Web of Life Conference

April 25-26, 2024

The UNIVERSITY of OKLAHOMA
HEALTH SCIENCES

Web of Life Conference

April 25-26, 2024

HEALTH SCIENCES CENTER
The UNIVERSITY of OKLAHOMA

Thursday, April 25, 2023
Nicholson Auditorium, OU Health Sciences Center

7:00 am – 8:00 am	Conference Registration & Breakfast

SESSION I: Welcome Addresses from University of Oklahoma Health Sciences' Administration (8:00 am – 9:00 am)

8:00 am – 8:05 am	**Priyabrata Mukherjee, PhD**, Co-Chair
8:05 am – 8:10 am	**Resham Bhattacharya, PhD**, Co-Chair
8:10 am – 8:20 am	**Robert Mannel, MD**, Director of the OU Health Stephenson Cancer Center
8:20 am – 8:30 am	**Darrin Akins, PhD**, Vice President for Research
8:30 am – 8:40 am	**Gary Raskob, PhD**, Senior Vice President and Provost
8:40 am – 9:00 am	**Joseph Harroz, Jr., JD**, President of the University of Oklahoma

BREAK (9:00 am – 9:05 am)

SESSION II (9:05 am – 11:00 am)

9:05 am – 9:20 am	Session Introduction **Jed Friedman, PhD**, Director of the Harold Hamm Diabetes Center, University of Oklahoma Health Sciences

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9:20 am – 9:45 am	Contextual Determinants of Pancreatic Tumorigenesis **Dafna Bar-Sagi, PhD**, NYU Langone Health
9:45 am – 10:10 am	MegaMolecules an Applications as Antibody Mimics **Milan Mrksich, PhD**, Northwestern University
10:10 am – 10:35 am	Immunometabolic Checkpoints of Aging **Vishwa Deep Dixit, DVM, PhD**, Yale University

POSTER SESSION (10:35 am – 11:35 pm)

LUNCH (11:35 pm – 12:45pm)

SESSION III
(12:45 pm – 2:40 pm)

12:45 pm – 1:00 pm	Session Introduction **Danny Dhanasekaran, PhD**, Director of the Center for Basic Cancer Research, University of Oklahoma Health Sciences
1:00 pm – 1:25 pm	The Importance of Understanding the Normal Brain to Uncover Disease Vulnerabilities in Late Life **Carol Barnes, PhD**, University of Arizona
1:25 pm – 1:50 pm	Transcriptional Elongation Control and Chromatin in Developmental Gene Expression, Aging, and Disease **Ali Shilatifard, PhD**, Northwestern University
1:50 pm – 2:15 pm	Biomaterials for Delivering on the Promise of Immunotherapy **Natalie Artzi, PhD**, Harvard Medical
2:15 pm – 2:40 pm	Mitochondrial Dynamics and Cardiometabolic Disease **E. Dale Abel, MD, PhD**, University of California – Los Angeles

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COFFEE BREAK (2:40 pm – 2:55 pm)

SESSION IV
(2:55 pm – 4:50 pm)

2:55 pm – 3:10 pm	Session Introduction **Leo Tsiokas, PhD**, Chair of the Department of Cell Biology, University of Oklahoma Health Sciences
3:10 pm – 3:35 pm	FGF21 and Alcohol: A Sobering Liaison **David Mangelsdorf, PhD**, UT Southwestern Medical Center
3:35 pm – 4:00 pm	Blood is a Tissue: Controlling Nanoparticles' Journey in Blood and Things Learned Along the Way **Lola Eniola-Adefeso, PhD**, University of Michigan
4:00 pm – 4:25 pm	How Cilia are Built and Signal **Jeremy Reiter, MD, PhD**, University of California – San Francisco
4:25 pm – 4:50 pm	Colon Cancer Checks in When Bile Acids Check Out **Ronald Evans, PhD**, Salk Institute

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Friday, April 26, 2023
Nicholson Auditorium, OU Health Sciences Center

7:00 am – 8:00 am	Conference Registration & Breakfast

SESSION V
(8:00 am – 10:05 am)

8:00 am – 8:15 am	Session Introduction **Anirban Maitra, MBBS**, Scientific Director of the Sheikh Ahmed Pancreatic Cancer Research Center, MD Anderson Cancer Center
8:15 am – 8:50 am	Structural Nanomedicine through Spherical Nucleic Acids **Chad Mirkin, PhD**, Northwestern University
8:50 am – 9:15 am	Cilia and Tumorigenesis; from the Cancer Cell to the Tumor Microenvironment **Erica Golemis, PhD**, Fox Chase Cancer Center
9:15 am – 9:40 am	Merging Models to Advance Our Understanding of Obesity and Breast Cancer **Paul MacLean, PhD**, University of Colorado
9:40 am – 10:05 am	The Challenge of Inelegant Solutions to Questions About the Evolutionary Origins of Senescence, Adiposity, and Sexual Reproduction **David Allison, PhD**, Indiana University

COFFEE BREAK (10:05 am – 10:20 am)

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SESSION VI
(10:20 am – 12:25 pm)

10:20 am – 10:45 am	Session Introduction **Resham Bhattacharya, PhD**, Co-Leader Cancer Biology Program, OU Health Stephenson Cancer Center, University of Oklahoma Health Sciences
10:45 am – 11:10 am	Cancer and Thrombosis **Gary Raskob, PhD**, University of Oklahoma Health Sciences
11:10 am – 11:35 am	Engineering Timing and Location for Next-Generation Vaccines **Darrell Irvine, PhD**, Massachusetts Institute of Technology
11:35 am – 12:00 pm	Can Cancer Metabolism be Exploited for New Treatments in Patients? **Celeste Simon, PhD**, University of Pennsylvania
12:00 pm – 12:25 pm	Pancreas Cancer: Metabolism & Immunity **Ronald DePinho, MD, PhD**, MD Anderson Cancer Center

ROUND TABLE LUNCH (12:25 pm – 1:30 pm)

SESSION VII
(1:30 pm – 3:00 pm)

1:30 pm – 1:45 pm	Session Introduction **Dev Mukhopadhyay, PhD**, Professor of Biochemistry & Molecular Biology, Mayo Clinic
1:45 pm – 2:10 pm	Targeting Transcription Factor Neo-Enhancesomes in Cancer **Arul Chinnaiyan, PhD**, University of Michigan
2:10 pm – 2:35 pm	How Do Cells Make Heat? **Shingo Kajimura, PhD**, Harvard Medical School

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2:35 pm – 3:00 pm	MYC, Circadian Clock, Metabolism & Tumor Immunity **Chi Van Dang, PhD**, Johns Hopkins University

COFFEE BREAK (3:00 pm – 3:20 pm)

SESSION VIII
(3:20 pm – 4:25 pm)

3:20 pm – 3:35 pm	Session Introduction **Mary Beth Humphrey, MD, PhD, FACP**, Associate Dean of Research, Department of Internal Medicine, University of Oklahoma Health Sciences
3:35 pm – 4:00 pm	Adoptive Cell Therapy for Cancer **Carl June, PhD**, University of Pennsylvania
4:00 pm – 4:25 pm	UBAP2: A Tale of Two Stories **Priyabrata Mukherjee, PhD**, University of Oklahoma Health Sciences

PRESIDENT

Joseph Harroz, Jr., JD
President
The Univeristy of Oklahoma

Serving the University of Oklahoma for over 26 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, twelve years as general counsel, and two years as vice president for executive affairs.

As president of OU, Harroz led the development of the university's Strategic Plan – a comprehensive strategy that positions OU as one of the nation's leading public research universities marked by a transformative student experience. At the heart of the Plan is the university's fundamental purpose – We Change Lives – three small but powerful words that carry deep meaning. The complete Strategic Plan is available at ou.edu/leadon.

Under Harroz's leadership, OU is making remarkable strides toward the fulfillment of the Strategic Plan. In fall 2022, OU welcomed its largest, most diverse, and highest academically qualified class in the school's 132-year history – more than a quarter of whom are first-generation college students. Research at OU has not only recovered from the challenges presented by the COVID-19 pandemic, its growth has exceeded the Strategic Plan's goal of sustained 7% annual growth in research expenditures over seven years, relative to FY2019. As of FY2021, research expenditures reached over $387.2 million university-wide, an increase of 25.3% since the FY2019 benchmark. In addition, the university has enjoyed historic fundraising, receiving a record $317 million in gifts and pledges during FY2022.

An abundance of other successes have come to life since the Strategic Plan's launch two years ago – the addition of premier freshman housing, the merger of OU Health, joining the SEC, and more. Altogether, these endeavors are sparking a new era of excellence at OU.

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.

PROVOST

Gary E. Raskob, PhD

Senior Vice President & Provost
Regents Professor of Epidemiology & Medicine
Univerity of Oklahoma Health Sceinces

Gary E. Raskob, Ph. D., is Senior Vice President and Provost at the University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, with overall responsibility for the educational and research programs of its seven colleges, and the Stephenson Cancer Center and the Harold Hamm Diabetes Center. He also serves on the Boards of the OU Health system and the University Hospitals Authority and Trust.

Dr. Raskob has academic appointments in the College of Public Health, and the College of Medicine, as a Regents Professor of Epidemiology and Medicine. He began his career at the OU Health Sciences Center 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, and he currently serves on the Board of Directors for the National Blood Clot Alliance (NBCA), the major patient advocacy organization in the United States for patients with venous thrombosis and pulmonary embolism. 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. He is active in public health service in his community, and is an immediate 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.

VICE PRESIDENT FOR RESEARCH

Darrin Akins, PhD

Vice President for Research
Professor, Department of Microbiology & Immunology
University of Oklahoma Health Sciences Center

Dr. Darrin Akins is the Vice President for Research and tenured full Professor in the Department of Microbiology & Immunology at the University of Oklahoma Health Sciences Center. Dr. Akins is an internationally recognized expert in Lyme disease and is an established biomedical research scientist with an excellent history of past and current NIH R01 research funding. Dr. Akins also has extensive successful administrative experience as the current Vice President for Research, previous Associate Vice President for Health Sciences Research, Associate Dean for Research in the College of Medicine, and Assistant Dean of the Graduate College, where in each position he had the ultimate responsibility for enhancing research programs on the OUHSC campus. Dr. Akins has been Principal Investigator of the Oklahoma IDeA Network of Biomedical Research Excellence (OK-INBRE) award since 2009. Dr. Akins' laboratory for the past two decades has primarily focused on identifying novel Lyme disease vaccine candidates or other disease modulating therapeutics. Most recently, his laboratory discovered two novel protein export systems in the organism that causes Lyme disease, which are currently being evaluated for the roles they play in this complex disease. He has been continually funded by multiple NIH awards since 2005 for his Lyme disease studies, and his peers have consistently recognized his work with national and regional awards.

DEAN - COLLEGE OF MEDICINE

Ian F. Dunn, MD
Executive Dean, College of Medicine
Professor & Chair, Department of Neurosurgery
OU Health and Sciences

Ian F. Dunn, M.D., FACS, FAANS, is Professor and Chair of the Department of Neurosurgery at the University of Oklahoma College of Medicine. He holds the Harry Wilkins, M.D. Chair in Neurosurgery and also serves on the OU Health Executive Leadership Team as Chief Physician Executive.

Before coming to OU Health, Dunn served as an Associate Professor in the Department of Neurosurgery at Harvard Medical School for eight years and director for the Center for Pituitary and Skull Base Surgery at Brigham and Women's Hospital.

He completed his clinical fellowship in skull base neurosurgery at the University of Arkansas for Medical Sciences/St. Vincent Infirmary Medical Center, Little Rock, after completing his postdoctoral fellowship in cancer genomics at the Dana-Farber Cancer Institute/Broad Institute, Boston. He completed his neurosurgery residency and served as chief resident at the Children's Hospital/Brigham and Women's Hospital, and general surgery internship at Brigham and Women's Hospital. He earned his medical degree from Harvard Medical School in Boston, MA.

Dunn is a member of numerous national professional societies and presents nationally and internationally on his central focus on complex brain tumors at the skull base, including those in the pituitary region. He has authored more than 200 peer-reviewed journal publications and 40 chapters of various scientific and/or medical publications in neurosurgery.

STEPHENSON CANCER CENTER

Robert S. Mannel, MD
Director
OU Health Stephenson Cancer Center
Professor, Department of Obstetrics & Gynecology
University of Oklahoma Health Sciences

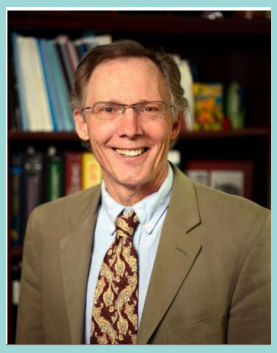
Robert Mannel, MD, is Director of the Stephenson Cancer Center and Professor in Obstetrics and Gynecology at the University of Oklahoma Health Sciences Center.

Since his appointment as cancer center Director in 2007, Dr. Mannel has overseen the Stephenson Cancer Center's emergence as a center recognized nationally for research, treatment, education and outreach activities. The Stephenson Cancer Center's major achievements during Dr. Mannel's tenure as Director include attaining Lead Academic Participating Site status within the National Cancer Institute (NCI)'s National Clinical Trials Network (NCTN) in 2014, achieving the prestigious NCI Designation status in 2018, competitively renewing NCI Designation in 2023, and being named a *US News and World Report* Top 50 "Best Hospital for Cancer" in the nation for 2019-20.

Dr. Mannel currently serves as a Chair for NRG Oncology, one of four national non-profit organizations that make up the NCI's National Clinical Trials Network (NCTN). The NCTN, the world's premier network for developing and conducting clinical trials to advance new cancer therapies, is composed of over 2,200 institutions nationwide. NRG Oncology is the largest group within the Network, placing more cancer patients on NCI clinical trials than any other organization.

