cooperation of co-amplified oncogenes in hepatocellular carcinoma (HCC)"

11:55 am – 12:15 pm	Ralf Janknecht, M.S., Ph.D. Professor, Department of Cell Biology, University of Oklahoma Health Campus

"Oncogenic Enigma and Potential Drug Target: The Nucleotide Hydrolase DNPH1"

Rajgopal Govindarajan, DVM, Ph.D.

Plenary Speaker

Professor and Chair, Department of Pharmaceutical Sciences

Ohio State University

I am Professor and Chair of the Division of Pharmaceutics and Pharmacology, OSU College of Pharmacy. I am a participating member of the Translational Therapeutics program in the OSU Comprehensive Cancer Center (OSUCCC). I have nearly 20 years of experience in preclinical anti-cancer drug development. My research program is broadly focused on nucleoside analog developmental therapeutics in cancer, viral, and certain rare human genetic disorders. We have been particularly working on understanding the role of solute carrier (SLC) nucleoside transporters in mechanisms governing the hematopoietic homeostasis, stemness, and therapeutic drug efficacy and toxicity in pancreatic cancer. My training is in the areas of veterinary medicine (DVM), cancer biology (PhD), and drug pharmacology (PKPD) (Postdoc) and has extensively used preclinical rodent models and analytical methods (e.g., LC-MS/MS based metabolomics) to evaluate investigative therapeutic agents. At Ohio State University Comprehensive Cancer Center (OSUCCC), we have collaborative ties with expert medicinal chemists, gastroenterologists, oncologist, statisticians, and immunologists which support our current research projects.

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) exhibits remarkable metabolic adaptability, leveraging both de novo and salvage nucleotide synthesis pathways to sustain proliferation under nutrient-limited conditions. While inhibitors of dihydroorotate dehydrogenase (DHODH)—a key enzyme in de novo pyrimidine biosynthesis—have shown promising preclinical efficacy in certain cancers, their clinical success has been limited, particularly in PDAC. In this study, we introduce Hosu-53, a novel and potent DHODH inhibitor with broad activity across PDAC models. Differential responses to Hosu-53 were driven by compensatory mechanisms. Mechanistic investigations revealed that DHODH inhibition in sensitive PDAC lines triggered apoptosis, ferroptosis, and G_2/M cell cycle arrest. In contrast, resistant lines circumvented the blockade through upregulation of the nucleoside salvage pathway, autophagy, and macropinocytosis. Functional assays confirmed that activation of the salvage pathway mediates resistance by recycling extracellular nucleosides, thereby bypassing the need for de novo synthesis. In orthotopic syngeneic PDAC mouse models, dual inhibition of DHODH and equilibrative nucleoside transporter 1 (ENT1) significantly suppressed tumor growth and metastatic spread. Notably, this combination therapy also induced broad immunomodulatory changes within the tumor microenvironment, shifting it toward a more pro-inflammatory and immune-active (“hot”) state, indicative of enhanced antitumor immune engagement. These findings underscore

the potential of metabolic targeting to disrupt tumor-intrinsic survival pathways while simultaneously reshaping the immune landscape to favor antitumor immunity. Dual inhibition of de novo and salvage nucleotide synthesis emerges as a promising therapeutic strategy to overcome resistance and potentiate immune responses in PDAC.

Min Yu, Ph.D.

Speaker

Professor, Department of Pharmacology and Physiology

University of Maryland School of Medicine

I am a tenured Professor with research focuses on understanding the genetic, epigenetic and microenvironmental regulations of circulating tumor cells (CTCs) that lead to initiation of cancer metastasis in various organs. The overarching goal is to leverage on the knowledge to improve the detection, treatment and prevention of metastasis.

Hematogenous metastasis is initiated by a rare subset of CTCs in the blood stream, but the identity and properties of those metastasis-initiating cells are not well understood. This gap of knowledge is largely due to the challenge in isolating and analyzing those rare cells in the blood. I have made significant contribution to the improved technologies for isolating and analyzing the properties of CTCs in the blood streams of cancer patients. I performed the first RNA-seq analysis of CTCs and functionally validated the pro-metatatic role of a candidate found in CTCs (*Yu, et al., Nature 2012*). I showed dynamic epithelial and mesenchymal characteristics in patients' CTCs and their correlation with treatment responses (*Yu, et al., Science 2013*). We pioneered long-term *ex vivo* cultures of patient-derived CTCs and performed the first individualized drug susceptibility testing (*Yu, et al., Science 2014*), which subsequently also helped elucidating other novel insights related to CTCs and metastasis. My laboratory has performed detailed analyses of the patient-derived CTC lines in xenograft assays and showed that they can recapitulate the major metastatic patterns as seen in corresponding patients. Further functional studies also led to new understanding of underlying mechanisms for brain metastasis, including drivers for crossing the blood-brain-barrier and colonization at the brain (*Klotz, et al, Cancer Discovery, 2020*). To understand the complex interactions of CTCs with the tumor microenvironment, we have discovered various mechanisms promoting metastatic propensity of CTCs, including microenvironment-triggered TAK1 kinase-mediated autocrine signals (*Iriondo, et al, Nature Communications, 2018*), long term hypoxic memory of suppressing type I interferon signaling (*Iriondo, et al, Cancer Research, 2024*), and a truncated KRT81 that alters biomechanics of the cells and promote CTC clustering (*Kang, et al, Advanced Science, 2023)*. We also continue to improve the technologies and methods for single CTC analysis (*Kamal, et al, Scientific Reports 2019; Teng, et al, MCR, 2020; and Kamal, et al, Cancers, 2023)*. Combining the unique resource of patient-derived CTC lines and our expertise in analyzing CTCs and modeling cancer metastasis, we aim to decipher the mechanisms and identify therapeutic targets for cancer metastasis in the metastatic precursors. Our recent effort has deeply focused on using new single cell technologies to understand human brain metastasis and mechanisms of stress-resistance in CTCs, as well as hypoxic memory impact on CTCs and metastasis.

I have established many models, tools and collaborations related to metastasis, supervised trainees to publish independently, managed many funding awards, and participated in collaborative research and grants. Therefore, I have the training and experience to support my role in this grant.

ABSTRACT

The interactions of tumor cells with the brain microenvironment to either suppress or promote brain metastasis formation are poorly understood. We took advantage of single-cell multiomics sequencing of human brain metastases to profile the molecular and cellular dynamics in tumor cells and associated microenvironment. Among different primary cancer types, notably with a prevalence of breast cancer, our data suggest that there are conserved yet distinct tumor cell subpopulations, governed by specific changes in gene expression, chromatin accessibility and tumor-stroma interactions. We identified and validated a tumor intrinsic transcription factor, together with the microenvironmental niche providing its ligand, to suppress brain metastasis outbreak, via both intrinsic and extrinsic mechanisms.

Devanand Sarkar, MBBS, Ph.D.

Speaker

Professor, Department of Cellular, Molecular and Genetic Medicine

Virginia Commonwealth University

Devanand Sarkar is a Professor in the Department of Cellular, Molecular and Genetic Medicine at Virginia Commonwealth University. His research focuses on hepatocellular carcinoma (HCC) and metabolic dysfunction-associated steatotic liver disease (MASLD). The laboratory studies molecular mechanisms of these diseases and evaluates novel and targeted treatment strategies using mouse models. His research has been continuously funded by NCI, NIDDK, DOD and other foundations. He is the Associate Director for Cancer Research Training and Education Coordination (CRTEC) of VCU Massey Comprehensive Cancer Center. He co-directs the PhD program in Clinical and Translational Sciences and is the contact PI of a T32 grant funded by NIH/NCATS.

ABSTRACT

Hepatocellular carcinoma (HCC), the primary malignancy of hepatocytes, is the sixth most common cancer and the third most common cause of cancer-related deaths globally with an increasing incidence. Most HCC cases are diagnosed at advanced stages with an expected survival of <2 years. It is, therefore, necessary to better understand the molecular pathogenesis of HCC and develop novel, targeted therapeutic strategies. Gains and amplifications of chromosome 8q are frequently seen in HCC. The oncogene MYC, encoding the transcription factor c-Myc, at 8q24.21 is in this amplicon. Among the molecular subclasses of HCC, the S2 subclass is characterized by a MYC signature and poor survival. The focus of research in the laboratory is to study several genes which show consistent co-amplification with MYC in HCC and other cancers in The Cancer Genome Atlas (TCGA). These genes include AEG-1/MTDH, MDA-9/SDCBP, TAF2 and SLC25A32. We study cooperation between MYC and these genes in HCC development and progression using a variety of mouse models, analyze the function of these genes in physiology and disease, and evaluate combination of targeted inhibition of MYC and these genes as a potential therapeutic for HCC. For targeted inhibition we use small molecule inhibitors as well as targeted nanoparticles delivering siRNA for these oncogenes. Our goal is to translate the pre-clinical findings to clinical trials with a view to ameliorating the sufferings and prolonging survival of scores of HCC patients.

Ralf Janknecht, M.S., Ph.D.

Speaker

Professor, Department of Cell Biology

University of Oklahoma Health Campus

My research has centered on how dysregulation of signaling pathways, transcription factors or enzymes is involved in tumorigenesis and development. In addition to biochemical and cell culture studies, my laboratory has successfully employed xenograft, transgenic and knockout mouse models to reveal the importance of various proteins in tumor initiation and progression. Furthermore, my expertise in cancer research was recognized by my invitation to numerous peer review panels, including those operated by the Department of Defense and the National Institutes of Health. Lastly, my 128 published manuscripts were cited more than 16,000 times (h-index = 70; Google Scholar), which might serve as an indicator of impact of the accomplished research

ABSTRACT

Breast cancer is worldwide a prominent malignancy, yet its pathophysiology is still not fully understood. To ameliorate this knowledge deficit, we examined if the highly understudied DNPH1 (2'-Deoxynucleoside 5'-phosphate *N*-hydrolase 1) enzyme would affect breast tumorigenesis. DNPH1 was overexpressed in breast tumors correlating with increased metastasis and reduced survival. Downregulation of DNPH1 diminished the oncogenic potential of breast cancer cells. Further, *Dnph1* knockout impaired HER2-mediated mammary tumor formation in mice. Stimulation of angiogenesis and subduing AMP levels may contribute to DNPH1's tumor promoting activities. Lastly, we show that DNPH1 inhibition can augment the cytotoxic effects of PARP inhibitors. Altogether, these results suggest that DNPH1 inhibition could represent a novel stand-alone therapy in breast cancer or serve as an adjuvant to PARP inhibitors in various cancers.

EXTRACELLULAR VESICLES AND CANCER

SESSION III – EXTRACELLULAR VESICLES AND CANCER

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Kai Ping Burrows, Murali Ragothaman, Rajagopal Ramesh

2:00 pm – 2:05 pm	Session Introduction by Moderators
2:05 pm – 2:35 pm	**Plenary Speaker** – Raghu Kalluri, M.D., Ph.D. Professor, Department of Cancer Biology, UT MD Anderson Cancer Center

"Cancer without disease: Combining the concept of healthy living and aging with strategies to prevent malignant disease of cancer"

2:35 pm – 2:55 pm	Devika Soundara Manickam, Ph.D. Associate Professor, Department of Neurology, UT Health, Houston

"Delivery of mitochondria using large extracellular vesicles"

2:55 pm – 3:15 pm	Aijun Wang, Ph.D. Professor, Department of Biomedical Engineering and Surgery, University of California Davis

"Engineering stem cell derived extracellular vesicles for targeted delivery"

3:15 pm – 3:35 pm	Sunila Pradeep, Ph.D. Associate Professor, Department of Obstetrics and Gynecology, Medical College of Wisconsin

"Extracellular Vesicles Steer Immune Responses in the Tumor Microenvironment"

3:35 pm – 3:55 pm	Shailendra Dwivedi, Ph.D. Assistant Professor, Department of Obstetrics and Gynecology, University of Oklahoma Health Campus

"EV-Mediated Sarcoma-Carcinoma Crosstalk in Uterine Carcinosarcoma"

Raghu Kalluri, M.D., Ph.D.

Plenary Speaker

Professor, Department of Cancer Biology

MD Anderson Cancer Center

Dr. Kalluri's research team is focused on performing innovative research to unravel how cells and their environment communicate to maintain organ health, and how such communication networks are altered in cancer and other diseases.

Current areas of research in the Kalluri laboratory include cancer biology and metastasis, the tumor microenvironment, tissue injury and regeneration and the biology of exosomes in health and disease. We investigate the biology of cancer with an implicit mission to develop new strategies for diagnosis and therapy. Dr. Kalluri's laboratory is a fertile training ground for the next generation of scientists and physician-scientists.

ABSTRACT

Cancer is not always lethal. Many cancers remain a contained and dormant group of abnormal cells, never progressing to invasive, malignant, or clinical disease. It is estimated that up to 35% of adults over the age of 40 may already have these contained cancers, or carcinoma in-situ. Individuals with these lesions can be said to have 'cancer without disease.' This talk will explore the question of what factors contribute to cancer remaining silent, and how can we exploit these factors to extend lifespan and continued good health? Early detection of in-situ carcinomas carries the risk of overdiagnosis and overtreatment, and the future of oncology must challenge and redefine cancer classification and treatment strategies. The next leap forward in cancer care will involve approaches to keep cancer contained, stave off clinical illness, and outlive the disease resulting from cancer.

Devika Soundara Manickam, Ph.D.

Speaker

Associate Professor, Department of Neurology

UT Health, Houston

Devika S Manickam received her Ph.D. in Pharmaceutical Sciences from Wayne State University (Detroit, MI). Her talk will focus on the development of extracellular vesicles for the delivery of mitochondria as a platform technology for treating a wide range of diseases associated with mitochondrial dysfunction. She has published 50 papers in leading drug delivery journals. She is one of the recipients of the 2022 Young Innovator award in Cellular and Molecular Bioengineering and also received the 2023 Young Investigator award in Bioengineering from the Controlled Release Society. Her research is currently supported by the National Institutes of Health and the Department of Defense.

ABSTRACT

Extracellular vesicles (**EVs**) are natural carriers of cellular cargo. EVs play a role in intercellular communication via transfer of their internal components, including lipids, proteins and nucleic acids. We study EV subsets that are either large or small: **lEVs** or **sEVs** isolated from human or mouse brain endothelial cells (**BECs**). Large EVs naturally incorporate mitochondria during their biogenesis. Our work has demonstrated that (1) lEVs but not sEVs contain mitochondria, (2) lEVs transfer mitochondria into recipient BECs and cortical and hippocampal neurons in mouse brain slices, (3) lEVs increase cellular ATP levels and mitochondrial function in the recipient oxygen-glucose deprived (**OGD**) BECs. Interestingly, recipient OGD BECs treated with lEVs displayed superior mitochondrial function (oxygen consumption- and extracellular acidification rates) compared to BECs treated with control sEVs that lack mitochondria. Moreover, lEVs isolated from donor BECs with compromised mitochondrial function failed to increase ATP levels in the recipient BECs—suggesting that the increased bioenergetics in the lEV-treated cells is a function of innate lEV mitochondria. (4) BEC-derived lEVs transfer their innate mitochondria that subsequently localized with recipient cell mitochondria in primary human BECs, suggestive of mitochondrial fusion and (5) mice injected with lEVs demonstrated a 50% reduction in infarct volume and improved neurological functions (scored as behavioral recovery) compared to vehicle-injected mice in a mouse middle cerebral artery occlusion model of ischemia/reperfusion injury (stroke). We, for the first time, have demonstrated the therapeutic efficacy of the larger, mitochondria-containing EVs, in a mouse model of transient ischemic stroke. Delivery of functional mitochondria is an effective approach to protect the post-ischemic blood-brain barrier—and therefore is a promising strategy to decrease long-term neurological dysfunction post-stroke.
Leveraging on our works developing BEC-derived lEVs containing mitochondria, we have also developed neuron-derived EVs and have demonstrated that (1) neuron-derived lEVs but not sEVs

contain mitochondria, (2) lEV-treated recipient heat-stressed neurons showed increased cell survival, and (3) intramuscularly-injected mitochondria-containing lEVs were delivered to spinal cord motor neurons in an EV dose-dependent manner in healthy mice. These findings suggest that lEV mitochondria may decrease motor neuron degeneration via increasing mitochondrial function and thereby decrease early muscle denervation in a mouse model of amyotrophic lateral sclerosis. Overall, our works highlight the broad therapeutic potential of innate lEV mitochondria to treat a variety of nervous system pathologies associated with mitochondrial dysfunction.

Aijun Wang, Ph.D.

Speaker

Professor, Department of Biomedical Engineering and Surgery

University of California Davis

Dr. Aijun Wang is a Chancellor's Fellow Professor of Surgery and of Biomedical Engineering at the University of California, Davis (UC Davis). He is the Vice Chair for Translational Research, Innovation and Entrepreneurship for the Department of Surgery, Co-founder and Co-Director of the Center for Surgical Bioengineering (CSB) and the inaugural Dean's Fellow in Entrepreneurship at the UC Davis School of Medicine. Dr. Wang's research focuses on developing tools and technologies that combine molecular, cellular, tissue and biomaterial engineering to promote regeneration and restore function. The Wang Group integrates single cell spatial multi-omics (transcriptomics, proteomics, and metabolomics) to study disease mechanisms and developmental process, and engineers and develops stem cell/gene therapy, extracellular vesicles/nanomedicine, and extracellular matrix/biomaterial scaffolds to treat a wide spectrum of congenital conditions and acquired diseases. Dr. Wang specializes in bringing therapeutics from bench to bedside, through innovative discovery, translational and investigational new drug (IND)-enabling studies, current Good Manufacturing Practice (cGMP) manufacturing, and conducting clinical trials in both human and companion animal patients.

ABSTRACT

Stem cell–derived extracellular vesicles (EVs) hold tremendous promise as therapeutic and regenerative platforms. Yet their translation for central nervous system (CNS) disorders has been constrained by limited blood–brain barrier (BBB) penetration and rapid degradation or diffusion following systemic administration. Our group has developed an integrated suite of EV engineering technologies to overcome these constraints and enable precise, cell-type–specific targeting within the CNS. Building on our *in utero* stem cell therapy program using placenta-derived mesenchymal stromal cells (PMSCs)—currently under clinical evaluation in a first-in-human, Phase 1/2a CuRe Trial—we identified that PMSC-derived EVs (PMSC-EVs) efficiently deliver neuroprotective cargo and confer functional benefits across multiple model systems. These include *in vitro* neuroprotection assays, a rodent model of multiple sclerosis, and an ovine model of spina bifida. We recently established a near-term ovine model of neonatal hypoxic-ischemic encephalopathy (HIE) and demonstrated that intranasally delivered PMSC-EVs safely achieve robust brain biodistribution, bypass the BBB, and exert disease-modifying effects with a strong safety profile. To further enhance CNS targeting, we engineered EV surfaces with cell-type– and extracellular matrix–specific ligands (e.g., peptides, aptamers). Using single-EV analytical platforms, we quantified surface conjugation efficiency and optimized modification strategies to tailor *in vivo* biodistribution. In parallel, we developed a novel hybrid EV technology by fusing membranes from distinct EV sources. Super-resolution microscopy and quantitative proteomics confirmed successful hybridization and revealed synergistic improvements in brain-cell targeting, neuroprotection, and immunomodulatory activity. Together, these advances demonstrate a modular and versatile platform for engineering and hybridizing EVs to achieve precision CNS delivery. This work outlines a translational path toward next-generation EV therapeutics for neurological injury and disease.

Sunila Pradeep, Ph.D.

Speaker

Associate Professor, Department of Obstetrics and Gynecology

Medical College of Wisconsin

I am an Associate Professor in the Department of Obstetrics and Gynecology at the Medical College of Wisconsin (MCW), Milwaukee, Wisconsin. My previous studies identified the underlying mechanisms utilized by ovarian cancer cells to metastasize through the hematogenous route (***Cancer Cell,*** *2014)*. In addition, we discovered an unexpected novel finding in tumor progression and metastasis: Erythropoietin, a widely used agent for treating anemia in cancer patients, binds to Ephrin B4 (***Cancer Cell****, 2015)*. I have established an active and externally funded research program that characterizes unknown functions of *extracellular vesicle proteins and immune cell reprogramming* in the ovarian cancer microenvironment (***Advanced Science***, 2022, 2025). Throughout my career, I have published several *manuscripts* in respected journals *like Cancer Cell*, *Cell Metabolism*, Advanced Science, *Nature Communications*, *Cancer Discovery, and Cancer Research*. I have an intense research and technical background in tumor immunology, exosome biology, ovarian cancer biology, and mouse tumor model systems. *Studies in my lab are primarily focused on the role of immune cells in ovarian cancer metastasis, the role of extracellular vesicles on immune cells, and their metabolic adaptation in the tumor microenvironment in ovarian cancer, and how to improve immunotherapy.*

ABSTRACT

Epithelial ovarian cancer (EOC), which represents nearly 90% of ovarian malignancies, remains the most lethal gynecologic cancer due to late-stage diagnosis, high recurrence rates, and limited responsiveness to immunotherapy. Although immune checkpoint blockade targeting PD-1/PD-L1 has transformed treatment for several malignancies, response rates in ovarian cancer remain below 5%, underscoring a critical gap in understanding how the tumor microenvironment (TME) subverts immune defense. Growing evidence identifies extracellular vesicles (EVs) as central mediators of oncogenic communication and immune suppression in EOC. We demonstrate that ovarian cancer cells secrete EVs enriched with the translation initiation factor eIF4E and the lipid kinase SPHK1, among other bioactive molecules. These vesicles are readily taken up by immune cells, particularly macrophages, where they enhance protein synthesis, metabolic reprogramming, and cholesterol efflux, fostering a pro-tumorigenic, immunosuppressive phenotype. EV-packaged SPHK1 catalyzes the extracellular generation of sphingosine-1-phosphate (S1P), activating S1PR1 signaling in both tumor and immune cells. Pharmacologic inhibition of HMG-CoA reductase (HMGCR) or SPHK1 mitigates these effects, reducing PD-L1 expression, limiting infiltration of immunosuppressive macrophages, and restoring antitumor immunity. Together, these findings reveal a unifying mechanism whereby tumor-derived EVs integrate translational and sphingolipid signaling to remodel the TME, promoting immune evasion and metastatic progression.

Shailendra Dwivedi, Ph.D.

Speaker

Assistant Professor, Department of Obstetrics and Gynecology

University of Oklahoma Health Campus

Dr. Shailendra Dwivedi is an Assistant Professor in the Gynecologic Oncology Section of the Department of Obstetrics and Gynecology at the University of Oklahoma Health Sciences Campus (OUHSC) in Oklahoma City, Oklahoma. An early-career investigator with broad expertise in cancer biology, cell signaling, noncoding RNA, and nuclear receptor signaling, his research integrates basic and translational approaches to elucidate molecular mechanisms underlying gynecologic malignancies, particularly uterine carcinosarcoma (UCS) and ovarian cancer.

Since joining OUHSC in 2013, Dr. Dwivedi has established a productive and well-funded research program supported by competitive awards, including grants from OCAST, PHF, the NCI (R21), and the DOD (Early Cancer Investigator Award). He has authored more than 45 peer-reviewed publications and a book chapter and plays an active role in mentoring graduate students and research fellows within the Graduate Program in Biomedical Sciences (GPiBS).

Dr. Dwivedi's early work helped uncover the critical role of transforming growth factor-beta (TGF-β) signaling in driving epithelial–mesenchymal transition (EMT) and disease progression in UCS. Building on these findings, his independent research now focuses on how the UCS tumor microenvironment and extracellular vesicle–mediated communication contributes to EMT, metastasis, and therapeutic resistance. His long-term goal is to identify novel biomarkers and targeted therapeutic strategies to improve outcomes for women with aggressive gynecologic cancers.

ABSTRACT

Background: Uterine carcinosarcoma (UCS), is a rare but highly aggressive uterine malignancy characterized by its high rates of metastasis and recurrence. Although UCS represents less than 5% of uterine cancers, it accounts for 16.4% of uterine cancer–related deaths, underscoring its disproportionate lethality. Current therapeutic options, including surgery, radiation, and chemotherapy, offer limited benefit in advanced disease. While metastatic UCS lesions are predominantly carcinomatous, accumulating evidence indicates that the sarcomatous compartment plays a key role in driving tumor progression by promoting epithelial–mesenchymal transition (EMT), lymphovascular invasion, and remodeling the tumor microenvironment. However, the molecular mechanisms underlying this sarcoma–carcinoma crosstalk remain largely unexplored, representing a critical gap in understanding UCS biology.

Methodology: To address this, we investigated whether sarcoma-derived extracellular vesicles (EVs) influence carcinoma proliferation, invasion, and EMT and identified potential molecular mediators. UCS cell lines (CS99, JHUCS1) modeled the sarcomatous, mesenchymal compartment, while Ishikawa cells represented the

epithelial carcinoma component. EVs (~150 nm) were isolated, characterized (CD9, CD63, Flotillin), and applied to Ishikawa cells. Functional assays assessed proliferation, invasion, EMT markers, and Akt/ERK signaling, and EV proteomics identified candidate mediators.

Results: UCS-conditioned media promoted carcinoma proliferation and invasion, with EVs as key mediators, as EV-depleted media has only limited effects. EVs isolated from both UCS cell lines induced proliferation, EMT, and migration. Mechanistically, EVs activated Akt and ERK signaling independently of EGFR, with SRC phosphorylation as a potential upstream event. Pharmacologic inhibition of Akt or ERK reduced EV-induced invasion.

Conclusion: Sarcoma-derived EVs are potent drivers of UCS carcinoma proliferation, invasion, and EMT, revealing a novel mechanism of sarcoma–carcinoma communication. Linking specific EV cargo to pro-tumorigenic signaling identifies the sarcoma compartment as a critical determinant of UCS aggressiveness and a promising therapeutic target. Targeting EV-mediated signaling may provide a strategy to limit UCS progression and improve outcomes.

Keywords: Uterine carcinosarcoma, extracellular vesicles, sarcoma–carcinoma crosstalk, proliferation, invasion, EMT, Akt, ERK.

Acknowledgement: Research is supported by the startup funds by OUHC to SD.

TRANSCRIPTOMICS AND DATA SCIENCE

SESSION IV – TRANSCRIPTOMICS AND DATA SCIENCE

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Pankaj Singh, Takemi Tanaka, Marmar Moussa

4:15 pm – 4:20 pm	Session Introduction by Moderators
4:20 pm – 4:50 pm	**Plenary Speaker** – Denis Wirtz, Ph.D. Professor, Department of Chemical and Biomolecular Engineering, Johns Hopkins University

"3D multi-omic mapping of precancerous lesions and tumors"

4:50 pm – 5:10 pm	Jun Li, Ph.D. Professor and Chairman, Department of Molecular Genetics and Genome Sciences, University of Oklahoma Health Campus

"Mechanism or Prediction - have we delivered?"

5:10 pm – 5:30 pm	Sooryanarayana Varambally, Ph.D., MBA Professor, Department of Pathology, University of Alabama Birmingham

"From Big Data to Discoveries: Comprehensive Cancer Proteogenomic Platforms for Data Analysis and Target Discovery"

5:30 pm – 5:50 pm	Tae Gyu Oh, Ph.D. Assistant Professor, Department of Oncology Science, University of Oklahoma Health Campus

"Uncovering the Molecular Landscape of Rare Diseases through Spatial Technologies"

Denis Wirtz, Ph.D.

Plenary Speaker

Professor, Department of Chemical and Biomolecular Engineering

Johns Hopkins University

Denis Wirtz is the Theophilius H. Smoot Professor of Engineering and Science Wirtz received a physics engineering degree from the Free University of Brussels in 1988, and MSc and PhD in Chemical Engineering from Stanford University in 1993. Wirtz has been the Vice Provost for Research of Johns Hopkins University since 2014.Through research at the interface of physics, engineering, and oncology, Wirtz has made seminal contributions in cancer cell migration, mechanobiology, 3D imaging, and immuno-oncology. He has developed quantitative methods, including particle-tracking microrheology, multi-compartment organoids and high-throughput cell migration assays. He has introduced CAR T technology to enhance solid tumor infiltration. Recently, he has developed CODA, a, AI-based method to image large volumes of tissues and tumors in 3D dimensions. Denis Wirtz has founded the Johns Hopkins Institute for NanoaBioTechnology (INBT). He is the Director of the NCI-funded postdoctoral training program in nanotechnology for oncology and. Director of the NCI-funded Physical Sciences-Oncology Center (PS-OC) and the Johns Hopkins Cellular Cancer Biology Imaging Cancer (CCBIR) Center. Wirtz is author and co-author of 275 peer-reviewed articles published in journals such as Science, Nature, Cell, Nature Reviews Cancer, and Nature Cell Biology. Wirtz received the NSF Career award in 1995; he is fellow of the Institute for Medical and Biological Engineering (AIMBE), the American Association for the Advancement of Science (AAAS), the American Physical Society (APS), and member of the Royal Academy of Medicine of Belgium.

ABSTRACT

Our group has recently developed CODA, an AI-based platform to map whole diseased and healthy organs and organisms in 3D and at single-cell resolution. CODA solves the challenge of imaging large volume samples, while preserving high spatial resolution. Through integration with other multi-omic approaches – such as spatial transcriptomics and proteomics - CODA allows for unprecedented cellular and molecular profiling of tissues. I will discuss the new biological insights into tumor onset and progression gained from the use of CODA, including ovarian and pancreatic cancers, and associated biomedical implications for early detection of cancer. I will also introduce our new CAR T therapies that exploit synthetic velocity receptors that dramatically increase the ability of traditional CAR T cells to readily infiltrate fibrotic tumors. We demonstrate their enhanced effectiveness in pancreatic, ovarian, and lung cancer.

Jun Li, Ph.D.

Speaker

Professor and Chairman, Department of Molecular Genetics and Genome Sciences

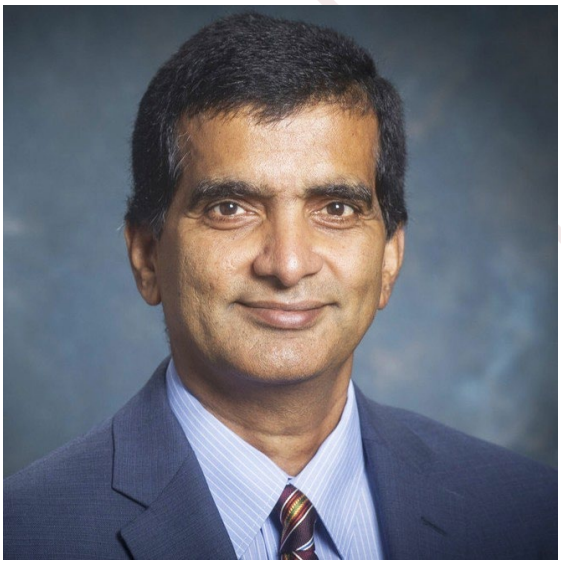
University of Oklahoma Health Campus

Dr. Jun Li is Professor and Founding Chair of the newly established Department of Molecular Genetics and Genome Sciences in the College of Medicine (COM) at the University of Oklahoma Health Sciences. Before joining OU in April 2025, he was a Professor of Human Genetics and Professor and Associate Chair of Computational Medicine & Bioinformatics at the University of Michigan Medical School, where he worked for nearly 18 years. His background includes physics (BSc, Peking University), and biophysics/electrophysiology (PhD, Caltech), and genetics/genomics (postdoc, Stanford). As a computational biologist Dr. Li has led many studies to extract knowledge from genetic, genomic, and phenotype data generated from disease cohorts, patient families, or relevant model systems. His group has built expertise in statistical inference (pattern recognition, classification) and bioinformatics. In recent years his team has developed strong collaborations to study cancer genomics, genetics and epigenetic of drug abuse, and cell and developmental biology of the reproductive system. He was experienced at leading research initiatives in Michigan Medicine, and has been elected as an AAAS Fellow and AIMBE Fellow.

ABSTRACT

Over the past two decades, cancer genomics has witnessed dramatic expansions in sample size, technologies, and data modalities: from analyses of bulk tumor tissues to studies of intratumor heterogeneity, and then to single-cell profiling; from primary tumors to metastatic and drug-resistant samples; from somatic genomes to transcriptomes, proteomes, metabolomes, and integrated multi-omic investigations; from subclone lineage tracing to mapping the functional characteristics of these lineages; and, finally, to spatially resolved analyses of cells and cell communities, sometimes across multiple omic layers. This forward rush to collect and analyze increasingly large and complex datasets has created serious bottlenecks in interpretation, and interpretation itself has taken many forms. My talk will argue for the central importance of delivering either **mechanisms** that can be falsified in the laboratory, or **predictions** that demonstrably improve upon current clinical or computational predictors. I will illustrate this point with two examples. First, multi-omic analyses of bulk GBM samples revealed new subtypes and generated mechanistic hypotheses emerging from refined classification. Second, predictors of drug response in cancer cell lines should focus on within-tumor-class prediction, because conflating intra- and inter-class variation can undermine both network analysis and “foundation model” performance, leading to exaggerated accuracy estimates. Future

progress will require rigorous, statistically grounded approaches to strengthen our mechanistic understanding of cancer evolution, each within its proper tissue context.



Sooryanarayana Varambally, Ph.D., MBA

Speaker

Professor, Department of Pathology

University of Alabama Birmingham

My research focus is to understand the molecular basis of cancer using integrative genomic, epigenetic, proteomic and cancer biology approach. Our groups translational cancer research involves transferring the basic research discoveries to develop disease detection markers as well as targeting. I have worked extensively in the area of solid tumor genomics, biomarker discovery, biology, and therapeutic targeting.

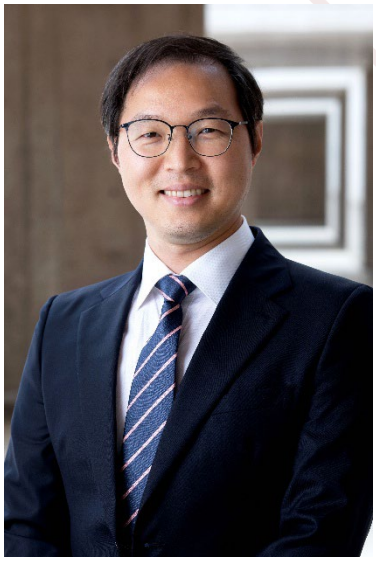
Our research helps better understand the molecular alterations during the initiation and progression of multiple human malignancies. We perform integrative analysis to identify the best targets and work towards developing agents/drugs for specific causative targets. Many of my publications describe the identification of new targets for various cancers. We would like to develop collaborations in order to hasten the pace of cancer research and discovery by team science approach. In order to enhance the cancer research/target discovery, we built a target discovery platform called UALCAN (https://ualcan.path.uab.edu) for cancer genomic and proteomic data analysis, making cancer research a worldwide team effort. This portal has been visited well over a 1.75 Million times and related articles cited over 7,500 times from researchers across the globe since its release in 2017. Recently, we have released the "UALCAN Mobile", free android and Apple app for gene expression analysis. Recently , we have developed and released a comprehensive breast cancer molecular database called "MammOnc-DB (http://resource.path.uab.edu/MammOnc-Home.html). Some of the candidate therapeutic targets that I have identified include Histone Methyltransferase EZH2, AMACR, TPD52, MTA1, ERG gene fusion, Wnt receptor FZD8, SPINK1, CtBP1, RAF kinase gene fusions, GOLM1, GLYATL1 and JAGGED1 in prostate cancer, GATA3, AGTR1, EZH2, CCN6 (WISP3) in breast cancer, MTHFD1L, TRIP13, PAICS, P4HA1, BZW2 in colorectal cancers, TRIP13, PAICS in pancreatic cancers and MTHFD1L, PAICS and PAK4 in bladder cancer among others. I have patents for targeting histone methyltransferase EZH2 and MMSET.

My research has resulted in prolific output with over 175 published articles and many of them in high impact factor (IF), prestigious journals including Science, Nature, New England Journal of Medicine, Nature Medicine, Cancer Cell, Cancer Discovery, Blood, PNAS, Cancer Research, Oncogene among others. Our research has been highly cited and our work has been cited by leading cancer researchers and biologists worldwide with over 50,300 citations. I was a member of the team that won the Inaugural American Association for Cancer Research (AACR) Team Science Award for the prostate cancer gene fusion discovery in 2007. I am the recipient of the Research Faculty Recognition Award

from the University of Michigan in 2009. In 2021, I received the outstanding achievement award from the Society of American Asian Scientists in Cancer Research (SAASCR). In 2023, I received the UAB Heersink School of Medicine Deans Excellence award for exceptional achievements in research. I am actively involved in teaching and serve as Co-Director of the Cancer Biology Theme of UAB-Graduate Biomedical Sciences (GBS). I directed the GBS-728, Cancer Genomics, Epigenetics and Therapy course, as the director of this course. It was designed to educate the students on the basic and novel concepts to understand cancer. I also organize the Translational Research Group Meeting, a tri-Departmental interactive seminar series. Recently, I had the honor of graduating with MBA degree with marketing major from Collat School of Business at the University of Alabama at Birmingham.

ABSTRACT

Cancers exhibit diverse morphological, histological, and molecular alterations during their initiation, progression, and metastasis. Not all cancers are similar, and even cancers of the same organ show molecular heterogeneity. Advances in molecular profiling, sequencing technologies, and proteomics have resulted in the generation of massive datasets. Availability of these data has presented promising avenues for cancer research, especially for identification of new therapeutic targets and precision targeting. However, mining of these data in meaningful ways and utilizing them to their full potential requires the development of intuitive, innovative, and user-friendly platforms. Multiple “Omics” data from patients can help stratify cancers based on their mutational status, gene expression, and survival patterns. Additionally, these molecular alterations can have relevant associations with stage, race/ethnicity, histologic subtypes, genetic aberrations, and other clinicopathologic parameters that can be further stratified. In this era of precision medicine, it is imperative that, to inhibit cancer growth, researchers and clinicians have the capability to identify candidate, subclass-specific cancer biomarkers through early diagnosis, prediction of disease recurrence, identification of molecular determinants for therapeutic targeting, and re-purposing of drugs. Our work focuses on the use and dissemination of BIG cancer data. We have developed integrative bioinformatics tools that harnesses the power of these large datasets and allows researchers to discover biological insights for specific tumors. Detailed data analyses and visualization can be accomplished through use of our researcher-centric, distinctive, and continuously evolving platform, **UALCAN** (https://ualcan.path.uab.edu, and “**UALCAN Mobile” App**) as well as through our breast cancer-focused data platform, **MammOnc-DB** (https://resource.path.uab.edu/MammOnc-Home.html). Our goals are (a) to make large cancer molecular datasets available for easy analysis by cancer researchers; (b) to make cancer research a global team effort; and (c) to facilitate discoveries of cancer targets and development of biomarkers.



Tae Gyu Oh, Ph.D.

Speaker

Assistant Professor, Department of Oncology Science

University of Oklahoma Health Campus

My research focuses on using bioinformatics and molecular biology to uncover disease mechanisms, with emphasis on metabolic disorders, fibrosis, NASH, cancers, and more recently, rare diseases. In my graduate work, I studied the interaction between the transcription factor RORγ and the epigenetic regulator PRMT6 in breast cancer, developing pipelines to analyze RNA-seq and ChIP-seq data. As a postdoctoral researcher in the Evans laboratory at the Salk Institute, I expanded into advanced computational approaches, including a machine-learning model for diagnosing inflammation-associated metabolic diseases. I also established a metagenomic analysis pipeline that identified a microbiome-based diagnostic signature for fibrosis and cirrhosis (Oh et al., Cell Metabolism, 2020 & 2021), validated across international cohorts and recognized by the AASLD Fellow Research Award. In addition, I have contributed bioinformatics expertise to collaborative studies in diverse areas, such as transcriptional regulation in colon cancer, single-cell profiling of human islet organoids for diabetes, ribo-tag profiling of neural cells in opioid response, and epigenomic mapping of inflammation-responsive macrophages. Building on this foundation, my current work focuses on spatial transcriptomic and multi-omic technologies to map the molecular landscape of rare diseases. By integrating high-dimensional spatial data with clinical cohorts, I aim to uncover hidden mechanisms and advance precision diagnostics and treatments for rare disease populations.

ABSTRACT

Spatial multi-omics is a critical advancement in understanding complex disease mechanisms, allowing us to profile molecular events while preserving essential cellular context and local interactions. We utilized the 10x Genomics Xenium In Situ Platform to conduct high-resolution, multiplex profiling in models of liver diseases and rare cancers. Our work primarily focused on leveraging the spatial transcriptome to precisely define tissue structure and zonation in pathological states, demonstrating exceptional power in the accurate identification of inflammation regions and the delineation of associated gene expression boundaries. A key finding in damaged liver models was the distinct and concentrated upregulation of the factor Annexin A2 (Anxa2), which was highly highlighted within the damaged central areas of the tissue, suggesting its potential role as a spatially-defined marker of localized injury. Beyond transcription, we established a crucial **protein and transcriptome joint profiling workflow** within the same platform, enabling direct, concurrent comparison of mRNA and protein expression across the tissue space. Analysis of this joint dataset confirmed a general positive correlation between mRNA and protein levels for a large number of genes, validating the

workflow's utility. Importantly, we identified a notable subset of genes exhibiting no correlation between mRNA and protein abundance (e.g., CD4), a finding that underscores the significant role of post-transcriptional and translational regulatory mechanisms in disease, which would be entirely masked by single-omic approaches. In conclusion, the application of Xenium-based spatial multi-omics provides unprecedented insights into the molecular and structural basis of liver diseases and rare cancers, using precise localization and the identification of mRNA-protein expression discordance to generate high-value, spatially-resolved therapeutic hypotheses.

DRUG DISCOVERY, DEVELOPMENT AND RESISTANCE

SESSION I – DRUG DISCOVERY, DEVELOPMENT AND RESISTANCE

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: C.V. Rao, Dongin Kim, Raid Aljumaily

8:00 am – 8:05 am	Session Introduction by Moderators
8:05 am – 8:35 am	**Plenary Speaker** – Trever Bivona, M.D., Ph.D. Professor, Department of Medicine, University of California San Francisco

"New insights into lung cancer pathogenesis and therapy resistance"

8:35 am – 8:55 am	Naoko Takebe, M.D., Ph.D. Professor, Department of Medicine, University of Oklahoma Health Campus

"Evolutionary-Revolutionary: Berathomics for Early Cancer Detection"

8:55 am – 9:15 am	Shwetal Mehta, Ph.D. Professor; Department of Translational Neuroscience; Barrow Neurological Institute

"Breaking the Barrier: PK/PD anchored Hybrid Early Phase Clinical Trials for CNS Cancers"

9:15 am – 9:35 am	Abdul Rafeh Naqash, M.D. Associate Professor, Department of Medicine, OU Health Stephenson Cancer Center

"Integrated molecular and clinical characterization of pulmonary large cell neuroendocrine carcinoma"

9:35 am – 9:55 am	Jie Wu, Ph.D. Professor, Department of Pathology, University of Oklahoma Health Campus

"Progress and challenge in RET-targeted cancer therapy"

Trever Bivona, M.D., Ph.D.

Plenary Speaker

Professor, Department of Medicine

University of California San Francisco

I am a cell and molecular biologist, a medical oncologist, and a laboratory-based physician scientist. I lead a basic and translational research program focused on signal transduction, cancer genetics and molecular therapeutics, and the molecular basis of tumor initiation and progression. My discoveries have provided insight into the function and regulation of critical cancer-driving proteins including oncogenic receptor tyrosine kinases and RAS pathway genes. Of note, recent work uncovered a distinct mode of kinase-mediated RAS signaling in cancer via membraneless cytoplasmic protein granules. My work also uncovered drug resistance programs mediated by NF-kappaB and Hippo-YAP pathway signaling and lineage plasticity switches in lung cancer and cancer dormancy. The overall goal of my research program is to understand the regulatory principles underlying cell signaling pathways, cancer growth, and metastasis through hypothesis-driven investigations in order to improve cancer therapy and patient survival. I direct the NCI-funded U54 Bay Area Drug Resistance and Sensitivity Center within the Cancer Moonshot program. I have successfully mentored over 20 individuals into independent academic and industry positions over the last 10 years and serve as co-PI on the UCSF NCI-funded K12 translational oncology training program. I am a Chan-Zuckerberg Biohub Senior Investigator and an elected member of the ASCI and was recently selected for an International Association of Lung Cancer Scientific Achievement Award in Basic and Translational Cancer Biology. I also serve on the AACR International Lung Cancer Task Force Steering Committee, and the NCI Think Tank: Studying the Context and Complexity of Oncogenes and Oncogene Addiction Paradigms in Malignancies (SCOPE).

Naoko Takebe, M.D., Ph.D.

Speaker

Professor, Department of Medicine

University of Oklahoma Health Campus

Naoko Takebe, MD, PhD, joined the Stephenson Cancer Center, University of Oklahoma (OU), as the Associate Director of Clinical Research and Chief, Solid Tumor Oncology Section in the Department of Medicine, OU College of Medicine, in May 2024. Previously, she spent 17 years at the National Cancer institute, NIH as a Translational Science Section Head of the Early Clinical Trials Development Program, Associate Chief Developmental Therapeutics Clinic, and a Senior Investigator in the Cancer Therapy Evaluation Program (CTEP). Prior to joining NCI, she was a faculty member in the Department of Medicine and Pathology at the University of Maryland School of Medicine, Blood and Marrow Transplant Program. Dr. Takebe received her M.D. and Ph.D. degrees from Hirosaki University School of Medicine, Japan. She completed her Medical Hematology/Oncology Clinical and a Post-doctoral Fellowship at Memorial Sloan-Kettering Cancer Center, New York. As a physician-scientist, she conducts bench-to-bedside, first-in-human, and early-phase biomarker-driven tissue-agnostic clinical trials in solid tumors, especially pancreatic cancer, in collaboration with Dr. Min Li and Dr. Pankaj Singh. She also collaborates with OU-Norman colleagues, including Dr. Wei Chen for immunotherapy and Dr. Thirumalai Venkatesan for breath-based volatile organic compounds (VOCs) for early cancer detection.

ABSTRACT

The primary tools for cancer screening—blood tests, imaging, endoscopy, and biopsy—have been noted to present significant access barriers for patients through bodily discomfort, travel requirements, and costs. The field of breathomics, the study of exhaled volatile organic compounds (VOC) as markers of healthy and disease states, offers an alternative approach to disease screening. Pioneered by Linus Pauling in 1971, breathomics has been steadily evolving over the decades to its revolutionary next step today of becoming a viable early cancer detection system. The BACHS (Breath Analyzed Compounds for Health Screening) platform, co-developed at OU, represents this next step as a portable, real-time, non-invasive diagnostic platform for early disease detection. Exhaled breath is analyzed for disease-specific VOC, and this platform has demonstrated the ability to distinguish between patients with COVID-19, lung cancer, or tuberculosis from healthy individuals. To date, VOC capture and detection technology has involved large, expensive, and immobile equipment, often introducing artifacts and confounders from sample breakdown or external contaminants, with limits of detection ranging from parts per million (ppm) to parts per billion (ppb). By contrast, the BACHS platform: 1) uses reliable soft-ionization Proton Transfer Reaction Time-Of-Flight Mass Spectrometry (PTR-TOF-MS) to reduce VOC breakdown during detection; 2) increases the limit of detection to parts per trillion (ppt) through the introduction of a specialized breath Inlet which limits environmental distortions; 3) eliminates confounders through causal AI; and 4) with multi-modal fusion compresses the

acquisition and analysis of data (and therefore time to diagnosis) from days or weeks to minutes while boosting early-detection rates above 95%. Commercial proof of concept has been demonstrated in first-generation PTR-TOF-MS platforms deployed in several countries outside the US for COVID-19 screening at airports. Current work aims for further development of the BACHS platform towards FDA approval, which involves the collection of breath VOC data from Stephenson Cancer Center (SCC) esophageal, hepatocellular, ovarian, and pancreatic cancer patients and from age- and sex-matched controls. Two-thirds of each group will be used to develop a training set to define cancer-specific VOC signatures, and the final third will be used to validate these signatures. Machine learning (ML)/Artificial Intelligence (AI) is utilized extensively in the BACHS platform to analyze the raw breath data for the presence of and amounts of VOC, and then determine a pattern, signature, linked to a healthy or disease state. Collection of large numbers of signatures from a variety of cancers will lead to multi-cancer detection algorithms. Following the successful completion of this work, future studies will engage larger numbers of healthy, at-risk, cancer patients in a multi-center clinical trial to determine the predictive potential of these VOC signature algorithms against the standard of care early cancer detection tests.

Shwetal Mehta, Ph.D.

Speaker

Professor, Department of Translational Neuroscience

Barrow Neurological Institute

Dr. Shwetal Mehta is a Professor of Translational Neuroscience at Barrow Neurological Institute. She also serves as the Deputy Director and CSO of the Ivy Brain Tumor Center. Research in the Mehta Laboratory focuses on understanding the molecular mechanisms underlying therapeutic resistance in GBM, alongside the PK/PD-driven drug discovery through the early phase clinical trials program. By integrating advanced molecular profiling, functional studies, and patient-derived models, the lab aims to identify vulnerabilities in tumor biology and develop targeted strategies to improve patient outcomes. This approach bridges laboratory discovery with early-phase clinical evaluation, ultimately advancing personalized therapies for individuals affected by malignant brain tumors.

ABSTRACT

Glioblastoma (GBM) remains one of the most aggressive and treatment-resistant brain tumors in adults. Despite decades of extensive genetic and molecular characterization, there have been no new drugs approved for GBM over last two decades. There are several valid narratives describing the challenges to GBM drug development, including inadequate blood-brain penetration, extensive inter- and intra-tumoral heterogeneity, highly immunosuppressive tumor environment, and multiple driver mutations. To side-step these difficulties, Ivy Brain Tumor Center utilizes tissue-based, PK/PD-driven studies to assess brain penetration of drugs and develop novel drug candidates through the early phase 'hybrid' clinical trials pipeline. This approach allows timely assessment of target engagement and proof-of mechanism in human GBM tissues prior to therapeutic dosing of patients.

Abdul Rafeh Naqash, M.D.

Speaker

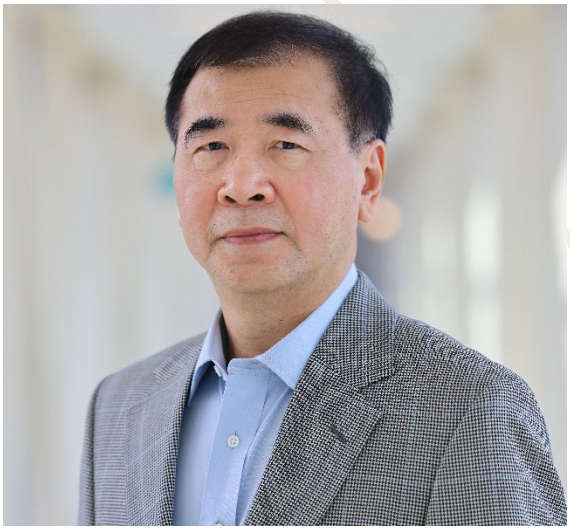
Associate Professor, Department of Medicine

OU Health Stephenson Cancer Center

Abdul Rafeh Naqash, MD received his medical degree at the Government Medical College Srinagar, Kashmir. He completed Internal Medicine residency training at the University of Buffalo/Catholic Health. Subsequently, Dr. Naqash completed his sub-specialty clinical training in Hematology/Oncology at East Carolina University, Greenville, NC, and an early phase clinical trial fellowship at the National Cancer Inst, Bethesda, in the developmental therapeutics clinic. As an Associate Professor in the Medical Oncology/ phase 1 program at Stephenson Cancer Center, Dr. Naqash is focusing his interest in drug development and incorporating a genomically driven approach to early phase clinical trials. He is also interested in Lung Cancer, immunotherapy biomarkers, understanding resistance patterns to Immunotherapy and immune toxicities. Dr. Naqash has led and collaborated extensively with national and international leaders in the field of immunotherapy. Some of this work has been published in high-impact journals such as the NEJM, Journal of Clinical Oncology, Cancer Cell, Nature Communications , lancet Oncology, among others. Dr. Naqash has been the recipient of several coveted nationally recognized awards such as the 2023 NIH Directors Award The NCI Directors Award, Conquer Cancer Award, The 2022 40 under 40 in Cancer Award, among several others.

ABSTRACT

Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare, aggressive lung tumor marked by significant molecular heterogeneity. In a study of 590 patients across two independent cohorts, we observed comparable overall survival across treatment regimens (chemotherapy, chemoimmunotherapy, immunotherapy) without unexpected adverse events. Genomic analysis identifies distinct non-small cell lung cancer-like (NSCLC-like, *KEAP1*, *KRAS*, *STK11* mutations) and SCLC-like (*RB1*, *TP53* mutations) LCNEC subtypes, with 80% aligning with SCLC transcriptional profiles. Serial sampling revealed stable mutational but shifting transcriptomic landscapes over time. Here we show, elevated FGL-1 (a LAG-3 ligand) and SPINK1 expression in NSCLC-like LCNECs, and higher levels of DLL3 in SCLC-like LCNECs. Immunofluorescence confirms FGL-1 expression in NSCLC-like LCNECs, and H&E slide analyses indicates fewer tumor-infiltrating lymphocytes in LCNECs versus other lung cancers. These findings highlight LCNEC's distinct immunogenomic profile, supporting future investigations into LAG-3, SPINK1, and DLL3-targeted therapies. Ongoing spatial analyses comparing LNCEC to SCLC to compare and contrast the tumor microenvironment will be presented at the meeting.



Jie Wu, Ph.D.

Speaker

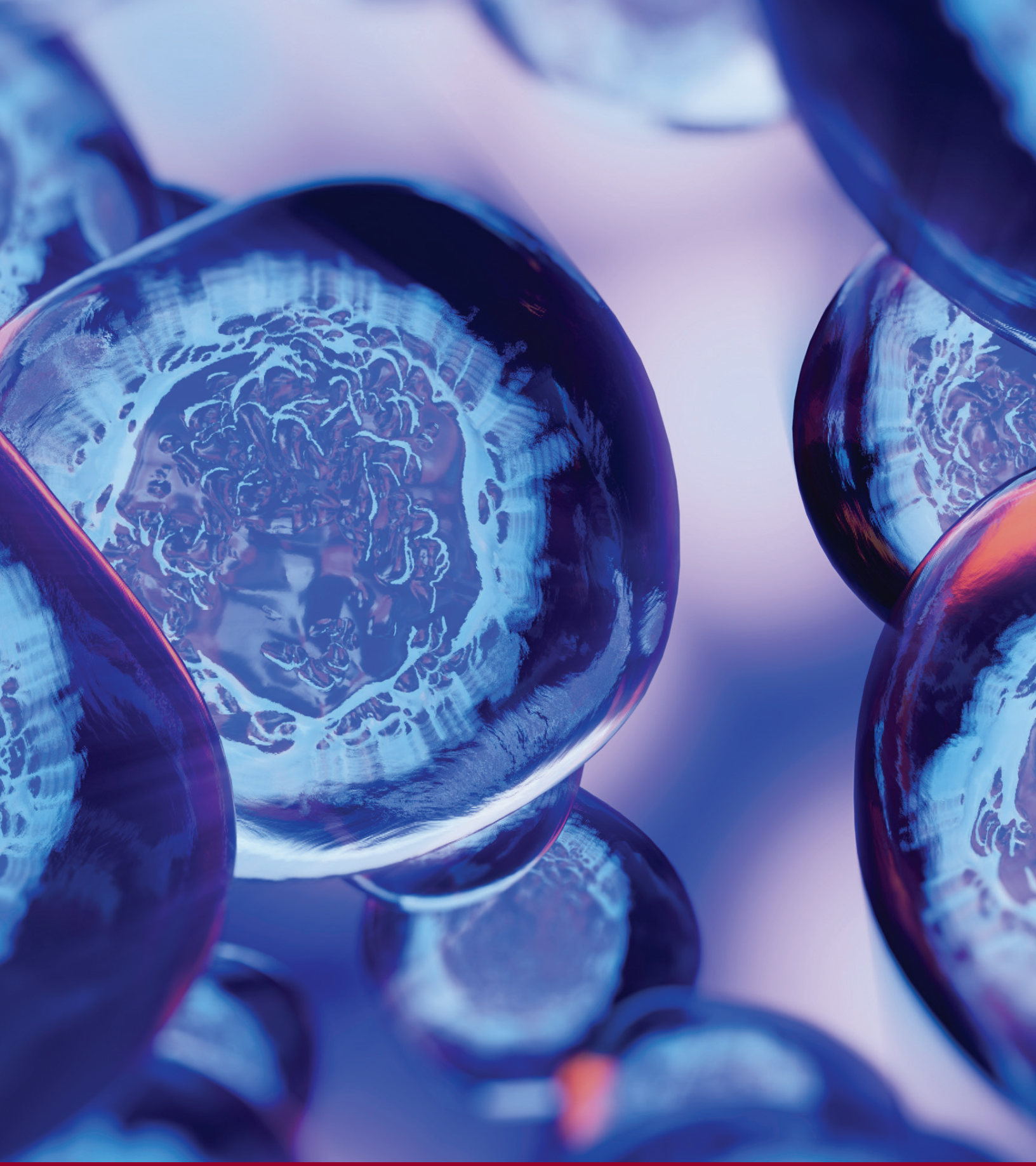
Professor, Department of Pathology

University of Oklahoma Health Campus

Dr. Wu received his undergraduate education in Xiamen University. After a brief graduate education at the Shanghai Institute of Cell Biology in Chinese Academy of Sciences, he completed his graduate education in Biochemistry at the University of Kansas Medical Center. During postdoctoral research at the Memorial Sloan-Kettering Cancer Center and University of Virginia, Dr. Wu made seminal contribution in delineating the MAP Kinase pathway. Dr. Wu established his independent laboratory at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, where he was a Senior Member and a tenured Professor prior to relocating his lab to the University of Oklahoma Health Sciences Center. Currently, Dr. Wu is a professor in the Department of Pathology and the Peggy and Charles Stephenson Endowed Chair in Cancer Translational Research at the University of Oklahoma Health Sciences Center. His laboratory conducts research in cancer biology and therapy focusing on protein tyrosine kinases and phosphatases. Dr. Wu has published over 90 original research papers in addition to review articles and book chapters. His research projects at OUHSC have been supported by NCI, PHF, and OCAST grants.

ABSTRACT

Oncogenic RET mutations and gene fusions are found mostly in thyroid and non-small cell lung cancer, but also at lower rates in other types of cancer. Selpercatinib (Loxo-292) and pralsetinib (Blu-667) are the first-in-class RET-selective protein tyrosine kinase inhibitors (TKIs) approved for treating advanced and metastatic RET-altered cancers. Selpercatinib and pralsetinib gave durable, high overall response rates. However, few patients achieved a complete response. Drug-tolerated residual tumors persistent in most patients inevitably evolve to drug resistance through acquired on-target mutations or off-target mechanisms. Selpercatinib and pralsetinib occupy both the front and back pockets of RET kinase by wrapping around the essential gate wall K758 residue, rather than passing through the gate between gatekeeper V804 and gate wall K758 residues. This allows selpercatinib and pralsetinib to inhibit gatekeeper V804L/M mutations, which are resistant to prior multikinase RET TKIs. Preclinical and clinical studies identified RET solvent-front G810C/R mutations as the predominant on-target resistant mechanism for both selpercatinib and pralsetinib. Pralsetinib, but not selpercatinib, also subjects to resistance by RET roof L730I/V mutations. Efforts are underway to develop the next-generation RET TKIs capable of inhibiting RET solvent-front mutants. Acquired NTRK3 and ALK fusions have been identified in selpercatinib-treated patients. Combination treatments of selpercatinib with NTRK and ALK kinase inhibitors are feasible. Nevertheless, subsequent on-target resistant mutations on one of these kinases renders the combination ineffective. While managing acquired resistance prolongs the duration of disease control, a cure requires elimination of drug-tolerated residual tumor cells. Analysis of RET TKI tolerated persister cells indicated that they are genetically heterogeneous. Thus, combination of a RET TKI with a drug targeting the shared phenotypical vulnerability, rather than a secondary genetic alteration, would offer a better chance to eliminate the residual tumors.



CANCER METABOLISM – BIOLOGY AND TARGETS

SESSION II_– CANCER METABOLISM – BIOLOGY AND TARGETS

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Kamiya Mehla, Surender Shukla, Min Li

10:10 am – 10:15 am Session Introduction by Moderators

10:15 am – 10:45 am **Plenary Speaker** – John Blenis, Ph.D.
Professor, Department of Pharmacology, Weill Cornell Medical College
"Mechanisms linking diet and metabolism to cancer development & progression"

10:45 am – 11:05 am Ramandeep Rattan, Ph.D.
Professor, Department of Pharmacology and Chemical Biology, University of Pittsburgh
"Feeding the Fight: Reprogramming Macrophages Through Diet in Ovarian Cancer"

11:05 am – 11:25 am Todd W. Miller, Ph.D.
Professor, Department of Pharmacology and Toxicology, Medical College of Wisconsin
"Leveraging metabolic vulnerabilities in ER+ breast cancer."

11:25 am – 11:45 am Amber Vu, Ph.D.
Staff Scientist, Department of Radiation Oncology, University of Oklahoma Health Campus
"CMLD-2-mediated inhibition of HuR induces mitochondrial dysfunction and autophagy in cancer cells"

11:45 am – 12:05 pm Srinivas Malladi, Ph.D.
Associate Professor, Department of Pathology, UT Southwestern Medical Center
"Targetable Metabolic Dependencies of Brain Metastatic Cells"

12:05 pm – 12:25 pm Simon Grelet, Ph.D.
Assistant Professor, Department of Biochemistry and Molecular Biology, University of South Alabama
"Lineage Tracing and Fate Mapping of Nerve-to-Cancer Cell Transfer of Mitochondria During Metastasis"

John Blenis, Ph.D.