A graduate of the University of Texas College of Medicine at Galveston, Dr. Mannel completed his residency in Obstetrics and Gynecology at Scott and White Hospital in Temple, Texas. After his residency he pursued a Gynecologic Oncology Fellowship at the University of California, Irvine and joined the faculty at the OU Health Sciences Center in 1989.

He served as Chairman of the OU Department of Obstetrics and Gynecology from 1997 to 2013, and he was instrumental in developing the Section of Gynecologic Oncology at the OU Health Sciences Center into one of the top gynecologic cancer programs in the country.



Jacob (Jed) Friedman, PhD
Director, Harold Hamm Diabetes Center
Chickasaw Nation Chair & Professor, Physiology, Biochemistry & Molecular Biology, Pediatrics
Associate Vice-Provost, Diabetes Programs
University of Oklahoma Health Sciences

Jacob E. (Jed) Friedman, PhD, is Director of the Harold Hamm Diabetes Center, Chickasaw Nation Chair and Professor of Physiology, Biochemistry and Molecular Biology, and Pediatrics, Associate Vice-Provost for Diabetes Programs at the University of Oklahoma Health Sciences Center. Dr. Friedman was recruited in 2019 and has a long-standing interest in understanding the causes and consequences of obesity and diabetes impact on developmental programming of metabolic disease during the first 1000 days. Previously he served as Director of the Colorado NIH-Nutrition and Obesity Research Center (NORC) Molecular and Cellular Analytical core lab and has 30 years of experience in clinical-translational research in mouse, monkey, and humans.

Dr. Friedman is an internationally recognized leader in clinical-translational and basic investigations in developmental programming and Gestational Diabetes with 30 years of uninterrupted NIH funding in mouse, monkey, and man. Dr. Friedman's research integrates basic and human clinical research involving diabetes, obesity, and fetal developmental origins of obesity and Non-Alcoholic Fatty Liver Disease (NAFLD), a disease that affects up to 40% of obese children. His lab was the first to describe prenatal fatty liver in human infants born to obese mothers using MRI/MRS. Dr. Friedman went on to discover that a gut microbial imbalance in human infants born to obese mothers, when transferred to germ-free mice, reduced macrophage phagocytosis and provokes obesity and NAFLD. This has advanced the field and set the stage for pre-natal interventions designed to prevent the consequences of maternal obesity and diabetes in youth where obesity, diabetes are rapidly increasing.

Dr. Friedman's work has led to clinical trials in collaboration with clinical investigators in Ob-Gyn, Neonatology, and Endocrinology. These studies in humans and Non-Human Primates are now designed to investigate how specific metabolic targets impact maternal metabolism and fetal metabolic systems at the molecular, endocrine, and epigenetic levels in infant stem cells, liver, and the microbiome. He has published >180 original papers, books, and invited reviews in top journals including JCI, PNAS, Nature Communications, Nature Reviews, Hepatology, and Diabetes. Dr. Friedman has mentored **59** post-docs, MD fellows, and students, (9 Ks, 4 F32s, 7 RO1s), including 9 who hold faculty positions (Instructor, or above) at the University of Colorado or in biomedical research institutes elsewhere. He has won numerous awards nationally and internationally, including the 2014 ADA Norbert Freinkel Award for outstanding lifetime contributions to the field of diabetes and pregnancy and the University of Colorado Award for outstanding mentorship.

OMRF PRESIDENT

Andrew Weyrich, PhD
President
Oklahoma Medicial Research Foundation

Dr. Andrew Weyrich became president of OMRF in 2022. An internationally recognized leader in blood clotting whose discoveries have facilitated key advances in the field of hematology, Dr. Weyrich came to the foundation from the University of Utah. There, he was vice president for research, professor of internal medicine, and held the H.A. & Edna Benning Presidential Endowed Chair, as well as president of the University of Utah Research Foundation and Innovation District.

Originally an exercise physiologist, Dr. Weyrich joined the University of Utah as a postdoctoral researcher and, over the next 28 years, built his scientific reputation on the investigation of how blood cells impact human thrombotic and inflammatory diseases. He has authored more than 150 peer-reviewed articles and has been funded by the National Institutes of Health for over 25 years.

Dr. Weyrich is a member of the advisory council to the NIH's National Heart, Lung, and Blood Institute, an associate editor for the medical journal Blood Advances, and a former member of the editorial board for the medical journal Blood. Among his numerous honors is the American Society of Hematology's prestigious William Dameshek Prize for outstanding contributions leading to a new fundamental understanding of hematology.

In 2023, Dr. Weyrich kicked off "77 for 77," a campaign to celebrate OMRF's 77th anniversary and increase awareness of the foundation across all 77 Oklahoma counties. Through August 2024, Dr. Weyrich and OMRF leadership, staff and scientists are crisscrossing the state, touching each of Oklahoma's counties and hosting events to reconnect with the communities that came together to build the foundation in the 1940s.

A native of Ohio, Dr. Weyrich received his undergraduate degree in biology from Baldwin-Wallace College, his master's degree in health and exercise science from Wake Forest University, and his doctorate in physiology and pharmacology from the Bowman Gray School of Medicine at Wake Forest

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Danny Dhanasekaran
Elizabeth Wellberg
Jed Friedman
Kathleen Moore
Robert Mannel
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SESSION I

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8:10 am – 8:20 am	**Robert Mannel, MD**, Director of the OU Health Stephenson Cancer Center
8:20 am – 8:30 am	**Darrin Akins, PhD**, Vice President for Research
8:30 am – 8:40 am	**Gary Raskob, PhD**, Senior Vice President and Provost
8:40 am – 9:00 am	**Joseph Harroz, Jr., JD**, President of the University of Oklahoma

SESSION II

9:05 am – 9:20 am	Session Introduction **Jed Friedman, PhD**, Director of the Harold Hamm Diabetes Center, University of Oklahoma Health Sciences
9:20 am – 9:45 am	Contextual Determinants of Pancreatic Tumorigenesis **Dafna Bar-Sagi, PhD**, NYU Langone Health
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Jacob (Jed) Friedman, PhD

Director, Harold Hamm Diabetes Center
Chickasaw Nation Chair & Professor, Physiology, Biochemistry & Molecular Biology, Pediatrics
Associate Vice-Provost, Diabetes Programs
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Dafna Bar-Sagi, PhD

Saul Farber Professor of Biochemistry & Molecular Pharmacy
Executive Vice President & Vice Dean for Science
Chief Sceintific Officer
New York Univeristy

Dr. Bar-Sagi is a cancer biologist widely recognized for her work on pathophysiological processes that drive the initiation and progression of mutant Ras tumors. She has made fundamental contributions to the understanding of the mechanisms that couples extracellular signals to Ras activation of effector pathways that control cell proliferation and survival. Dr. Bar-Sagi is also credited with the discovery of Ras oncogene-dependent mechanisms that enhance tumor cell fitness via immune evasion and metabolic adaptation.

Dr. Bar-Sagi is the Saul Farber Professor of Biochemistry and Molecular Pharmacology. Aside of leading her research program, Dr. Bar-Sagi is Executive Vice President and Vice Dean for Science, Chief Scientific Officer of NYU Langone Health. Prior to joining NYU Grossman School of Medicine in 2006 as chair of the Department of Biochemistry, Dr. Bar-Sagi headed the Department of Molecular Genetics and Microbiology at SUNY at Stony Brook.

Contextual Determinants of Pancreatic Tumorigenesis

Pancreatic cancer, in its most common form - pancreatic ductal adenocarcinoma (PDAC) - is one of the most lethal cancers with overall 5-year survival of 11%. Approximately 61,000 new cases of PDAC were diagnosed in the US in the past year, and the incidence is rising at a rate of 0.5% to 1.0% per year. On this trajectory, PDAC is projected to become the second most common cause of cancer-related deaths in the US. The evolution of PDAC is driven by a network of complex molecular and cellular alterations that affect the tumor cells themselves and the environment that surrounds them. The focus of our efforts has been to define the context-dependent contribution of these alterations to the pathophysiological characteristics of PDAC with the goal of leveraging this information to identify actionable vulnerabilities in this disease.

Milan Mrksich,

Henry Wade Rogers Professor, Departments of Biomedical Engineering, Chemistry, & Cell & Development Biology
Northwestern University

Milan Mrksich is the Henry Wade Rogers Professor with appointments in the Departments of Biomedical Engineering, Chemistry, and Cell & Developmental Biology. He served as Northwestern's Vice President for Research, was the Founding Director of the Center for Synthetic Biology and an Associate Director of the Robert H. Lurie Comprehensive Cancer Center. He earned a BS degree in Chemistry from the University of Illinois and a PhD in Chemistry from Caltech. He then served as an American Cancer Society Postdoctoral Fellow at Harvard University before joining the Chemistry faculty at the University of Chicago in 1996, where he remained until his move to Northwestern in 2011. His honors include the Camille Dreyfus Teacher-Scholar Award, the TR100 Innovator Award, the Arthur C. Cope Scholar Award, the Illinois Bio ICON Innovator Award, the Pittsburgh Analytical Chemistry Award, and election to the American Institute for Medical and Biological Engineering. Dr. Mrksich is a leader in the science and engineering of materials that contact biological environments. His laboratory has pioneered several technologies, including strategies to integrate living cells with microelectronic devices, the SAMDI biochip technology for high throughput experiments, and the megamolecule approach to making synthetic proteins for therapeutic applications.

MegaMolecules and Applications as Antibody Mimics

This talk will describe an approach for synthesizing molecules that have sizes greater than 100 nm and yet are structurally perfectly defined. The approach relies on the selective and covalent reaction of an enzyme domain with an irreversible linker. Fusion proteins containing two or more of the enzyme domains are treated with linkers terminated in two or more of the irreversible inhibitors, leading to the rapid reaction of the partners and efficient assembly of the megamolecule. Several enzyme-inhibitor pairs have been developed, and used to prepare megamolecules that are linear, cyclic, branched, and that have molecular weights greater than 500,000 Dalton, and sizes greater than 100 nm. The talk will describe the use of this approach to create antibody mimics that include multiple affinity domains, including domains having different specificities. Applications of the megamolecule antibodies include enzyme conjugates for localized treatment, for imaging, and for recruitment of T-cells to tumors. These examples demonstrate the many opportunities for creating functionalized molecular scaffolds for a broad range of applications

Vishwa Deep Dixit, DVM, PhD

Waldemar Von Zedtwitz Professor of Pathology
Professor of Immunobiology
Director, Yale Center for Research on Aging (Y-Age)
Yale University

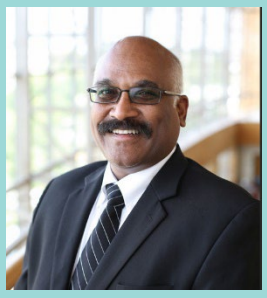
Son of teachers, Deep grew up in Hisar (northwest India). He studied veterinary medicine in India, and did PhD research at the University of Hannover, Germany, and postdoctoral research at Morehouse School of Medicine, in Atlanta, and the National Institute on Aging (of the National Institutes of Health), in Baltimore. He currently holds the Waldemar Von Zedtwitz endowed chair and is a professor in the departments of Pathology, Comparative Medicine, and Immunobiology at Yale University. Dixit is also director of the Yale Center for Research on Aging (Y-Age) at Yale School of Medicine.

The Dixit lab studies the interactions between immune and metabolic systems that control inflammation and the process of aging. His team helped establish NLRP3 inflammasome activation as a key mechanism of “inflammaging” and immunosenescence that leads to age-related degenerative conditions including metabolic dysfunction. Dixit and his collaborators have identified that switching the metabolic state from utilization of glucose to generation of fat-derived ketone bodies inhibits inflammation by deactivating the NLRP3 inflammasome and reduces immunopathology. Through its recent work, his laboratory discovered that the moderate restriction of calories in middle-aged humans, which induces negative energy balance, reveals endogenous targets that reign in inflammation and may play a role in enhancing healthy lifespan. Ongoing research in Dixit’s lab is focused on interrogating how the nutrient and energy-sensing mechanisms in a host can be harnessed to identify immunometabolic checkpoints to enhance health and longevity. Dixit’s research has been published in leading scientific journals, and he has been recognized for his work by numerous awards from scientific societies including the National Institute on Aging. Research in the Dixit laboratory is funded in part by the Cure for Alzheimer’s Foundation and the National Institutes of Health.

Immunometabolic Checkpoints of Aging

SESSION III

12:45 pm – 1:00 pm	Session Introduction **Danny Dhanasekaran, PhD**, Director of the Center for Basic Cancer Research, University of Oklahoma Health Sciences
1:00 pm – 1:25 pm	The Importance of Understanding the Normal Brain to Uncover Disease Vulnerabilities in Late Life **Carol Barnes, PhD**, University of Arizona
1:25 pm – 1:50 pm	Transcriptional Elongation Control and Chromatin in Developmental Gene Expression, Aging, and Disease **Ali Shilatifard, PhD**, Northwestern University
1:50 pm – 2:15 pm	Biomaterials for Delivering on the Promise of Immunotherapy **Natalie Artzi, PhD**, Harvard Medical School
2:15 pm – 2:40 pm	Mitochondrial Dynamics and Cardiometabolic Disease **E. Dale Abel, MD, PhD**, University of California – Los Angeles



Danny Dhanasekaran, PhD

Professor, Department of Cell Biology
Samuel Roberts Noble Foundation Endowed Chair in Cancer Research
Associate Director for Basic Research, Stephenson Cancer Center
Director, SCC-COBRE & Center for Basic Cancer Research
University of Oklahoma Health Sciences

Dr. Danny Dhanasekaran earned his Ph.D. in Biochemistry from the Indian Institute of Science, India and postdoctoral training at the University of Wisconsin-Madison and the National Jewish Center for Immunology and Respiratory Medicine. He has served in tenured professorships at both the Temple University School of Medicine and the University of Oklahoma Health Science Center, where he is currently a Professor of Cell Biology, Associate Director for Basic Cancer Research, and the Director of NIH-funded MTCRO-Center of Biomedical Research Excellence. Recognized with the prestigious Acres of Diamond Award and the Million Dollar Research Award from Temple University, Dr. Dhanasekaran has also served as WCU Professor at Seoul National University, South Korea, and Visiting Professor at the University of Tokyo Medical and Dental University, Japan, and Università del Piemonte Orientale, Italy. He has served as a Charter Member of the NIH/CSR Study Section on Tumor Cell Biology and continues to review grants for NIH, DOD, and AHA. He also serves as editor and editorial board member for several international journals. Dr. Dhanasekaran's research is focused on uncovering transcriptomic and metabolomic variations in ovarian cancer, including omics analysis in diverse populations. Aiming to identify and leverage novel diagnostic and therapeutic targets, his work is dedicated to enhancing our understanding of cancer pathogenesis and creating personalized treatment approaches that significantly improve patient outcomes.