Plenary Speaker

Professor, Department of Pharmacology

Weill Cornell Medical College

Dr. John Blenis is the Anna Maria and Stephen Kellen Professor of Cancer Research and Professor of Pharmacology in the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine. He is also the Associate Director of Basic Science and Shared Resources at The Sandra and Edward Meyer Cancer Center as well as the director of the pharmacology Ph.D. program. Dr. Blenis earned his B. A. from University of California, Berkeley and his Ph.D. from Michigan State University. His postdoctoral research in the Department of Cellular and Developmental Biology at Harvard University was immediately followed by an appointment as Assistant Professor at Northwestern University Medical School in 1987. In 1989, he joined the faculty of Harvard Medical School and remained there until moving to Weill Cornell Medicine in 2014.

Dr. Blenis has made pioneering contributions to our understanding of signal transduction. He discovered key components of the PI3K-mTOR-S6K, and Ras-ERK/MAPK pathways, arguably the most often altered signaling systems in cancer, set the conceptual framework for how they are organized and regulated, and identified therapeutic targets and inhibitors now being evaluated in clinical studies. In the early days of cancer signaling, he purified and identified S6K, and defined its regulation by mitogens, tumor promoters and oncogenes. He demonstrated that S6K activation is dependent on PI3-kinase and sensitive to rapamycin, thus establishing it as the first component of what we now call the mTORC1 pathway. He played a major role in defining the canonical pathway for mTORC1 activation via PI3K-Akt, Ras-RSK, RHEB GTPase and the tumor suppressor complex TSC1/2. More recently, he has extended this pathway by identifying downstream kinases including SRPK2 and GSK3, and is investigating their downstream functions as mTORC1 effectors. He has been characterizing how this pathway regulates transcription, mRNA biogenesis, translation and cell metabolism, to promote cell growth and survival. Dr. Blenis also defined Ras-dependent regulation of ERK and RSK. He discovered that Raf, ERK, and RSK form a Ras-modulated kinase pathway, that ERK and RSK translocate into the nucleus to mediate signaling from the cell surface, through the cytoplasm and into the nucleus to regulate gene expression and other nuclear functions. Further, he has shown how ERK and RSK signal strength, duration and location are central to cell fate decisions. Recently, he has uncovered mechanisms by which ERK2 regulates metabolism and signaling that contributes to cancer metastasis including the recent discovery that propionate metabolism promotes metastatic progression. His

fundamental discoveries have been critical for understanding how ERK and RSK regulate gene expression, cell survival, proliferation and metastasis. Dr. Blenis continues to identify biomarkers, therapeutic targets, and drug resistance mechanisms that will enable future treatment strategies. Dr. Blenis has received a number of awards including the ACS Junior Faculty award, AHA Established Investigator award, the Rothberg Courage Award, the LAM Foundation Established Investigator award, the NIH/NCI MERIT award and the Siegel Family Award for Outstanding Medical Research. Additionally, he has received two awards related to teaching and mentoring; The Academy at Harvard Medical School Excellence in Tutoring Award and Weill Cornell Medicine Pharmacology Outstanding Teaching & Mentoring Award.

ABSTRACT

We previously discovered a role for **propionate metabolism** in metastatic progression of several tumor types. Multiple enzymes downstream in the pathway are down-regulated by factors that promote metastasis such as TGFβ, ERK2, hypoxia and nutrient deprivation in breast and lung cancer. These changes promote the accumulation of upstream metabolites, methylmalonyl-CoA and propionyl-CoA. The accumulation of methylmalonyl-CoA results in elevated levels of methylmalonic acid (MMA). MMA, which is also an aging-associated metabolite, is secreted in extracellular vesicles (EVs) and promotes tumor progression to an aggressive phenotype. In aggressive prostate cancer, propionyl-CoA levels are also elevated. Propionate metabolism is sensitive to dietary branched-chain amino acids (BCAAs) and propionate. How dietary BCAAs and propionate promote prostate cancer progression will be discussed.

We have also shown that the essential dietary **omega-6 fatty acid (linoleic acid, LA)**, promotes triple negative breast and prostate cancer progression. Omega-6 LA is significantly elevated in the unhealthy “Western diet” as compared to the healthier Mediterranean diet. We have demonstrated that LA binds to the fatty acid transporter, FABP5, and this complex promotes the activation of mTORC1 at lysosomes and mitochondria. Preliminary data show that 3T3-L1 adipocytes secret FABP5-EVs which can accumulate in cancer cells with low FABP5 expression. These insensitive breast cancer cells then become sensitive to LA, suggesting a link between obesity and breast cancer progression.

Ramandeep Rattan, Ph.D.

Speaker

Professor, Division of Gynecologic Oncology, HFH-MSU Health Sciences,

Henry Ford Health, Detroit, MI

Dr. Ramandeep Rattan is a Principal Investigator at Henry Ford Health (HFH-MSU health Sciences), where her laboratory studies the metabolic and immunometabolic mechanisms that drive ovarian cancer progression and shape immune responses. She earned her Bachelor's degree in Clinical Laboratory Medicine from PGIMER (Chandigarh, India), master's degree in Microbiology from CRI (Kasauli, India), and PhD in Molecular and Cellular Pathobiology from the Medical University of South Carolina (Charleston, SC), followed by a postdoctoral fellowship in ovarian cancer at the Mayo Clinic (Rochester, MN). Her lab investigates how dietary and metabolic interventions, including caloric restriction, influence tumor-associated macrophages and T cells to promote antitumor immunity. Other areas of emphasis include targeting myeloid-derived suppressor cells to alleviate immunosuppression in ovarian cancer and understanding the metabolic consequences of PARP inhibition in BRCA-positive ovarian cancer. Dr. Rattan's research is supported by the NIH/NCI and the Department of Defense Ovarian Cancer Research Program, and she has received multiple national and foundation awards recognizing her contributions to ovarian cancer research.

ABSTRACT

Calorie restriction (CR) or reducing calorie intake without malnutrition to create a negative energy balance, is being recognized as a potential adjuvant intervention for preventing and inhibiting cancer. However, its effect on anti-tumor immune response is not known. Here we investigated the impact of 30% CR on anti-tumor immune response in syngeneic mouse ovarian cancer models. Using ID8p53-/-, ID8p53-/-,BRCA1 and STOSE ovarian tumor models subjected to CR or regular diet (RD), we observed that CR significantly reduced tumor growth and improved survival in contrast to mice on RD. Immune profiling indicated a significant modulation of the macrophage population. Interestingly there was an increase in M1-like marker CD38 expression and decrease in tumor associated M2-like markers CD206 and EGR; which translated to an increase in M1/M2 ratio. The role of macrophages in mediating CR's anti-tumor effect was validated by testing in nude mice which still showed tumor inhibitory effect despite T cell absence and macrophage depletion studies where CR failed to inhibit tumors. The shift to M1-like phenotype was accompanied by increase in glycolysis and phagocytosis of tumor cells. CR educated macrophages showed decreased expression of the don't eat me- SIRP1a marker.

Combination of SIRP1a inhibition with CR, increased tumor cell phagocytosis by macrophages and further improved survival. Our results suggest CR enables metabolic reprogramming of pro-tumor macrophages into anti-tumor phenotype and facilitates tumor phagocytosis.

Todd Miller, Ph.D.

Speaker

Professor, Department of Pharmacology and Toxicology

Medical College of Wisconsin

Todd's research interests center on the development of treatment strategies for breast and other cancers, and the identification of mechanisms of therapeutic resistance. He completed his B.S. in Physiology & Neurobiology at the University of Connecticut in 1998, and his Ph.D. in Biomedical Sciences at the University at Albany in 2004. Following a postdoctoral fellowship in the laboratory of Carlos Arteaga at Vanderbilt University, he joined the Geisel School of Medicine at Dartmouth and the Dartmouth Cancer Center in 2012. He rose to the rank of Professor with tenure at Dartmouth in 2023, and then transitioned to the Medical College of Wisconsin Cancer Center in 2023.

ABSTRACT

Recurrence and progression of estrogen receptor alpha (ER)-positive breast cancer are prevented by endocrine therapies that inhibit ER transcriptional activity. However, approximately one-third of patients experience disease recurrence, recurrences are often metastatic, and metastatic breast cancer is usually ultimately fatal. Cancer cells that tolerate endocrine therapy and persist despite treatment are a cause of tumor recurrence. We therefore sought to identify mechanisms underlying endocrine-tolerant persistence. Endocrine-tolerant persister ER+ breast cancer cells exhibited oxidatively stress during endocrine therapy. Proteomic analysis revealed upregulation of antioxidant-driving enzymes including glutathione peroxidase 4 (GPX4) in persisters. Relief of oxidative stress via antioxidant buffering enhanced persister fitness under endocrine therapy. The increased oxidative state of persisters drove lipid peroxidation and ferroptosis. Persisters had an altered lipidome with increased levels of polyunsaturated fatty acids prone to peroxidation, which was attributable in part to increased lysophosphatidylcholine acyltyransferase 3 (LPCAT3, MBOAT5) expression via loss of ER-mediated repression during endocrine therapy. LPCAT3 overexpression increased polyunsaturated fatty acid incorporation into cells and sensitized to ferroptosis. Pharmacological inhibition of GPX4 enhanced the anti-persister effects of endocrine-based therapies in cultured cells and xenograft-bearing mice. These findings supporting the development of therapeutic strategies for ER+ breast cancer that leverage the oxidative stress induced by endocrine-based therapies and drive ferroptosis.

Amber Vu, Ph.D.

Speaker

Staff Scientist, Department of Radiation Oncology

University of Oklahoma Health Campus

Amber is a staff scientist, with a background in molecular virology and gene therapy. She completed her Ph.D. in the laboratory of Dr. Richard Roller at The University of Iowa, studying herpes simplex virus type 1 (HSV-1) mediated nuclear lamina re-organization and nuclear egress of viral capsids. She performed her postdoctoral work in the laboratory of Dr. Paul McCray at The University of Iowa, with projects focusing on gene therapy for cystic fibrosis and lentiviral vector glycoprotein manipulation to increase transduction to the airway epithelium.

Her research is currently focused on the studying effect of HuR on mitochondrial dynamics and cellular metabolism.

Outside of lab, she enjoys spending time with her family, reading science fiction/fantasy novels, and gardening.

ABSTRACT

Human antigen R (HuR) is an RNA-binding protein commonly overexpressed in various cancers and plays a key role in regulating genes associated with tumor progression, angiogenesis, cell cycle, and resistance to chemotherapy. Elevated HuR expression has been linked to aggressive tumor growth, increased invasiveness, and unfavorable clinical outcomes. Both pharmacologic and genetic inhibition of HuR have demonstrated antitumor effects *in vitro* and *in vivo* across multiple cancer types. These effects are primarily mediated through molecular mechanisms such as cell cycle arrest, increased reactive oxygen species (ROS) production, and enhanced DNA damage leading to apoptotic cell death. Despite these findings, HuR's role in regulating cancer cell metabolism and mitochondrial dynamics remains poorly understood. In this study, we examined the impact of CMLD-2, an HuR inhibitor, on glycolysis, mitochondrial function, ROS generation, and mitophagy in human breast (MDA-MB-231) and lung (H1299) cancer cell lines. HuR inhibition led to reductions in both glycolytic activity and mitochondrial respiration. Metabolomic profiling revealed cell-type specific alterations in glycolytic and tricarboxylic acid (TCA) cycle intermediates, along with accumulation of acylcarnitines. suggesting mitochondrial overload, TCA cycle bottlenecks, and impaired fatty acid oxidation. CMLD-2 treatment induced multiple markers of mitochondrial dysfunction, including mitochondrial fragmentation, elevated production of mitochondrial superoxide production, reduced mitochondrial membrane potential, and cleavage of mitochondrial fusion protein L-OPA1. Moreover, CMLD-2 activated autophagy and mitophagy signaling, increased autophagic structure formation and enhanced colocalization of mitochondria with the autophagosome marker LC3. Together, these findings demonstrate that HuR inhibition leads to mitochondrial dysfunction and significantly alters cancer cell metabolism, revealing a novel therapeutic potential of HuR-targeted cancer therapy.

Srinivas Malladi, Ph.D.

Speaker

Associate Professor, Department of Pathology

UT Southwestern Medical Center

Dr. Srinivas Malladi leads a metastasis research program at UT Southwestern Medical Center focused on identifying and targeting disseminated cancer cells in minimal residual disease, a critical but underexplored window for preventing relapse. His laboratory employs integrated molecular, genetic, biochemical, and metabolic approaches, combined with clinically relevant models, to investigate the mechanisms governing metastatic latency, immune evasion, and recurrence. Using pioneering preclinical systems that recapitulate clinical disease manifestations, his group has revealed that metastasis-initiating cells adopt stem-like traits, suppress immune-activating pathways, and exploit metabolic diversity to sustain long-term survival and metastatic competence. Trained at UT Austin and as an American Cancer Society postdoctoral fellow with Dr. Joan Massagué at Memorial Sloan Kettering, Dr. Malladi established his independent laboratory at UT Southwestern in 2017. Since then, he has cultivated a dynamic team of graduate students and postdoctoral fellows and fostered broad collaborations with leading investigators in cancer metabolism, pathology, and translational oncology. Through this work, Dr. Malladi is advancing fundamental understanding of metastasis biology while driving efforts to translate these insights into strategies for early detection and therapeutic intervention.

ABSTRACT

Breast cancer patients with metachronous brain metastases have poor survival rates, which can be attributed to disseminated residual cells surviving current therapies. However, little is known about how these cells remain dormant for extended periods before initiating metachronous metastasis. Through a phenotypic screen in mice, we isolated HER2+ latent and brain metastatic cells. Transcriptomic and metabolic profiles of these brain-tropic breast cancer cells identified actionable dependencies and unique therapeutic opportunities. Brain-tropic Lat and metastatic cells have distinct metabolic profiles that determine their metastatic fitness. Both latent and metastatic cells survive in equilibrium with innate immune surveillance, oxidize glutamine and maintain cellular redox homeostasis through the anionic amino acid transporter xCT. In addition, latent metastatic cells in the brain uptake, store, and utilize fatty acids secreted by tumor-associated reactive astrocytes to meet their cellular energetic needs. Fatty acid oxidation and peri-droplet mitochondria enable utilization of fatty acids and promote survival of latent metastatic cells. Attenuating fatty acid oxidation by genetic and pharmacological inhibition disrupted mitochondrial dynamics and limits metastatic incidence. Likewise, depleting dynamin-related protein 1 altered mitochondrial dynamics that results in lipid droplet accumulation and attenuated metastatic latency and relapse in HER2+ breast cancer brain metastatic models. Furthermore, pharmacological inhibition of DRP1 decreases brain metastatic burden in preclinical models. We have now developed TNBC subtype specific brain metastasis models and are investigating their metabolic dependencies. In sum, our studies highlight the therapeutic potential of targeting cellular plasticity programs in phenotypically distinct and metabolically diverse brain-tropic latent and metastatic cells to prevent brain metastatic recurrences.

Simon Grelet, Ph.D.

Speaker

Assistant Professor, Department of Biochemistry and Molecular Biology

University of South Alabama

My research program is dedicated to understanding how the tumor microenvironment shapes cancer progression, with a particular emphasis on the interplay between cancer cells, the nervous system, and cellular metabolism.

In my earlier work, I investigated the functional roles of long non-coding RNAs (lncRNAs) in cancer. This research uncovered novel mechanisms by which these transcripts regulate gene expression through the alternative splicing of protein-coding genes (Grelet et al. *Nature Cell Biology*, 2017). I demonstrated that this regulation leads to the generation of functionally active lncRNAs that promote cancer cell plasticity and aggressiveness. Through integrative transcriptomic analyses and functional assays, I contributed to identifying a set of lncRNAs reactivated during breast cancer plasticity and showed how they modulate the expression of axon guidance molecules (Grelet et al. *Life Science Alliance*, 2022). These findings revealed a mechanistic link between tumor innervation and cancer cell plasticity, establishing a foundation for the study of neuro-cancer interactions.

Building on this molecular insight, my current research focuses on cancer innervation, the infiltration of tumors by nerves, and its impact on cancer cell behavior. I am particularly interested in how neural inputs influence cancer cell metabolism, survival under stress, and the acquisition of metastatic traits. By developing novel *in vitro* and *in vivo* models, my group is uncovering key mechanisms that drive nerve-mediated tumor progression, with the goal of identifying therapeutic targets. We developed a CRISPR/Cas9-based reporter system to monitor cancer-induced axonogenesis in live cells (Galappaththi et al. *Cancers*, 2022). We confirmed the association between cancer cell plasticity and tumour innervation in this high-throughput setup.

Currently, a central focus of the laboratory is the phenomenon of intercellular mitochondrial transfer. We have shown that neurons can donate mitochondria to cancer cells, a process that enhances the bioenergetic capacity and stress resilience of the recipient cells (Hoover et al. *Nature,* 2025). Ongoing work aims to define the molecular mediators of this exchange, assess its contribution to metastatic dissemination *in vivo*, and explore strategies to disrupt this metabolic symbiosis for therapeutic gain.

ABSTRACT

The nervous system plays a pivotal role in cancer biology, and pathological investigations have consistently linked intratumoral nerve density to cancer aggressiveness and metastasis. However, the precise impact of cancer-associated neurons on cancer cell biology and the communication channels established at the interface between nerves and cancer remain poorly known. We show that cancer-

associated neurons contribute to cancer metabolic plasticity through the transfer of mitochondria from nerves to cancer cells. Breast cancer denervation and nerve-cancer coculture models confirmed the role of cancer-associated neurons in improving tumor energetics in the breast cancer context. Neurons stimulated by cancer cells in coculture undergo metabolic reprogramming, exhibiting a significant increase in mitochondrial mass coupled with the transfer of their mitochondria into neighboring cancer cells. To precisely track the fate of recipient cancer cells, we developed MitoTRACER, a novel reporter of the cell-cell transfers of mitochondria that permanently mark recipient cancer cells and their progeny. Lineage tracing and fate mapping of cancer cells having acquired mitochondria from neuronal donors in the primary tumor revealed their selective enrichment at metastatic sites following cancer dissemination.

Collectively, our data highlight the enhanced capacities of cells that receive mitochondria from neurons in the primary tumor to successfully form distant metastases, shedding light on how the nervous system supports cancer metabolism and metastatic dissemination.

IMMUNO-ONCOLOGY

SESSION III_– IMMUNO-ONCOLOGY

SAMIS CONFERENCE ROOM (LEVEL 2)

Moderators: Maureen Cox, Dinesh Thotala, Venkateshwar Madka

2:00 pm – 2:05pm — Session Introduction by Moderators

2:05 pm – 2:35 pm — **Plenary Speaker** – David A. Barbie, M.D.
Professor, Dana Farber Cancer Institute
"Unleashing cGAS-STING signaling to promote cancer immunogenicity"

2:35 pm – 2:55 pm — Sean Lawler, Ph.D.
Associate Professor, Department of Pathology and Laboratory Medicine, Brown University
"Designing new approaches for glioblastoma: from drug delivery to antiviral therapies"

2:55 pm – 3:15 pm — Chih-Chi Andrew Hu, Ph.D.
Professor, Houston Methodist Neal Cancer Center
"Secretory IgM drives malignant progression of B cell leukemia"

3:15 pm – 3:35 pm — Rajagopal Ramesh, Ph.D
Professor, Department of Pathology, University of Oklahoma Health Campus
"Rekindling the Innate Immunity Signaling Through HuR-Targeted Therapy in Medulloblastoma"

3:35 pm – 3:55 pm — Wei Chen, Ph.D.
Professor and Director, School of Biomedical Engineering, University of Oklahoma
"Local Ablative Immunotherapy for Cancer"

David Barbie, M.D.

Plenary Speaker

Professor

Dana Farber Cancer Institute

Dr. Barbie is the Director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute and an Associate Professor of Medicine at Harvard Medical School. He is also Associate Director of the Belfer Center for Applied Cancer Science and an Associate Member of the Broad Institute. Dr. Barbie earned his undergraduate degree at Harvard College and M.D. degree at Harvard Medical School and was a Howard Hughes Medical Investigator Program Medical Student Research Fellow in Dr. Edward Harlow's laboratory at the MGH Cancer Center. He then completed an MGH internal medicine residency and chief medical residency, a Dana-Farber Partners Oncology fellowship, and performed his post-doctoral work in Dr. William Hahn's laboratory at DFCI and the Broad Institute. Currently, he is the principal investigator of his own laboratory at DFCI while also seeing patients in the Lowe Center for Thoracic Oncology.

ABSTRACT

A substantial fraction of cancers silence Stimulator of Interferon Genes (STING)-Interferon (IFN) signaling, which evolved to detect cytosolic DNA and trigger antiviral immune response. Therapeutic reactivation of this program via STING agonists, epigenetic, or DNA-damaging therapies can restore antitumor immunity in multiple preclinical models. Our laboratory has demonstrated that small cell lung cancer and KRAS-STK11/LKB1 mutant non-small cell lung cancer evade response to immune checkpoint blockade by epigenetically silencing STING but remain vulnerable to cancer immunotherapy upon its reactivation. However, low level STING signaling has also been shown to be pro-tumorigenic, and the mechanisms that restrain the degree STING-IFN signaling in tumors have remained elusive. Recently, we characterized a novel mechanism whereby activation of downstream IFN induces the expression of three-prime exonuclease 1 (TREX1), the major cytosolic DNA exonuclease. Induction of TREX1 downstream of STING-IFN signaling in tumor cells limits upstream dsDNA sensing by cGAS and prevents excessive pathway activation. Genetic inactivation of TREX1 in tumor cells thus unleashes cGAS-STING activity, driving robust downstream IFN and STAT1 pathway activation. Co-culture of TREX1 deficient tumor cells with NK cells further amplifies this effect due to additional STAT1 activation by NK cell derived IFNγ, promoting robust apoptosis. TREX1 knockout in multiple mouse syngeneic tumor models further demonstrates that PD-1 blockade or STING agonism can enhance T cell and NK cell infiltration downstream of tumor cell STING-IFN signaling, resulting in robust anti-tumor activity in vivo. These findings identify TREX1 as an important cancer innate immune checkpoint and a druggable therapeutic target.

Sean Lawler, Ph.D.

Speaker

Associate Professor, Department of Pathology and Laboratory Medicine

Brown University

Sean Lawler PhD is an Associate Professor at Brown University, where he co-Directs the Brain Tumor Research Program.

His lab research is at the intersection of biology and therapy for brain tumors, where his group studies new methods for effective drug delivery to glioblastoma, and how cytomegalovirus affects tumor growth and could serve as a therapeutic target.

ABSTRACT

Glioblastoma is an aggressive brain tumor and is still lacking effective therapies despite remarkable progress in understanding its mutational underpinnings and tumor biology in recent years. Here, I will discuss two approaches under current investigation in my lab. First, drug delivery to the brain is a major challenge that needs to be overcome for effective approaches to be implemented. I will discuss our work on BBB penetrant peptide drug conjugates, as well as a new approach to enhance drug accumulation in tumors through modulation of the blood brain tumor barrier using small molecule protein kinase inhibitors. Second, I will discuss another key project in the lab, to investigate the role of cytomegalovirus (CMV) in glioblastoma progression. We have developed a mouse model which demonstrates elevated tumor growth in the presence of CMV infection. We have found that antiviral drugs reverse this effect and can result in improved survival in preclinical models suggesting a pathway to new clinical approached for this challenging disease.

Chih-Chi Andrew Hu

Speaker

Professor

Houston Methodist Neal Cancer Center

Chih-Chi Andrew Hu, PhD, earned his Bachelor's degree from China Medical University and Master's degree from National Sun Yat-Sen University in Taiwan. During his military service as a second lieutenant, he taught histology and performed research at the National Defense Medical Center. Dr. Hu pursued his doctoral training with Dr. Tung-Tien Sun at the New York University School of Medicine (2001-2006) to study membrane protein assembly on the surface of the urinary bladder. Dr. Hu pursued his postdoctoral training with Dr. Hidde L. Ploegh, at the Whitehead Institute/Massachusetts Institute of Technology (2006-2010) to study the functions of the endoplasmic reticulum in normal B cells. He became an Assistant Professor at the Moffitt Cancer Center/University of South Florida (2010-2014) and was later recruited to the Wistar Institute/University of Pennsylvania as an Associate Professor (2014-2019) where he was heavily involved in the training and education program. He was promoted to Full Professor at the same institute in 2020 and recruited to the Houston Methodist Research Institute in December 2020.

Dr. Hu is the Associate Director for Cancer Research Training and Education Coordination (CRTEC) at the Houston Methodist Neal Cancer Center (HMNCC). He works on building the infrastructure within the HMNCC to prepare for the next generation of cancer researchers. He has also implemented the predoctoral and postdoctoral trainee research-in-progress seminar series and will spearhead the submissions of institutional training and education grants. Dr. Hu's laboratory investigates the biology of the endoplasmic reticulum (ER) in normal and malignant B cells. The work from his laboratory establishes that inhibiting the IRE-1/XBP-1s pathway of the ER stress response and activating IRE-1's interacting protein, STING, are effective therapeutic strategies for B cell cancer and graft-versus-host disease. His laboratory develops novel small molecules to target these pathways and continues to identify and characterize ER-resident proteins that can be targeted for therapy of human diseases.

ABSTRACT

Chronic lymphocytic leukemia (CLL) is a cancer derived from mature B cells. Both mouse and human CLL cells can produce and secrete immunoglobulin M. We investigated the roles of secretory IgM (sIgM) in CLL progression by crossing the Eμ-TCL1 mouse model of CLL with MD4 transgenic mice whose B cells produced B-cell receptor (membrane-bound IgM) and sIgM with monospecificity for hen egg lysozyme (HEL). CLL cells developed in these MD4/Eμ-TCL1 mice reactivated a parental Ig gene allele and produced membrane-bound IgM and sIgM incapable of recognizing HEL. The MD4/Eμ-TCL1

mice had reduced survival, increased myeloid-derived suppressor cells (MDSCs), and decreased numbers of T cells. We next investigated whether sIgM could contribute to the accumulation of MDSCs by crossing μS-/- mice, which could not produce sIgM, with Eμ-TCL1 mice. The μS-/-/Eμ-TCL1 mice survived longer than Eμ-TCL1 mice and developed decreased numbers of MDSCs which were less capable of suppressing the proliferation of T cells. The IRE-1/XBP-1s pathway of the endoplasmic reticulum (ER) stress response had been shown to regulate the production of sIgM in B cells. Specifically, XBP-1s-deficient B cells showed drastically downregulated production of sIgM as a result of regulated IRE-1-dependent decay. Thus, we targeted the synthesis of sIgM by deleting XBP-1s specifically from CLL cells and the resultant XBP-1 knockout Eμ-TCL1 mice indeed produced low levels of sIgM, which was accompanied by decreased numbers and reduced functions of MDSCs. In addition, it is worth noting that XBP-1s plays an intrinsic role in promoting the growth of CLL cells; however, the factor that activates XBP-1s in CLL cells is unknown. By generating and investigating the activation-induced cytidine deaminase (AID) knockout Eμ-TCL1 CLL mouse model, we showed that AID-deficient Eμ-TCL1 CLL cells produced and secreted increased levels of sIgM, accompanied by increased expression levels of XBP-1s. When compared with these AID-deficient CLL cells, sIgM-deficient CLL cells from μS-/-/Eμ-TCL1 mice produced barely detectable levels of XBP-1s. Altogether, these data suggest that sIgM can exert both extrinsic and intrinsic effects to drive malignant progression of CLL.

Rajagopal Ramesh, Ph.D.

Speaker

Professor, Department of Pathology

University of Oklahoma Health Campus

Rajagopal Ramesh, PhD is a Professor in the Department of Pathology at the OU Health Stephenson Cancer Center (OU-SCC) on the University of Oklahoma Health Sciences Center campus in Oklahoma City, OK. He serves as Associate Director for its Cancer Training, Education, and Coordination (CRTEC) program, Co-Director of the Nanomedicine Program, and Director of the Small Animal Imaging Core program. He is the Presbyterian Health Foundation Presidential Professor and holds the Jim and Christy Everest Endowed Chair in Cancer Developmental Therapeutics.

Dr. Ramesh is a distinguished oncologist and cancer researcher. His research focuses on cancer biology, gene and drug delivery, and immune modulation for lung cancer patients with an emphasis on translational cancer research. Using lipids, biodegradable polymers, and gold, he leads a team of specialists that develop nanoformulations for developing and testing gene and drug delivery carriers. His research also focuses on testing the antitumor activities of tumor suppressor genes and small molecule inhibitors. More recently, his research has focused on investigating extracellular vesicles as a biomarker source and drug delivery vehicle.

Dr. Ramesh has contributed substantially to gene-based drug delivery and therapeutic innovations that have significantly advanced the field of oncology. Funded through a continuous stream of NIH R01 support, his research efforts have led to the translation of four of his laboratory studies to the clinic for the treatment of lung cancer and other solid tumors.

As Associate Director for CRTEC, he has developed numerous educational, training and career development programs whose trainees span the range from midde school students to Assistant Professors. In this capacity, he serves as the Program Director for seven cancer-specific summer programs at OU-SCC.

Dr. Ramesh's extensive contributions to the field of oncology are marked by his leadership in serving as Chair or member of several grant study sections for the NIH, DOD, ACS, Komen, and Wellcome Trust. He served as the Chair of the Nanotechnology Study Section of the NIH from 2020 to 2022. He is an active member of the American Association of Cancer Research, International Society of Extracellular Vesicles, American Society of Gene and Cell Therapy, and International Association for the Study of Lung Cancer. He serves board member for the American Cancer Society for Oklahoma, Cancer Biology Training Consortium, and the Indian Society of Extracellular Vesicles.

Throughout his career, Dr. Ramesh has been recognized for his expertise, leadership, and dedication to advancing biomedical research and care. His passion for making a difference in the lives of cancer patients drives his ongoing efforts to contribute to the global fight against cancer.

ABSTRACT

HuR is an RNA binding protein overexpressed in multiple human cancers and plays a role in tumorigenesis, invasion and metastasis. Genetic and pharmacologic inhibition of HuR demonstrated antitumor activity establishing HuR as a molecular target for cancer therapy. However, little is known about HuR's role in modulating the innate immune system. The cytoplasmic double-stranded DNA (dsDNA) sensing, cyclic GMP-AMP synthase (cGAS)- stimulator of interferon genes (STING) signaling pathway is crucial for host defense against cancer. Activation of the cGAS-STING signaling cascade triggers the production of proinflammatory cytokines and type I interferons, thereby enhancing antitumor immunity. In the present study, we investigated the effect of CMLD2, a small molecule inhibitor targeting HuR, on the proliferation of medulloblastoma (MB) cells and elucidated the mechanistic relationship between HuR and STING in the regulation of the innate immune response in MB.