Carol Barnes, PhR

Regents' Professor, Psychology, Neurology and Neuroscience
Evelyn F. McKnight Chair for Learning and Memory in Aging
Director, Evelyn F. McKnight Brain Institute
Director, Division of Neural Systems, Memory and Aging
University of Arizona

Carol A. Barnes is a Regents Professor in the Departments of Psychology, Neurology and Neuroscience, the Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging, and Director of the Evelyn F. McKnight Brain Institute at the University of Arizona. She earned her B.A. in Psychology from the University of California at Riverside, and her M.A. and Ph.D. from Carleton University in Ottawa, Canada. She did postdoctoral training in neurophysiology in the Department of Psychology at Dalhousie University, The Institute of Neurophysiology, University of Oslo, and in the Cerebral Functions Group at University College London. Barnes is past president of the 38,000-member Society for Neuroscience, is a Fellow of the American Association for the Advancement of Science, an elected member of the National Academy of Sciences and an elected Foreign Member of the Royal Norwegian Society of Sciences and Letters. She is the recipient of the 2013 Gerard Prize in Neuroscience and the 2014 American Psychological Association Award for Distinguished Scientific Contributions.

The central goal of Barnes' research program is to understand how the brain changes during normative aging and what the functional consequences of this are for information processing and memory. Her research program has involved behavioral, electrophysiological and molecular biological approaches to the study of young and aged rodents and non-human primates. This work provides a basis for understanding the basic mechanisms of normal brain aging, a prerequisite for a deeper understanding of neurodegenerative diseases that occur during aging. Most recently she is the PI of a large project (the Precision Aging Network) that studies normative human brain aging, with the goal of discovering methods to optimize cognitive healthspan across the lifespan. Working with interdisciplinary teams she has published a number of manuscripts that are now classic references on brain aging and behavior.

The Importance of Understanding the Normal Brain to Uncover Disease Vulnerabilities in Late Life

Some past myths and current ideas about normative brain and cognitive aging will be reviewed. One focus of my research is to serve as PI of a group based at the University of Arizona, with collaborators across the US, which we call the "Precision Aging Network".The NIH sponsors this 5-year project through the National Institute on Aging. The PAN group is committed to building a foundation of knowledge about normative aging that can be used by the scientific community to optimize brain health in normal aging populations as well as to inspire new treatment approaches for neurodegenerative diseases. This grant has allowed us to launch the studies in our Precision Aging Network, that include very large samples of cognitive performance across the lifespan (18 – 90+ years) from individuals across the United States through the web-based MindCrowd testing platform (we currently have data from ~500,0000 people) as well as genetic, lifestyle, environment and other variables that will enable determination of what factors, on a more individualized basis can optimize brain health as we age. The Precision Aging network is based on the principle of team-based science, as we include people with basic neuroscience and cognitive science backgrounds as well as bio- and computer- engineers, geneticists biocheists, molecular biologists, epidemiologists and bioinfomaticians to help us collect, analyze and integrate the complex data we are collecting. To do this we are taking a precision medicine approach to brain aging, much like the field of cancer biology pioneered. With this information we have the goal of predicting, preventing or slowing the decline of brain aging on an individual basis, to increase quality of life for diverse groups of individuals as they age.

Ali Shilatifard, PhD

Chair, Department of Biochemistry & Molecular Genetics
Director, Simpson Querrey Institute for Epigenetics
Northwestern University

Dr. Shilatifard is a world-renowned biochemist and molecular geneticist and a respected expert in the field of transcription and epigenetics, specifically as it relates to cancer biology. Shilatifard has an immense interest in understanding the intricate molecular mechanisms of the regulation of gene expression, the mechanisms that activate or suppress a particular gene's trait. As a Jane Coffin Childs postdoctoral fellow at the Oklahoma Medical Research Foundation, Shilatifard made a seminal contribution to the field of leukemia biology by identifying the first function of any of the MLL translocation partners as an RNA Polymerase II elongation factor and linking transcription elongation control to cancer pathogenesis. This study also demonstrated that elongation stage of transcription is a key regulatory step in gene expression. Since then, his laboratory has continued to contribute to the field of gene expression and epigenetics and its link to cancer biology through many discoveries including the purification of the first histone H3K4 methyltransferase Set1/COMPASS and the MLL/COMPASS family. His studies also identified the Super Elongation Complex (SEC) as a complex containing many of the MLL's translocation partners found in leukemia in one complex regulating the elongation stage of transcription. His fundamental biochemical studies demonstrated a role for chromatin and the elongation stage of transcription as the central mechanisms for cancer development. The Shilatifard lab's focused studies over the past 30 years have made significant inroads to understanding the cause of childhood leukemia, and his studies are leading to the development of extremely promising target-specific drugs for childhood leukemia and other forms of cancers. Currently, the inhibitors and pathways identified in Shilatifard's laboratory towards the COMPASS and SEC families are being tested for the treatment of childhood leukemia, brain cancer, bladder cancer, and triple negative breast tumors.

For his contributions to our understanding of cancer epigenetics and chromatin biology, Dr. Shilatifard has been recognized by the Leukemia and Lymphoma Society as a Scholar, as the recipient of the Sword of the American Cancer Society, and the AMGEN Award by the American Society of Biochemistry and Molecular Biology. He has been funded through several major grants from the National Institutes of Health, and National Cancer Institute and was selected as an inaugural recipient of the Outstanding Investigator Award from the National Cancer Institute in 2015 and recently renewed this funding until 2030. He has served as a Senior Editor for the journal *Science*, Editor for Molecular and Cellular Biology and as the founding Editor for *Sciences* open access journal, *Science Advances* between 2014-2023. Shilatifard also has served on the Scientific Advisory Boards of Genentech, the Max Planck Society, the Searle Foundation, and as a member of the jury for the BBVA Foundation Prize in Medicine.

Transcriptional Elongation Control and Chromatin in Developmental Gene Expression, Aging, and Disease

Chromosomal translocations are major drivers of cancer. The 11q23 translocation, which fuses the *Mixed Lineage Leukemia* (*MLL*) gene with any of dozens of other genes on different chromosomes, drives the pathogenesis of pediatric hematological malignancies including the majority of infant leukemias. In 1996 we demonstrated that one of these *MLL* oncofusion partners, the *ELL* gene, encodes a factor controlling the rate of transcriptional elongation by RNA Polymerase II. At the time it was thought that gene expression was only regulated at the level of transcriptional initiation, but our study suggested that transcriptional elongation control is a key regulatory step in gene expression, and its link to leukemia suggested that transcriptional elongation dysfunction could drive disease pathogenesis. Through a series of biochemical purifications of MLL oncofusion proteins, we then determined that ELL and many other MLL oncofusion partners are all subunits of the same macromolecular complex containing the longation-promoting kinase CDK9. We named this complex the Super Elongation Complex (SEC). This discovery solidified a role for elongation control as a key regulatory step in gene expression and is malfunction drives rearranged leukemias by demonstrating that translocation of MLL into subunits of SEC result in defect in transcriptional elongation checkpoint control. Discovery of SEC as a major transcription elongation factor also provides a potential therapeutic targets controlling this process. We have continued to dissect the mechanisms by which not only SEC but also many other transcriptional regulatory complexes (such as BRD2-4, BRDT, PAF1c, SPT complexes, NELF and ELOA family) all function together to regulate the activity of RNA Pol II as components of a dynamic and complex transcriptional elongation machinery. Through chemical biology screening, we have also developed small molecules that can be used as tools to study transcription elongation control *in vivo* by disruption of these elongation factor complexes. These compounds serve as lead tools for further development of clinical therapies targeting transcriptional elongation control in disease. I will share our recent findings regarding the mechanistic complexity of transcription elongation control, its roles in development and impacts on aging and disease, and how my lab leverages our molecular studies to generate targeted therapeutic approaches.

Natalie Artzi,

Associate Professor of Medicine
Harvard Medical School

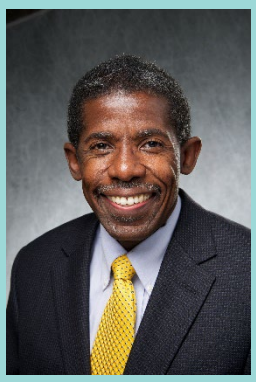
Dr. Artzi is an Associate Professor of Medicine at Harvard medical School. She is a Principal Research Scientist at MIT, Associate Faculty at the Wyss Institute for Biologically Inspired Engineering, and an Associate Member of the Broad Institute of Harvard and MIT. She completed her postdoctoral studies at MIT focusing on studying tissue: biomaterial interactions and designing smart biomaterials for therapy and diagnosis applications.

Dr. Artzi is the recipient of multiple grants and awards, including the inaugural Kabiller Rising Star Award in Nanotechnology and Nanomedicine, the Acta Biomaterialia Silver Medal award, the Clemson Award for Applied Science, One Brave Idea award, Stepping Strong Innovator Award, Controlled Release Society Young Investigator Award, Mid-Career Award from the Society for Biomaterials, Bright Futures Prize, and the Massachusetts Life Science Center for women entrepreneurs. Dr. Artzi was recently inducted to the Controlled Release Society College of Fellows.

Currently, Dr. Artzi directs multiple research venues aiming to integrate science, engineering, and medicine to rationally design personalized materials to improve human health, and has co-founded a startup company, BioDevek, which develops the next-generation biomaterials to improve outcomes following internal surgeries.

Biomaterials for Delivering on the Promise of Immunotherapy

Immunomodulatory therapies have advanced to clinical trials over the past decade for the treatment of a range of diseases and disorders, from cancer to diabetes to transplant rejection. However, the efficacy of these therapies remains limited, as challenges associated with off-target drug toxicity, poorly controlled drug pharmacokinetics, and an incomplete understanding of real-time therapy responses prevent effective therapeutic windows from being realized. Here, we highlight some of our work on the design, fabrication, and characterization of biomaterial-based delivery technologies for the controlled delivery of immunotherapies and for the non-invasive monitoring of their associated immune responses for the treatment of cancer and autoimmune disease. We show that the design of materials and their delivery context can influence therapeutic outcomes and alter the spatiotemporal characteristics of the incited immunomodulatory responses. By adroitly designing and utilizing our material delivery platforms, we can deliver immunotherapies with tailorable pharmacokinetics and enhanced efficiency to improve long-term therapeutic outcomes and tolerability, and enable studying basic questions in immunobiology as we seek to generate a ‘living’ therapeutics.



E. Dale Abel, MD, PhD

William S. Adams Distinguished Professor of Medicine
Chair and Executive Medical Director
Department of Medicine
David Geffen School of Medicine and UCLA Health

Professor E. Dale Abel is the William S. Adams Distinguished Professor and Chair for the Department of Medicine, David Geffen School of Medicine and Executive Medical Director UCLA Health. Dr. Abel graduated with Distinction from the University of the West Indies School of Medicine, obtained a DPhil from Oxford University as a Rhodes Scholar, trained in Internal Medicine at Northwestern University, where he was chief resident and in endocrinology at the Beth Israel Deaconess Medical Center, Harvard Medical school. Dr. Abel has had a distinguished career in endocrine, metabolism and cardiovascular research. His pioneering work on glucose transport and mitochondrial metabolism launched his current research interests: molecular mechanisms responsible for cardiovascular complications of diabetes. Dr. Abel has published more than 250 peer reviewed publications in competitive journals, his work has been highly cited and has shaped much of current understanding of the metabolic mechanisms underlying heart failure, particularly in obesity and diabetes.

Dr. Abel is the recipient of numerous awards for scholarship and mentorship, including awards and endowed lectureships such as the Fred Conrad Koch Lifetime Achievement Award of the Endocrine Society, the 2018 African American Museum of Iowa History Makers Award. He is an elected member of the American Association of Physicians (AAP), the American Society for Clinical Investigation (ASCI), the American Clinical and Climatological Association (ACCA), the National Academy of Medicine (NAM) and the National Academy of Sciences (NAS). He is past President of the Endocrine Society and the Association of Professors of Medicine.

Mitochondrial Dynamics and Cardiometabolic Disease

Mitochondria undergo repeated cycles of fusion and fission, a process known as mitochondrial dynamics. Mitochondrial fission is mediated by a family of proteins including Dynamin related proteins (DRP1) and Fission 1 (Fis 1). Outer mitochondrial membrane fusion is mediated by the mitofusin family of GTPases (MFN1 and MFN2) and inner mitochondrial membrane fusion by the protein optic atrophy 1 (OPA1). We have been exploring the relationship between mitochondrial dynamics and cardiometabolic disorders, by focusing on OPA1. We have discovered novel interactions between OPA1, estrogens and thrombosis risk in humans, and links between OPA1 function in adipose tissue and the generation of circulating mitokines that regulate systemic metabolic homeostasis. By studying >25,000 patients with inactivating mutations of OPA1, presenting clinically with autosomal dominant optic atrophy (ADOA), we have observed that OPA1 dysfunction increases the risk of thromboembolic disease in men and post-menopausal females and increases the risk for metabolic dysfunction associated fatty liver disease (MAFLD), type 2 diabetes, dyslipidemia and hypertension, all hallmarks of the metabolic syndrome. Major adverse cardiovascular events were also significantly increased despite good control of hypertension, diabetes and dyslipidemia. Thus, primary defects in mitochondrial dynamics predispose to cardiometabolic disease.

SESSION IV

2:55 pm – 3:10 pm	Session Introduction **Leo Tsiokas, PhD**, Chair of the Department of Cell Biology, University of Oklahoma Health Sciences
3:10 pm – 3:35 pm	FGF21 and Alcohol: A Sobering Liaison **David Mangelsdorf, PhD**, UT Southwestern Medical Center
3:35 pm – 4:00 pm	Blood is a Tissue: Controlling Nanoparticles' Journey in Blood and Things Learned Along the Way **Lola Eniola-Adefeso, PhD**, University of Michigan
4:00 pm – 4:25 pm	How Cilia are Built and Signal **Jeremy Reiter, MD, PhD**, University of California – San Francisco
4:25 pm – 4:50 pm	Colon Cancer Checks in When Bile Acids Check Out **Ronald Evans, PhD**, Salk Institute

David Mangelsdorf, PhD

Alfred G. Gilman Professor
Chair, Department of Pharmacology
University of Texas Southwestern Medical Center

David J. Mangelsdorf is the Alfred G. Gilman Professor and Chair of the Department of Pharmacology at the University of Texas Southwestern Medical Center in Dallas and Investigator of the Howard Hughes Medical Institute, and he is a member of the National Academy of Sciences. Dr. Mangelsdorf received his B.S. from Northern Arizona University, his Ph.D. from the University of Arizona, and his postdoctoral training at The Salk Institute for Biological Studies. During his career, he discovered the hormonal ligands and biological pathways for several nuclear receptors, including RXR, LXR, FXR, and DAF-12. Dr. Mangelsdorf currently runs a joint laboratory with Dr. Steven Kliewer that more recently has discovered two signaling pathways mediated by the endocrine factors FGF19 and FGF21, which regulate metabolism and behavior in response to nutrient stress. Their work on work on the nuclear receptor, DAF-12, uncovered the mechanism that governs nematode parasitic infections. Together their research has led to several therapeutic targets that are being developed to treat a diverse range of diseases, including cholestasis, cancer, fatty liver disease, nematode parasitism, pancreatitis, and alcohol abuse.

FGF21 and Alcohol: A Sobering Liaison

Fibroblast growth factor 21 (FGF21) is an endocrine and paracrine factor that is produced in response to nutrient and metabolic stress and is known to have diverse roles in maintaining lipid and glucose homeostasis. In both animals and humans, the most potent inducer of circulating FGF21 is alcohol consumption, a finding that is supported by human genetic studies. In response to alcohol, FGF21 is made and released from the liver into circulation, and then enters discrete brain regions where it acts to suppress further alcohol intake, increase drinking pure water, and decrease alcohol-induced sedation. Loss of FGF21 or its receptor makes animals more prone to increased alcohol intake, dehydration, and inebriation. Pharmacologic administration of FGF21 greatly enhances both its anhedonic and amethystic properties by reversing the desire to consume alcohol and markedly reversing the intoxication of drunk mice. The diverse actions of FGF21 are mediated through a unique receptor complex that is composed of a classic FGF receptor and an essential co-receptor, b-Klotho. Investigation into the CNS regions required for FGF21's effects has revealed the existence of complex neural endocrine circuits, which in addition to regulating metabolism, also govern reward behaviors and arousal in response to alcohol.

Lola Eniola-Adefeso, PhD

Vennema Endowed Professor, Department of Chemical Engineering
Associate Dean for Graduate & Professional Education
University Diversity & Social Transformation Professor
University of Michigan – Ann Arbor

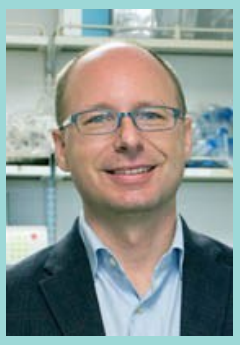
Dr. Omolola (Lola) Eniola-Adefeso is the CSO and a Co-founder of Asalyxa Bio, a company that develops a therapeutic that addresses the issues of ARDS in a novel manner. Her research looks to design biocompatible functional particles for targeted drug delivery.

She is the Vennema Endowed Professor of Chemical Engineering and the University Diversity and Social Transformation Professor of Chemical Engineering at the University of Michigan-Ann Arbor. She serves as Michigan Engineering's Associate Dean for Graduate and Professional Education and has appointments in Biomedical Engineering as well as Macromolecular Science and Engineering.

She received a doctoral degree (2004) in Chemical and Biomolecular Engineering at the University of Pennsylvania. Since she arrived at Michigan, Dr. Eniola-Adefeso has published over 70 research articles and received several honors and awards, including the NSF CAREER Award, American Heart Association (AHA) Innovator Award, and most recently, the Biomedical Engineering Society (BMES) MIDCAREER Award. She is a fellow of the American Institute for Medical and Biological Engineering (AIMBE), the Biomedical Engineering Society, the American Heart Association, the Controlled Release Society (CRS), a senior member of the National Academy of Inventors (NAI), and serves as Deputy Editor for Science Advances. Additionally, she was recently elected to a two-year term as the president of AIMBE. Her research is currently funded by multiple grants from the NIH NHLBI, the American Heart Association, and the National Science Foundation.

Blood is a Tissue: Controlling Nanoparticles' Journey in Blood and Things Learned Along the Way

Our work focuses on probing the role of particle geometry, material chemistry, and blood rheology/dynamics on the ability of vascular-targeted drug carriers to interact with the blood vessel wall - an important consideration that will control the effectiveness of drug targeting regardless of the targeted disease or delivered therapeutically. This presentation will highlight the carrier-blood cell and cell-cell interactions that affect drug carriers and immune cells binding to the vascular wall and how these interactions can alter important neutrophil functions in various diseases.



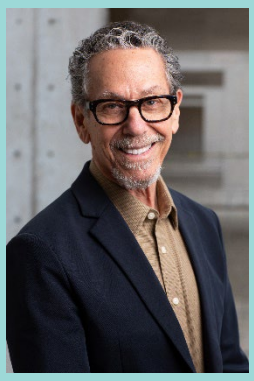
Jeremy Reiter, MD, PhD

Professor & Chair, Department of Biochemistry & Biophysics
School of Medicine
Univeristy of California, San Francisco

Dr. Jeremy Reiter, MD, PhD, is a professor at the University of California, San Francisco (UCSF). His work focuses on how cells build cilia and how cilia function in intercellular communication and has included elucidating the mechanisms by which cilia transduce signals such as Hedgehogs, demonstrating that cancer cells can be addicted to their cilia, and discovering the role of the transition zone in gating the ciliary localization of receptors. His studies help reveal how cilia signal, how defective ciliary signaling causes ciliopathies (e.g., cystic kidney diseases), how ciliary defects contribute to diseases not normally considered ciliopathies (e.g., obesity, Hedgehog-associated cancers), and how cilia function in postnatal tissues with a particular focus on the hypothalamic regulation of feeding behavior. In addition, he has been the Chair of the Department of Biochemistry and Biophysics.

How Cilia are Built and Signal

Primary cilia are solitary, immotile sensory organelles present on most cells. Over the last two decades, we have learned how primary cilia play important roles in intercellular communication, physiology and human diseases called ciliopathies. Cilia are unique environments for signal transduction, with tight control of protein, lipid and second messenger concentrations within a small compartment, enabling cilium-specific forms of reception, transmission and integration of biological information. Emerging molecular understanding of how cilia transduce multiple intercellular signals provides the opportunity to therapeutically intervene in diseases as diverse as retinal degeneration, polycystic kidney disease and obesity.



Ronald Evans, PhD

Professor
Director, Gene Expression Laboratory
March of Dimes Chair, Development & Molecular Biology
Salk Institute for Biological Studies

Ronald M. Evans, Ph.D. is a Professor at the Salk Institute for Biological Studies, Director of the Gene Expression Laboratory, and holds the March of Dimes Chair in Developmental and Molecular Biology. His landmark paper in 1985 revealed the first complete sequence for the glucocorticoid receptor (GR) launching a molecular era of hormone signaling and gene control. He showed that non-steroidal molecules such as vitamin A and thyroid hormone were structurally related to the GR leading to his proposal for a Nuclear Receptor Superfamily. This launched a second wave of discovery that opened many new branches of physiology. Evans' discovery of FXR revealed that bile acids are unexpectedly a family of hormones that control digestion and metabolism by activating an FXR gene network. Globally, the receptor super-family helps to regulate sugar, salt, calcium, cholesterol and fat metabolism, mitochondrial proliferation, circadian rhythm and basal metabolic rate. They are primary targets in breast, prostate, and pancreatic cancer, and leukemia treatment, and have FDA-approved therapeutic roles in chronic inflammation, osteoporosis, asthma and Types 1 & 2 diabetes. His muscle metabolism studies on PPARd led to the discovery of 'exercise mimetics,' oral drugs which promote the benefits of fitness without training. Exercise mimetics will help battle the obesity epidemic, diabetes, heart disease and frailty. His work on stem cell differentiation includes the in vitro generation of immunologically 'invisible' Human Islet Like Organoids (HILOs) that rescue diabetes in mice with human insulin without need for a device. Evans is a co-leader of 4 Stand Up to Cancer Dream Teams. Awards include the Albert Lasker Basic Medical Research Award in 2004, the Wolf Prize in Medicine in 2012 and the Japan Prize in 2024. He is a member of the NAS, NAM and NAI.

Colon Cancer Checks in when Bile Acids Check Out

The discovery of the bile acid receptor FXR launched a new branch of physiology which demonstrated bile acids are not simply digestive surfactants but also act as potent hormones by controlling metabolic gene networks. Indeed, high levels of FXR expression in tongue, gut, liver, pancreas and islets, kidney, adrenal, gall bladder, stomach and adipose makes it a potent regulator of body-wide metabolism. Unexpectedly, we found that selective activation of intestinal FXR both protects mice against diet-induced weight gain and lowers colorectal cancer progression. This impact on cancer led us to next explore FXR's potential to manage the increasing prevalence of Inflammatory Bowel Disease (IBD) which includes Ulcerative Colitis and Crohn's Disease. Finally, I'll also show how FXR signaling modulates the microbiome and the role of the microbiome and reciprocally the role of the microbiome in modulating bile acid signaling

SESSION V

8:00 am – 8:15 am	Session Introduction **Anirban Maitra, MBBS**, Scientific Director of the Sheikh Ahmed Pancreatic Cancer Research Center, MD Anderson Cancer Center
8:15 am – 8:50 am	**Keynote:** Structural Nanomedicine through Spherical Nucleic Acids **Chad Mirkin, PhD**, Northwestern University
8:50 am – 9:15 am	Cilia and Tumorigenesis; from the Cancer Cell to the Tumor Microenvironment **Erica Golemis, PhD**, Fox Chase Cancer Center
9:15 am – 9:40 am	Merging Models to Advance Our Understanding of Obesity and Breast Cancer **Paul MacLean, PhD**, University of Colorado
9:40 am – 10:05 am	The Challenge of Inelegant Solutions to Questions About the Evolutionary Origins of Senescence, Adiposity, and Sexual Reproduction **David Allison, PhD**, Indiana University

Anirban Maitra, MBBS

Professor, Department of Anatomical Pathology
Division of Pathology
MD Anderson Cancer Center

Dr. Maitra is a Professor of Pathology and Translational Molecular Pathology, and Scientific Director of the Sheikh Ahmed Pancreatic Cancer Research Center at UT MD Anderson Cancer Center, Houston (since August 2013). Dr. Maitra is the Principal Investigator of an NCI-funded laboratory dedicated to pancreatic cancer research. Dr. Maitra has trained over three dozen postdoctoral fellows and graduate students, many of whom are now in independent faculty positions in the United States or worldwide.

The arc of his research career has been defined by contributions made in the spheres of genetics and molecular pathology of pancreatic cancer and its precursor lesions, in both human and cognate mouse models of pancreatic neoplasia. Dr. Maitra is deeply committed towards identifying and implementing translational research opportunities in pancreatic cancer that can improve the survival of patients stricken with this disease, with a particular focus on early detection and cancer interception. Dr. Maitra has been a leader on numerous programmatic efforts in pancreatic cancer, funded through both the NCI and foundations such as Stand-Up-To-Cancer/AACR.

KEYNOTE SPEAKER

Chad Mirkin, PhD

Professor, Department of Chemistry
International Institute for Nanotechnology
Northwestern University

Chad Mirkin is a chemist and a world-renowned nanomedicine expert, known for his invention of spherical nucleic acids, or SNAs, and their development as diagnostic and therapeutic tools; >1,800 products are based upon SNAs, including the Verigene system, SmartFlares, and SNA drugs in seven human clinical trials based on gene regulation and cancer immunotherapy. He has authored >870 manuscripts and >1,200 patent applications worldwide (>430 issued). He has founded 10 companies, most recently, Flashpoint Therapeutics. He has been recognized with >250 awards and elected into all three US National Academies. Mirkin served on PCAST (Obama) for eight years.