Bioinformatics analysis using the UALCAN web-portal revealed an inverse correlation between HuR and STING protein expression in MB. Immunohistochemical staining of MB TMA further confirmed this relationship, showing that tissues with high HuR expression exhibited low or undetectable STING levels, consistent with the bioinformatics findings. *In vitro* studies showed CMLD2 treatment (20μM and 30μM) induced time and dose-dependent cytotoxicity in MB cell lines compared to DMSO-treated controls. Molecular studies revealed CMLD2 treatment suppressed HuR expression while markedly upregulating key proteins in the cGAS-STING pathway (p-STING^{Ser366}, p-TBK1^{Ser172}, and p-IRF3^{Ser396}) at the two drug concentrations tested, Furthermore, CMLD2 treatment significantly increased the secretion of cGAS-STING-associated chemokines (CXCL10 and CCL5) and the cytokine IL-6 compared to DMSO-treated controls. Although the magnitude of induction varied among the cell lines, the overall trend was consistent with the activation of the cGAS-STING pathway following HuR inhibition. Our findings indicate that CMLD2-mediated HuR inhibition induces cytotoxicity in MB cells and simultaneously activates the cGAS-STING pathway. Elucidating how HuR suppression modulates STING signaling and influences immune cell activity will facilitate the development of novel HuR-targeted therapies to enhance anti-tumor immune responses in MB.

Wei Chen, Ph.D.

Speaker

Professor and Director, School of Biomedical Engineering

University of Oklahoma

Dr. Wei R. Chen received his BS degree in physics from Shandong University, Jinan, China, in 1982. He received his PhD degree in theoretical high-energy particle physics from the University of Oregon in 1988. He changed his research from physics to cancer research in the early 1990s. Currently, he is Stephenson Endowed Chair and Professor, and Director of the Stephenson School of Biomedical Engineering at the University of Oklahoma. Dr. Chen is a pioneer in the field of immunophotonics. His group developed localized ablative immunotherapy for metastatic cancers using the combination of local laser ablation and local administration of a novel immunostimulant, with promising outcomes in pre-clinical studies and preliminary clinical trials. Dr. Chen has published 200+ peer-reviewed articles (with an h-index of 63). He has been awarded 11 US patents and multiple international patents. Dr. Chen has received more than $10 million in funding from state and federal agencies, foundations, as well as from industrial sponsors. He was elected as a SPIE (International Society of Optics and Photonics) Fellow in 2007, an AIMBE (American Institute for Medical and Biomedical Engineering) Fellow in 2022, and a Senior Member of NAI (National Academy of Inventors) in 2024. He received the 2008 US Professor of the Year award and the 2011-2012 US Fulbright Lecturing/Research Award. He also won the Medal for Excellence in Teaching from the Oklahoma Foundation for Excellence in 2011 and the SPIE Educator Award in 2012. Dr. Chen is a co-founder and a board director of Immunophotonics, Inc. The company received the US FDA approval in April 2023 for a phase 1b/2a multicenter clinical trial for patients with late-stage colorectal cancer, non-small cell lung cancer, and soft-tissue sarcoma, using the novel therapy developed by Dr. Chen's team.

ABSTRACT

The biggest challenge in cancer treatment is metastasis, due to the failure of the host immune system to detect and destroy cancer cells, particularly metastatic tumor cells. In fact, about 90% of cancer deaths are caused by metastasis. Unfortunately, we have limited options for treating metastatic cancers. Given the immunological root cause of cancer, the ideal solution is immunotherapy to activate, enhance, and direct the host immune system to systemically eradicate cancer and prevent recurrence. We developed an immunophotonics-based novel approach: localized ablative immunotherapy (LAIT). LAIT combines targeted photothermal therapy with a locally administered novel immunostimulant to induce systemic immune responses aimed at treating metastatic tumors. In this talk, I will discuss LAIT-induced immune responses at the transcriptomic level using single-cell RNA sequencing. Then, I will present our clinical results using LAIT for the treatment of patients with melanoma, breast cancer, and other late-stage cancers.

POSTER PRESENTATIONS

Poster #:	Last Name:	First Name:	Institution:	Academic Position:	Abstract Title
1	Haines	Delila	YES Oklahoma	High School Student	A Closer Look: OCT Imaging of Cystic Dilations
2	Satepauhoodle	Hezakiya	El Reno High School	High School Student	Precision Medicine in a Gel: Safer Chemotherapy for Brain Tumors
3	Nichols	Paisley	YES Oklahoma	High School Student	Drosophila Model of HPV Reveals Vulnerability to Oropharyngeal Cancer cells to proteasome inhibition
4	Frings	Avrey	YES Oklahoma	High School Student	The Chemistry and Uses of Different DNA Quantification and Visulaization techniques
5	Viso	Ashley	Northeastern State University	Undergraduate Student	Near-IR Gold Nanorod Combined Photothermal and Photodynamic Therapy
6	Sears	Christian	Oklahoma Christian University	Undergraduate Student	In Vitro Evaluation of Mebendazole Against Cisplatin-Resistant Ovarian Cancer Cells
7	Daniel	Dennis	University of Oklahoma	Undergraduate Student	Safety and Degradation of an Injectible Hydrogel, Optimized for Brain Delivery to Glioblastoma
8	Calhoun	Henley	University of Oklahoma	Undergraduate Student	Tracking Nanoparticle Spatiotemporal Distributions in OVCAR8 Ovarian Cancer Spheroids using Expansion Microscopy
9	Williams	Kaitlyn	University of Oklahoma	Undergraduate Student	Evaluating PEGDA's Influence on Brain-Mimetic Bioink Mechanics and Assessment of Photopolymerization-Induced Oxidative Stress Response
10	Brambila	Laura	Dallas Baptist University	Undergraduate Student	MIR497HG: A Promising Candidate in Ovarian Cancer Therapeutic Development
11	Atiyeh	Paul	University of Oklahoma	Undergraduate Student	Systematic Evaluation of an Anionic Poly(methacrylic acid)-Based Nanogel Library for Macrophage Cytocompatibility and Immunomodulation
12	Le	Vincent	University of Oklahoma Health Campus	Undergraduate Student	The Biological Effects of MDR Exosomes on P-gp Expression in Cancer Cells
13	Street	Charles	University of Oklahoma	Undergraduate Student	Computational tumor progression analysis via seriation based trajectory inference
14	Sumrell	Collin	University of Oklahoma	Undergraduate Student	Predicting Sequential Somatic Mutations in Colon Adenocarcinoma Using LSTM and ARIMA Models
15	Pandit	Kaustubh	University of Oklahoma	Undergraduate Student	Dual-Modality Photoacoustic and Ultrasound Localization Microscopy for Kidney Viability Assessment
16	Nguyen	Tuan	University of Oklahoma	Undergraduate Student	Central Genes: A novel centrality-based ab initio approach for informative gene selection in single cell RNA-seq analysis
17	Eissa	Ahmed	University of Oklahoma	Post-bacc	Super-Resolution Imaging of Nanoparticle Spatial Distributions in Entire 2D and 3D Tumor Models
18 **Abstract omitted**	Reeves	Hope	University of Oklahoma Health Campus	Post-bacc	Empower Patients with HPV-associated Disease to Promote HPV Vaccination (Empower): Protocol for developing and pilot testing an educational component for patients with HPV-related oropharyngeal cancer or dysplasia
19	Owens	Iman	University of Oklahoma Health Campus	Post-bacc	Testing Leukemia-Essential Genes via Somatic Transgenesis and Scale Allo-Transplantation
20	Lewis	Seth	University of Oklahoma Health Campus	Post-bacc	Chronic Exposure to Chromium and Nickel Alters Viability and Promotes Stemness in Oral Squamous Cell Carcinoma
21	Jahir Hussain	Afsana Parveen	Oklahoma State University	Graduate Student	Silent Messengers of Resistance: Exosomes Rewired by Therapy Pressure
22	Akomea	Angelina	University of Oklahoma Health Campus	Graduate Student	Generating Tumor-Targeting Monoclonal Antibodies using Pancreatic Cancer Exosomes

23	Mutembei	Bornface	University of Oklahoma	Graduate Student	Predicting Kidney Post-Transplantation Function from Optical Coherence Tomography Images Using Machine Learning
24	Bueltel	Brandon	University of Oklahoma	Graduate Student	Multi-Agent Drug Delivery from Hydrogel for Use in Local Treatment of Glioblastoma
25	Chakrabarty	Brototi	University of Oklahoma Health Campus	Graduate Student	Targeted Delivery of Sodium Thiosulfate-Loaded Lipid Nanoparticles Prevents Cisplatin-Induced Ototoxicity: From Bench to Zebrafish
26	Liu	Junyuan	University of Oklahoma	Graduate Student	Based on Static-Compression Optical Coherence Elastography, Quantitative Elasticity Assessment Metrics are Provided for Biological Tissues
27	O'Connor	Kelly	University of Oklahoma Health Campus	Graduate Student	Exploring the role of exosomes on ovarian cancer cell growth
28	Amani	Kiana	University of Oklahoma	Graduate Student	Optimal Routing for Mobile Lung Cancer Screening Vehicle Guided by Incidence Rates: A Case Study in Oklahoma
29	Sekhri	Malika	University of Oklahoma Health Campus	Graduate Student	Exploring the Role of Obesity-Associated Extracellular Matrix in Local Breast Cancer Progression
30	Ghanbariabdolmaleki	Marjan	University of Oklahoma	Graduate Student	Evaluation of Nuclei Isolation Techniques for Single-Nucleus RNA Sequencing in Tissue and Cell Suspensions
31	Firouzi	Maryam	University of Oklahoma Health Campus	Graduate Student	Cancer-Derived Small Extracellular Vesicles as a Platform for Generating Cancer–Targeting Antibodies
32	Mohammadnejad	Mobina	University of Oklahoma	Graduate Student	Understanding nanoparticle–cell interactions
33	Ghanbari Mehrabani	Mojtaba	University of Oklahoma	Graduate Student	Payload-Free Macrophage Modulation by Synthetic Nanogels: Correlation of Particle Core Chemistry with Immunological Outcome
34	Oladapo	Olajumoke	University of Oklahoma	Graduate Student	AtlasCollect: A Single Cell Data Atlas platform and Unified Platform for Datasets Collection and Integration
35	Ohene-Marfo	Phoebe	University of Oklahoma Health Campus	Graduate Student	Role of Hepatocyte MLKL in the progression of obesity driven- MASLD-related HCC
36	Subramanian	Poorvi	Oklahoma State University	Graduate Student	Novel molecular driver directed proteomic shift silence immune activation favoring survival over surveillance
37	Zhang	Qinghao	University of Oklahoma	Graduate Student	Optical Coherence Tomography Evaluation of Mebendazole Therapeutic Efficacy in Ovarian Cancer Xenografts
38	Bennett	Rachel	University of Oklahoma	Graduate Student	Understanding and Predicting Care Gaps in Childhood Cancer Survivors Using Machine Learning-Based Survival Models
39	Miller	Reegan	University of Oklahoma Health Campus	Graduate Student	Pancreatic tumor cells modulate the mast cell transcriptome and metabolome
40	Salim	Sabir	Oklahoma State University	Graduate Student	Shifting Immune Signatures Define Bladder Cancer Progression and Prognostic Potential
41	Chakraborti	Sampurna	University of Oklahoma	Graduate Student	Advancing Treatment for Triple-Negative Breast Cancer: Integrating Photothermal Therapy with Immunomodulation in a Preclinical Model
42	Pandey	Shriya	University of Oklahoma Health Campus	Graduate Student	Development of proteolysis targeting chimera (PROTAC) for degradation of oncogenic RET protein tyrosine kinase
43	Narayanan	Sivasubramani	Oklahoma State University	Graduate Student	Lipid Metabolic Reprogramming in Cancer: Uncovering a New Genetic Determinant Pathway

44	Mohanvelu	Sreenidhi	Oklahoma State University	Graduate Student	Site-specific post translational rearrangement in tumor suppressor PML cemented oncogenic addiction in deadly extracranial solid tumors in infants.
45	Turner	Sydney	University of Oklahoma	Graduate Student	Gas vesicles conjugated to antibodies for tumor characterization via ultrasound imaging
46	Bhattacharjee	Adree	University of Oklahoma	Graduate Student	Improved visualization of tumor vasculature using an automatic eigen-image based signal extraction method
47	Flores Arce	Federico Jesus	University of Oklahoma	Graduate Student	Targeted Annexin A5–Mertansine Conjugate for Leukemia Therapy
48	He	Furong	University of Oklahoma Health Campus	Graduate Student	CD151-mediated deacetylation of α-tubulin contributes to colorectal cancer cell' motility and macropinocytic uptake
49	Kakwambi	Enos	University Of Oklahoma	Graduate Student	A novel approach to highly variable genes selection for scRNA-Seq analysis
50	Liu	Ronghao	University of Oklahoma	Graduate Student	Optical Coherence Tomography Detects Biliary Microstructural Alterations for Evaluating Bile Duct Viability in Liver Transplatation
51	Kapoor	Suryaveer	University of Oklahoma	Graduate Student	Building Clustering Consensus and Exploring the Immune Landscape in Mouse Spleen in Single-Cell Resolution
52	Cloud	Elijah	University of Oklahoma	Medical School Student	Enhanced Diagnostic Indication via Novel Claudin-4 Targeting Peptide in Breast Cancer
53	Sammur	Lana	University of Oklahoma	Medical School Student	Exploring C-Myc and its Relationship with DCLK1 in Ovarian Cancer
54	Khastgir	Rumaish	University of Oklahoma Health Campus	Medical School Student	Selective Inhibition of HUR and EZH2 Reveals Potential Crosstalk in Medulloblastoma
55	Abbas	Anser	University of Oklahoma	Medical School Student	Investigating Pancreatic Tumor Cell-Induced Epigenetic Modification in Neutrophils
56	Dey Bhowmik	Arpan	University of Oklahoma Health Campus	Post-Doctoral Fellow	Targeting Ovarian Cancer Stemness and Chemoresistance via Auro-Liposome miR-195 Delivery
57	Aijaz	Ayesha	University of Oklahoma Health Campus	Post-Doctoral Fellow	Non-infectious sarcoid-like inflammatory granulomatous conditions (NSIGC) associated with Immune checkpoint inhibitors (ICIs) for cancer: Pan-tumor Results from the International ICARUS (Immune Checkpoint Associated Rare and Unique Side effects) Consortium
58	Penta	Dhanamjai	University of Oklahoma Health Campus	Post-Doctoral Fellow	Targeting chemoresistance in Ovarian Cancer
59 **Abstract omitted**	Amirmahani	Farzaneh	University of Oklahoma Health Campus	Post-Doctoral Fellow	WNT16 promotes phenotypic plasticity and radiation resistance in glioblastoma
60	Mortan	Laura	University of Oklahoma Health Campus	Post-Doctoral Fellow	Identification and Experimental Validation of Triosephosphate Isomerase 1 as a Functional Biomarker of SHetA2 Metabolic Inhibition of Ovarian Cancer Cells.
61	Periyasamy	Loganayaki	Oklahoma State University	Post-Doctoral Fellow	Targeted Nanodeliverables Remodel the Aggressive Neuroblastoma Microenvironment and Suppress Tumor Progression
62	Jagadish	Natesh	University of Oklahoma Health Campus	Post-Doctoral Fellow	Synergistic Antitumor Effects of SHetA2 and Myc Inhibitor in Cervical Cancer
63	Thomas	Nisha	University of Oklahoma Health Campus	Post-Doctoral Fellow	Tamoxifen Effects on Adipocyte Progenitors Link Breast Cancer Endocrine Therapy to Diabetes Risk

64	Shaw	Pallab	University of Oklahoma Health Campus	Post-Doctoral Fellow	Inhibition of Cystathionine B-Synthase abrogates Anoikis Resistance in detached Ovarian Cancer cells by attenuating SP1–ITGB1 Axis and impairing spheroidogenesis
65	Selvarani	Ramasamy	University of Oklahoma Health Campus	Post-Doctoral Fellow	The Impact of Mitochondrial Haplotype on Inflammation, Fibrosis, and Liver Cancer in Novel OKC-HETB/W Rats
66 **Abstract omitted**	Gor	Ravi	University of Oklahoma Health Campus	Post-Doctoral Fellow	Passive Smoking Promotes Cancer Stemness in Head and Neck Squamous Cell Carcinoma
67	Sriramanujam	Sandeepkumar	University of Oklahoma Health Campus	Post-Doctoral Fellow	Enhancing Immunotherapy Efficacy in Glioblastoma by Targeting CXCR1/2-Mediated Immunosuppression
68	Pani	Sarita	University of Oklahoma Health Campus	Post-Doctoral Fellow	Therapeutic Targeting of Ferroptosis in USPC: SHetA2 Induces TFRC Expression and Potentiates Paclitaxel Efficacy
69	Derangula	Somasekhara	University of Oklahoma	Post-Doctoral Fellow	Atovaquone Attenuates Pancreatic Cancer–Induced Cachexia
70	Voddu	Suresh	University of Oklahoma Health Campus	Post-Doctoral Fellow	Lipophagy-Dependent Fatty Acid Oxidation is a Metabolic Vulnerability for KRAS Signaling Inhibition in Pancreatic Cancer
71	Chumak	Vira	University of Oklahoma Health Campus	Post-Doctoral Fellow	OGT1 reprograms tumor-associated macrophages in pancreatic adenocarcinoma tumor model
72	Sambasivam Ramakrishnan	Yogaraj	University of Oklahoma Health Campus	Post-Doctoral Fellow	Hypoxia-Responsive Targeted Polymersome Drug Delivery in Patient-Derived Xenograft Models of Triple-Negative Breast Cancer
73	Ahmed	Zoheb	University of Oklahoma Health Campus	Post-Doctoral Fellow	DCLK1 Orchestrates Hepatocyte-Macrophage Dysregulation to Drive Liver Fibrosis and Hepatocarcinogenesis
74	Garcia-Contreras	Lucila	University of Oklahoma Health Campus	Faculty	Pharmacokinetics of exosome-encapsulated doxorubicin after administration by different routes
75	Moussa	Marmar	University of Oklahoma	Faculty	Predicting T-Cell Receptor specificity and phenotype using integrated classical and pre-trained Protein Language Models
76	Darden	Paul	University of Oklahoma Health Campus	Faculty	Rural Children with Overweight or Obesity Face Barriers to Identification and Treatment
77	Yoon	Sang	University of Oklahoma	Faculty	Molecular imaging to visualize cancer biomarkers
78	Thavasi	Velmurugan	University of Oklahoma	Staff	Breath-Based Lung Cancer Detection Using PTR-MS and Machine Learning
79	Cruddas	KeAnna	Laureate Institute	Research Assistant	Neuronal-enriched extracellular vesicle microRNA associations with inflammation and neurotoxicity in major depressive disorder

*** NOTE: Some abstracts have been omitted from in the Program Book per presenters' request.**

A CLOSER LOOK: OCT IMAGING OF CYSTIC DILATIONS

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OCT is an imaging technique that uses light to image nanometers beneath tissue. It is not commonly used in most medical fields as of now but has many applications in gastrointestinal imaging. Many organs and tissues, such as livers and kidneys, can be imaged using the OCT to highlight structural abnormalities like tumors or disease that may go unseen by traditional imaging techniques. One of these structural abnormalities include cystic dilations of the liver. Cystic dilations occur when there is an obstruction of blood to the liver, damaging the liver's ability to regenerate itself. Cystic dilations are difficult to detect via MRI or ultrasound. When left untreated, cystic dilations can lead to infection and even cancer. OCT's abilities to detect these small abnormalities lend it to a wide range of applications. As of now, OCT is not commonly used because of expenses and lack of training on the matter, but it is expected to be seen in the foreseeable future to be used as a common imaging technique.

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PRECISION MEDICINE IN A GEL: SAFER CHEMOTHERAPY FOR BRAIN TUMORS

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Abstract: In Dr. Clegg's lab there is a search for better drug delivery to brain tumors such as glioblastomas. The way this is being done is by loading chemotherapeutics into nano particles which are then loaded into a biocompatible gel. The methods used for analysis are things such as rheology, histology, high pressure liquid chromatography, dynamic light scattering, and drug release study. All these methods provide information to make sure the method of delivery is doing its job safely and sufficiently. This is a bright future method for drug delivery.

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A DROSOPHILA MODEL OF HPV REVEALS VULNERABILITY TO OROPHARYNGEAL CANCER CELLS TO PROTEASOME INHIBITION

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Drosophila flies show how certain genes in job are interacting to cause tumors growth. Proteins Alpha and Beta were used to induce cell death in unhealthy cells and had no effect on healthy cells

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THE CHEMISTRY AND USES OF DIFFERENT DNA QUANTIFICATION AND VISUALIZATION TECHNIQUES

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DNA quantification and visualization techniques are commonly used to determine the concentration and size of DNA in a sample. This research goes over the uses of gel electrophoresis, the Qubit (a fluorometer), and the Tapestation (an automated capillary electrophoresis platform). While completing this research, each of these techniques were used to quantify and visualize the DNA of nematodes and their digestive system's microbiome.
Although there was evidence of extracted DNA from the gel electrophoresis, there was not enough to obtain a concentration from the Qubit and the Tapestation. These skills are important because they can help researchers check the quality of their work and improve their results. It would be exceptionally useful if a researcher is sequencing DNA from cancer cells.

NEAR-IR GOLD NANOROD COMBINED PHOTOTHERMAL AND PHOTODYNAMIC THERAPY

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Cancer is a disease that is constantly evolving, so novel methods of treatment are required to combat it. We desperately need cancer treatments that destroy cancer cells yet spare healthy ones. Gold nanorods might hold the key to a future of localized cancer therapies. Gold nanorods (GNRs) have shown great promise in medical applications over the last decades due to their unique and tunable interaction with light and their potential for surface functionalization. These properties allow for photothermal therapy (PTT), in which light elevates the temperature of the GNRs within a biological setting. Additionally, GNRs can be coated with light-reactive chemotherapeutic agents, allowing for photodynamic therapy (PDT). These functions are particularly relevant for near-infrared (NIR) light absorption given the extended biological window of up to 2 cm because it could allow for non-invasive treatments, especially of cancers just beneath the skin. However, these particles are formed in the surfactant CTAB via a seed-mediated growth mechanism, which is toxic in the human body. Here, we describe recent efforts to synthesize NIR absorbing GNRs bifunctionalized with both folic acid and hydroxamate-based histone deacetylase (HDAC) inhibitors, like vorinostat (SAHA). Many tumors are known to overexpress folic acid receptors, so this overexpression will aid in concentrating the GNRs solely at cancer sites. Irradiation with NIR light will create a hyperthermic environment promoting two localized responses: thermal cell degradation and detachment of the drug coated on the GNR surface, thereby targeting the irradiated area and distributing the drug solely onto the tumor. These pharmacologically active compounds will be bound to the GNR surface through cuACC “click” chemistry, which will allow for relatively easy swapping of surface coatings. This combined therapy approach will allow for multiple simultaneous targeted therapies of shallow tumors through a noninvasive and nontoxic pathway.

We gratefully acknowledge financial support from the Department of Physical Sciences and the Gregg Wadley College of Science and Health Professions at Northeastern State University.

IN VITRO EVALUATION OF MEBENDAZOLE AGAINST CISPLATIN-RESISTANT OVARIAN CANCER CELLS

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Introduction: Ovarian cancer is the deadliest gynecological malignancy, primarily due to late-stage diagnosis, development of resistance to current platinum-based chemotherapies, and frequent recurrence. Although maintenance therapies have shown clinical benefits, they are considerably toxic, expensive, and have low response rates. Thus, novel therapeutic strategies are urgently needed. Repurposing drugs is an increasingly popular strategy in oncology due to the financial and logistical constraints of new drug development. Recently, mebendazole (MBZ), an anti-parasitic drug, has gained much attention in oncology due to its favorable biosafety profile and potent anti-cancerous activity seen in several human malignancies, including ovarian cancer. In this study, we examined MBZ efficacy against cisplatin-resistant (CPR) ovarian cancer cells.

Methods: MBZ's efficacy was assessed in cisplatin-sensitive (WT) and CPR OVCAR8 human ovarian cancer cells using an MTT cell viability assay. To assess whether MBZ enhances cisplatin sensitivity, MBZ-treated ovarian cancer cells were treated with cisplatin and analyzed for cell viability. Spheroid and colony formation assays were conducted to assess MBZ's impact on ovarian cancer cell stemness, and western blotting was used to examine stemness and therapy-related molecular markers.

Results: MBZ significantly reduced viability in both WT and CPR ovarian cancer cells, with an IC_{50} below 1 µM for 72 hours. MBZ pretreatment markedly enhanced cisplatin sensitivity in ovarian cancer cells. It also inhibited colony formation ability in both WT and CPR ovarian cancer cells, as evidenced by reduced spheroid size and structural disruption in the MBZ treatment group compared to controls. Additionally, MBZ downregulated key stemness markers (CD133 and SOX2) and inhibited the Wnt/β-catenin signaling pathway by reducing β-catenin expression in these spheroids.

Conclusion: Our study strongly supports the therapeutic potential of MBZ for chemoresistant ovarian cancer and its ability to enhance cisplatin sensitivity, offering a promising avenue for overcoming resistance in treatment-refractory patients.

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SAFETY AND DEGRADATION OF AN INJECTIBLE HYDROGEL, OPTIMIZED FOR BRAIN DELIVERY TO GLIOBLASTOMA

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Abstract: Glioblastoma (GBM) is the most common and lethal brain tumor, with a 5-year patient survival rate of 5%. The current standard of care, consisting of surgical debulking of accessible tumors and systemic temozolomide, is inadequate and fundamentally limited by the inability of most chemotherapies to cross the blood-brain barrier. Our research seeks to close this technology gap through the development of an injectable hydrogel that delivers different chemotherapeutics directly to the tumor site. Our team invented this injectable hydrogel, called "ParenchyGel" (US patent pending). The present study evaluates the biodegradation kinetics and safety profile of ParenchyGel and its components. To assess safety, each gel component was administered to L929 fibroblasts (ISO 10993-5 test), followed by MTS and LDH toxicity assay to detect the potential for cell membrane damage or changes in metabolism. Gel degradation was also measured by submerging gels in a 0.9% saline solution at 37 C, and measuring changes in stiffness and mass over six weeks. Rheology was performed using a compression test and an amplitude sweep on n=3 hydrogels (weekly sampling). Three raw components (i.e., chemically modified hyaluronic acid, LAP photoinitiator, poly(ethylene glycol)) showed no significant toxicity differences relative to untreated cells, and a significantly greater metabolism and cell membrane integrity relative to a lysis positive control ($p<0.01$), providing strong evidence for cytocompatibility. Over six weeks, ParenchyGel's swollen mass, dry mass, and Young's modulus decreased by 14.5%, 47.2%, and 6.2%, respectively. Although the dry mass decreases by half, the more modest decrease in both swollen mass and stiffness suggests that the gel maintains integrity in a hydrated form over the intended duration of drug delivery in the brain/body (~1 month). Together, our data strongly suggests that ParenchyGel is cytocompatible and suitable for month-term drug delivery to Glioblastomas in the brain tissue environment.

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TRACKING NANOPARTICLE SPATIOTEMPORAL DISTRIBUTIONS IN OVCAR8 OVARIAN CANCER SPHEROIDS USING EXPANSION MICROSCOPY

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Ovarian cancer affects 10.5 individuals per 100,000 people per year in Oklahoma and 10.1 individuals per 100,000 people per year in the country. There is a need to explore treatments that are safer and more effective. We focus in this study on gold nanoparticles as a model system for ovarian cancer nanomedicines. Using 3D super-resolution microscopy, we track the spatiotemporal distribution of these nanoparticles in multicellular OVCAR8 ovarian cancer spheroids. The spheroids were exposed to nanoparticles in cell culture for up to seven days. After fixation, the spheroids were processed using an expansion microscopy procedure, which includes the infusion of swellable hydrogels. Once the hydrogels were polymerized, the spheroid-hydrogel hybrids were stained with fluorescent NHS-dyes to label the proteome of the spheroids. Upon submerging the stained spheroid-hydrogel hybrids in deionized water to swell the hydrogels, we achieved expansion factors of up to 10 times. This expansion process enables the 3D super-resolution microscopy of entire OVCAR8 spheroids with lateral resolutions approaching 20 nm using conventional confocal laser scanning microscopy systems. Using this workflow, we track the time-dependent accumulation of gold nanoparticles in these spheroids with 3D intracellular context. We hypothesize that the majority of internalized gold nanoparticles will actively interact with ovarian cancer cells rather than being passively distributed across the extracellular matrix. Additionally, we hypothesize that gold nanoparticles are more likely to reach the spheroid center when incubated for extended periods. Our research underscores the significance of using 3D cancer model systems with in vitro tumor environments that more closely mimic those found in humans, as well as the importance of combining these cancer models with advanced 3D super-resolution microscopy. Our approach may serve as a general workflow for evaluating nanoparticle-tumor interactions across various malignancies, with the ultimate goal of developing next-generation cancer nanomedicines that are safer and more effective.

Acknowledgments

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EVALUATING PEGDA'S INFLUENCE ON BRAIN-MIMETIC BIOINK MECHANICS AND ASSESSMENT OF PHOTOPOLYMERIZATION-INDUCED OXIDATIVE STRESS RESPONSE

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The semi-permeable nature of the blood-brain barrier (BBB) limits the delivery of therapeutics to treat neurological cancers, such as glioblastoma. Developing physiologically relevant BBB models is therefore critical for studying brain tumor biology and drug transport, for which three-dimensional (3D) bioprinting offers a promising approach. Since brain tissue stiffness varies across pathological states, bioinks must exhibit tunable viscoelastic properties, as well as maintain neural cell health during photopolymerization. This study investigated how incorporating polyethylene glycol diacrylate (PEGDA) into a composite bioink influences its viscoelastic properties and how photopolymerization time affects cytocompatibility. The bioink was comprised of methacrylated hyaluronic acid (HAMA), methacrylated gelatin (GelMA), and PEGDA, with lithium phenyl (2,3,6-trimethylbenzoyl) phosphinate (LAP) as a photoinitiator for UV crosslinking at 365 nm. Rheological testing showed that PEGDA had minimal effects on viscous flow, yield behavior, and temperature stability, while increasing GelMA concentration enhanced stiffness of the gel. The yield strain was approximately 102% for the low GelMA concentration hydrogels while the storage moduli consistently increased for high GelMA concentration formulations. All hydrogels demonstrated optimal printability between 30-40 °C. To assess cytocompatibility, DCFDA assays were performed using human primary astrocytes seeded within the hydrogel prior to UV exposure. Mean fluorescence intensity (MFI) values increased proportionally to UV exposure time, indicating increasing reactive oxygen species levels. However, increased MFI in hydrogels with LAP may indicate the oxidation of DCFDA by free radicals produced during the photopolymerization process, causing background fluorescence. Overall, PEGDA contributed little to mechanical modulation compared to GelMA, and the DCFDA results suggest that photopolymerization may cause oxidative stress to astrocytes. These results underscore the importance of fine-tuning GelMA content and UV exposure to create bioprinted BBB models that can accurately mimic the tumor microenvironment and serve as reliable in vitro platforms for evaluating therapeutic delivery and resistance mechanisms in glioblastoma.

MIR497HG: A PROMISING CANDIDATE IN OVARIAN CANCER THERAPEUTIC DEVELOPMENT

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Ovarian cancer (OvCa) is one of the most lethal gynecologic malignancies, driven by late-stage diagnosis, rapid metastasis, and high recurrence rates. The need for novel therapeutic targets is urgent. Long non-coding RNAs (lncRNAs) have gained attention for their roles in cancer progression and regulation. Among them, LncRNA **MIR497HG**, the host gene of tumor-suppressive **miR-497** and **miR-195**, is found to be downregulated in many cancers and poorly characterized in OvCa. Therefore, unraveling the cause of **MIR497HG** downregulation is of utmost importance, and we hypothesized that there might be involvement of **epigenetic regulation** by means of promoter methylation. Gene expression of **MIR497HG** and **miR-195** was analyzed in normal ovarian surface epithelial cells (OSE) and OvCa cell lines (COV318, OVCAR3, OVCAR8, OVSAHO, COV362, TYK-nu, TYK-nu CpR) using qRT-PCR. RNA interference (siRNA) was utilized to silence **MIR497HG** and assess the expression of **miR-195**. We also evaluated pre- and mature RNA levels of **MIR497HG** and **miR-195** in both untreated and DNA methyltransferase inhibitor (**DNMTi 5-Azacytidine, 20µM**) treated OVCAR8 and OVSAHO cell lines after 96 hours. Both precursor and mature forms of **MIR497HG** were significantly downregulated in ovarian cancer (OvCa) cell lines (COV318, OVCAR3, OVSAHO, COV362, TYK-nu, TYK-nu CpR) compared to the normal ovarian surface epithelial (OSE) cell line. A **positive correlation** was observed between **MIR497HG** and **miR-195** expression levels. Knockdown of **MIR497HG** resulted in a marked reduction in both its pre- and mature transcripts, accompanied by a significant downregulation of **miR-195**, suggesting a **direct regulatory relationship**. Given that **promoter methylation** is a known mechanism for gene silencing, we investigated its role and found that treatment with the DNA methyltransferase inhibitor **5-Azacytidine** significantly restored **MIR497HG** expression, implicating **epigenetic repression** in its downregulation. Our study highlights that **MIR497HG** is markedly downregulated in OvCa and its expression positively correlates with **miR-195 levels**. The reactivation of **MIR497HG** by **DNMTi treatment** strongly supports a role for **epigenetic silencing** in its suppression. These findings suggest that restoring **MIR497HG** and **miR-195** expression may serve as a potential therapeutic strategy to inhibit tumor progression in ovarian cancer.

SYSTEMATIC EVALUATION OF AN ANIONIC POLY(METHACRYLIC ACID)-BASED NANOGEL LIBRARY FOR MACROPHAGE CYTOCOMPATIBILITY AND IMMUNOMODULATION

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Biodegradable nanogels are promising platforms for macrophage-targeted immunomodulation due to their tunable chemistry, hydrophilicity, and biocompatibility. In cancer and other inflammatory conditions, macrophages internalize nanogels, making them ideal for designing charge-dependent responses. This study developed an anionic poly(methacrylic acid)-based nanogel library to evaluate how composition influences RAW 264.7 and bone-marrow-derived macrophage (BMDM) viability and phenotype. Nanogels were synthesized via inverse emulsion polymerization with *N,N'-bis(acryloyl)cystamine (BAC)* as the degradable crosslinker. Acrylamide (AAm), 2-hydroxyethyl methacrylate (HEMA), and methacrylic acid (MAA) were copolymerized in varying ratios, generating three anionic nanogel families—P(AAm-co-MAA), P(HEMA-co-MAA), and P(HEMA-co-AAm-co-MAA). Dynamic light scattering (DLS) evaluated pH-responsive swelling and surface charge and assessed the nanogels' colloidal stability under biological conditions. FTIR and ^{1}H NMR confirmed polymer composition and purity. To assess cytocompatibility, RAW 264.7 and BMDMs were treated with increasing nanogel concentrations (0.001875-1.5 mg/mL) for 24 hours. LDH and MTS assays quantified cytotoxicity and metabolic activity. Flow cytometry assessed macrophage phenotype using surface (CD86, MHC II, CD206, CD163) and intracellular (iNOS, Arg1) markers. DLS revealed nanogel diameters between 70–100 nm, with pH-dependent swelling as pH increased, and high colloidally stability. LDH assays showed that no formulation exhibited significant dose-dependent cytotoxicity ($p>0.05$). MTS assays demonstrated up to 25 % higher metabolic activity relative to untreated groups for P(HEMA-co-MAA) and P(HEMA-co-AAm-co-MAA) formulations ($p<0.05$). Flow-cytometric analysis revealed composition and dose-dependent modulation of macrophage phenotype, with increased CD86, MHC II, and CD206 expression. These findings demonstrate that anionic nanogels containing higher MAA content maintain macrophage viability while enhancing metabolic and activation markers, suggesting a mild pro-regenerative immunomodulatory effect. These results establish a foundation for linking charge-dependent nanogel properties with macrophage phenotype and signaling, informing future therapies for inflammatory conditions such as cancer. Ongoing efforts include 2D NMR characterization, flow-cytometric profiling of polarization markers, and BMDM-focused secretome and transcriptome analyses using NanoString.

THE BIOLOGICAL EFFECTS OF MDR EXOSOMES ON P-GP EXPRESSION IN CANCER CELLS

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A major challenge addressed in chemotherapy is the development of multidrug resistance after treatment among various cancer cells. This resistance is often caused by the high levels of P-glycoprotein (P-gp). The mechanism of P-gp is pumping out foreign substances, including the drug you are using, thereby reducing its efficacy. Exosomes are nanosized, extracellular vesicles released from the cell. They play a big role in cell-to-cell communication and contain information from the cell's origin. Recent studies have observed that exosomes are responsible for transferring resistance to other untreated cancer cells. This study investigates the potential role of exosomes, their transfer of their resistance through the various treatments to cancer cells, and observations of P-gp levels on the cells. In a previous study, exosomes were isolated and characterized from an ovarian cancer cell line called Kuramochi (KU) treated with 1µM and 2µM doxorubicin. Cell Counting Kit-8 (CCK-8) was used to determine cell viability and analyzed after treatment with different exosome concentrations on sensitive KU cells. Afterwards, different doses of doxorubicin were injected onto the treated cell at different time conditions, and results were visualized through immunocytochemistry. Currently, a different cell line called MES-SA and its multidrug derivative MES-SA/MX2 are used. KU cells were revealed to have shown changes in P-gp expression following exosome treatment. CCK-8 indicated a concentration- and time-dependent effect of resistant KU-derived exosomes on sensitive KU cells. The previous study with KU cells suggests that exosomes derived from drug-resistant cancer cells may affect the level of P-gp and mediating resistance among sensitive cancer cells. However, various dosages of MDR exosomes may induce cytotoxicity to the cells, and further research needs to be conducted to understand deeply how they respond. Results from different cell lines can change, but current findings highlight the observations of cells mediating MDR through exosome transfer.

COMPUTATIONAL TUMOR PROGRESSION ANALYSIS VIA SERIATION BASED TRAJECTORY INFERENCE

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Precise lineage or evolution path determination play a crucial role in discerning the dynamic developmental or temporal progression patterns observed in single cell RNA-Seq data. In this work, we present a novel computational approach for progression pattern inference of normal or tumor cell populations that are actively progressing along a dynamic pathway in single cell resolution. This is achieved via ordering the cellular transcriptional profiles identifying the progression of cell populations along differentiation, signaling, or tumor evolution paths. Here, we developed a seriation-based progression pattern inference method using optimally reordered hierarchies and provide advanced principal-curves-based visualization of the inferred paths in three-dimensional latent space representation of scRNA-Seq data. Additionally, we present novel metrics for evaluating the reconstructed order and identified pathways and evaluate our approach using real single cell transcriptomics datasets.

PREDICTING SEQUENTIAL SOMATIC MUTATIONS IN COLON ADENOCARCINOMA USING LSTM AND ARIMA MODELS

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Accurate prediction of tumor evolution and the sequential appearance of somatic mutations can improve our understanding of cancer progression. In this study, we compare a Recurrent Neural Network (RNN) model based on Long Short-Term Memory (LSTM) against a classical time-series model, Autoregressive Integrated Moving Average (ARIMA), for predicting the presence of a mutation in a specific gene in a colon adenocarcinoma sample based on a sequence of temporally-ordered mutations. While both approaches yielded high overall accuracy, both struggled with low true positive rates (TPR) due to high class imbalance. Notably, ARIMA achieved a higher TPR, but had a positive predictive value (PPV) much lower than that of LSTM, indicating a more liberal assignment of positives. Counter to expectations, improvements to the architecture of the LSTM model did not improve performance. To refine predictions, we applied hierarchical clustering to group samples according to their mutational burden, producing improvements in both TPR and PPV within clusters.

DUAL-MODALITY PHOTOACOUSTIC AND ULTRASOUND LOCALIZATION MICROSCOPY FOR KIDNEY VIABILITY ASSESSMENT

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Assessing deep-tissue oxygenation and perfusion in human organs is critical for monitoring kidney viability during preservation and evaluation protocols. Ex vivo normothermic machine perfusion (NMP) presents a promising platform for maintaining organ function and evaluating kidney health. However, current assessment methods are limited, as they rely on global perfusate biomarkers (e.g., oxygen consumption and blood perfusion) and single-point measurements, which lack spatial resolution and quantitative data on both organ metabolism and hemodynamics. On the other hand, photoacoustic imaging (PAI) enables deep-tissue mapping of blood oxygen saturation (sO_2), which is advantageous over the shallow and single-point detection of pulse oximetry. Meanwhile, ultrasound localization microscopy (ULM) offers a super-resolution assessment of microvascular architecture and blood flow, enabling visualization of perfusion at the capillary level, a scale inaccessible to conventional Doppler ultrasound. In this study, we propose a novel multi-modal imaging strategy for the comprehensive, non-invasive assessment of ex vivo perfused human kidneys using PAI and ULM. We demonstrated the first application of this integrated platform in an ex vivo perfused human kidney under physiological conditions. PAI-derived sO_2 maps were validated against the standard pulse oximetry. ULM's super-resolution microvasculature images and quantitative flow velocity maps were correlated with the absolute flow rate of the perfusion system. Our results demonstrated the feasibility of this dual-modality approach, capturing how the perfused kidney utilized oxygen and distributes blood flow. This strategy holds significant translational potential for enhancing organ viability assessment, advancing research in renal physiology, and improving understanding of organ perfusion dynamics.

CENTRAL GENES: A NOVEL CENTRALITY-BASED AB INITIO APPROACH FOR INFORMATIVE GENE SELECTION IN SINGLE CELL RNA-SEQ ANALYSIS

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The influx of high dimensional single cell RNA-Seq (scRNA-seq) data requires feature selection methods to reduce noise and distinguish informative features in order to perform effective analysis [3]. Current methods for excluding noise and uninformative features focus on preserving features of high variance or attempt to highlight 'rare' features. Other existing probabilistic approaches are differential gene expression analysis or deep learning-based feature importance prioritization to identify marker genes or features; however such methods require prior knowledge about the cluster labels. Here, we propose Central Genes, a graph-based approach which selects informative genes based on centrality measures. The method constructs a gene network to preserve each feature relation to one another. We select genes of significance depending on its role within the network denoted by a centrality measure such as betweenness [1,2] or closeness [2]. To validate our method, we compare against current feature selection methods such as highly variable genes and TF-IDF [4] across various publicly available datasets for accuracy in clustering, cell type identification and pre-selecting marker genes in differential expression analysis among other analyzes. Our current results suggest that our novel approach outperforms common feature selection methods by providing robust capabilities against noise while maintaining biological interpretability.

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SUPER-RESOLUTION IMAGING OF NANOPARTICLE SPATIAL DISTRIBUTIONS IN ENTIRE 2D AND 3D TUMOR MODELS

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Nanoparticles play a vital role in cancer therapy and diagnostics, serving as vehicles for targeted drug delivery and imaging contrast agents. Despite significant clinical success—particularly with mRNA lipid nanoparticle (LNP) vaccines—the efficient and precise delivery of nanoparticles to tumor tissues remains a major challenge. Most existing studies emphasize biodistribution at the organ or tissue level, yet critical knowledge gaps persist regarding the fate of nanoparticles once they enter tumor microenvironments. Little is known about how these particles distribute, aggregate, or release their payloads within tumors, or how their interactions with cancer and immune cells affect delivery efficiency.

Conventional optical microscopy lacks the resolution necessary to resolve these nanoscale interactions. Expansion Microscopy (ExM), when combined with fluorescence labeling, provides a powerful super-resolution platform capable of physically expanding biological samples for nanoscale visualization. Leveraging this approach, we aim to directly observe the uptake, trafficking, and payload release of organic nanoparticles within cancer and immune cells.

Using 4T1 murine triple-negative breast cancer cells and RAW 264.7 macrophages as a preliminary two-dimensional model, we employ fluorescently labeled liposomes as a representative nanoparticle system. This allows us to visualize both hydrophobic and hydrophilic cargo within the bilayer and track their intracellular fate using ExM. By combining precise fluorophore/nucleic acid pre-labeling with high-resolution expansion imaging, we can map nanoparticle localization and payload survival at unprecedented detail.

This work bridges a critical gap in nanomedicine by elucidating how nanoparticles behave inside tumor cells, providing insight into intracellular delivery mechanisms, and informing future three-dimensional and in vivo models. Ultimately, these findings will support the rational design of targeted mRNA-lipid-based therapeutics for metastatic triple-negative breast cancer.

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TESTING LEUKEMIA-ESSENTIAL GENES VIA SOMATIC TRANSGENESIS AND SCALE ALLO-TRANSPLANTATION

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Leukemia is a hematologic cancer and the most common childhood malignancy. Zebrafish and humans share similar adaptive immune systems and key immunologic and oncologic pathways, making zebrafish useful to study ALL (Acute Lymphoblastic Leukemia) biology. Our lab uses zebrafish with transgenic human MYC (*hMYC*) controlled by a lymphoblast-specific promoter (*rag2*) to drive ALL. We pair this with lineage-specific markers (e.g., *lck*:*mCherry*, *cd79a*:*GFP*) in multi-transgenic fish, creating fish with color-coded B- and T-lineage ALL. MYC drives oncogenesis, but cannot cause ALL in isolation; other genes also contribute, making them potential therapeutic targets. To test candidate genes putatively essential to ALL initiation and progression *in vivo*, we sought a method to rapidly enhance or ablate genes in only ALL cells. We selected TEAZ (Transgene Electroporation in Adult Zebrafish), a somatic transgenesis system. TEAZ introduces DNA into some—but not all—cells, creating competing populations of modified vs. unmodified ALL cells. TEAZ can introduce transgenes that enhance, or CRISPR components to ablate, gene function. Traditionally, TEAZ directly injects plasmids into tissues of living fish, but to 'scale up' TEAZ, we are piloting a new method: We harvest ALL-infiltrated scales from a donor fish, perform TEAZ on scales *ex vivo*, and then implant TEAZ'd scales into immunosuppressed recipients. One donor fish provides dozens-to-hundreds of ALL-infiltrated scales, so we can test many genes in parallel simultaneously, comparing otherwise-identical ALL cells to find those crucial to ALL survival and growth. Scale abundance also allows transplants with large cohorts to achieve statistically-significant results quickly. Thus, scale transplants permit functional target testing to ascertain which genes merit development of novel ALL therapeutics. We will present an overview of our project's schema and current progress.

CHRONIC EXPOSURE TO CHROMIUM AND NICKEL ALTERS VIABILITY AND PROMOTES STEMNESS IN ORAL SQUAMOUS CELL CARCINOMA

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Background: Electronic cigarettes (e-cigarettes) have gained widespread popularity as perceived safer alternatives to combustible tobacco. However, e-cigarette aerosols contain toxic heavy metals such as hexavalent chromium (Cr^{6+}) and nickel (Ni^{2+}), which are systemically absorbed and can elicit cytotoxic and proliferative cellular responses. Given the considerable deposition of these metals in the oral mucosa, investigating their long-term oncogenic potential is essential for comprehensively assessing the health risks associated with e-cigarette use.

Hypothesis: We hypothesize that chronic exposure to e-cigarette user-relevant concentrations of Cr^{6+} and Ni^{2+} alters oral cancer cell viability and enhances stemness characteristics. This study aims to evaluate the impact of prolonged low-dose exposure on oral squamous cell carcinoma viability and stemness properties.

Methods: WSU-HN6 cells were treated every other day for 14 days with Cr^{6+} (0.75, 1.5, and 3 µg/L) or Ni^{2+} (2.5, 5, and 10 µg/L), reflecting plasma concentrations reported in e-cigarette users. Cell viability was assessed by MTT assay 96 hours post-exposure, while stemness was quantified via tumorosphere formation in ultra-low attachment plates over five days. Statistical analysis was performed using ANOVA and *t*-tests.

Results: Chromium and nickel exposure at plasma-relevant concentrations observed in e-cigarette users led to a concentration dependent decrease in cell viability, Notably, both metals significantly ($p<0.05$) enhanced tumorsphere formation, suggesting that the chronic exposure increases cancer stemness.

Conclusions: Preliminary findings suggest that chronic low-dose exposure to Cr^{6+} and Ni^{2+} at levels considered environmentally "safe" increases cancer stemness in oral squamous cell carcinoma and may facilitate a more aggressive cellular phenotype. These results underscore potential oncogenic risks associated with e-cigarette use and highlight the necessity for mechanistic investigations into how persistent metal exposure promotes stemness and tumor progression.

Keywords: e-cigarettes, heavy metals, chromium, nickel, oral cancer, cancer stemness

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SILENT MESSENGERS OF RESISTANCE: EXOSOMES REWIRED BY THERAPY PRESSURE

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Exosomes are potent mediators of systemic cellular communication, orchestrating tumor evolution through the dynamic transfer of genetic and molecular cargo. In pediatric neuroblastoma (NB), a highly lethal embryonal malignancy characterized by hematogenous dissemination and acquired resistance with therapy pressure remains a critical barrier to durable clinical outcomes. To interrogate the proteomic landscape of exosomes under therapeutic pressure, we profiled exosomal cargo derived from NB patients, primary and metastatic site derived diagnostic (DX) cells (CHLA 15, CHLA 42) and matched progressive disease (PD) cells (CHLA 20, CHLA 90) that survived therapy-induced stress. Exosomes were isolated from serum-free cultures, characterized via nanoparticle tracking analysis (NS300), and subjected to global proteomic profiling using data independent acquisition-based mass spectrometry. Spectronaut was used for precise peptide quantification and applied $\log_2$ fold change and –log2 (Padj) thresholds with FDR correction for robust protein-level inference. Of the total 4,004 exosomal proteins realized, PD-derived exosomes displayed loss of 476 proteins and distinct expression of another 281 candidates when compared with DX counterparts. Functional annotation in Omics Playground V4 (BigOmics Analytics) revealed enrichment of therapy-induced exosomal proteins regulating apoptosis (*BCAP31, TXNIP, PEA15, IGF2R*), epithelial-to-mesenchymal transition (*BMP7, HGF, LIMS1, TGFB1, LOXL3*), multidrug efflux-mediated chemoresistance (*ABCD3, ABCB6, ABCA3, ABCC1*), immune evasion (*ICAM2, CD99, ZMPSTE24, FGL1, CD276*) and metastasis (*SRSF2, PHF5A, SNRPD2*) signaling. PD-derived exosomes are enriched in SUMOylation of chromatin organization proteins (*TPR, CHD3, HDAC1*) that reprogram gene expression to support therapy resistance. These findings uniquely reveal that therapeutic pressure drives a profound shift in exosomal cargo toward a pro-survival, pro-metastatic, and immune-evasive proteomic signature. Crucially, exosomal proteins in PD actively transmit molecular determinants that reinforce chemoresistance and promote disease progression, positioning these exosomal proteomics as the promising biomarkers and, further paves way for the development of novel molecular targeted therapeutic strategies for deadly progressive NB.

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GENERATING TUMOR-TARGETING MONOCLONAL ANTIBODIES USING PANCREATIC CANCER EXOSOMES

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) remains notoriously lethal due to its rapid and aggressive progression, late diagnosis, and resistance to current therapies. Our study investigates a novel approach to addressing this challenge by using exosomes, small extracellular vesicles (sEVs) derived from pancreatic cancer to generate antibodies that selectively target the cancer cell.

Method: In this study, exosomes were isolated from Panc-1 cell line and characterized by nanoparticle tracking analysis (NTA), confirming an average size of ~100 nm and concentration of $1.6x10^{11}$ particles/ml. Mice were then immunized by three intraperitoneal (IP) injection of Panc-1 exosomes ($5 x10^{9}$ particles/dose with adjuvant) at 2-week intervals. Following administration, antibody production in mice serum were visualized by immunocytochemistry against Panc-1 cells. Hybridoma cells were then generated by fusing the splenic B-cells from the immunized mice with myeloma cells. Antibody screening was conducted by testing the supernatants from multiple hybridomas with binding affinity to Panc-1 cells. Single-cell cloning was subsequently used to isolate hybridomas capable of producing monoclonal antibodies with selective targeting to pancreatic cancer cells.

Results/Conclusions: Our results shows that pancreatic cancer derived exosomes can be used to generate specific monoclonal antibodies that bind strongly to Panc-1 cells. These antibodies could enable ligand discovery for future development targeted therapeutics in PDAC. Future studies will focus on optimizing exosome formulations and exploring their applications in pancreatic cancer treatment.

PREDICTING KIDNEY POST-TRANSPLANTATION FUNCTION FROM OPTICAL COHERENCE TOMOGRAPHY IMAGES USING MACHINE LEARNING

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Abstract: Delayed graft function (DGF) is a post-transplant complication in recipients of deceased donor kidneys. This study investigates the effectiveness of machine learning approaches in predicting DGF using texture features extracted from optical coherence tomography (OCT) images, supplemented with Kidney Donor Profile Index (KDPI) scores. To address significant class imbalance between immediate graft function (IGF) and DGF, three strategies were evaluated: threshold optimization, data balancing via the synthetic minority oversampling technique with Tomek links, and cost-sensitive learning. We demonstrate that classifiers trained on KDPI scores alone underperformed compared to those trained OCT derived texture features. Classifiers trained on KDPI alone showed moderate improvements after adjusting the threshold but incorporating OCT-derived texture features markedly enhanced model performance across all classifiers. These findings underscore the utility of OCT imaging in assessing kidney allograft quality and predicting post-transplant outcomes, highlighting the potential of machine learning classifiers to estimate the risk of delayed graft function (DGF) in deceased donor kidneys prior to transplantation.

MULTI-AGENT DRUG DELIVERY FROM HYDROGEL FOR USE IN LOCAL TREATMENT OF GLIOBLASTOMA

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Abstract: Glioblastoma (GBM) is the most common metastatic brain tumor, affecting approximately 12,000 new patients annually in the United States, with fewer than 900 surviving five years. The current standard of care, the Stupp protocol, combines surgical resection with systemic temozolomide; however, achieving therapeutic peritumoral concentrations remains limited by the blood–brain barrier (BBB). Local delivery systems such as the Gliadel® Wafer bypass the BBB but fail to sustain therapeutic drug levels and are poor mechanistic matches with brain tissue. Our hydrogel delivery system suspends polymeric nanoparticles within the hydrogel matrix, allowing the modulation of drug loading into either the nanoparticle or aqueous phase depending on solubility and desired release kinetics. *In-vitro* release studies analyzed the system's ability to sustain release of therapeutics effective against GBM cells but restricted *in vivo* by BBB transport. Fasudil, Interferon-γ (IFNγ), and various sized Fluorescein Isothiocyanate (FITC) Dextran—used as analogs for neutrally charged, polar drugs—were loaded into 50-µL hydrogels and allowed to release over three weeks into release media. Fasudil concentrations were quantified via ultra-performance liquid chromatography, IFNγ with CQBCA Protein Quantification assays, and FITC via fluorescence spectroscopy. Inclusion of unloaded nanoparticles yielded significantly more uniform release kinetics without altering cumulative release. Average coefficients of variation were reduced by 53% for Fasudil and 43% for IFNγ compared to gels without nanoparticles. Fasudil exhibited the highest cumulative release (~70%), whereas IFNγ released only ~3%. FITC–Dextran release scaled inversely with size, confirming diffusion-limited transport and demonstrating preferential delivery of small, electrostatically neutral molecules. Initial *in-vivo* safety evaluation in nude mice (n=10) using doxorubicin-loaded gels extended survival at 60 days (50% vs 20% for saline controls) without peripheral organ toxicity. Collectively, this data demonstrates that my hydrogel is a safe and effective delivery platform for small, uncharged drugs both *in-vitro* and *in-vivo* to treat GBM.

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TARGETED DELIVERY OF SODIUM THIOSULFATE-LOADED LIPID NANOPARTICLES PREVENTS CISPLATIN-INDUCED OTOTOXICITY: FROM BENCH TO ZEBRAFISH

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Abstract

Platinum-based chemotherapeutic agents cause irreversible loss of sensory hair cells in the cochlea, impairing the conversion of sound vibrations into electrical signals and leading to chemotherapy-induced ototoxicity and associated hearing loss. Our study aimed to develop a biomaterial-based localized drug delivery system to protect cochlear hair cells from cisplatin (CisPt)-induced ototoxicity. Sodium thiosulfate (STS)-loaded solid lipid nanoparticles (SLN) termed STS-SLNs were rationally designed and synthesized using a double emulsion solvent-evaporation method and characterized by DLS, NTA, TEM, and HPLC. The optimized STS-SLNs exhibited optimal physicochemical properties, stability, and uniform spherical morphology, including average particle size (~92.3 ± 0.8 nm), low polydispersity (<0.3), zeta potential (−13.2 ± 2.1 mV), and encapsulation efficiency (45.5 ± 5.9%). STS-SLNs showed sustained release of STS from SLNs with an n value of 0.09 (Fickian diffusion) determined using the Korsmeyer–Peppas model. Cellular uptake studies with House Ear Institute-Organ of Corti (HEI-OC1) cells using Coumarin-6-tagged STS-SLNs showed a maximum uptake at 1 hour via clathrin-mediated endocytosis. STS-SLNs displayed antioxidant potential in ROS scavenging assays, and enhanced cell viability in live/dead assays compared to CisPt treatment alone. The molecular signaling pathways were investigated by assessing the expression of STAT3, P-STAT3 and Nrf2 pathways in HEI-OC1 cells. STS-SLNs significantly reduced STAT3 and P-STAT3 expression compared to the CisPt-treated group, suggesting a protective effect against CisPt-induced oxidative stress via the STAT3 pathway. To assess *in vivo* efficacy, zebrafish embryos (5–6 days post-fertilization) were preincubated with STS-SLNs (50 µM–0.64 nM) prior to CisPt exposure (400 µM). STS-SLN treatment markedly preserved neuromast morphology and prevented hair cell loss at concentrations ≥2 µM, demonstrating significant otoprotective potential. In summary, STS-SLNs effectively protected auditory cells from damage in both cellular and preclinical models, highlighting their promise as a localized therapeutic strategy for preventing cisplatin-induced oxidative stress and associated hearing loss.

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BASED ON STATIC-COMPRESSION OPTICAL COHERENCE ELASTOGRAPHY, QUANTITATIVE ELASTICITY ASSESSMENT METRICS ARE PROVIDED FOR BIOLOGICAL TISSUES

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Abstract: Optical coherence elastography (OCE)- as an extension of optical coherence tomography (OCT)-enables quantitative characterization of the mechanical properties of biological tissues. Within OCE, static (quasi-static) compression OCE (SCOCE) is a comparatively simple approach that requires no external excitation; it characterizes tissue mechanics by computing phase changes in the OCT signal between pre- and post-compression states. The elastic modulus of the specimen is then quantified by comparison with reference phantoms of known mechanical properties, measured under identical loading and imaging conditions. We have already achieved promising results in tumor margin detection, quantitative assessment of tissue elasticity, and tissue classification.

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EXPLORING THE ROLE OF EXOSOMES ON OVARIAN CANCER CELL GROWTH

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Exosomes, or small extracellular vesicles, are small membrane-bound cells produced by cancer cells that carry proteins, lipids, and nucleic acids, which can affect the parent cell (cancer cell) viability. This study aimed to evaluate the exosome effects on their parent cells. This was done with the ovarian cancer cell lines OVCAR-3, COV362, and OVSAHO . The cells were cultured in complete media. After cells reached about 80% confluency, they were cultured in FBS-deficient media to collect exosomes. The exosomes underwent centrifugation and ultrafiltration to purify. Using these purified exosomes, we performed the cell viability assay (CCK8 assay). We used different doses of exosome numbers and different exosome treatment times (24, 48, and 72 hours). We observed and concluded that the exosomes had different results depending on their respective cell lines. For OVCAR-3, the cells were able to proliferate with all tested concentrations. For COV362 the cells were able to proliferate until the 10^9 dose in which the cells started to die. For OVSAHO, the cells proliferated until 10^7. This shows that different types of ovarian cancer cell lines are responding differently to their exosomes.

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OPTIMAL ROUTING FOR MOBILE LUNG CANCER SCREENING VEHICLE GUIDED BY INCIDENCE RATES: A CASE STUDY IN OKLAHOMA

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Oklahoma ranks 8th in the U.S. for age-adjusted lung cancer incidence (63.3 cases per 100,000) and 5th for lung cancer mortality (45.3 deaths per 100,000), making it one of the most adversely impacted states nationally. Evidence from large randomized clinical trials such as the National Lung Screening Trial (NLST) has demonstrated that low-dose CT (LDCT) remains a superior screening modality compared to chest X-ray, yielding a 20% reduction in lung cancer mortality among eligible high-risk individuals. As a result, the US. Preventive Services Task Force (USPSTF) has issued a Grade B recommendation for LDCT screening, requiring full coverage without cost sharing by Medicare and most private insurers. However, lung cancer screening uptake across the U.S. remains persistently low, and Oklahoma performs even worse: recent Oklahoma data show participation of less than 11%, compared to approximately 16% nationally. To address this, several hospital systems in the nation have begun implementing mobile LDCT screening units intended to directly bring screening to rural and underserved regions, which have limited access to fixed screening centers. However, many current mobile programs operate in an “on-request” manner in which the unit is dispatched in response to requests for screening, rather than being proactively allocated to regions with the highest expected benefit. The effectiveness of mobile screening is therefore fundamentally tied to geographic targeting, uncertainty in participation, and travel logistics. In this work, we develop a routing optimization model for a mobile lung cancer screening under uncertainties in screening participation and outcomes. The model is informed by the county-stratified incidence rates from the Oklahoma Central Cancer Registry and geo-spatial characteristics of Oklahoma. We demonstrate the results of our model when applied to counties with limited access to LDCT facilities and quantify the outcomes of the optimized mobile screening program.