Structural Nanomedicine Through Spherical Nucleic Acids

Modern medicine is driven by the development of complex biological therapies, and nanomedicine plays a pivotal role in overcoming the limitations of traditional drugs. Structural nanomedicine, which manipulates therapeutic entities at the nanoscale, is particularly promising. Spherical Nucleic Acids (SNAs), with their dense, radial oligonucleotide arrangement, offer superior cellular uptake, nuclease resistance, and target affinity compared to linear nucleic acids. This unique architecture enables the precise attachment of multiple functional components, including diverse oligonucleotide sequences, peptides, and proteins.

By controlling the nanoscale placement of elements like vaccine components, SNAs can induce potent, programmable immune responses. This approach has the potential to revolutionize cancer vaccines. Beyond vaccines, structural nanomedicine offers exciting possibilities for improving the delivery and efficacy of antisense, siRNA, and CRISPR-based gene editing therapies. Our laboratory at Northwestern University (NU) and Flashpoint Therapeutics, an NU startup specializing in structural nanomedicine, is leveraging the SNA platform to create breakthrough therapeutics in these areas. This presentation will explore how designed nanoscale architectures can transform the future of medicine.

Erica Golemis, PhD

Professor
Vice President
Associate Director for Systemwide Intergration
Chair, Department of Cancer & Cellular Biology
Wiiliam Wikoff Smith Chair in Cancer Research
Fox Chase Cancer Center – Temple Health

Dr. Erica Golemis, Ph.D. is the William Wikoff Smith Chair in Cancer Biology and serves as Associate Director for System Integration at Fox Chase Cancer Center, as well as Chair of the Department of Cancer and Cell Biology at the Lewis Katz School of Medicine at Temple University. Her research interests lay in the study of signaling networks that influence therapeutic response to cancer and ciliopathies. Prior to joining Fox Chase, Dr. Golemis received her doctorate from the Department of Biology at the Massachusetts Institute of Technology and received postdoctoral training at the Massachusetts General Hospital and Harvard Medical School. Dr. Golemis is a Fellow of the AAAS, Editor-in-Chief at *Cancer & Metastasis Reviews*, and a frequent peer-reviewer for the NIH, DOD, and other agencies.

Cilia and Tumorigenesis; From the Cancer Cell to the Tumor Microenvironment

In adult humans, most differentiated cell types express a primary monocilium (also known as a cilium) comprising a central microtubule-based axoneme extended from a basal body, encompassed by a specialized membrane. The basal body is derived from the mother centriole as part of a “ciliary cycle” that commences following mitosis; cilia protrude from the cell in G0/early G1 but are reabsorbed as cells move towards and through S phase, with the released centriole differentiating as a centrosome, to function as part of a mitotic organizing center. Often described as cellular “antennas”, cilia provide hubs for receipt of physical and molecular cues.

Over the past 20 years, numerous developmental disorders have been linked to genetic defects that impair ciliary structure and/or signaling. More recently, relationships between ciliary function and cancer are also emerging. Specific growth regulatory pathways, including notably Hedgehog, depend on a ciliary-localized receptor system. Medulloblastomas and other cancers that depend on activation of the Hedgehog pathway are influenced by ciliary integrity. For pancreatic ductal adenocarcinomas (PDACs), asymmetric signaling between the unciliated cancer cell and ciliated cancer-associated fibroblasts contributes to tumor progression and restrains tumor metastasis. The ciliary cycle is governed through the activity of growth factor and cell cycle pathways that are frequently oncogenic in cancer; drugs targeting these pathways can influence ciliary integrity and function, potentially contributing to unexpected drug activities. Intriguingly, recent studies have also identified cilia as mediators of metabolism, adipogenesis, and inflammation, through action both on cancer cells and those in the tumor microenvironment. These processes are well established as influencing tumor progression. Based on these complex activities, greater consideration of ciliary status as a modulator of tumor risk and prognosis is merited.

Paul MacLean, PhD

Professor, Medicine & Pathology
School of Medicine
University of Colorado

Dr. MacLean is Professor of Medicine and Pathology at the University of Colorado School of Medicine with 25 years of experience studying obesity and its metabolic complications. He currently serves as the Director of the Colorado Nutrition Obesity Research Center and the Director of Research and Education Integration for the Anschutz Health and Wellness Center. His research interests include the biological drivers of weight regain after weight loss, exercise as a strategy for weight loss maintenance, and understanding how obesity affects key aspects of women's health across the lifespan. He has a particular interest in how obesity and its treatments affect the risk and incidence of breast cancer. Over the past several years, Dr. MacLean has worked with program staff at the National Institutes of Health to lead the ADOPT Core Measures Project, an interdisciplinary effort to develop personalized approaches for the treatment of obesity. Dr. MacLean's overarching research objective is to translate the wealth of knowledge generated from mechanistic basic science studies of energy balance to clinically relevant concepts and applications in obesity therapeutics.

Merging Models to Advance Our Understanding of Obesity and Breast Cancer

Despite new treatment modalities, the incidence of breast cancer has remained steady in recent years with >250,000 new diagnoses and >40,000 deaths annually in the US. Concurrently, over two-thirds of US women are afflicted with overweight or obesity. Obesity and metabolic disease increase breast cancer incidence and worsen patient outcomes in women of all ages. Premenopausal women with obesity are at increased risk of triple negative breast cancer (lacking any targetable factors). Postmenopausal women with obesity incur more estrogen receptor (**ER**) positive breast cancer and are more likely to develop resistance to endocrine therapies. While estrogen is clearly an important part of this relationship, two key observations suggest that there may be estrogen-independent mechanisms at play: 1) obesity is accompanied by worse *prognosis* for estrogen-independent triple negative breast cancer; and 2) anti-estrogen therapies are less effective against ER+ breast tumors in women with obesity. Regardless of tumor subtype and menopausal status, excess weight is associated with poor outcomes for breast cancer patients. We have merged preclinical models of obesity, menopause, and breast cancer, to examine estrogen-independent mediators of this relationship, to study the underlying mechanisms of the resistance to endocrine therapies, and to pursue novel strategies for prevention and treatment. Our studies have led us to study a novel role for cancer-associated fibroblasts in this relationship and how intermittent energy restriction may be able to eliminate obesity-associated tumor progression.

David Allison, PhD
Dean, Distinguished Professor, and Provost Professor
School of Public Health
Indiana University - Bloomington

David B. Allison, Ph.D., is Dean, Distinguished Professor, and Provost Professor at Indiana University–Bloomington School of Public Health. Continuously NIH-funded as a PI for over 25 years, he has authored or co-authored more than 700 scientific publications. Awards include the Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring (2006); the Friends of Albert (Mickey) Stunkard Lifetime Achievement Award (The Obesity Society, 2021); and the Harry V. Roberts Statistical Advocate of the Year Award (American Statistical Association, 2018). In 2022 he was named a Distinguished Lecturer by Sigma Xi and received the Hoebel Prize for Creativity (Society for the Study of Ingestive Behavior). He received the 2023 Bodil M. Schmidt-Nielsen Distinguished Mentor and Scientist Award (American Physiological Society). In 2023, he was elected as a Fellow of Sigma Xi the Scientific Honor Society, elected as member of the International Statistical Institute, and elected and inducted into the Academy for Health and Lifespan Research, the first global non-profit group focused on accelerating breakthroughs in the expansion of the human health span. Elected to the National Academy of Medicine in 2012, he also serves as co-chair of the National Academy of Sciences' Strategic Council on Research Excellence, Integrity, and Trust. Dr. Allison is a staunch advocate for rigor in research methods and the uncompromisingly truthful communication of research findings.

The Challenge of Inelegant Solutions to Questions About the Evolutionary Origins of Senescence, Adiposity, and Sexual Reproduction

It was said by Dobzhansky that "nothing in biology makes sense except in the light of evolution" (see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9830543/). This thinking often seems to be represented by investigators in ipse dixit statements about our presumed evolutionary past's circumstances that led to selection pressures which would produce our modern characteristics, that most if not all characteristics (phenotypes) have indeed been the subject of (usually directional) selective pressures, and that a single selective force is the sole or primary evolutionary factor which influenced the current trait. Building on ideas expressed by others (e.g., https://link.springer.com/article/10.1007/s40656-023-00604-4, https://www.hup.harvard.edu/books/9780674504622, https://nick-lane.net/books/life-ascending-the-ten-great-inventions-of-evolution/, https://scientistseessquirrel.wordpress.com/2015/09/28/is-biology-beautiful/), I will offer that a richer understanding of aging (senescence), adiposity (obesity), and sexual reproduction will emerge if we embrace inelegant multifactor solutions in thinking about evolutionary origins of interconnected characteristics. Accepting that evolution is a tinkerer and not a designer, that 'selected' is not 'selected for', that evolutionary forces other than selection exist, and that optimization may be seen as a messy democracy of traits and entities with sometimes competing fitness interests may be inelegant, but it may lead to additional insights and…will be fun.

SESSION VI

10:20 am – 10:45 am	Session Introduction **Resham Bhattacharya, PhD**, Co-Leader Cancer Biology Program, OU Health Stephenson Cancer Center, University of Oklahoma Health Sciences
10:45 am – 11:10 am	Cancer and Thrombosis **Gary Raskob, PhD**, University of Oklahoma Health Sciences
11:10 am – 11:35 am	Engineering Timing and Location for Next-Generation Vaccines **Darrell Irvine, PhD**, Massachusetts Institute of Technology
11:35 am – 12:00 pm	Can Cancer Metabolism Be Exploited for New Treatments in Patients? **Celeste Simon, PhD**, University of Pennsylvania
12:00 pm – 12:25 pm	Pancreas Cancer: Metabolism & Immunity **Ronald DePinho, MD, PhD**, MD Anderson Cancer Center

Resham Bhattacharya, PhD

Professor, Department of Obstetrics & Gynecology

Co-Leader, Cancer Biology Program, OU Health Stephenson Cancer Center

University of Oklahoma Health Sciences

Dr. Bhattacharya is a Professor in the Department of Obstetrics and Gynecology and the co-leader of the Cancer Biology program at the Stephenson Cancer Center. Dr. Bhattacharya's cancer biology work in gynecologic cancers has led to novel target discovery and her bench-side work has been translated into clinical trials. Dr. Bhattacharya has demonstrated fundamental aspects of endothelial signaling that are instrumental in regulating vessel homeostasis. Additional contributions have been in elucidating how protein persulfidation contributes to mitochondrial bioenergetics, metabolism and regulation of the hypoxia inducible factor (HIF).

Gary e. Rraskob, PhD

Senior Vice President and Provost

Regents Professor of Epidemiology and Medicine

University of Oklahoma Health Sciences

Dr. Gary Raskob is Senior Vice President and Provost for the University of Oklahoma Health Sciences with overall responsibility for the educational and research programs of its seven colleges, the Stephenson Cancer Center and the Harold Hamm Diabetes Center. He also serves on the Boards of the OU Health system and the University Hospitals Authority and Trust. He holds academic appointments as Regents Professor of Epidemiology and Medicine with research interests in the prevention and treatment of deep-vein thrombosis and pulmonary embolism, clinical trials, and antithrombotic drug development. Dr. Raskob served as a an advisor on thrombosis and hemostasis for the National Heart, Lung and Blood Institute, and for the Centers for Disease Control and Prevention. 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.

Cancer and Thrombosis

Thrombosis is a common and serious complication in patients with cancer. Anticoagulant drugs are the preferred treat for patients with cancer-associated thrombosis. These patients have both a high risk of recurrent thrombosis and an increased risk of bleeding complications compared with non- cancer patients with thrombosis. Such complications often interrupt or delay the progress of definitive cancer therapy. Recent advances in understanding of the biochemistry of blood coagulation have led to the development of potentially safer anticoagulant drugs. This presentation will review these advances and outline clinical trials currently ongoing to improve the care of patients with cancer-associated thrombosis.

Darrell Irvine, PhD

Professor, Departments of Biological Engineering and Materials Science & Engineering
Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology
Ragon Institute of MGH, MIT, and Harvard
Investigator, Howard Hughes Medical Institute

Darrell Irvine, Ph.D., is a Professor at the Massachusetts Institute of Technology and an Investigator of the Howard Hughes Medical Institute. He also serves on the steering committee of the Ragon Institute of MGH, MIT, and Harvard. His research is focused on the application of engineering tools to problems in cellular immunology and the development of new materials for vaccine and drug delivery. Major efforts of the laboratory are directed toward vaccine development for HIV and cancer immunotherapy. Dr. Irvine's work has been recognized by numerous awards, including election as a Member of the National Academy of Medicine, Fellow of the Biomedical Engineering Society, Fellow of the American Institute for Medical and Biological Engineering, and appointment as an investigator of the Howard Hughes Medical Institute. He is the author of over 200 publications, reviews, and book chapters and an inventor on numerous patents.

Engineering Timing and Location for Next-Generation Vaccines

Following infection, even "acute" viral and bacterial infections are often accompanied by prolonged antigen and/or inflammatory cue exposure, which can extend weeks after infectious pathogen is cleared. This is in contrast the relatively short duration of antigen/inflammation that accompanies many subunit vaccines. Further, the structural integrity of vaccine antigens is critical for the priming of protective humoral immunity, but following protein immunization, antigens are rapidly degraded in the subcapsular sinus, paracortex, and interfollicular regions of lymph nodes. To overcome these challenges, we have developed immunization strategies and vaccine delivery technologies that prolong the delivery of antigen/adjuvant cues to lymphoid tissues, alter antigen uptake/capture in lymph nodes, and target antigens to B cell follicles. These approaches modulate diverse aspects of the immune response, expanding the repertoire of responding B cells, augmenting germinal center reactions, and promoting enhanced memory B cell and plasma cell development. Applications of these approaches to enhance vaccine responses to HIV and coronaviruses will be described.

Celeste Simon, PhD

Scientific Director, Abramson Family Cancer Research Institute
Associate Director, Cancer Center, Perelman School of Medicine
University of Pennsylvania

M. Celeste Simon, Ph.D. is the Scientific Director of the Abramson Family Cancer Research Institute and an Associate Director of the Cancer Center at the Perelman School of Medicine at the University of Pennsylvania. Dr. Simon's research is focused on how cells sense and respond to changes in the availability of molecular oxygen and nutrients. This affects normal development, physiology, and numerous diseases, such as the growth of solid tumors. The Simon Laboratory is studying how O_2 sensing impacts tumor inflammation, metabolism, metastasis, and overall disease progression. She accesses animal models and cancer patient samples with the ultimate goal of developing novel strategies to treat tumors such as pancreatic cancer, soft tissue sarcoma, hepatocellular carcinoma, and renal cancer. Dr. Simon currently directs a laboratory of 20 individuals, including graduate students, postdoctoral fellows, clinical fellows, and research technicians. She was an HHMI Investigator for twenty years, and has received numerous awards recognizing her research, such as the Fouad Bashour Award for Distinguished Physiologists, Stanley N. Cohen Award for Biomedical Research, and Elliot Osserman Award from the Israel Cancer Research Fund. In 2014, she was elected to the American Academy of Arts and Sciences, and the National Academy of Medicine in 2018. She received an NCI Outstanding Investigator Award in 2017 and was named a Fellow of the AACR Academy in 2021. She was also elected to the National Academy of Sciences in 2021, named the AACR-G.H.A. Clowes Award for Outstanding Basic Cancer Research in 2023, and received a FASEB Lifetime Achievement Award for her research, leadership, and mentoring. In 2023, she was named an HHMI Emeritus Investigator.

Can Cancer Metabolism be Exploited for New Treatments in Patients

Our laboratory investigates responses to changes in oxygen availability, as well as cancer cell adaptations to microenvironmental stresses that significantly contribute to advanced disease. Solid tumors frequently develop areas subjected to hypoxia and growth factor/nutrient deprivation, due to vascular insufficiency. I will discuss how this influences tumor progression.

Ronald DePinho, MD

Professor, Department of Cancer Biology
Harry Graves Burkhart III Distinguished University Chair, Cancer Biology
MD Anderson Cancer Center

Ronald A. DePinho, M.D. is the past president and distinguished university professor at MD Anderson Cancer Center in Houston, Texas. He studied biology at Fordham University, received his M.D. degree with distinction from the Albert Einstein College of Medicine, and performed his residency and postdoctoral training at Columbia-Presbyterian Medical Center. His research career began at Einstein as the Feinberg Senior Faculty Scholar in Cancer Research and an ACS Research Professor. He then joined the Dana-Farber Cancer Institute and Harvard Medical School where he was the founding Director of the Belfer Institute for Applied Cancer Science. During his 6-year tenure as MD Anderson's, president, Dr. DePinho conceived and launched the Cancer Moon Shots Program recruited many world-class faculty including its first Nobel, and expanded its global network to reach one-third of the human population. His research program has made fundamental contributions to our understanding of cancer, aging, and degenerative disorders, and these discoveries have led to clinical advances. He is a leader in the development and use of genetically engineered mouse models for various human cancers including colorectal cancer, pancreas, prostate, GBM, MDS, myeloma, and melanoma. His laboratory defined the role of telomeres and telomerase in cancer, aging, and Alzheimer's Disease. For his contributions to science and healthcare, Dr. DePinho has received the AACR Clowes Memorial Award, the Albert Szent-Gyorgyi Prize, the Ellis Island Medal of Honor, Portugal's Order of Saint James of the Sword, among other awards and honors. He is a member of the National Academy of Medicine and the National Academy of Science, and a fellow of the American Academy of Arts and Sciences, the American Association of the Advancement of Science, and the American Association of Cancer Research.

Understanding & Taming Pancreas Cancer

In PDAC, oncogenic KRAS (KRAS*) drives glycolysis in cancer cells, leading to glucose depletion and massively elevated lactate levels within the TME. This metabolic landscape exerts a profound inhibitory effect on glycolysis-dependent CD8+ T cells and M1-like inflammatory TAMs while fosters a favorable environment for OXPHOS-dependent immune suppressive myeloid cells such as Tregs, MDSCs, and M2-like anti-inflammatory TAMs, thereby creating an immunosuppressive TME. Genetic or pharmacological inhibition of KRAS* yields profound tumor regressions across diverse PDAC models, partially attributed to the attenuated tumor-infiltrating MDSCs and M2-like TAMs and the augmented tumor-infiltrating T cells. However, the emergence of acquired resistance poses a substantial challenge, as evidenced by the inevitable relapse of tumors, highlighting the imperative of combining KRAS* inhibitors with adjunctive therapies for more durable responses in PDAC. Our previous studies have uncovered cancer cell-intrinsic and TME-mediated mechanisms of escape from KRAS* inhibition, providing actionable co-targeting strategies to enhance the effectiveness of KRAS* inhibitors. Here, we combined KRAS* inhibition with agents targeting the major arms of the immunity cycle: CXCR1/2 inhibitor for myeloid cells, antagonistic anti-LAG3 antibody for T cells, and agonistic anti-41BB antibody for dendritic cells. This combination elicited robust anti-tumor activity in iKPC mice bearing large autochthonous tumors. While vehicle/isotype-treated mice succumbed within 3 weeks, sustained treatment led to durable complete tumor regression and prolonged survival in 36% of mice at 6 months. Mechanistic analyses revealed enhanced T cell infiltration and activation, depletion of immunosuppressive myeloid cells, and increased antigen cross-presentation by dendritic cells within the tumor core. These findings highlight the promise of KRAS* inhibitors alongside immunotherapy as a potential PDAC treatment avenue, warranting clinical investigation.

SESSION VII

1:30 pm – 1:45 pm	Session Introduction **Dev Mukhopadhyay, PhD**, Professor of Biochemistry & Molecular Biology, Mayo Clinic
1:45 pm – 2:10 pm	Talk Title **Arul Chinnaiyan, PhD**, University of Michigan
2:10 pm – 2:35 pm	How Do Cells Make Heat? **Shingo Kajimura, PhD**, Harvard Medical School
2:35 pm – 3:00 pm	MYC, Circadian Clock, Metabolism & Tumor Immunity **Chi Van Dang, PhD**, Johns Hopkins University

Dev Mukhopadhyay, PhD

Professor, Department of Biochemistry & Molecular Biology

Mayo Clinic

Debabrata (Dev) Mukhopadhyay, Ph.D., has a broad background in tumor microenvironment with training and expertise in angiogenesis, cancer, cardiovascular diseases and diabetes. Dr. Mukhopadhyay and his team are using pancreatic and renal cancer disease models to examine how tumors develop and particularly how they induce the angiogenic response that is essential for their survival.

Vascular permeability factor (VPF), also known as vascular endothelial growth factor (VEGF), has been implicated in the new vessel development found in most tumors. Although the mechanism of these complex processes remains unclear, Dr. Mukhopadhyay and his team are investigating the importance of VPF-VEGF as well as its signaling pathways to elucidate the mechanisms by which VPF-VEGF function in a variety of tumor models.

Moreover, Dr. Mukhopadhyay and his team are stuying the role of other angiogenic-related factors in tumor angiogenesis and metastasis, such as vascular endothelial growth factor C (VEGFC), vascular endothelial growth factor D (VEGFD) and phosphatidylinositol glycan anchor biosynthesis class F protein (PIGF).

Additional research interests include stellate cell biology, new drug delivery systems and nanotechnology, and incorporating the use gold nanoparticles and other bioconjugates as messengers to deliver reagents capable of manipulating the angiogenic response in vivo.

Arul Chinnaiyan, MD, PhD

Director, Michigan Center for Translational Pathology
S.P. Hicks Endowed Professor of Pathology
Investigator, Howard Hughes Medical Institute
American Cancer Society Research Professor
Univeristy of Michigan

Dr. Chinnaiyan is a molecular pathologist and physician scientist at the leading edge of translational cancer research and precision oncology. He is an Investigator of the Howard Hughes Medical Institute, American Cancer Society Research Professor, and Director of the Michigan Center for Translational Pathology. He has received several honors including the Paul Marks Prize for Cancer Research and the NCI Outstanding Investigator Award; he was also inducted into the AACR Academy Class of 2020. He is a member of the American Society for Clinical Investigation, Association of American Physicians, American Academy of Arts and Sciences, National Academy of Inventors, National Academy of Medicine, and the National Academy of Sciences. Most recently he was awarded the 2022 Sjöberg Prize for cancer research by the Royal Swedish Academy of Sciences.

Dr. Chinnaiyan is best known for the discovery of TMPRSS2-ETS gene fusions in a majority of prostate cancers, the first causative gene fusion in a common solid tumor. This landmark discovery was made using a bioinformatics approach to detect outlier genes in an aggregated tumor gene expression database developed by his group. In 2011, he established the first integrative, comprehensive clinical sequencing approach for advanced cancer patients called MI-ONCOSEQ, which has served as a paradigm for cancer precision medicine. He has also been taking advantage of integrative sequencing efforts to understand the non-coding genome of cancer especially in the area of biomarker and therapeutic development.

Targeting Transcription Factor Neo-Enhancesomes in Cancer

Shingo Kajimura, PhD

Investigator, Howard Hughes Medical Institute
Professor, Harvard Medical School, Beth Israel Deaconess Medical Center
Division of Endocrinology, Diabetes & Metabolism
Harvad University

Dr. Kajimura is a Professor of Medicine at Harvard Medical School, Beth Israel Deaconess Medical Center, and Investigator at Howard Hughes Medical Institute. His research focuses on understanding the molecular basis of bioenergetics, with an emphasis on energy homeostasis. His research led to the discovery of new pathways controlling thermogenesis and therapeutic targets for metabolic diseases.

How Do Cells Make Heat?

Thermogenesis is fundamental to mammals. Dysregulation of the process is closely linked to several pathologies, such as metabolic disease and hyper/hypo-metabolism. This presentation will discuss the recent advance regarding the molecular mechanisms of thermogenesis. A special focus will be on a recently identified non-canonical thermogenic mechanism in brown/beige fat, *a.k.a.* UCP1-independent thermogenesis. The therapeutic opportunities of this pathway will be discussed.

Chi Van Dang, MD, PhD

Ludwig Institute for Cancer Research, New York, NY
Bloomberg-Kimmel Institute for Cancer Immunotherapy,
Departments of Oncology and Biochemistry & Molecular Biology,
Johns Hopkins University, Baltimore, MD

Dr. Chi Van Dang is scientific director of the Ludwig Institute for Cancer Research and Bloomberg Distinguished Professor of Cancer Medicine. He is also Professor of Oncology, Cell Biology, and Biochemistry and Molecular Biology at Johns Hopkins University. Dang's research helped define the complex functions of the *MYC* oncogene, a central switch in human cancer, identifying key domains that mediate its transcription factor activity. The Dang Lab also established the first mechanistic link between MYC and cellular energy metabolism, contributing to the concept that genetic alterations re-program energy utilization and render cancer cells addicted to certain energy sources. His Lab further documented that MYC could disrupt circadian metabolism and is exploiting these concepts for therapeutic targeting of cancer cell metabolism as a new anticancer strategy. He is the editor-in-chief emeritus of *Cancer Research*, a member of the National Academy of Medicine and fellow of the American Academy of Arts & Sciences and the American Association for Cancer Research Academy. He received his B.S. in chemistry from the University of Michigan and a Ph.D. in chemistry from Georgetown University, followed by an M.D. degree from the Johns Hopkins University School of Medicine. He is board-certified in Internal Medicine and Medical Oncology.

MYC, Circadian Clock, Metabolism & Tumor Immunity

The MYC oncogene drives a transcriptional program that stimulates proliferative metabolism and immune evasion, rendering normal cells neoplastic when tumor suppressor mechanisms are diminished. As a transcription factor, MYC is a member of E-box binding factors that include the clock master regulator Bmal1-CLOCK heterodimer, which regulates metabolism is a circadian manner and is disrupted by high levels of MYC. As such, when MYC is deregulated, circadian metabolic oscillation ceases and proliferative metabolism is activated, driving increased mitochondrial function, protein synthesis, and glycolysis. MYC deregulation results in reliance on key metabolic pathways, such as glycolysis, glutaminolysis, and de novo fatty acid synthesis that expose tumor vulnerabilities. Inhibiting deregulated fatty acid synthesis can curb growth of MYC induced kidney tumors. Inhibiting glutaminase curbed growth MYC-induced liver tumors. However, targeting glycolysis by inhibiting lactate dehydrogenase has efficacy in the syngeneic MC38 colon tumor model, but with on-target, off-tumor effects. The role of the circadian clock in tumorigenesis is often conflicting. We found that hypoxia inhibits the clock through acidity and that Bmal1's role in melanoma tumorigenesis is cell-state dependent, such that loss of Bmal1 reduces YUMM2.1 melanoma tumor growth, whereas overexpressed Bmal1 sequesters myosin Myh9, shifts YUMM2.1 to a more mesenchymal, immunotherapy resistant state associated with increased MRTF-SRF and AP1 activity. Given that Myc and Bmal1 both regulate metabolism, we sought to determine their roles in tumor sensitivity to dietary changes such as alternate day fasting, which alters systemic immunity and significantly reduces tumorigenesis in the MC38 model and a potentially Myc-dependent way in the YUMM2.1 model. These studies suggest that the combination of dietary perturbation and metabolic inhibitors could add to the efficacy of immunotherapy.