TITLE: EXPLORING THE ROLE OF OBESITY-ASSOCIATED EXTRACELLULAR MATRIX IN LOCAL BREAST CANCER PROGRESSION

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Breast cancer is the most prevalent invasive cancer in women. Obesity is a key risk factor implicated in the progression of ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC). Importantly, while breast cancer is often diagnosed as DCIS, it is unknown which lesions will progress to potentially lethal IDC, especially in obesity. Limited in vitro models hinder understanding of obesity's role in early cancer invasion. In a retrospective study on human breast specimens, we analyzed gene expression in DCIS and IDC from women with varying BMI. Obesity-associated DCIS showed increased ECM remodeling and EMT, suggesting ECM-driven progression. Many of the ECM-derived signals are relayed to cancer cells through the YAP pathway. Previous studies in our lab have focused on estrogen and fibroblast growth factor 1 (Fgf1) as obesity associated factors promoting breast cancer growth. We developed 2D and 3D in vitro models to explore how ECM remodeling by estrogen and Fgf1 promotes breast cancer. In the **3D model**, ECM was isolated and denatured from lean and obese mouse mammary glands. Human MCF7 spheroid size and growth rates were analyzed in this ECM. Spheroids in obese ECM were larger, showed invasive morphology, and had greater levels of nuclear YAP, suggesting pathway activation. Mass Spectrometry revealed greater ECM protein levels in obese ECM indicating fibrosis. In our **2D model**, mouse adipose precursor cells were treated with estrogen or Fgf1, allowed to produce ECM for 2 days, followed by decellularization. MCF7 control or YAP-KD were seeded on precursor cells ECM for gene expression and morphological analyses. MCF7 control cells had more YAP nuclear localization on ECM from Fgf1 treated precursors and upregulated FN and LOX compared to YAP KD cells, suggesting YAP-mediated ECM signaling. Our study highlights a crucial role for obesity-associated ECM remodeling in breast cancer cell growth and DCIS progression and suggests ECM targeting as a therapeutic strategy in obese breast cancer patients.

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EVALUATION OF NUCLEI ISOLATION TECHNIQUES FOR SINGLE-NUCLEUS RNA SEQUENCING IN TISSUE AND CELL SUSPENSIONS

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The nucleus, the largest organelle in eukaryotic cells, encloses DNA within a double-membrane envelope that organizes chromatin for compaction and gene regulation, thereby shaping both epigenetic and transcriptomic profiles [1]. Single-nucleus RNA sequencing (snRNA-seq) provides a powerful approach to investigate cellular diversity within complex tissues. By isolating nuclei instead of whole cells, snRNA-seq overcomes key limitations of conventional single-cell RNA-seq [2]. A central step in this process is the isolation of intact nuclei. Multiple protocols have been developed for nuclei isolation from both tissues and cell suspensions, and each source presents its own unique challenges and limitations. To address these complexities, this review examines and compares some of the most evaluated protocols across diverse biological systems, including human umbilical cord blood (CD34+ cells) [3], kidney tissue [4], organoids [5], mouse brain [6], heart tissue [7], and plant tissue [8]. Our analysis highlights that the choice of nuclei isolation method is a critical experimental variable influencing snRNA-seq data quality, with direct implications for the reliability, reproducibility, and interpretability of downstream analyses. Ultimately, this review aims to provide guidance for selecting the most appropriate nuclei isolation protocol, thereby ensuring robust data generation and advancing transcriptomic studies across a wide range of biological contexts.

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CANCER-DERIVED SMALL EXTRACELLULAR VESICLES AS A PLATFORM FOR GENERATING CANCER–TARGETING ANTIBODIES

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Targeted cancer therapy remains limited by the lack of tumor-specific ligands, largely due to the heterogeneity of tumor antigens. To address this challenge, we developed a strategy that uses ovarian cancer–derived small extracellular vesicles (sEVs) as immunogens to generate monoclonal antibodies that target tumor cells. Since sEVs mirror the structure of their parent cells, antibodies generated against these vesicles have the inherent potential to target the cancer cells from which they originate. Using this approach, we identified a lead antibody (AB) with strong tumor-targeting specificity against ovarian cancer cells.

sEVs isolated from OVCAR-8 cells were injected into mice to induce an antigen-specific immune response, followed by hybridoma generation and monoclonal antibody screening. The resulting lead antibody demonstrated strong specificity toward ovarian cancer cells relative to non-cancerous HOSE cells. To evaluate therapeutic potential, the antibody was conjugated to paclitaxel-loaded $CD8^+$ T cell–derived exosomes (AB-TSEV/P), forming a targeted drug delivery platform.

In vitro, both paclitaxel-loaded exosomes and antibody-decorated exosomes produced significantly greater cytotoxicity than free paclitaxel, confirming the delivery advantage of exosomal formulations. In vivo studies using an OVCAR-8 xenograft model revealed that AB-TSEV/P induced marked tumor regression over an 80-day study period ($p<0.0001$) without affecting body weight, demonstrating strong efficacy and tolerability. Biodistribution analyses using IVIS imaging showed significantly enhanced tumor accumulation of antibody-decorated exosomes ($p<0.0001$). Mechanistic studies with bulk RNA sequencing and spatial transcriptomics demonstrated downregulation of proliferative drivers such as MYC and LIF, along with enrichment of apoptotic, immune, T-cell receptor–related, and antigen receptor–related pathways.

Together, these findings establish cancer-derived sEVs as a platform for generating tumor-targeting antibodies and show that antibody-decorated exosomes deliver chemotherapy with enhanced precision, efficacy, and mechanistic impact, while providing a foundation for future personalized cancer therapy.

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LABEL-FREE AND HIGH-THROUGHPUT QUANTIFICATION OF NANOPARTICLE-CELL INTERACTIONS AT THE SINGLE-CELL LEVEL WITH FLOW CYTOMETRY

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Understanding the nanoparticle-cell interactions at the single-cell level is essential for improving nanomedicine design and delivery efficiency. Here, we present a label-free flow cytometric approach for the quantification of nanoparticles across complex physiological models. By correlating side scatter intensity shifts with nanoparticle exposure and validating these results qualitatively and quantitatively with Confocal Laser Scanning Microscopy and Inductively Coupled Plasma Mass Spectrometry, we looked into the uptake of nanoparticles in immune cells and cancer cells under mono-culture, co-culture, and mixed-cell model. Our results demonstrate that this label-free method not only enables accurate detection of nanoparticle uptake in complex systems but also reveals biologically relevant behaviors. This approach provides a realistic and high-throughput approach for understanding nanoparticle-cell interactions and offers new opportunities to evaluate nanoparticle behavior in physiologically relevant environments.

PAYLOAD-FREE MACROPHAGE MODULATION BY SYNTHETIC NANOGELS: CORRELATION OF PARTICLE CORE CHEMISTRY WITH IMMUNOLOGICAL OUTCOME

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Macrophage polarization critically shapes cancer progression and therapy response. While nanoparticles are often viewed as inert carriers, emerging evidence shows carrier chemistry alone can program innate immunity. We engineered a 20-member library of PEG-shelled, disulfide-crosslinked nanogels by ARGET-ATRP, systematically varying cationic content [DEAEMA vs DMAEMA] and hydrophobic comonomers (MMA, BzMA, CHMA, tBMA, BMA) at 75:25 or 25:75 cationic:hydrophobe. FT-IR and 1D/2D NMR confirmed high monomer incorporation. Quantitative NMR with external calibration resolved distinct TCEP and TCEP-oxide peaks after disulfide cleavage, enabling absolute crosslinker quantification, consistent with feed ratios. Nanogels were colloidally stable (DLS <200 nm) and pH-responsive, with reduced ζ-potential at alkaline pH. Cytocompatibility assays showed ≥80% RAW264.7 viability at 50–200 µg/mL. Functionally, high-charge (75%) formulations—especially DEAEMA—drove robust pro-inflammatory phenotypes: CD86 increased ~5-fold and iNOS ~73-fold versus untreated cells, accompanied by a ~33-fold rise in IL-6. Lower-charge (25%) variants suppressed IL-6. Targeted transcriptomics (NanoString, 163 genes) revealed that 75% DEAEMA nanogels clustered with IFNγ+LPS, upregulating CCL2/4/5, CXCL10/11, TNF, and IL6, consistent with NF-κB/STAT1 engagement. In primary bone marrow-derived macrophages, DEAEMA-rich nanogels elicited an "alert-yet-remodeling" program: immune activation co-occurred with antioxidant, ECM, and proliferation pathways, highlighting context-dependent plasticity. Together, these results identify cationic charge density—modulated by core chemistry—as a first-order design handle to program macrophage state without payload. Chemistry-encoded, payload-free nanogels could serve as tunable adjuvants or immunomodulatory biomaterials for cancer immunoengineering and combination therapies.

ATLASCOLLECT: A SINGLE CELL DATA ATLAS PLATFORM AND UNIFIED PLATFORM FOR DATASETS COLLECTION AND INTEGRATION

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Single-cell datasets typically represent heterogeneous populaKons and require meKculous computaKonal approaches for in-depth analysis, but more importantly, given the explosion in single cell data generaKon, a crucial need arises for integraKon of data and analysis on atlas levels. Several tools exist to collect experimental single-cell data in the form of raw sequencing data files and experiment-level metadata, such as GEO Archive and Sequence Read Archive (SRA)[3]. Other tools or packages are available for performing cell-level analysis of individual datasets, such as Loupe Browser (10x Genomics), Seurat[5], and SC1[4]. Finally, there are ”atlases,” which typically display datasets as one integrated dataset with extensive cell-level metadata and ’pseudo-bulk’ level insights. However, there are currently no atlas development tools that allow for interacKve and dynamic aggregaKon of single cell datasets that comprehensively collect and curate single cell sequencing datasets while simultaneously allowing for interacKve datasets integraKon and assessment of integraKon effects. In this work we present ’AtlasCollect’, an innovaKve web-based interacKve pla`orm designed to streamline the collecKon, mapping, and live integraKon of single cell RNA sequencing (scRNA-seq) data developed using the Next.js framework as well as R custom code and packages. Our tool provides a user-friendly interface that simplifies complex data management using SQLite and file systems, automates exploratory analysis workflows for data validaKon and visualizaKon, and offers a centralized hub for various integraKon algorithms. A key strength of this pla`orm lies in its interfacing with mulKple established dataset integraKon methods, including CCA [6], Harmony[2], Joint PCA [6], and RPCA [1]. Furthermore, our pla`orm facilitates seamless integraKon with downstream comprehensive analysis pla`orms and frameworks such as Seurat[5] and SC1[4] and addresses challenges related to batch effects. To conclude, the AtlasCollect pla`orm aims to empower researchers with varying levels of computaKonal experKse to gain immediate insights into cellular heterogeneity and gene expression dynamics of dataset collecKves.

Keywords
single cell RNA-Seq, web-based tool, data integraKon, batch effect

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NON-NECROPTOTIC ROLE OF MLKL IN PROGRESSION OF MASLD- RELATED HCC

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Mixed Lineage Kinase Domain-Like (MLKL), the executioner of necroptosis, is upregulated in metabolic-associated steatotic liver disease (MASLD) and hepatocellular carcinoma (HCC). While systemic MLKL manipulation showed complex, dose-dependent effects in diet-induced obesity models, the hepatocyte-specific role of MLKL in driving MASLD progression to HCC remains poorly defined, particularly under chronic Western diet (WD) stress. We employed hepatocyte-specific MLKL knockout mice (*Mlkl*^{HepKO}) fed a long-term WD to model MASLD-driven HCC progression. We analyzed MASH pathology, tumor burden, cell proliferation, cancer stemness, and mitochondrial respiration. Findings were validated in human HCC cell lines using genetic knockdown and the human MLKL inhibitor, necrosulfonamide (NSA). WD feeding robustly increased hepatic MLKL, yet canonical necroptosis markers (RIPK3, P-MLKL oligomers) were absent. Strikingly, *Mlkl*^{HepKO} mice exhibited reduced hepatocarcinogenesis, showing fewer and smaller tumors, decreased proliferation (Ki67), and suppressed cancer stem markers (DCLK1, OCT4). This anti-tumor effect occurred independently of obesity, liver inflammation, fibrosis, or liver injury, suggesting a dissociation between steatohepatitis severity and tumor progression. Mechanistically, MLKL loss protected against mitochondrial dysfunction and induced remodeling of mitochondrial dynamics, resulting in improved basal and maximal cellular respiration. Clinically, high MLKL expression in human HCC correlated with poor patient survival, and NSA phenocopied genetic MLKL knockdown in HepG2 cells, suppressing proliferation and improving respiration. Our data reveal a novel hepatocyte-intrinsic, non-necroptotic role for MLKL as a tumor progression factor in MASLD-driven HCC. MLKL promotes tumorigenesis by coupling altered mitochondrial dynamics and cellular respiration to cancer cell survival and stemness. Our studies reveal MLKL as a druggable biomarker and therapeutic target for metabolic liver cancer.

NOVEL MOLECULAR DRIVER DIRECTED PROTEOMIC SHIFT SILENCE IMMUNE ACTIVATION FAVORING SURVIVAL OVER SURVEILLANCE

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Neuroblastoma (NB) is an aggressive embryonal malignancy that evolves under therapy pressure, rewiring its cellular machinery to survive, evade, and persist. We identified **Retinal Degeneration 3 (RD3)** as a novel immunogenetic regulator whose loss reshapes NB's genomic landscape, driving immune escape and tumor evolution. While the genomic blueprint suggests RD3-dependent tumor immunogenicity, we sought to define its translational and functional consequences by performing global untargeted proteomics using Omics Playground V4 (BigOmics Analytics), mapping RD3-dictated proteome-wide changes in neuroblastoma. Patient-derived clones obtained from high-risk (stage 4) NB at diagnosis (Dx, $RD3^{+}/^{+}$; n=2), progressive disease (PD, $RD3^{-}/^{-}$; n=3), and their RD3 reverse-engineered counterparts (stable silencing in Dx and reinstatement in PD clones, n=5) were analyzed on an Orbitrap Exploris 480 in DIA mode. Spectronaut was used for robust peptide identification and quantification applying stringent thresholds (log_2 fold change, $-log_{10}$(Padj) FDR correction). RD3 diminution induced proteomic asymmetry (and none downregulated), mapping to hallmarks of tumor evolution, metabolic rewiring, survival adaptation, immune modulation, and metastatic competence. Conversely, stable restoration of RD3 precisely reversed the induced effects. Immune functional analysis exhibited negative enrichment, indicating an immune-suppressed flow. Key effectors of T-cell receptor signaling, including NEMO, AGO1, and CUL5, were regulated, signifying a collapse of immune engagement machinery. Consistent with our prior identification of RD3 regulated 27-gene signature, **QPCT** abundance profoundly increased with RD3-loss affirming its regulatory role consistently both at transcriptomic and translational levels. Critically, **HLA-A** displayed RD3-loss dependent decrease, while increasing **CD276** (B7-H3). Critically, our findings revealed a paradoxical chaos: RD3-deficient tumors host a directed proteomic shift, while selectively silencing immune activation favoring survival over surveillance. This study, for the first-time ventures how RD3-deficiency dictates a proteomic collapse that fuels immune dysfunction in deadly progressive NB. Decoding this landscape uncovers actionable targets for immune reprogramming strategies to reprime NB to immunotherapy.

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OPTICAL COHERENCE TOMOGRAPHY EVALUATION OF MEBENDAZOLE THERAPEUTIC EFFICACY IN OVARIAN CANCER XENOGRAFTS

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Abstract

Epithelial ovarian cancer represents a significant therapeutic challenge due to its distinctive progression trajectory and frequent development of chemotherapeutic resistance. Despite initial treatment approaches demonstrating 80% remission rates, long-term survival remains below 50%, largely attributed to late diagnosis. Mebendazole (MBZ), a repurposed antiparasitic drug, has emerged as a promising therapeutic candidate due to its well-documented safety profile and microtubule-modulating mechanisms. This study employed spectral-domain optical coherence tomography (SD-OCT) to evaluate the therapeutic efficacy of mebendazole in OVCAR-8 ovarian cancer xenografts, with mice divided into control, mebendazole, cisplatin, and combination treatment groups. We implemented a comprehensive texture analysis framework comprising 26 parameter categories, extracting 2,562 quantitative features from OCT images, and identified 60 optimal features through Recursive Feature Elimination with Cross-Validation (RFECV). Using a nested leave-one-out cross-validation (LOOCV) framework, we evaluated the classification performance of six machine learning models (DT, RF, SVM, KNN, MLP, AB), providing a novel non-invasive approach for assessing the efficacy of repurposed mebendazole in ovarian cancer treatment.

UNDERSTANDING AND PREDICTING CARE GAPS IN CHILDHOOD CANCER SURVIVORS USING MACHINE LEARNING–BASED SURVIVAL MODELS

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Cancer mortality has steadily declined in recent decades, yet the number of newly diagnosed cases continues to rise. As a result, the population of childhood and adolescent cancer survivors has grown to nearly 500,000 in the United States as of 2020. While advances in diagnosis and treatment have improved survival rates, many survivors face lifelong health challenges, including cardiovascular disease, endocrine disorders, and secondary malignancies that stem from prior cancer therapies.

Long-term follow-up (LTFU) care is essential for early detection and management of these late effects. Consistent LTFU visits reduce emergency department utilization and improve outcomes. Clinical guidelines recommend that survivors attend at least one LTFU visit every two years to maintain optimal care. However, adherence remains suboptimal due to logistical, financial, and social barriers.

To better understand and predict these care gaps, this study applies machine learning–based survival models to identify survivors at elevated risk of LTFU non-adherence and estimate when they may drop out of care. Using clinical and demographic data, we compare multiple models and employ post-hoc interpretability techniques to explain predictions and identify key factors influencing early dropout across subgroups. Our findings highlight the potential of machine learning to uncover hidden drivers of care discontinuity and enable targeted, proactive interventions, ultimately improving long-term outcomes and advancing precision survivorship care for childhood cancer survivors.

PANCREATIC TUMOR CELLS MODULATE THE MAST CELL TRANSCRIPTOME AND METABOLOME.

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Pancreatic ductal adenocarcinoma (PDAC) is an extremely deadly disease with an overall 5-year survival rate of only 13%. Recent studies have highlighted how changes in nutrients in the tumor microenvironment can affect immune cell function, leading to uncontrolled tumor growth. However, there are many immune cell subsets that have yet to be investigated. Mast cells are myeloid-derived granulocytes that release pre-formed mediators and cytokines in response to stimuli. Mast cell infiltration in PDAC has been associated with decreased survival in patients, and depletion of mast cells *in vivo* decreases tumor size in mouse models, suggesting a role in tumor growth. However, the exact mechanisms by which this occurs are unknown. Therefore, we have developed an *in vitro* co-culture system using the murine mast cell line MC/9 and syngeneic pancreatic tumor cells to investigate how tumor cells influence mast cell function using bulk RNA-sequencing and metabolomic approaches. Co-cultured MC/9 cells show an activated phenotype indicated by increased expression of genes associated with mediators: *Tpsab1*, cytokines: *Il13, Il6*, and *Tnf*, and the activation marker *Cd69*. Furthermore, tumor cells co-cultured with MC/9 cells increase *Il13ra1* expression, which may prime them to respond to cytokines released by mast cells. As signaling through the IL13RA1/IL4R has been shown to increase tumor cell proliferation, this may be one mechanism by which mast cells promote tumor growth. Analysis of non-polar metabolomics show that co-cultured MC/9 cells increase vitamin B6 (VB6) levels and one carbon metabolism. Depleting VB6 levels in MC/9 media or blocking of PLP significantly reduced IL-13 production in these cells. Overall, these data indicate that mast cells may promote tumor growth via vitamin B6 uptake and subsequent IL-13 production.

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SHIFTING IMMUNE SIGNATURES DEFINE BLADDER CANCER PROGRESSION AND PROGNOSTIC POTENTIAL

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Bladder cancer (BC) is widely recognized for its strong immunogenicity and harbors the fourth highest overall mutational burden among all cancers, a feature that enhances its capacity to elicit robust anti-tumor immune responses. Despite this, BC patients often exhibit limited responsiveness to immunotherapy, regardless of disease stage. To better understand the immune contexture of BC, we analyzed the distribution of $CD4^+$ and $CD8^+$ T lymphocytes and CSF3R expression in tumors from 112 patients using a custom-archived tissue microarray (TMA). Multiplex confocal immunofluorescence was performed, and quantitative image analysis was conducted using QuPath (v0.5.1) with a multiplex fluorescence module. Comparative profiling revealed that $CD8^+$ cytotoxic T cell infiltration was more prominent in non-muscle-invasive BC (NMIBC) and early-stage disease, while reduced in muscle-invasive BC (MIBC), progressive disease (PD), and metastasis, suggesting a loss of effective immune surveillance in advanced stages. $CD4^+$ T cells exhibited a more complex pattern: elevated levels were observed in PD but were reduced in MIBC and metastasis, likely reflecting a shift toward immunosuppressive regulatory T cell phenotypes. CSF3R expression was consistently upregulated in MIBC, PD, and metastatic tumors compared to NMIBC, indicating its association with disease advancement. Trends suggested that higher $CD8^+$ T cell presence may be linked to more favorable clinical outcomes, while elevated CSF3R expression appeared to align with more aggressive disease features. These findings highlight the evolving immune landscape across BC progression, the immunomodulatory roles of $CD4^+$ and $CD8^+$ T cell subsets, and the potential of CSF3R as a therapeutic target. Integrative strategies that enhance cytotoxic T cell responses while mitigating immunosuppressive mechanisms may offer new avenues to improve immunotherapeutic efficacy in advanced BC.

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ADVANCING TREATMENT FOR TRIPLE-NEGATIVE BREAST CANCER: INTEGRATING PHOTOTHERMAL THERAPY WITH IMMUNOMODULATION IN A PRECLINICAL MODEL

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Triple-negative breast cancer (TNBC) is an aggressive disease with few options and high metastatic risk. Using an orthotopic 4T1 BALB/c model, we evaluated a multimodal regimen combining anti-PD-1, intratumoral imiquimod (IMQ) hydrogel, and near-infrared photothermal therapy (PTT), with or without surgery. 4T1 cells (1×10^5) were implanted in the fourth mammary fat pad. When tumors reached ~3 mm, mice received anti-PD-1 (days 0, 2, 7), IMQ (day 0), and intratumoral SWCNT–annexin A5 (day 3) followed by PTT delivered either as 45 °C for 5 min or immediate shut-off at 55 °C using a 980-nm laser; temperatures were monitored by thermal imaging. Surgery was performed on day 5 in designated groups. Tumor growth, survival (Kaplan–Meier), serum cytokines (day 7), splenic immune profiling (day 15), and toxicity (weights, organ ratios, H&E) were assessed. The combination of anti-PD-1 + IMQ + 45 °C/5-min PTT + surgery produced the strongest benefit: marked tumor regression and prolonged survival versus controls and other arms. Cytokine profiling showed elevated IFN-γ, TNF-α, IL-6, and IL-12, consistent with immune activation. Flow cytometry revealed increased $CD4^+$ and $CD8^+$ T cells and reduced MDSCs. Toxicity evaluations found no significant adverse effects. Notably, animals receiving anti-PD-1 + IMQ + PTT without resection later developed firm abdominal masses, suggesting residual tumor or fibrosis and underscoring the value of removing thermally primed lesions. Our goal is to develop a clinically translatable treatment regimen suitable for human pilot studies.

DEVELOPMENT OF PROTEOLYSIS TARGETING CHIMERA (PROTAC) FOR DEGRADATION OF ONCOGENIC RET PROTEIN TYROSINE KINASE

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Oncogenic mutations and fusions of the Rearranged during Transfection (RET) protein tyrosine kinase is a target for cancer therapy. Currently, two RET-selective protein tyrosine kinase inhibitors (TKIs), selpercatinib and pralsetinib, are approved for treating advanced and metastatic RET-altered cancers. While inhibiting RET kinase activity, selpercatinib or pralsetinib treatment increases the level of the CCDC6-RET fusion protein in human cancer cells. To overcome this drug-induced compensatory effect, we attempt to simultaneously inhibit the oncogenic RET kinase activity and degrade the oncogenic RET protein with a RET TKI-based degrader. A panel of RET PROTACs was synthesized and screened for degradation of CCDC6-RET protein in cell cultures by immunoblotting. Lead compounds were further characterized for their selectivity and potency in cell cultures and bioavailability in mice. A lead compound, YW-N-7, exhibited dual action of inhibiting and selectively degrading oncogenic RET proteins in cell cultures and in cell-derived xenograft tumors, and inhibited tumor growth. This study exemplifies the feasibility of simultaneously inhibiting and degrading oncogenic RET kinase for cancer therapy.

LIPID METABOLIC REPROGRAMMING IN CANCER: UNCOVERING A NEW GENETIC DETERMINANT PATHWAY

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Lipid metabolism is increasingly recognized as a key contributor to cancer progression and therapy resistance. In neuroblastoma (NB), an aggressive pediatric cancer, disruption in lipid metabolism correlates with poor clinical outcomes. Our previous studies identified Retinal degeneration protein 3 (RD3) as a crucial factor whose loss under treatment accelerates tumor growth and spread. RD3 deficiency is associated with increased lipid accumulation, suggesting its role in disrupting lipid regulation and maintaining metabolic balance. However, the mechanism by which RD3 impedes lipid dysregulation remains unknown. Herein, we conducted transcriptomic profiling in bed-to-bench and RD3-reverse engineered NB models. Genomic RNA-seq analysis in RD3-expressing clones (CHLA-42, CHLA-15, SHSY5Y) compared to RD3 knockout counterparts (CHLA-42 RD3-/-, CHLA-15 RD3-/-, SHSY5Y RD3-/-) using univariate analysis (log2 fold change with false discovery rate, FDR of log10Padj) revealed a conserved transcriptional signature of 315 upregulated and 259 downregulated genes across all three models (Novogene). Ingenuity Pathway Analysis (QIAGEN Inc. IPA) indicated a metabolic paradigm shift towards adipogenesis via enhanced transcription of FZD10 and FGF1, and cholesterol biosynthesis by downregulation of INSIG1. Additionally, glycerophospholipid metabolism was upregulated via coordinated regulation of MBOAT1, PLA2G4C, and CPNE7, and sphingolipid metabolism was promoted by A4GALT, ARSJ, and SPHK1, a key modulator upstream of ERK1/2 and PI3K/AKT signaling. Furthermore, both mitochondrial and peroxisomal fatty acid oxidation were activated through PPARα/RXRα signaling, driven by upregulation of AGT, ACOX2, PLCL1, ADRA2A, and TGFBR2, alongside downregulation of ACBD7 and NFYB transcription. For the first time, we identified RD3 as a central regulator of lipid metabolic homeostasis in NB. Therapeutic pressure-driven RD3 loss triggers coordinated reprogramming of lipid pathways, fueling adipogenesis and fatty acid oxidation while disrupting cholesterol balance. These shifts promote tumor progression and therapy resistance. Targeting this lipid-driven vulnerability offers a promising direction for next-generation diagnostics and treatments for high-risk, therapy-resistant NB.

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SITE- SPECIFIC POST TRANSLATIONAL REARRANGEMENT IN TUMOR SUPPRESSOR PML CEMENTED ONCOGENIC ADDICTION IN DEADLY EXTRACRANIAL SOLID TUMORS IN INFANTS.

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The malignant trajectory of high-risk neuroblastoma (HR-NBL), a deadly pediatric cancer is driven by reinforcing network of oncogenic signals and transcriptional dependency, that sustain aggressive behavior. Central to this axis are site-specific post-translational modifications that destabilize tumor suppressors and mediates tumor aggressiveness. Promyelocytic leukemia protein (PML), a nuclear-scaffold and master regulator coordinating apoptosis, senescence and transcriptional control is destabilized in HR-NBL through aberrant site-specific post-translational modifications. Herein, we investigated the function of unique serine (S^{518}) phosphorylation mediated feed-forward loop of PML destabilization in reinforcing oncogene addiction, wherein NBL progression is reliant on sustained S^{518} phosphorylation to amplify oncogenic transcriptional programs. We modeled phosphorylation dependent control systems of PML in clinically divergent NBL states through site-directed mutagenesis of S^{518} residue in PML. Tumor cells derived from patients with therapy-refractory/progressive disease was engineered to express a phospho-inert form of PML by substituting S^{518} with alanine (A^{518}). Conversely, cells obtained during diagnosis were programmed to express a phospho-mimetic variant by substituting S^{518} with glutamic acid (E^{518}), simulating constitutive phosphorylation. Stable integration and sequence validation confirmed fidelity of both constructs, establishing a platform to investigate the role of S^{518} phosphorylation driven transcriptional hierarchies that induce aggressive phenotypes in NBL. Oncogene addiction characterized by profiling of 88 oncogenes, revealed distinct transcriptional consequences of S^{518} phosphorylation. The phosphomimic variants exhibited significant upregulation of multiple oncogenic axes, consistent with a sustained dependency on malignant signaling. In contrast, phospho-inert constructs attenuated expression of oncogenic modulators, disrupting transcriptional circuitry that regulates aggressive phenotypes. These findings for the first time, recognized the PML S^{518} phosphorylation driven PML destabilization feed-forward loop that anchored oncogenic transcriptional programs in deadly developmental tumor. Critically the outcomes imply that, therapy pressure dictated S^{518} phosphorylation in the PML directs the evolution of therapy defying progressive disease and identify a novel candidate for molecular targeted maintenance therapy.

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GAS VESICLES CONJUGATED TO ANTIBODIES FOR TUMOR CHARACTERIZATION VIA ULTRASOUND IMAGING

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Introduction: According to the American Cancer Society, more than a million new tumors require imaging and characterization each year in our fight against cancer. Ultrasound imaging is a modular and versatile tool and with a capable targeting contrast agent, could be a noninvasive alternative to traditional biopsies. Gas vesicles (GVs) are stable nanometer size contrast agents with protein shells, making them readily available for chemical conjugation. In this study, we used click-chemistry to tag the GVs with antibodies (mAbs), chosen for their cell protein marker targeting exclusivity. This mAb-GV conjugate was first tested *ex vivo* on mouse tumor cells which were imaged with ultrasound after targeting. Next the conjugate was improved by switching to a site-specific antibody labeling technique and confirmed using multiple antibodies, including one currently being used in clinic, targeting multiple cancer cell lines. The conjugate was then further optimized and characterized using *in vitro* size, stability, and development efficiency tests as well as an *in vivo* biodistribution test.

Methods: The ultrasound experiments were conducted with a 128-element linear array transducer (L22-14vX, Verasonics) operating at a center frequency of 15 MHz. The GVs were isolated from *Anabaena flos-aquae* (AnaGV). We targeted human epidermal growth factor receptor 2 (HER2), programmed death ligand 1 (PD-L1), and Trophoblast cell surface antigen 2 (Trop2). The two click chemistry pairs used were phosphine-azide and azide-dibenzocyclooctyne (DBCO).

Results: The *ex vivo* ultrasound test showed a 75% targeting success, prompting the switch to site specific antibody labeling, which significantly improvements brightness for all 4 antibodies used. The optimizations and characterizations show efficient labeling, high stability, and healthy clearance. Through mAb-GV conjugate targeting and detection on cancer cells by ultrasound imaging, this study suggests the feasibility of a non-invasive ultrasound tumor characterization technique. *In vivo* tumor targeting tests are currently underway for further confirmation.