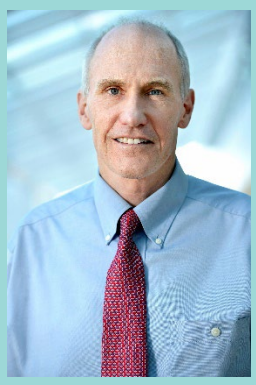
SESSION VIII

3:40 pm – 3:55 pm	Session Introduction **Mary Beth Humphrey, MD, PhD, FACP**, Associate Dean of Research, Department of Internal Medicine, University of Oklahoma Health Sciences
3:55 pm – 4:20 pm	Adoptive Cell Therapy for Cancer **Carl June, PhD**, University of Pennsylvania
4:20 pm – 4:45 pm	UBAP: A Tale of Two Stories **Priyabrata Mukherjee, PhD**, University of Oklahoma Health Sciences

Mary Beth Humphrey, MD, PhD, FACP

Associate Dean of Research
Professor of Medicine
McEldowney Chair in Immunology
Division Chief of Rheumatology, Immunology and Allergy
Department of Internal Medicine
University of Oklahoma Health Sciences

Dr. Humphrey grew up in Dallas, TX and completed her B.A. in Biology, magnum cum laude, at Austin College. She completed her MD, PhD in the Medical Science Training Program (MSTP) at Baylor College of Medicine. Dr. Humphrey subsequently completed Internal Medicine internship, residency, and Chief residency as well as Rheumatology fellowship at the University of California San Francisco. In 2007, she was recruited to the University of Oklahoma Health Sciences Center in the Department of Medicine, Division of Rheumatology. She was promoted to Associate professor with Tenure in 2012 and Professor in 2015. Beginning in 2013, she serves as the Division Chief of Rheumatology at OUHSC and in 2019 became the Associate Dean for Research for the College of Medicine. Dr. Humphrey was named the James R. McEldowney Chair in Immunology in 2009 and received the She has maintained research funding on myeloid cell contributions to osteoporosis, bone remodeling, and dementia since 2003. As a board-certified Rheumatology clinician, she proudly serves at the Oklahoma City Veterans Affairs Medical Center and at the OU Medical Center.



Carl June, MD

Richard W. Vague Professor in Immunotherapy, Department of Pathology
Director, Center for Cellular Immunotherapies
University of Pennsylvania

Carl June maintains a research laboratory that studies various mechanisms of lymphocyte activation that relate to immune tolerance and adoptive immunotherapy for cancer and chronic infection. In 2011, his research team published findings detailing a new therapy in which patients with refractory and relapsed chronic lymphocytic leukemia were treated with genetically engineered versions of their own T cells. The June laboratory has published more than >500 publications and has a google scholar h-index of 175 with >100,000 citations. He currently serves as the Richard W. Vague Professor in immunotherapy in the Department of Pathology and Laboratory Medicine and as the Director of the Center for Cellular Immunotherapies at the Perelman School of Medicine, as well as the Director of the Parker Institute for Cancer Immunotherapy at the University of Pennsylvania. He is the recipient of numerous awards and honors, including his election into the National Academies of Medicine and Science and the American Academy of Arts and Sciences.

Adoptive Cell Therapy for Cancer

Chimeric Antigen Receptor T-cell (CAR T) therapy represents a significant advance in cancer treatment, harnessing the body's own immune system to fight malignancies. This innovative form of immunotherapy involves genetically engineering a patient's T cells to produce receptors on their surface called chimeric antigen receptors (CARs). These receptors enable the T cells to recognize and attach to specific proteins or antigens on tumor cells, leading to their destruction. Recent advances in CAR T-cell therapy have shown promising results in the treatment of hematologic cancers such as leukemia, lymphoma, and myeloma with ongoing research exploring its potential in treating solid tumors. Despite challenges such as managing side effects and ensuring long-term efficacy, the clinical success of CAR T-cell therapy underscores its potential as a powerful tool in the fight against cancer.

Priyabrata Mukherjee, PhD

PHF Presidential Professor
Peggy and Charles Stephenson Endowed Chair in Laboratory Cancer Research
Professor of Pathology
Senior Director, Research Partnerships, Stephenson Cancer Center
Co-Director, Nanomedicine Program, Stephenson Cancer Center
Univeristy of Oklahoma Health Sciences Center

Mukherjee is a Professor in the department of Pathology and holds Peggy and Charles Stephenson Endowed Chair in Laboratory Cancer Research. Mukherjee also serves as the Senior Director of Research Collaboration and Partnership at the Stephenson Cancer Center.

His research has earned him several awards including, Outstanding Achievement Award by the Society of Asian American Scientists in Cancer Research (SAASCR), Fred G. Silva Award by the Department of Pathology and Presbyterian Health Foundation Presidential Professorship Award at OUHSC. He is also an elected Fellow of the Royal Society of Chemistry (FRSC), American Institute of Medical and Biological Engineering (FAIMBE), National Academy of Inventors (FNAI) and American Academy for the Advancement of Science (AAAS).

Mukherjee has been working at the interface of biology and materials science and made fundamental contributions on the application of nanoscience in biology. Mukherjee conceived the idea of self-therapeutic nanoparticle that are currently being utilized world-wide as a discovery tool to identify molecular targets for personalized medicine. Demonstrated fundamental aspects of cell-nanomaterial interaction currently being utilized to develop designer nanformulation for targeted therapy. Developed organo-inorganic hybrid nanomaterials as a general nucleic acid delivery system. Mukherjee also made fundamental contributions in the area of macropinocytosis, mitochondrial morphogenesis and tumor metabolism with respect to ovarian and pancreatic cancer.

UBAP2: A Tale of Two Stories

In recent years, significant effort has been devoted to develop nanotechnology for the delivery of small molecular weight drugs, as well as macromolecules such as proteins, peptides, or genes into cells and tissue. Another emerging and understudied area is the use of nanotechnology as a discovery tool to aid in fundamental understanding of the evolution of a disease. Using this approach Mukherjee group identified UBAP2 as a key regulator of one of the fundamental physiological processes. In this talk Mukherjee will discuss how UBAP2 resides at the crossroad of two fundamental physiological processes, aberrant activation of which promotes various pathophysiologies.

POSTER ABSTRACTS

Name (Last, First):	Institution:	Title:
Abbadi, Jumana	University of Oklahoma Health Sciences Center	ELUCIDATING THE CONTRIBUTION OF TUMOR DERIVED CALCITONIN GENE-RELATED PEPTIDE IN TUMOR GROWTH AND IMMUNE EVASION
Adewunmi, Eniola	University of Oklahoma Health Sciences Center	FUNCTIONAL CONSEQUENCES OF DEFECTIVE SKIN LIPID METABOLISM IN A RAT MODEL OF ERYTHROKERATODERMIA VARIABILIS
Ampadu, Felix	University of Oklahoma Health Sciences Center	A NOVEL PHARMACOLOGICAL INHIBITOR OF MAP4K4 CONFERS HEPATOPROTECTION AGAINST METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE
Bickel, Marisa	University of Oklahoma Health Sciences Center	IGF1R DEFICIENCY IN VASCULAR SMOOTH MUSCLE CELLS IMPAIRS VASCULAR AND COGNITIVE FUNCTION
Castillo-Castrejon, Marisol	University of Oklahoma Health Sciences Center	B CELLS ARE REGULATORS OF MENOPAUSE-ASSOCIATED WEIGHT GAIN, GLUCOSE METABOLISM AND ADIPOSE TISSUE DYSFUNCTION MAINLY THROUGH E2/ERA SIGNALING
Chandrasekaran Balaji	Texas A&M University	KK62 DISPLAYS POTENT ANTITUMOR ACTIVITY AGAINST CASTRATE-RESISTANT PROSTATE CANCER THROUGH ACTIVATION OF AUTOPHAGY
Chen, Chien-Yu	University of Pittsburgh	KNOCKING DOWN OF XKR8 ENHANCES CHEMOTHERAPY EFFICACY THROUGH MODULATING TUMOR IMMUNE MICROENVIRONMENT
Choudhary, Swati	University of Oklahoma Health Sciences Center	UNVEILING PRECISION TARGETS: OSBP AND ORP4 IN OVARIAN CANCER THERAPY WITH OSW-1 ANALOG COMPOUNDS
Clegg, John	University of Oklahoma, Norman	DELIVERY TECHNOLOGIES FOR CYTOKINE IMMUNOTHERAPY OF NEURO-INFLAMMATORY DISEASES
Deep, Gagan	Wake Forest	PROSTATE CANCER INDUCES COGNITIVE IMPAIRMENT VIA DELIVERING SPECIFIC MICRORNA CARGO LOADED IN SMALLER EXTRACELLULAR VESICLES
Fornalik, Michal	Oklahoma Medical Research Foundation	THE PROTECTIVE ROLE OF 17ALPHAE2 IN HEPATOCELLULAR CARCINOMA (HCC) DRIVEN BY NON-ALCOHOLIC STEATOHEPATITIS (NASH) IN MALE MICE
George, Kiran	University of Oklahoma Health Sciences Center	MOLECULAR MECHANISMS OF DESENSITIZATION AND INTERNALIZATION OF OXYTOCIN RECEPTOR IN NEURONS
Isingizwe, Zitha Redempta	University of Oklahoma Health Sciences Center	STUDIES OF DGLA EFFECTS ON PLATELET AND OVARIAN CANCER INTERATIONS
Jazir, Sabira Mohammed	University of Oklahoma Health Sciences Center	UNDERSTANDING THE LINK BETWEEN INFLAMMATION, NECROPTOSIS, AND AGING LIVER: IMPLICATIONS FOR NONALCOHOLIC FATTY LIVER DISEASE AND HEPATOCELLULAR CARCINOMA
Jonscher, Karen	University of Oklahoma Health Sciences Center	MATERNALLY SUPPLEMENTED PQQ TARGETS CERAMIDE METABOLISM IN OFFSPRING TO BLUNT DEVELOPMENTAL PROGRAMMING OF NAFLD
Khatri, Ujjwol	University of Oklahoma Health Sciences Center	ALLEVIATION OF TUMOR-INDUCED CACHEXIA BY RET-SELECTIVE INHIBITOR SELPERCATINIB
Luo, Zhangyi	University of Pittsburgh	INHIBITION OF IRHOM BY CD44-TARGETING NANOCARRIER FOR IMPROVED CANCER IMMUNOCHEMOTHERAPY

POSTER ABSTRACTS

Name (Last, First):	Institution:	Title:
Makuch, Magdalena	Oklahoma Medical Research Foundation	EFFEROCYTOSIS OF CANCER CELLS PERFORMED BY HUMAN MONOCYTE-DERIVED MACROPHAGES IS DIMINISHED UNDER HYPOXIA
Mensah Sankofi, Barbara	University of Oklahoma Health Sciences Center	FGF1 REGULATES GLYCOLYSIS THROUGH ETV4 IN OBESITY-ASSOCIATED BREAST CANCER CELLS
Mohanvelu, Sreenidhi	Oklahoma State University	PROGNOSTIC SIGNIFICANCE OF THE ACQUIRED LOSS OF RETINAL DEGENERATION PROTEIN 3 (RD3) IN CANCER STEM CELLS IN ENDOMETRIAL CANCER
Moore, Eric	University of Oklahoma Health Sciences Center	THE ROLE OF SENESCENCE AND INFLAMMATION IN MATERNAL OBESITY
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Zhang, Ziqian	University of Pittsburgh	GAS6-TARGETING MULTI-FUNCTIONAL NANOPARTICLES FOR ENHANCED CANCER THERAPY
Zyla-Jackson, Katarzyna	Oklahoma Medical Research Foundation	NUTRITIONAL KETOSIS AMELIORATES PATHOLOGIES IN A MOUSE MODEL OF MULTIPLE SCLEROSIS BY MODULATING TRYPTOPHAN, SEROTONIN, AND MELATONIN PATHWAYS ALONG THE GUT-CNS AXIS

ELUCIDATING THE CONTRIBUTION OF TUMOR DERIVED CALCITONIN GENE-RELATED PEPTIDE IN TUMOR GROWTH AND IMMUNE EVASION

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Cancer is a convoluted disease and the interactions happening within the tumor microenvironment **(TME)** are incredibly complex. Nerves represent a vital component in the TME, and most of what is known about this interaction is that cancer cells invade nerves. Recent evidence shows that nerves are more involved in the pathogenesis of tumors, for example, sensory nerves release important neuropeptides such as calcitonin gene-related peptide **(CGRP)** which influences the immune, cardiovascular, and other systems in the TME. The interaction between sensory nerves and cancer is complex and completely understudied, especially in the context of breast cancer. Breast cancer is the most common cause of cancer related deaths in women aged 20-49, with triple negative breast cancer, an aggressive subtype, being associated with a high mortality rate compared to other breast cancers. We have recently found that in murine triple negative breast cancer, tumor cells produce substantial amounts of CGRP even with the depletion of CGRP-releasing sensory neurons. Blocking CGRP signaling halts the growth of the tumor while enhancing anti-tumor immune responses. In this study, *we propose that tumoral CGRP is driving tumor progression and inhibiting the immune system*. We intend to explore the change in CGRP and CGRP receptors' expression within the tumor *in vitro* and during different developmental stages *in vivo*. We will provide a detailed analysis of how CGRP influences the immune system by studying the response of specific immune cells to CGRP treatment *in vitro*. Finally, we will study the consequences of blocking intra-tumoral CGRP signaling, using the CGRP receptor antagonist BIBN4096, on tumor growth and its effect on anti-tumor immune responses and whether we can synergize BIBN4096 with traditional immunotherapies to promote tumor regression. Testing the viability of CGRP inhibition as a novel therapeutic is a critical step in developing new treatments for aggressive breast cancers.