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IMPROVED VISUALIZATION OF TUMOR VASCULATURE USING AN AUTOMATIC EIGEN-IMAGE BASED SIGNAL EXTRACTION METHOD

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Introduction: Accurate visualization of tumor vasculature is critical for early cancer detection and monitoring. Super-resolution ultrasound imaging visualizes tumor vasculature using contrast agents such as microbubbles (MBs) and gas vesicles (GVs), with GVs additionally allowing deep tissue imaging. However, isolating MB and GV signals is challenging due to clutter and noise. Conventional thresholding methods rely on subjective or fixed thresholds, often retaining clutter and noise. To address this, we developed an eigen-image based signal extraction method that segments data into dominant components using changepoint detection, improving signal isolation and enhancing vascular visualization in tumors.

Materials and Methods: Radio-frequency data were acquired using a 128-element linear array transducer at 15 MHz and 500 Hz frame rate. MBs were imaged in an *in vivo* mouse tumor model. Data were decomposed by singular value decomposition into eigen-images, analyzed for intensity changes, and segmented using changepoint detection. The method was compared with elbow point and hard thresholding (HT) using vessel density (VD) and signal-to-noise ratio (SNR). For GV imaging, GVs embedded in gel were subjected to controlled motion and collapse sonication. GV signals were then localized with our method and compared to difference imaging.

Results and Conclusions: Our method effectively separated MB and GV signals from clutter and noise. In tumor imaging, VD increased to 38% with higher frame counts, outperforming elbow point (15.3%) and HT (18.6%), while SNR improved up to 8.7 dB, exceeding other methods. For GV imaging, the method accurately detected GV locations without pixel registration, whereas difference imaging struggled to separate motion-induced clutters from true GV signals. These results demonstrate that this method provides an automated and robust solution for contrast agent imaging, enabling accurate visualization of tumor vasculature.

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TARGETED ANNEXIN A5–MERTANSINE CONJUGATE FOR LEUKEMIA THERAPY

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Leukemia remains a global health burden, with over 460,000 new cases and 310,000 deaths annually. Acute Myeloid Leukemia (AML) predominates in adults, while Acute Lymphoblastic Leukemia (ALL) is most frequent in children. In the United States, AML causes 22,000 new diagnoses and 11,000 deaths yearly, whereas ALL accounts for 6,100 new cases. Despite progress in chemotherapy, relapse and resistance remain common due to non-specific cytotoxicity and poor tumor targeting.

Mertansine (DM1), a maytansinoid microtubule inhibitor, induces mitotic arrest and apoptosis at sub-nanomolar concentrations but suffers from hydrophobicity, rapid plasma clearance, and severe off-target toxicity. To address these limitations, annexin A5 (ANXA5) was conjugated to DM1 via a non-cleavable sulfo-SMCC linker to generate a targeted cytotoxic conjugate (ANXA5–DM1). ANXA5 binds phosphatidylserine (PS) a phospholipid abnormally externalized on malignant and apoptotic cells—with sub-nanomolar affinity in a calcium-dependent manner, enabling selective delivery of DM1 to leukemia cells.

Binding and cytotoxicity assays were performed on three murine leukemia cell lines: C1498 (myeloid AML), P388D1 (monocytic/lymphoid), and L1210 (lymphoid ALL). Specific binding was confirmed for all lines with dissociation constants (Kd) of 0.37 nM for C1498, 0.93 nM for P388D1, and 0.32 nM for L1210, consistent with strong PS-mediated targeting. Cytotoxicity, evaluated by Alamar Blue after 72 h exposure (100 µM–1 pM), revealed potent dose-dependent inhibition: IC_{50} = 1.03 nM (C1498), 1.20 nM (P388), and 0.26 nM (L1210). Compared to free DM1 (IC_{50} ≈ 4.5 nM for C1498; 264 nM for P388; 93 nM for L1210), the conjugate achieved a 4- to 350-fold increase in efficacy, validating its targeting advantage. Ongoing studies are assessing binding and cytotoxicity on normal PBMCs to confirm selectivity.

These results suggest that the ANXA5–DM1 conjugate represents a promising next-generation therapy for AML and ALL, combining high specificity, strong cytotoxicity, and reduced systemic toxicity, potentially improving patient outcomes beyond current chemotherapy standards.

CD151-MEDIATED DEACETYLATION OF A-TUBULIN CONTRIBUTES TO COLORECTAL CANCER CELLS' MOTILITY AND MACROPINOCYTIC UPTAKE

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CD151 is upregulated in various cancers and is usually considered a tumor promoter by encompassing cell motility. However, the role of CD151 and its related mechanisms are not well understood in colorectal cancer (CRC). By silencing CD151 in SW480 colon cancer cells, we found that CD151 facilitates collective and solitary migration, haptotactic and chemotactic migration, and invasion through various matrix environments. Mechanistically, CD151 knockdown results in upregulation of acetylated α-tubulin by inhibitingHDAC6 activity, which is the only deacetylase known to act on tubulin. Therefore, CD151 knockdown regulates the microtubule composition. Supportively, HDAC6 inhibitor played a role in diminishing the inhibitory effects of CD151 knockdown on cell movement. On the other hand, CD151-knocked-downcells exhibit less modernistic activity, which is an actin-dependent process initiated by growth factor-mediated activation of Ras and PI3-kinase signaling pathways to non-selectively engulf extracellular fluid and nutrients. But whether the reduced macropinocytic process under CD151 knockdown condition is induced by increased acetylated α-tubulin composition, how CD151 participates in this process and what's the role for HDAC6 needed to be addressed in the future.

A NOVEL APPROACH TO HIGHLY VARIABLE GENES SELECTION FOR SCRNA-SEQ ANALYSIS

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Single cell RNA-sequencing (scRNA-Seq) data are typically represented as cell-by-gene count matrices, which capture the expression of each gene as detected in the sampled cells; often a heterogeneous population of multiple different cell types or cell states. Almost all scRNA-Seq analysis workflows have a gene selection step prior to applying clustering algorithms which helps remove genes with low variability and hence reduce the high-dimensional gene space. A de-facto method for achieving this selection of highly variable genes (HVG) uses dispersion and mean expression scores to evaluate the variability of each individual gene. However, methods based on mean-variance relationship for gene selection suffer from arbitrary determination of number of genes to use and are susceptible to variance instability.

Here, we propose a novel method for selecting highly variable genes: "Principal Genes", that utilizes the rotations (or loadings) from Principal Component Analysis (PCA) to calculate a novel score per gene that we name "Principal Percentage Score (PPS)". We utilize Augmented Implicitly Restarted Lanczos Bidiagonalization methods to efficiently obtain PCs associated with the largest variance and their rotation scores. PPS helps weigh the genes based on their contribution in the PCA rotations and hence ranks the genes according to their variability.

To test the performance of our gene selection method, we use several validation strategies, including clustering of single cell RNA-Seq data with known 'ground truth'. Furthermore, we measure the performance of our method against the dispersion-based highly variable gene (HVG) selection approach. We use several validation metrics, including sensitivity and adjusted rand index scores for clustering based on genes selected using our method against genes selected using the HVG method; and our validation datasets include three single cell RNA-Seq labeled datasets: sorted PBMCs dataset with known ground truth labels, a labeled Mouse Motor Cortex dataset, and an Embryonic Stem Cells dataset.

Our findings show that our new method, Principal Genes, is comparable and in some cases, superior in selecting highly variable genes and achieves ultra-fast gene selection from PCA results.

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OPTICAL COHERENCE TOMOGRAPHY DETECTS BILIARY MICROSTRUCTURAL ALTERATIONS FOR EVALUATING BILE DUCT VIABILITY IN LIVER TRANSPLANTATION

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Abstract:
Biliary complications remain among the most frequent causes of graft loss after liver transplantation, yet current imaging modalities lack sufficient resolution to detect microstructural changes in donor bile ducts. This study aimed to evaluate whether optical coherence tomography (OCT) can non-invasively identify pathological alterations prior to transplantation. Twenty human bile ducts were imaged ex vivo using polarization-sensitive OCT, with findings validated by confocal microscopy and histology. OCT revealed multiple pathological features, including cystic dilation, periglandular injury, subepithelial edema, and wall thickening, all consistent with histological and confocal confirmation. These results demonstrate that OCT provides depth-resolved, real-time, three-dimensional visualization of bile duct pathology and may enhance pre-transplant donor duct evaluation while reducing post-transplant biliary complications.

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BUILDING CLUSTERING CONSENSUS AND EXPLORING THE IMMUNE LANDSCAPE IN MOUSE SPLEEN IN SINGLE-CELL RESOLUTION

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The spleen is the largest organ for filtering blood and plays a crucial role in the adaptive immune system. The spleen is the largest organ for filtering blood and plays a crucial role in the adaptive immune system. Numerous studies examined various cellular populations of the spleen especially in cancer immunological studies, however, often with a focus on one particular cell type like T or B cells. Studies that comprehensively characterize the full cellular landscape of the spleen including erythrocytes - which are often removed - remain uncommon. This study aims to build a comprehensive transcriptomic atlas of the spleen and characterize key processes at a single-cell resolution. We will employ single- cell RNA sequencing (scRNA-seq), a state-of-the-art technique for exploring the cellular landscape and composition of complex organs. The scRNA-seq analysis, coupled with trajectory inference and ligand–receptor interaction studies, will reveal the detailed immune landscape of the spleen and identify critical genes involved in its activation.

To ensure high granularity and accuracy in cell-type identification, we employed a novel computational strategy that integrates Term Frequency–Inverse Document Frequency (TF-IDF) and Shared Nearest Neighbor (SNN)–based clustering approaches that achieve superior results to applying these approaches individually. Additionally, we developed a new computational approach for building clustering consensus and validating cell type identification methods. This integrated framework not only enhances the precision of cell-type classification but also provides new insights into the cellular and molecular mechanisms in the spleen.

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ENHANCED DIAGNOSTIC INDICATION VIA NOVEL CLAUDIN-4 TARGETING PEPTIDE IN BREAST CANCER

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Introduction

Claudin-4, a tight junction protein, is a promising biomarker in breast cancer. We developed and tested a peptide probe targeted against claudin-4 for non-invasive diagnosis and image guided surgery.

Methods

Breast cancer cell lines T47D (ER^+), 2LMP(TNBC), ZR75-30 (ER^+/HER^+), MDA-MB-231(TNBC), MDA-MB-468(TNBC), and positive control ASPC1 were evaluated for claudin-4 expression via western blot. The peptide was synthesized via microwave chemistry, purified with flash chromatography, conjugated to amine Hilyte 555 or 750 dye, then dialyzed. Cell lines were treated with CL4-29-750 then imaged with NIR-fluorescence. CL4-29-555 was blocked with an antibody to identify probe specificity in MDA-MB-231 and T47D cells. Then examined via fluorescent microscopy.

Results

Western blot analysis revealed claudin-4 signal intensities normalized to ß-actin of 0.34, 0.30, 0.16, 0.06, 0.02, and 0.01 for cell lines ZR75-30, ASPC1, T47D, MDA-MB-468, 2LMP, and MDA-MB-231, respectively. NIR analysis has an 8-fold increase in intensity from MDA-MB-231 to ASPC1(positive control). Fluorescence microscopy showed probe binding in T47D cells have 46.6% higher signal than the MDA-MB-231 cells ($p<0.01$). CL4-29-555 was shown in the blocking group to have a reduced signal compared to unblocked in T47D cells ($p<0.01$).

Conclusion

Novel claudin-4 targeting probe can differentiate between high and low claudin-4 expressing breast cancer.

Funding

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EXPLORING C-MYC AND ITS RELATIONSHIP WITH DCLK1 IN OVARIAN CANCER

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Introduction: Ovarian cancer is the fifth leading cause of cancer-related deaths in women. Both doublecortin-like kinase 1 (DCLK1) and c-Myc are frequently overexpressed in ovarian cancer and linked to poor survival. Although DCLK1 affects several oncogenic pathways, its relationship with c-Myc in ovarian cancer has not been defined. Prior lab work demonstrates that c-Myc levels decrease in DCLK1 knockout cells and increase with wildtype DCLK1 overexpression, but not with kinase dead DCLK1 mutants. We hypothesize that c-Myc is elevated alongside DCLK1 in ovarian cancer, that inhibiting c-Myc will reduce DCLK1, and that DCLK1 regulates c-Myc.

Methods: Protein levels of total c-Myc and its phosphorylated forms (S62 and T58) were measured by western blot in ovarian cancer cell lines OVCAR8, OVCAR3, COV362, and MESOV, and in non-cancerous FTE188 and HOSE cells. To investigate whether c-Myc regulates DCLK1, OVCAR8 CPR cells were treated with a c-Myc inhibitor, MG 132, or vehicle control. DCLK1 expression was measured by western blot. In a separate experiment, c-Myc was knocked down using siRNAs, and DCLK1 expression was measured. To determine whether DCLK1 affects c-Myc, cells were treated with a DCLK1 inhibitor, and c-Myc expression was measured. Additionally, a c-Myc promoter luciferase reporter assay was used to measure c-Myc transcriptional activity after treatment with DCLK1 inhibitor, c-Myc inhibitor, the combination of both, and MG 132.

Results: Total c-Myc was elevated in HOSE, FTE188, MESOV, OVCAR3, and OVCAR8. Phosphorylated c-Myc (T58) was elevated in MESOV, OVCAR3, and COV362. Cells treated with c-Myc or DCLK1 inhibitors showed changes in DCLK1 and c-Myc levels. In the reporter assay, both c-Myc and DCLK1 inhibitors reduced c-Myc transcriptional activity.

Conclusion: These findings suggest that c-Myc and DCLK1 regulate each other in ovarian cancer. Targeting this pathway may offer new therapeutic strategies, but further research is needed to fully define their relationship.

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SELECTIVE INHIBITION OF HUR AND EZH2 REVEALS POTENTIAL CROSSTALK IN MEDULLOBLASTOMA

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Introduction: Medulloblastoma (MB) is the most common malignant pediatric brain tumor, yet treatment options remain limited. This highlights the need for novel molecular targets for therapy. HuR, an RNA-binding protein, is overexpressed in several cancers, contributing to tumorigenesis and poor prognosis. Similarly, EZH2, a histone methyltransferase and gene silencer, drives tumor progression by catalyzing the trimethylation of histone H3 at lysine 27 (H3K27me3), using S-adenosylmethionine (SAM) as a methyl donor. While both HuR and EZH2 are implicated in various cancers, their individual roles and potential interaction in MB remain unclear. In this study, we explored HuR and EZH2 as therapeutic targets in MB using small-molecule inhibitors- CMLD2 for HuR and GSK343 for EZH2.

Methods: Human Sonic Hedgehog (SHH)-activated Daoy cells ($1x10^5$/well) were seeded in 6-well plates and treated with CMLD2 (20 and 30 mM) or GSK343 (5 and 10 mm). DMSO-treated cells served as controls. Cell viability was assessed at 24- and 48-hours post-treatment using the Trypan blue assay. Protein levels of HuR, EZH2, H3K27me3, H3K27ac were assessed by Western blotting using β-actin as a loading control.

Results: Both CMLD2 and GSK343 significantly reduced cell viability in a dose-dependent manner at both the time points tested ($p < 0.05$). Western blot analysis revealed that CMLD2 reduced EZH2 expression levels, altered H3K27 modification patterns, while HuR levels remained unchanged. In contrast, GSK343 treatment resulted in a marked decrease in EZH2, H3K27me3, and HuR expression, accompanied by a concomitant increase in H3K27ac levels.

Conclusion: Our findings suggest a potential crosstalk between HuR and EZH2 signaling pathways, identifying both as promising targets for MB therapy. Further studies are needed to clarify their interaction and explore combinatorial treatment strategies for SHH-activated MB.

Funding: This work was supported by the ASCEND program, funded by the Stephenson Cancer Center and the Tobacco Settlement Endowment Trust.

INVESTIGATING PANCREATIC TUMOR CELL-INDUCED EPIGENETIC MODIFICATION IN NEUTROPHILS

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Introduction: Pancreatic adenocarcinoma (PDAC) has a poor prognosis and a high resistance to conventional chemotherapy, partially due to a treatment-resistant tumor microenvironment (TME). Epigenetic changes associated with PDAC mutations are potential targets for more effective diagnosis and treatment. These epigenetic modifications can also regulate the function of immune cells in PDAC TME. Histone lactylation is a recently discovered epigenetic modification tied to glycolytic metabolism. Histone lactylation has been found to influence CD8+ T-cell effector function and antitumor immunity. Thus, we interrogated whether these modifications also exist in neutrophils in the in vitro conditions mimicking the PDAC TME.

Methods: HL-60, a promyelocyte cell line, was differentiated into neutrophils using a 2% DMSO-containing cell media. Differentiation was confirmed morphologically using Wright-Giemsa staining, and via fluorescence-activated cell sorting (FACS). Once a neutrophil population was established, the neutrophils were co-cultured with CAPAN-2, a PDAC cell line and HPNE, a normal pancreatic epithelial cell line, and alone as a control. After 24 hours, the free-floating neutrophils were isolated from the supernatant and subsequently processed for histone isolation and analyzed via Western Blot and flow cytometry.

Results: Wright-Giemsa staining was optimized for HL-60 cells, confirming the successful differentiation of HL-60 into neutrophils at a rate of 88% over a six-day incubation period in 2% DMSO. FACS analysis also demonstrated increased expression of characteristic neutrophil markers (CD14+, CD11B+, CD16+). Western Blot and flow cytometry experiments to analyze the level of histone lactylation in the three neutrophil co-culture groups are ongoing.

Conclusion: HL-60 is a promising model for studying epigenetic changes in neutrophils under *in vitro* conditions mimicking the PDAC TME. Future studies are warranted to validate the cell line-based epigenetic data with tumor-infiltrating neutrophils from orthotopic tumor mice. If validated, these studies will allow in identifying the potential molecular mechanisms of these changes.

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TARGETING OVARIAN CANCER STEMNESS AND CHEMORESISTANCE VIA AURO-LIPOSOME MIR-195 DELIVERY

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Background:
Ovarian cancer (OvCa) remains the most lethal gynecologic malignancy, largely due to late-stage detection, early metastasis, drug-resistance. Cancer stem-like cells (CSCs) drive tumor recurrence and drug-resistance by sustaining cancer growth. WNT7A is highly overexpressed in OvCa and plays a critical role in maintaining CSC phenotypes and epithelial–mesenchymal transition (EMT) and drug-resistance whereas miR-195 is frequently downregulated. Here, we investigated whether re-expression of miR-195 could suppress cancer progression and enhance drug-sensitivity and developed a novel Auro-Liposome (AuLPs) delivery system for miR-195.

Methods:
miR-195 expression was assessed by qRT-PCR, functional assays were performed to observe the role of miR-195 on CSC markers, EMT. β-catenin activation and nuclear localization were analyzed by Western blot and immunofluorescence. An *in vivo* omental homing assay was performed to check miR-195's anti-metastatic potential.

Results:
Spheroid-derived CSCs showed enhanced expression of cancer stem cell markers. Interestingly in this spheroid, miR-195 expression was significantly decreased. miR-195 overexpression reduced stemness markers, impaired spheroid growth, and enhanced cisplatin-sensitivity. miR-195 directly targeted WNT7A, leading to decreased nuclear localization of active β-catenin and inhibition of WNT7A/β-catenin signaling, EMT pathway. Furthermore, *in vivo* homing assay demonstrated that stable miR-195 re-expression significantly reduced CP20 adhesion to the mice omentum, underscoring its potential to inhibit metastatic colonization. Novel Auro-Liposome (AuLPs) system conferred superior intracellular delivery of miR-195 compared to commercial agents and inhibition of oncogenic WNT7A/β-catenin pathway.

Conclusions:
miR-195 as a key suppressor of OvCa progression and enhancer of cisplatin-sensitivity via directly modulating WNT7A/β-catenin pathway.

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NON-INFECTIOUS SARCOID-LIKE INFLAMMATORY GRANULOMATOUS CONDITIONS (NSIGC) ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS (ICIS) FOR CANCER: PAN-TUMOR RESULTS FROM THE INTERNATIONAL ICARUS (IMMUNE CHECKPOINT ASSOCIATED RARE AND UNIQUE SIDE EFFECTS) CONSORTIUM.

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Abstract:

Background: ICIs can be associated with a broad range of toxicities; however, limited data exists on NSIGC secondary to ICIs. Herein, we assembled the first international cohort of patients with cancer who received ICIs and subsequently developed NSIGC.

Methods: We conducted a retrospective, multicenter study across 19 institutions worldwide, including patients with cancer treated with ICIs between 2015 and 2025 who subsequently developed biopsy-confirmed NSIGC. Patients were eligible if they received anti-programmed cell death protein-1/programmed death-ligand 1 (anti-PD-1/PD-L1) alone or in combination with additional anti-cancer therapies such as chemotherapy, targeted agents or anti-CTLA-4, or if they were treated with other immunotherapies.

Results: The study included 141 pts with biopsy-confirmed NSIGC post-ICI. Median age at cancer diagnosis was 59 years (interquartile range [IQR] 50-67.5 years). Most common cancers in the cohort were melanoma (51.1%; n=72/141), followed by non-small cell lung cancer (16.3%; n=23/141). Most frequent sites of biopsy were lymph nodes (45.4%, n=64/141), followed by skin (17%, n=24/141). The median time to the diagnosis of NSIGC after ICI initiation was 7 months (Range: 0.26-68.9 months). Of 141 pts, 43.3% (n=61/141) were diagnosed after they went off treatment. Among these, 37.7% (n=23/61) had completed their treatment. Among the remaining 56.7% (n=80/141) diagnosed during treatment, 36.2% (n=29/80) required permanent treatment discontinuation due to NSIGC and 6.2% (n=5/80) were re-challenged. Steroids were used for the treatment of NSIGC in 19.9% (n=28/141).

Conclusions and Relevance: To the best of our knowledge, this is the largest dataset to date demonstrating ICI-related NSIGC. NSIGC can occur both during active treatment where it can result in treatment discontinuation and after completion of ICI therapy. Biopsy confirmation, when clinically safe and feasible, is critical to prevent misdiagnosis, and further research is required to elucidate biology and risk factors.

TARGETING CHEMORESISTANCE IN OVARIAN CANCER

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Abstract

Introduction: Ovarian cancer (OvCa) is a highly aggressive malignancy characterized by frequent relapse and metastasis, both of which contribute to its high mortality rate. Although most patients initially respond to platinum-based chemotherapy, up to 80% eventually develop resistance, rendering OvCa largely incurable. Therefore, there is urgent need to identify new therapeutic targets and develop strategies to overcome chemoresistance. This study investigates molecular drivers of cisplatin resistance and evaluates the repurposing potential of the anthelmintic drug mebendazole (MBZ) for OvCa treatment.

Methods: Transcriptomic alterations associated with chemoresistance were assessed in OVCAR8 wild-type (WT) and cisplatin-resistant (CPR) OvCa spheroids using RNA sequencing. Differentially expressed selected genes were validated by qRT-PCR, and western blotting. The clinical relevance of identified genes was determined by analyzing publicly available datasets (GSE133859 and TCGA-OV) and through immunofluorescence staining on tissue microarrays (TMA) from primary and recurrent OvCa patient samples. Functional roles were further examined using genetic manipulations. MBZ efficacy against OvCa was evaluated using 2D and 3D viability, migration, and invasion assays in OVCAR8 WT/CPR cell lines and patient-derived ascites cultures. Preclinical efficacy was tested in both orthotopic and patient-derived xenograft (PDX) models.

Results: Transcriptomic profiling revealed ITGB4 overexpression and SERPINB2 downregulation in CPR spheroids, findings that were consistent with GEO, TCGA-OV datasets as well as TMA analysis of patient samples. High ITGB4 expression in platinum-resistant OvCa patients was significantly associated with worse overall and progression-free survival. CRISPR-mediated ITGB4 knockout resensitized OVCAR8 CPR cells to cisplatin and reduced their invasion and migration capacities. In contrast, SERPINB2 expression suppressed invasion. MBZ treatment downregulated ITGB4, upregulated SERPINB2, and inhibited TGF-β/SMAD signaling. Functionally, MBZ reduced spheroid growth, invasion, and migration in vitro, enhanced cisplatin sensitivity in OVCAR8 CPR cells, and suppressed tumor progression in orthotopic and PDX models without causing systemic toxicity.

Conclusion: These findings demonstrate that ITGB4 overexpression promotes invasion and chemoresistance, while SERPINB2 exerts tumor-suppressive effects. MBZ overcomes cisplatin resistance by regulating ITGB4 and SERPINB2 expression, inhibiting EMT-related signaling pathways, and reducing tumor growth in preclinical models. MBZ represents a promising repurposed therapeutic candidate for chemoresistant ovarian cancer and warrants further clinical evaluation.

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IDENTIFICATION AND EXPERIMENTAL VALIDATION OF TRIOSEPHOSPHATE ISOMERASE 1 AS A FUNCTIONAL BIOMARKER OF SHETA2 METABOLIC INHIBITION OF OVARIAN CANCER CELLS.

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Background: Our objective was to identify and validate proteins that could predict which patients with ovarian cancer would most likely benefit from SHetA2, an investigational new drug currently in a Phase 1 clinical trial in patients with advanced or recurrent solid tumors (clinicaltrials.gov: NCT04928508).

Methods: Cells were cultured from ascites collected from consented patients under an institutional review board-approved protocol. SHetA2 or olaparib sensitivities were determined with an ATP assay in ascites-derived cultures or ovarian cancer cell lines. Expression of 21 proteins previously identified in an ovarian cancer mouse model were measured using microcapillary electrophoresis and four were modulated by siRNA or overexpression vectors. Metabolites were measured using mass spectrometry.

Results: Four of the 21 proteins, including triosephosphate isomerase 1 (TPI1), were expressed at higher levels in SHetA2-sensitive compared to -resistant ascites-derived cultures (t-tests; $p<0.05$) and positively correlated with SHetA2 potency (linear regressions; $p<0.05$). This method identified a unique profile of sensitivities and biomarkers for olaparib. Reduction or overexpression of TPI1 reduced or increased SHetA2 potency, respectively, in two ovarian cancer cell lines (t-tests; $p<0.05$). SHetA2 blocked metabolism downstream of TPI1 and blocked the tricarboxylic acid cycle.

Conclusion: TPI1 is a candidate functional biomarker of SHetA2 sensitivity in ovarian cancer.

TARGETED NANODELIVERABLES REMODEL THE AGGRESSIVE NEUROBLASTOMA MICROENVIRONMENT AND SUPPRESS TUMOR PROGRESSION

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Deadly progressive neuroblastoma (pNB) persists impervious to intensive multi-modal therapy (IMCT), contributing to high pediatric cancer mortality and <2% long-term survival. Our studies uncovered therapy-induced loss of Retinal degeneration protein 3 (RD3) as a central molecular event driving disease progression and aggressiveness. Building on this mechanistic insight, we developed an RD3-restorative approach that alleviates therapy-driven disease acceleration and restores therapeutic responsiveness in pNB. A 16-amino acid RD3 peptide was custom-synthesized, chemically labeled, and terminally capped for enhanced cell penetrance and sustained bioactivity. For tumor-specific delivery, this peptide was encapsulated in GD2-targeted immunoliposomes (RD3[GD2]IL), characterized by uniform size distribution, structural integrity, and high encapsulation efficiency. pNB xenografts were established in athymic nude mice using CHLA-20 cells from stage 4 patient tumors. Mice received intravenous RD3[GD2]IL (5 µM) or plain liposomes three times a week for four weeks. RD3[GD2]IL exhibited strong tumor homing and retention (EPR effect), resulting in selective intratumoral accumulation and significant tumor regression compared to controls. Histopathology revealed well-differentiated architecture in RD3[GD2]IL-treated tumors versus highly proliferative, poorly differentiated controls. PAS staining showed depleted glycogen and mucin, indicating impaired anabolic matrix remodeling. PSR staining identified extensive collagen degradation and disorganized fibrils, denoting stromal relaxation. TUNEL assay confirmed increased apoptotic nuclei, highlighting restored tumor cell vulnerability. No treatment-related toxicity or pathological changes occurred in normal tissues, suggesting RD3[GD2]IL has a favorable safety profile. This nanotherapeutics approach integrates precision-guided delivery with tumor remodeling, suppresses progression, and reprograms the neuroblastoma microenvironment toward a differentiated, less aggressive state. RD3-based strategies may redefine therapeutic boundaries for refractory pediatric cancers.

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SYNERGISTIC ANTITUMOR EFFECTS OF SHETA2 AND MYC INHIBITOR IN CERVICAL CANCER

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Abstract

Introduction: SHetA2 (Sulfur heteroarotinoid A2) is an orally bioavailable drug in Phase I clinical trial (NCT04928508) for advanced solid cancers. We demonstrated potent anticancer activity of SHetA2 against cervical cancer without toxicity. SHetA2 inhibited cervical cancer growth by inducing mitochondrial damage and metabolic reprogramming towards glycolysis, and inhibition of compensatory glycolysis enhanced SHetA2's sensitivity without added toxicity. SHetA2 also upregulated c-Myc expression, a key glycolytic regulator. This study investigated SHetA2-induced metabolic changes in cervical cancer and whether Myc inhibition enhances its efficacy.

Methods: Metabolomic analysis was performed using liquid chromatography-mass spectrometry. Expression of glycolytic genes and Myc was assessed by qRT-PCR and immunoblotting. Lactate dehydrogenase activity, lactate production, and cellular ATP levels were measured using commercial assay kits. The synergistic effects of SHetA2 with various Myc inhibitors were evaluated by orthogonal matrix assay in cervical cancer cells. *In vivo* efficacy and toxicity of SHetA2 and the selective Myc inhibitor (Myci975) were assessed using a xenograft model.

Results: SHetA2 induced a distinct metabolic signature in cervical cancer cells with pathway enrichment indicating increased glycolysis/gluconeogenesis and pyruvate metabolism. SHetA2 upregulated glycolytic gene expressions (GPI, PDK1, HK1, LDHA, GLUT1), enhanced LDH activity and lactate production, and reduced ATP levels under glycolytic inhibition, indicating heightened reliance on aerobic glycolysis. SHetA2 also significantly increased Myc expression in cervical cancer cell lines tested. The combination of SHetA2 and Myc inhibitor demonstrated synergistic/additive effects *in vitro*. *In vivo*, the SHetA2-MYCi975 combination significantly reduced tumor weight compared to either agent alone, without notable toxicity.

Conclusion: SHetA2 promotes glycolysis and Myc upregulation in cervical cancer cells, though the link between these effects remains under investigation. Myc inhibition enhanced SHetA2's antitumor activity, supporting a combinatorial metabolic strategy for cervical cancer therapy. Further studies are underway to elucidate the mechanistic basis and translational potential of this synergy.

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TAMOXIFEN EFFECTS ON ADIPOCYTE PROGENITORS LINK BREAST CANCER ENDOCRINE THERAPY TO DIABETES RISK

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Women diagnosed with estrogen receptor-positive breast cancer who receive endocrine therapy have 30% increased risk of developing type 2 diabetes (T2D) when compared to those receiving other breast cancer treatments. Of all the T2D cases diagnosed after breast cancer treatment, 48% are attributable to the prescribed therapy, largely due to tamoxifen treatment. Endocrine therapy aims to block ER signaling, to suppress ovarian function and lower hormone levels, or to inhibit the enzyme that produces estrogen throughout the body. Estrogen and endocrine therapies also interact with nuclear and extranuclear estrogen receptors in the metabolic tissues; therefore, any treatment that blocks ER will impact whole-body metabolism. We recently found that tamoxifen and estrogen deprivation therapy impaired glucose tolerance, promoted weight gain, and increased hepatic steatosis in obese but not lean female mice. In adipose tissue from obese female mice, endocrine therapies depleted subcutaneous adipocyte progenitors and promoted mature adipocyte hypertrophy, providing a plausible mechanism through which endocrine therapies can promote T2D in breast cancer survivors. Single-cell RNA sequencing of subcutaneous adipose stromal cells revealed that, in obese female mice, endocrine therapy inhibited expression of Wisp2, which helps maintain adipocyte precursor populations. In isolated subcutaneous adipocyte precursor cells, Esr1 and Wisp2 were highly expressed in progenitors compared to the committed preadipocytes. Estrogen treatment induced Wisp2 expression in an ERα dependent manner in adipose precursor cells. Estrogen and Wisp2 treatment increased the progenitor cell population, while tamoxifen decreased the proliferation of these cells. Wisp2KO in adipocyte precursor cells upregulated markers of inflammation and senescence, similar to tamoxifen treatment. The effects of tamoxifen on genes associated with inflammation and senescence are inhibited by cotreatment with exogenous Wisp2 protein. This study reveals the potential mechanism of ER signaling that support adipose tissue expansion, a contributing factor to the excess risk for T2D in breast cancer survivors after endocrine therapy.

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INHIBITION OF CYSTATHIONINE B-SYNTHASE ABROGATES ANOIKIS RESISTANCE IN DETACHED OVARIAN CANCER CELLS BY ATTENUATING SP1–ITGB1 AXIS AND IMPAIRING SPHEROIDOGENESIS

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Anoikis resistance i.e., the ability of cancer cells to evade apoptosis triggered upon detachment from extracellular matrix is a defining feature of cancer dissemination. In ovarian cancer (OvCa), where the major cause of mortality is metastasis, its dissemination occurs through the peritoneal cavity, where exfoliated tumor cells must evade cell death in the peritoneal fluid before invading secondary sites. OvCa cells exhibit anoikis resistance by aggregating into multicellular spheroids, wherein greater spheroidal compactness is directly associated with increased viability and invasiveness. In this study, we identify cystathionine β-synthase (CBS), a hydrogen sulfide (H_2S)–producing enzyme, as a regulator of anoikis resistance and invasiveness in OvCa metastatic units. Our results demonstrated that CBS silencing in both 2D monolayer and in 3D spheroids, caused apoptosis along with abrogation of spheroid compactness. CBS silenced spheroids showed activation of apoptotic markers and downregulation of stemness and EMT factors. Mechanistically, CBS maintains anoikis resistance by stabilizing the transcription factor SP1 through H2S-mediated persulfidation, sustaining integrin β1 (ITGB1) expression and therefore adding to spheroid compactness. Hence, these findings establish the role of CBS as a critical mediator of anoikis resistance in ovarian cancer spheroids, linking its function to metastatic competence. This association was further substantiated by our in-house tissue microarray (TMA) analysis, where high CBS expression positively correlated with the occurrence of omental metastasis, and by our preclinical murine model, in which CBS-silenced spheroidal cells exhibited reduced omental homing capacity. Collectively our study consolidates the candidature of CBS as a therapeutic target to attenuate OvCa transcoelomic metastasis.

THE IMPACT OF MITOCHONDRIAL HAPLOTYPE ON INFLAMMATION, FIBROSIS, AND LIVER CANCER IN NOVEL OKC-HET$^{B/W}$ RATS

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Non-resolving chronic inflammation is a key contributor to aging and plays a significant role in the development of many age-associated diseases, including chronic liver diseases such as metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, and liver cancer. However, limited information is available on how the host environment such as the mitochondrial haplotype (mt-haplotype) influences inflammation, fibrogenesis, and liver cancer. While previous studies have demonstrated that mitochondrial dysfunction is important in age-related pathologies/diseases, this is the first study to directly test the impact of mt-haplotypes on factors that play a role in cancer. We developed a novel rat model (OKC-HET) by crossbreeding four inbred rat strains-Brown Norway (BN), Fischer 344(F344), Lewis (LEW), and Wistar Kyoto (WKY)-in a heterogeneous nuclear background resulting in two different mitochondrial haplotypes are OKC-HET^{B} and OKC-HET^{W}, differing by 94 nucleotides. These rats were fed a Western diet (WD) for 6 months. Liver samples were collected from chow-diet fed and WD fed male OKC-HET^{B} and OKC-HET^{W} rats. We observed elevated inflammation (e.g., TNFα, IL-1β, IL-6), and fibrosis (Col3α, TGFβ, Colα1), TUNEL staining, Ki67, fat accumulation and collagen fiber by trichrome, PSR staining in the WD fed male rats of both B- and W-haplotypes compared to their chow-fed counterparts. These phenotypes were increased significantly in W-haplotype compared to the B-haplotype. In conclusion, our findings indicate an increase in chronic inflammation, fat accumulation, and fibrosis in WD fed rats, with the effect being affected by the mt-haplotype, i.e., more in the W-haplotype than the B-haplotype. This study reveals for the first time that mitochondrial haplotype affects metabolic pathways driving liver disease and cancer.

ENHANCING IMMUNOTHERAPY EFFICACY IN GLIOBLASTOMA BY TARGETING CXCR1/2-MEDIATED IMMUNOSUPPRESSION

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Abstract:

Background: Glioblastoma (GBM), the most common and aggressive brain tumor, has a median survival of just 14–16 months despite surgery, radiation therapy (RT), and temozolomide (TMZ). RT, though essential for tumor control, contributes to immunosuppression. We found that RT promotes the expansion of MDSCs and upregulates CXCR2 expression, amplifying immune suppression in GBM. Checkpoint inhibitors, effective in other cancers, have shown limited success in GBM due to immunosuppressive tumor microenvironment (TME). Our research focuses on evaluating the role of CXCR2 in radiation-induced MDSC expansion and its impact on immune suppression.

Methods: Using a syngeneic orthotopic GBM mouse models (CT2A and GL261), we evaluated the effects of targeting CXCR1/2 in combination with radiation and anti-PD-1, on survival, immune organ dynamics, and tumor progression. The study included comprehensive immune profiling using multi-color flow cytometry, along with functional assays to evaluate CXCR2 mediated MDSC expansion.

Results: We found that fractionated RT (2 Gy × 5 days) reduced $CD4^+$ and $CD8^+$ T cells while increasing MDSCs with higher CXCR2 expression, indicating that RT enhances immune suppression. Targeting CXCR1/2 with the small molecule inhibitor SX-682 significantly reduced MDSCs recruitment in TME and enhanced the survival in GBM mouse models. Furthermore, combining SX-682 with anti-PD-1 (αPD-1) therapy enhanced T-cell activation and extended survival in orthotopic GBM mouse models.

Conclusion: Our finding demonstrated that RT exacerbates immunosuppression by expanding MDSCs populations and reducing T-cell activity. Targeting CXCR1/2 with the small molecule inhibitor SX-682 effectively reduced MDSCs recruitment and restored T-cell function in the TME. Combining SX-682 with anti-PD-1 therapy further enhanced T-cell activation and prolonged survival in preclinical GBM models, highlighting a promising strategy for overcoming immune suppression and improving treatment outcomes in GBM.

THERAPEUTIC TARGETING OF FERROPTOSIS IN USPC: SHETA2 INDUCES TFRC EXPRESSION AND POTENTIATES PACLITAXEL EFFICACY

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Ferroptosis, a recently described form of programmed cell death driven by iron-dependent lipid peroxidation, plays a significant role in multiple diseases, including cancer. Inducing ferroptosis in cancer cells presents a promising avenue for therapeutic intervention. Consequently, ferroptosis-inducing agents are gaining increasing interest in the context of cancer treatment. In this study, we show that the novel compound SHetA2 is an effective inducer of ferroptosis in endometrial cancer cell lines. SHetA2 exhibited potent anticancer activity by promoting cell death and inhibiting cancer cell migration. Mechanistically, SHetA2 triggered ferroptotic cell death, as evidenced by elevated reactive oxygen species, enhanced lipid peroxidation, and reduced glutathione levels. Importantly, the ferroptosis inhibitor ferrostatin-1 effectively prevented SHetA2-induced cell death, confirming the involvement of ferroptosis. Notably, SHetA2 treatment resulted in significant upregulation of transferrin receptor (TFRC) expression in endometrial cancer cell lines as well as in ascites from endometrial cancer patients, indicating increased iron uptake. In line with this, we observed substantial iron accumulation in xenograft tumor tissues treated with SHetA2, further supporting a ferroptosis-driven mechanism. Crucially, silencing TFRC using siRNA effectively blocked SHetA2-induced cell death, demonstrating that TFRC-mediated iron uptake is essential for ferroptosis activation by SHetA2. These findings highlight iron metabolism as a key therapeutic target in SHetA2-induced ferroptosis. Metabolomic profiling further revealed distinct metabolic reprogramming, with increased glutamine, cysteine–glutathione disulfide, and nucleotides, and decreased TCA cycle intermediates such as citrate, succinate, and fumarate. These alterations suggest disrupted mitochondrial metabolism and redox imbalance, thereby creating a metabolic environment that enhances susceptibility to ferroptosis.

ATOVAQUONE ATTENUATES PANCREATIC CANCER–INDUCED CACHEXIA

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Abstract

Cancer-associated cachexia is a multifactorial metabolic syndrome characterized by systemic inflammation, progressive skeletal muscle wasting, and poor therapeutic outcomes. Pancreatic cancer is among the malignancies most frequently associated with cachexia, contributing significantly to patient mortality. Given the lack of FDA-approved therapies to counteract cachexia, drug repurposing offers a promising alternative strategy. Atovaquone, an FDA-approved antimalarial compound with potent anti-inflammatory properties, has previously been shown to inhibit STAT3 activation—a key driver of cancer-induced wasting.

In this study, we evaluated the anti-cachectic potential of atovaquone in pancreatic cancer–induced cachexia using both in vitro and in vivo models. Treatment of myotubes with S2013 pancreatic cancer cell–conditioned media (CM) induced classical cachectic responses, including upregulation of *atrogin-1* and *MuRF1* and downregulation of myosin heavy chain. Co-treatment with atovaquone reversed these effects, as confirmed by real-time PCR and Western blot analysis, indicating attenuation of muscle degradation. Mechanistically, atovaquone inhibited mitochondrial oxidative phosphorylation, leading to a reduced oxygen consumption rate (OCR) and activation of a compensatory glycolytic shift. This was evidenced by an increase in extracellular acidification rate (ECAR), glucose uptake, and lactate production. Enhanced glycolysis restored cellular energy balance and suppressed catabolic signaling, thereby protecting against CM-induced myotube atrophy. Inhibition of glycolysis with 2-deoxy-D-glucose (2-DG) abrogated the protective effects of atovaquone, underscoring the importance of glycolytic compensation in its mechanism of action.

Collectively, our findings demonstrate that atovaquone mitigates cancer-induced muscle wasting by reprogramming myotube metabolism from oxidative phosphorylation to glycolysis, thus preserving muscle mass and function. These results highlight atovaquone as a promising metabolic intervention for managing pancreatic cancer–associated cachexia.

Keywords: Atovaquone • Cancer cachexia • Mitochondrial oxidative phosphorylation • Glycolytic shift • Muscle wasting

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LIPOPHAGY-DEPENDENT FATTY ACID OXIDATION IS A METABOLIC VULNERABILITY FOR KRAS SIGNALING INHIBITION IN PANCREATIC CANCER

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ABSTRACT: Pancreatic ductal adenocarcinoma (PDAC) is characterized by frequent KRAS mutations, which activate the MAPK pathway to promote PDAC progression. Here, we explored metabolic vulnerabilities of PDAC by assessing initial metabolic reprogramming upon ERK inhibition using metabolomics, lipidomics, and isotope-tracing experiments. ERK inhibition enhanced lipid turnover and fatty acid oxidation while inhibiting glycolysis, glucose oxidation, and glutamine metabolism in PDAC cells. Moreover, lipophagy, but not cytosolic lipolysis, was responsible for the increased lipid turnover and fatty acid oxidation upon ERK inhibition. Mechanistically, we found that this metabolic shift was not mediated by classical cytosolic lipolysis but rather by lipophagy, a selective autophagic process that degrades lipid droplets to release free fatty acids. ERK inhibition promoted nuclear translocation and transcriptional activation of TFEB, a master regulator of lysosomal biogenesis and autophagy, thereby stimulating lipophagy and fueling FAO to maintain cellular energy homeostasis under metabolic stress. Importantly, pharmacological blockade of FAO abrogated this adaptive response and synergized with $KRAS^{G12D}$/MEK/ERK inhibitors, leading to a significant reduction in cell proliferation and enhanced cell death in PDAC cell lines and organoid models. The combination decreased tumor burden and improved survival in orthotopic cell line and patient-derived xenograft PDAC models. Overall, this study provides mechanistic insights into the development of metabolic resistance to KRAS signaling inhibition and demonstrates that fatty acid oxidation is a metabolic vulnerability following KRAS signaling inhibition that can be utilized as an effective therapeutic target to treat PDAC.

OGT1 REPROGRAMS TUMOR-ASSOCIATED MACROPHAGES IN PANCREATIC ADENOCARCINOMA TUMOR MODEL

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O-linked β-N-acetylglucosamine modification (O-GlcNAcylation) is a post-translational modification that plays a crucial role in development, normal physiology, and the pathophysiology of various diseases, including pancreatic cancer. This process is catalyzed by the enzyme O-GlcNAc transferase (OGT). The hexose biosynthesis pathway provides the necessary substrate, O-GlcNAc, for this reaction. However, the role of O-GlcNAcylation in tumor-associated macrophages has not been extensively studied. The hypoxic tumor microenvironment leads to increased glucose uptake, enhanced glycolysis, and promotes the polarization of macrophages toward the non-inflammatory M2-like phenotype. Additionally, macrophages undergo significant metabolic changes in this environment. We found that hexose biosynthesis metabolites are regulated in bone marrow-derived macrophages (BMDMs) cultured with tumor-conditioned media (TCM) *in vitro*.

To investigate the role of OGT1 in tumor-associated macrophages (TAMs), we created a mouse strain, LysM-Cre; $Ogt^{fl/fl}$, which features OGT1 loss specifically in macrophages. We showed that Ogt loss in macrophages changed pancreatic tumor growth dynamics. LysM-Cre; $Ogt^{fl/fl}$ mice developed significantly smaller tumors compared to LysM-Cre age and sex matched mice. Moreover, we observed the prolonged survival of tumor-bearing LysM-Cre; $Ogt^{fl/fl}$ mice, which might be explained by the decreased level of Ki-67 in the tumor tissue.

Ogt deletion in TAMs reprograms the myeloid cell population in the pancreatic tumor microenvironment. The total number of macrophages, dendritic cells, and activated dendritic cells is significantly increased in tumors implanted in LysM-Cre; $Ogt^{fl/fl}$ mice compared to LysM-Cre control mice.

These findings suggest a potential role of OGT1 and O-GlcNAcylation in the interplay between macrophages and lymphocytes within the pancreatic adenocarcinoma TME. The data indicate that OGT1 may inhibit the immune components of the tumor microenvironment. This knowledge could pave the way for innovative strategies aimed at shifting the balance towards a more effective anti-tumor immune response.

This study was in part supported by R37CA276924 (KM) from the National Cancer Institute of the National Institute of Health.

HYPOXIA-RESPONSIVE TARGETED POLYMERSOME DRUG DELIVERY IN PATIENT-DERIVED XENOGRAFT MODELS OF TRIPLE-NEGATIVE BREAST CANCER

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Introduction: Eliminating triple-negative breast cancer (TNBC) resistance to neoadjuvant chemotherapy is a critical unmet clinical need. Napabucasin (NAPA, a small organic molecule) is known to kill cancer stem cells by targeting the STAT3 signaling pathway. Our previous *in vitro* results showed significant effects with hypoxia-responsive targeted polymersomes compared to control in MDA-MB-231 and Patient-Derived Xenograft (PDX) TNBC cells. Further, we observed increased NRP-1 expression in TNBC patient-derived xenograft (PDX) cells under hypoxic (0.2% oxygen) conditions compared with normoxic (21% oxygen) conditions. Hence, we hypothesize that targeted hypoxia-responsive polymersome drug therapy would reduce the tumor growth of the PDX mouse model of TNBC.

Methods: We have established the TNBC PDX mouse model in two phases: an initial propagation phase (F1-F3) and a final study phase (F3-F6). TNBC tumor samples received from Sanford Broadway Clinic, Fargo, with IRB approval. PDX tumor-bearing female NSG (Jackson Lab) mice were administered polymersome-encapsulated drug (doxorubicin and other groups) by intravenous injection twice a week for 4 weeks. The percentage of tumor volume growth was calculated for these treatment groups and compared to the vehicle. The tumors from all the groups were excised and dissected after the treatment and fixed in 10% formalin for histological evaluation.

Results: TNBC PDX mouse model treated with DOX alone and a combination of encapsulated DOX with NAPA showed significant weight loss compared to the control (over 4 weeks). DOX-alone-treated mice showed reduced tumor growth and a significant difference compared to the control group. Notably, the targeted combination polymersome demonstrated a much lower tumor volume and displayed a marked difference compared to non-targeted vehicles, free-DOX, and saline.

Summary and Conclusion: Overall, the hypoxia-responsive targeted polymersomes showed potent antitumor activity in the novel TNBC PDX animal model. With further developments, the targeted polymersomes might have translational potential as drug carriers for treating TNBC.

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DCLK1 ORCHESTRATES HEPATOCYTE-MACROPHAGE DYSREGULATION TO DRIVE LIVER FIBROSIS AND HEPATOCARCINOGENESIS

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Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the third leading cause of cancer-related deaths worldwide. It typically develops in the setting of chronic liver injury, inflammation, and cirrhosis. Despite substantial progress made in the treatment of HCC, most patients are unresponsive and ultimately succumb to their disease, underscoring the urgent need for new treatment strategies. Lineage-tracing models have established hepatocytes as the cell of origin for HCC. We previously demonstrated that the cancer stem cell marker doublecortin-like kinase 1 (DCLK1) is highly induced in chronic liver disease but absent in normal liver. Here, we show that hepatocyte DCLK1 is essential for polarizing Kupffer cells and peripheral blood monocytes into a previously undefined M2-like hybrid macrophages with inflammatory and immunosuppressive characteristics, co-expressing CD206, S100A9, PD-L1, and DCLK1. Using a hepatocyte-specific Dclk1 knockout murine model (HSD1-KO), we demonstrated that hepatocyte Dclk1 drives profibrotic and carcinogenic responses including macrophages polarization into hybrid phenotype subsets. Pharmacological inhibition of DCLK1 suppressed both proinflammatory (TNF-α, IL-1β, IFN-α/β/γ) and immunosuppressive (IL-10) cytokines in cocultures, revealing DCLK1's central role in immune dysregulation. Mechanistically, DCLK1 activates a distinct DCLK1/β-catenin(p48)/cyclin D1 oncogenic signaling axis that differs from the canonical Wnt/β-catenin(p92) pathway, which is required for normal liver regeneration. Quantitative proteomics of HSD1-KO versus control livers identified DCLK1-dependent regulation of toxicity, inflammation, immune signaling, and cell cycle progression. Collectively, these findings uncover a novel DCLK1-regulated hepatocyte-macrophage partnership as a key driver of liver carcinogenesis and establish DCLK1 as a promising therapeutic target for the prevention and treatment of HCC.

PHARMACOKINETICS OF EXOSOME-ENCAPSULATED DOXORUBICIN AFTER ADMINISTRATION BY DIFFERENT ROUTES

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Exosomes are a natural alternative to conventional nanoparticles due to their biocompatibility, low immunogenicity, stability in biological fluids, and better internalization into cancer cells. Exosomes derived from CD8+ cytotoxic T cells possess some of the cytotoxic properties of the native T cells, which together with a drug could lead to synergistic cytotoxic effects on cancer cells. The goal of the project was to test this hypothesis on the triple negative breast cancer (TNBC) lung metastasis mouse model. Using doxorubicin (Dox) as a model drug, the aim of the study was to determine the influence of encapsulating Dox into exosomes (DoxEx) on its pharmacokinetics (PK). Female Balb/C mice were dosed either with Dox solution by the IV and IP routes (2mg/kg) or with DoxEx by the IP (2mg/kg) and Pulmonary (PUL, 0.5 mg/kg) routes. DoxEx was aerosolized directly into the airways of mice using a MicroSprayer. Mice were euthanized at 0.25, 1 and 3h after the dose and blood and tissues collected. Dox concentrations were determined by fluorescence and PK parameters calculated from the concentration vs time data. Dox (DoxEx) was eliminated (Ke) at a much slower rate (0.013 h^{-1}) after PUL than after IP (0.2449 h^{-1} solution; 0.2608 h^{-1} DoxEx) or IV (0.2041 h^{-1}), which resulted in a significantly longer half-life after PUL (53.29 h), than after IP or IV (2.7-3.4 h). Likewise, the area under the drug concentration curve (AUC) was 10x-50x larger after PUL than after IV or IP administration. Encapsulation of Dox in exosomes did not appear to affect either Ke (0.2449 h^{-1} vs. 0.2608 h^{-1}) or half-life (2.83h vs 2.67h), but it appears to reduce the AUC after IP administration (0.2522 µg/ml·h vs 0.1426 µg/ml·h). Studies are underway to evaluate the efficacy of DoxEx in treating lung metastasis in the TBNC mouse model.

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PREDICTING T-CELL RECEPTOR SPECIFICITY AND PHENOTYPE USING INTEGRATED CLASSICAL AND PRE-TRAINED PROTEIN LANGUAGE MODELS

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Heterogeneity of T Cell Receptors (TCRs), encoded primarily via V(D)J recombination allows the immune system to recognize a wide range of pathogens and cancer neoepitopes, however several computational challenges arise when tailoring treatments to an individual's unique TCR repertoire. Here we present a modularity-based method to identify local TCR antigen-specificity groups, and we benchmark classical and machine learning based approaches for modeling TCR specificity and phenotype. T-Cell Receptors (TCRs) are at the heart of the immune system's response to antigens. The hyper-heterogeneity of TCRs, encoded primarily via V(D)J recombination, allows for the immune system to recognize a wide range of pathogens and cancer antigens and neoepitopes. Several computational challenges arise in precision medicine when tailoring treatments to an individual's unique TCR repertoire. These include mapping TCR sequences, precisely the CDR3b sequences - the major driver of antigen specificity – to their respective antigens. Modeling the functional and phenotypical effects of TCR diversity, as well as integrating TCR sequencing data with other modalities in single cell resolution are further active areas of research. Here we present TCRClass , a comprehensive method for analyzing the immune repertoire and predicting receptor-antigen specificity. First, we introduce a novel modularity optimization-based method that utilizes the concept of split-penalty in graph theoretical algorithms to identify local TCR antigen-specificity groups in active immune cell repertoires. Additionally, we propose a new algorithm for predicting and modeling TCR phenotypes and specificity to cancer antigens that utilizes classic k-mer based featurization integrated with a novel approach using transfer learning via pre-trained Protein Language Models. We use antigen and epitope-specific single cell TCR sequencing data of publicly available epitope databases as well as putative cancer neoepitopes presented on MHC-I to extract and engineer CDR3 sequence-based features. We benchmark the top existing protein language model on their ability to produce embeddings with locality preserving characteristics that can accurately model TCR in downstream classification and specificity identification tasks. Additionally, our work provides full integration with single cell RNA-Seq modality for comprehensive functional analysis and integration with SC1 single cell analysis workflow.

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RURAL CHILDREN WITH OVERWEIGHT OR OBESITY FACE BARRIERS TO IDENTIFICATION AND TREATMENT

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Background: Obesity is a risk factor for cancer and disproportionately affects children living in rural America. Treatments for overweight or obesity (OW/OB) require recognition and tracking. A key tool is BMI percentile for age growth charts. CDC BMI growth charts for children from 2000 (CDC 2000) are not adequate for classification and tracking of most obese children.

Objective: Identify processes and experience in diagnosing and treating rural children with OW/OB in primary care clinics.

Methods: An obesity clinical trial was held in 4 states (Kansas, Nebraska, Oklahoma, and South Carolina) totaling 16 clinics caring for rural children. Data included: clinic manager interviews concerning obesity related resources, billing and practices, and random sampling of 80 medical records in 13 clinics. Eligibility for review were children 6-11 years old, a BMI percentile for age ≥ 85, rural residency, and followed in the clinic for ≥ 1 year. Data included demographics and the most recent well child and/or obesity visit.

Results: Clinics reported using BMI growth charts with 12 (80%) using CDC 2000 growth charts. We reviewed 919 eligible medical records, 841 (92%) had a BMI growth chart, with 66% CDC 2000, 558 (61%) had a diagnosis of well child and/or OW/OB; 234 (42%) well child only, 75 (13%) OW/OB only and 249 (45%) both well child and OW/OB. Of 386 patients with an OW/OB diagnosis 83% had only a Z code, 11% had an E code and 5% had both E and Z codes. Only 46 (8%) of patients had planned a follow-up visit. Patients with follow-up visits were more likely to have a diagnosis of OW/OB (87% (N=40) versus 13% (N=6), P<.01).

Conclusions: Multiple issues impede the recognition and treatment of rural overweight or obese children. Improvements should include updating EHRs with extended BMI-for-age growth charts, provider training and insurer reimbursement for ICD-10 codes for obesity, and provider support for implementing a guideline-based treatment.

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MOLECULAR IMAGING TO VISUALIZE CANCER BIOMARKERS

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Tumor imaging is crucial for cancer diagnosis and monitoring of patients under therapy. Ultrasound has been one of the first line imaging modalities for these purposes due to its portability and convenience. Recent advances on functional and molecular imaging capabilities of ultrasound imaging will further advance the utility of ultrasound imaging. Ultrasound can be used in combination with biomarkers to characterize the tumors with increased resolution and improved specificity without the need for invasive diagnostic procedures. Human epidermal growth factor receptor 2 (HER2) and programmed cell death ligand 1 (PD-L1) are surface cell protein markers that are both commonly expressed in tumors, making them an impactful target for cancer diagnosis and the monitoring of patient response to therapy. To target these biomarkers, we have used monoclonal antibodies (mAb) to conjugate with gas vesicles (GV) via click chemistry to make HER2 and PD-L1 targeting conjugates (mAb-GV). GVs are stable and have a life of span measured in years unlike microbubbles. Click chemistry is famous for its efficiency, bioorthogonality, and long last binding. To visualize mAb-GV targeting to specific biomarkers, we have developed an imaging approach to localize them using eigen-image based method using singular value decomposition (SVD). The goal was to identify threshold for transition from clutter and system noise to signals from GVs. We used eigen-images that can be extracted from the left singular matrix after SVD of original radio frequency (RF) data. mAb-GV conjugates efficiently target HER2 and PD-L1 expressing cells and the proposed eigen-image based GV localization approach efficiently extract GV signals from noisy background. From molecular engineering to signal processing for localization of point targets, we expect that our discovery will advance noninvasive way of cancer diagnosis and therapy to improve patient survival rate.

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BREATH-BASED LUNG CANCER DETECTION USING PTR-MS AND MACHINE LEARNING

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Early lung cancer detection depends on fast, noninvasive screening. We developed a breath-based diagnostic pipeline that quantifies volatile organic compounds (VOCs) reflecting metabolic activity using proton-transfer reaction mass spectrometry (PTR-MS). The cohort comprised 50 individuals with lung cancer and 190 healthy controls. VOCs were ranked by effect size (Cohen's d) between lung cancer and healthy controls, and the top 20 were retained as a biomarker panel. These features were used in a multi-stage classifier cascade to improve specificity against non-cancer respiratory disease. In the study dataset, k-nearest neighbors achieved 96.0% accuracy for lung cancer versus non-cancer, with support vector machines reaching 94.7%. The performance of this compact biomarker set supports a robust, scalable approach to noninvasive lung cancer screening. Coupling PTR-MS with machine learning offers a rapid path toward accessible testing in clinical and high-risk settings, pending external validation.

NEURONAL-ENRICHED EXTRACELLULAR VESICLE MICRORNA ASSOCIATIONS WITH INFLAMMATION AND NEUROTOXICITY IN MAJOR DEPRESSIVE DISORDER

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Major depressive disorder (MDD) remains a global health concern. The pathogenesis remains unknown, as multiple factors seem to have an influence on the disorder. Dysregulated immune signaling, including elevated pro-inflammatory cytokines, has been consistently reported in MDD and may contribute to neurotoxicity. MicroRNAs (miRNAs) play key roles in regulating gene expression, including inflammatory pathways. In MDD individuals, these regulatory mechanisms appear to be disrupted. Neuronal-enriched extracellular vesicles (NEEV) provide a minimally invasive method to assess brain-associated molecular signals in peripheral blood. In this study, we examined whether NEEV miRNAs are associated with inflammatory status and may reflect neurotoxic processes in inflammatory subtypes of MDD, stratified by C-reactive protein (CRP) concentrations. MDD subjects were stratified into High (CRP > 3mg/L, *n*=44) and Low (CRP < 3mg/L, *n*=44) inflammation groups and matched on age, sex, BMI, smoking status, and exercise using propensity scores. EV was isolated from plasma using a polymer-based kit. NEEV was enriched by a magnetic streptavidin bead immunocapture kit against the neural adhesion marker biotinylated antibody. NEEV small RNAs were purified and sequenced. Statistical analyses on NEEV miRNAs were conducted in R. Scaled miRNA data (counts per million) were log-transformed due to their non-Gaussian distributions determined by Shapiro-Wilks tests. Outliers were defined as z = ±3 across subjects and set as missing. Independent sample t-tests were used to assess differences between MDD-High and MDD-Low. In addition, Pearson' correlation was used to explore the relationship between NEEV miRNAs that showed group differences between MDD-High and MDD-Low and CRP concentrations. MDD-High exhibited higher NEEV miR-1-3p (*p*=.017, *d*=.52) and miR-221-3p (*p*=.013, *d*=.54) expressions than MDD-Low, in contrast, NEEV miR-425-5p expression was lower in MDD-High than MDD-Low (*p*=.008, *d*=.59). Within MDD, higher NEEV miR-1-3p (*r* =.27, *p*=.013) and miR-221-3p (*r* =.31, *p*=.003) expressions were correlated with higher CRP concentration, and higher NEEV miR-1-3p expressions were associated with lower CRP concentration (*r* =-.26, *p*=.013). These findings suggest that MDD with elevated CRP exhibited altered NEEV miRNA profiles. Given the roles of these miRNAs in regulating inflammation and multiple stages of neurotoxicity, their dysregulation in MDD may reflect underlying neuroimmune disturbances. While miR-1-3p and miR-221-3p have been linked to inflammatory responses in other conditions, their relevance in MDD remains understudied. Further testing could be conducted to establish a correlation between dysregulated expressions of miRNAs, inflammation, and neurotoxic effects.

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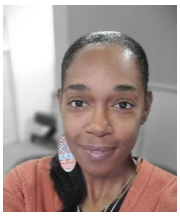

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