Funding sources:
This work is supported by the National Institute of General Medical Sciences (grant nos. P20GM103447 and P20GM103639)

FUNCTIONAL CONSEQUENCES OF DEFECTIVE SKIN LIPID METABOLISM IN A RAT MODEL OF ERYTHROKERATODERMIA VARIABILIS

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Funding: NIH (R01EY030513), NIH (R21AR076035) and Presbyterian Health Foundation (PHF)

Introduction: Fatty Acid-Elongase-4 (ELOVL4) mediates the biosynthesis of very long-chain fatty acids (VLC-FA) critical for the skin barrier. Several heterozygous ELOVL4 mutations cause Erythrokeratodermia Variabilis (EKV), a severe dry, itchy skin condition. We generated a mutant ELOVL4 knock-in rat model of EKV that recapitulated the human EKV. To understand how defective ELOVL4 function contributes to EKV, we test the hypothesis that altered ELOVL4-mediated VLC-FA biosynthesis contributes to defective lipid barrier maturation that affects skin function.

Methods: We analyzed lipid composition of skin and keratinocytes isolated from EKV and wild-type (WT) rats. We measured skin barrier integrity of the rats using N-hydroxysuccinimide-biotin. To understand how loss of functional ELOVL4 affects keratinocyte maturation, we used CRISPR/Cas9 mediated approach to knockout *ELOVL4* in N-TERT1 keratinocytes and validated ELOVL4 knockout using Western blot. We differentiated keratinocytes into 3D skin models to evaluate VLC-FA supplementation-mediated rescue without a functional ELOVL4.

Results: Our lipidomics analyses revealed depletion of VLC-FAs in keratinocytes isolated from EKV rats compared to WT. Histology and immunohistochemistry showed epidermal hyperkeratosis, and enlarged Sebaceous glands with elevated ELOVL4 expression in EKV rats. We observed biotin leakage into stratum corneum of EKV rats compared to wild-type rats. Our 3D organotypic models mimic human skin and present us with a unique opportunity to determine the effect of loss of ELOVL4 function on skin proliferation and differentiation.

Conclusion: The mutant ELOVL4 is defective in VLC-FA biosynthesis, which contributes to the defective skin barrier in the EKV rat model. Our data suggest a crucial role of ELOVL4 and VLC-FAs in keratinocyte proliferation and maturation. The 3D skin models will enable us to determine how the loss of ELOVL4 and VLC-FAs cause skin barrier defects and factors that contribute to disease severity. This will in turn enable us to explore potential therapeutic targets for the treatment of mutant-ELOVL4 causing skin disorders.

A NOVEL PHARMACOLOGICAL INHIBITOR OF MAP4K4 CONFERS HEPATOPROTECTION AGAINST METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

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Mitogen-activated protein kinase kinase kinase kinase-4 (MAP4K4) is a serine/threonine protein kinase belonging to a broad family of protein kinases related to yeast STE20p (sterile 20 protein) kinase. MAP4K4 is an upstream regulator of mitogen-activated protein kinases (MAPK) involved in multiple physiological processes, including cell migration, proliferation, and adhesion. MAP4K4 activity is implicated in various pathologies, including systemic inflammation, type-2 diabetes, and cardiovascular diseases. However, its role in metabolic dysfunction-associated steatotic liver disease (MASLD) is not fully unraveled. Recent studies suggest a correlation between MAP4K4 expression and MASLD progression. Moreover, inhibition of MAP4K4 in human primary hepatocytes using RNA interference protected against lipotoxicity. These observations provided an impetus for the synthesis of Glucose Pyrrolo Pyridinone (GPPD) – a novel pharmacological inhibitor of MAP4K4 as potential therapeutics against MASLD. Prophylactic effects of GPPD on oleic acid-induced *in-vitro* and a high-fat, high-fructose, high-cholesterol diet (MASH diet) -fed *in vivo* metabolic dysfunction-associated steatohepatitis (MASH) models were investigated. GPPD protected against hallmarks of steatosis *in vitro*. *In vivo*, administration of GPPD reduced body weight, liver weight, and subcutaneous and visceral fat accumulation in MASH-diet-fed mice. GPPD treatment attenuated hepatic steatosis, inflammation, ballooning, and fibrosis. Gene expression analyses showed that GPPD reduced the expression of CD36, DGAT1, F4/80, COL1A, and MCP-1. Preliminary studies into the molecular mechanisms underlying the effects of GPPD showed obliteration of hepatic JNK pathway, a downstream target of MAP4K4 signaling potentially involved in hepatoprotection. In conclusion, pharmacological inhibition of the MAP4K4 pathway by GPPD offers protection against MASH pathology. Moreover, this study lays a groundwork for future research, which will investigate role of hepatic MAP4K4 in MASH and characterize comprehensive mechanism of GPPD-mediated hepatoprotection, which will be instrumental in developing GPPD as a novel future small-molecule therapeutics targeting fatty liver and other metabolic diseases.

IGF1R DEFICIENCY IN VASCULAR SMOOTH MUSCLE CELLS IMPAIRS VASCULAR AND COGNITIVE FUNCTION

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Cerebrovascular pathologies are key contributors to cognitive decline in the elderly, leading to vascular cognitive impairment and dementia (VCID). Levels of circulating insulin-like growth factor 1 (IGF-1), a vasoprotective hormone, decrease during aging. VCID is associated with numerous vascular pathologies including increased blood brain barrier (BBB) permeability, impaired myogenic autoregulation and neurovascular coupling, increased vascular fragility, cerebral microhermorrhages (CMH), microvascular rarefaction, etc. Vascular smooth muscle cells (VSMCs) are important for maintaining cerebral blood flow, BBB integrity, and overall vascular integrity for healthy brain function. Increased VSMC fragility has been implicated as a contributing factor to cerebral microhemorrhages and subsequent vascular pathologies seen in Alzheimer's disease and other VCIDs. **We hypothesize that decreases in IGF-1 signaling impair adoption of protective VSMC phenotypes resulting in VSMC dysfunction and increased vascular fragility, ultimately contributing to cognitive decline**. We used a hypertension-based model of cerebrovascular dysfunction in mice with VSMC-specific IGF-1 receptor (*Igf1r*) deficiency and evaluated the development of cerebrovascular pathologies and cognitive dysfunction. VSMC-specific *Igf1r* deficiency led to impaired cerebral myogenic autoregulation, independent of blood pressure changes, decreased neurovascular coupling, impaired spatial learning and memory, impaired motor learning and increased BBB permeability. These studies suggest that VSMCs are key targets for IGF-1 in the context of cerebrovascular health, playing a role in vessel stability alongside other cells in the neurovascular unit, and that VSMC dysfunction in aging likely contributes to VCID.

This work was supported by grants from the National Institute of Health (R01AG070915, R03AG070479, K01AG073614, P30CA225520, T32AG052363) the Cellular and Molecular GeroScience CoBRE (1P20GM125528), and the Presbyterian Health Foundation

B CELLS ARE REGULATORS OF MENOPAUSE-ASSOCIATED WEIGHT GAIN, GLUCOSE METABOLISM AND ADIPOSE TISSUE DYSFUNCTION MAINLY THROUGH E2/ERA SIGNALING

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Loss of estrogen during menopause leads to increased adiposity and altered glucose metabolism, mechanistically linked to obesity and diabetes onset. Immune cell infiltration is a hallmark of adipose tissue (AT) metabolic dysfunction. However, the effects of loss of immune cell estrogen signaling in menopause-associated weight gain and glucose metabolism is unexplored. We tested the hypothesis that loss of E2/ERα signaling in B cells contributes to menopause-associated weight gain and metabolic dysfunction.

To model menopausal weight gain we ovariectomized (OVX) wild-type (WT, n=9), mice lacking B cells (B-null, n=9) and a constitutive B cell ERα knockout mice (BERαKO, n=9) and BERαWT (n=9) mice. 17β-estradiol (+E2) replacement groups per genotype served as controls. We assessed body composition, glucose tolerance test, inflammatory markers, AT expansion, liver lipid deposition, and pancreatic histopathology.

Under high-fat/high-sucrose diet, B null mice gain less weight when compared to WT mice following OVX (-37%) and remain sensitive to beneficial effects of E2 replacement: normal GTT, improved fasting glucose (-23%), increased lean mass (+22%) and decreased fat mass (-33%). E2 replacement prevented weight gain (-42%,) increased lean mass (+22%) and decreased fat mass (-26%) in BERαWT mice. E2 effects were abrogated in BERαKO mice with equivalent weight gain as BERαWT OVX-only mice. E2 replacement in BERαKO also had no beneficial effect on body composition. AT analysis from BERαKO showed hyperplasia (+40%), hypertrophy (+56% adipocyte diameter), and inflammation compared to BERαWT+E2.

B cell-deficient female mice showed protection for weight gain and improved glucose metabolism after OVX. B cell ERα ablation modifies the E2 effect on whole body metabolism. Our findings suggest that post-OVX weight gain, changes in body composition, AT dysfunction, and glucose metabolism are partially dependent on B cells estrogen signaling. This reveals a potential immune regulation of metabolism during menopause and the subsequent risk of developing age-related diseases.

This work is supported in part by an award from Harold Hamm Diabetes Center at the University of Oklahoma and the Oklahoma Center for Advancement of Science & Technology.

KK62 DISPLAYS POTENT ANTITUMOR ACTIVITY AGAINST CASTRATE-RESISTANT PROSTATE CANCER THROUGH ACTIVATION OF AUTOPHAGY

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Targeting androgen receptor (AR) by pharmacologic intervention is one of the practical approaches for the treatment of castration-resistant prostate cancer (CRPC). Hence, this study aimed to develop novel molecules that employ multiple mechanisms to inhibit AR expression and curtail the growth of CRPC. The target antiandrogen-equipped histone deacetylase inhibitors were synthesized, adapting the convergent chemistry we used to synthesize the first-generation compounds. The final compounds were characterized using 1H-NMR, 13C-NMR, and high-resolution mass spectrometry. We synthesized and analyzed several compounds, in which KK62 emerged as the lead compound. KK62 significantly inhibits a panel of CRPC cell lines in nanomolar concentrations without causing toxicity to healthy prostate epithelial cells. The molecular analysis suggested that inhibition of AR and AR-splice variants was evident, followed by downregulation of PSA expression in AR-positive CRPC cell lines. Further analysis confirmed that KK62 overcomes dihydrotestosterone (DHT) induced AR signaling and enzalutamide-resistant CRPC cells by downregulating AR and AR-splice variants in CRPC cells. Subsequent analysis confirmed that KK62 induces autophagy signaling by upregulating autophagosome (LC3B) and lysosome (LAMP1) markers expression and facilitating the autophagosome and lysosome fusion, which resulted in the induction of apoptosis in all AR-positive CRPC cell lines. The pro-apoptotic markers, such as BAX and cleaved caspase, were upregulated, whereas the downregulation of pro-survival markers was evident in KK62-treated CRPC cells. Our ongoing castrated and non-castrated xenotransplanted CRPC tumors and Patient-derived xenograft in vivo studies would validate our in vitro findings and confirm that KK62 is a potent compound that may improve therapeutic advances in treating CRPC.

Acknowledgement of Funding: We acknowledge support from the NIH/NCI-RO1CA266013 to AKO and CD.

KNOCKING DOWN OF XKR8 ENHANCES CHEMOTHERAPY EFFICACY THROUGH MODULATING TUMOR IMMUNE MICROENVIRONMENT

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Scramblase Xkr8 regulates phosphatidylserine (PS) externalization of cells during apoptosis, which plays an important role in mediating tumor immunosuppression. Our previous study showed that targeting Xkr8 in combination with chemotherapy is a novel approach to increase antitumor immune response. Here, we further evaluated this strategy using a clinically relevant orthotopic model and elucidated how targeting Xkr8 modulates tumor immune microenvironment through in depth single cell RNAseq analysis. We first demonstrated that knocking down Xkr8 enhanced the therapeutic effect of chemo prodrug FuOXP in two s.c. pancreatic cancer models (Panc02 and KPC) that responded differently with respect to the FuOXP-mediated Xkr8 induction. Co-delivery of Xkr8 small interference RNA (siRNA) and FuOXP further showed promising therapeutic efficacy in Panc02 orthotopic model. The combination of siXkr8 and FuOXP increased macrophage signaling and proliferation of NK cells. Single cell cluster and trajectory analysis revealed that combined treatment resulted in CD8+ T cells following a differentiation route from stem-like to cytotoxic rather than to exhausted cells. Our study shields new insight into the effect of Xkr8 knockdown on tumor immune microenvironment and further supports the combination of Xkr8 knockdown with chemotherapy as a new strategy to improve pancreatic cancer immunochemotherapy.

This work was supported by the National Institute of Health grants R01CA219399 and R01CA223788.

UNVEILING PRECISION TARGETS: OSBP AND ORP4 IN OVARIAN CANCER THERAPY WITH OSW-1 ANALOG COMPOUNDS

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Ovarian cancer (OC) is a highly deadly gynecologic tumor, with more than 20,000 new cases diagnosed annually. Due to the limited long-term survival of OC patients, it is crucial to develop effective, personalized treatment approaches. Our research has indicated that oxysterol-binding protein (OSBP) and OSBP-related protein 4 (ORP4) could be promising targets for precision cancer treatment in OC. OSBP is a critical factor in lipid transport, serving roles in both cholesterol movement and viral replication. Conversely, ORP4 appears to be a significant player in leukemia and cancer cell proliferation, although the exact mechanisms are not yet clear. We have demonstrated that the natural compound OSW-1, by targeting OSBP and ORP4, exhibits stronger anti-cancer effects against ovarian cancer cell lines and spheroids than conventional chemotherapy drugs like cisplatin and paclitaxel. In this context, our lab has synthesized analogs of OSW-1 with the goal of enhancing the effectiveness of targeted therapies. My primary aim is to comprehensively investigate the impact and underlying mechanisms of these OSW-1 analogs in both 2D and 3D ovarian cancer cell models. Encouragingly, initial findings have shown significant anti-cancer effects in both settings, further highlighting the potential of these analogs in the fight against OC. Ultimately, our overarching objective in this research is to uncover the role of oxysterol-binding proteins in ovarian cancer growth and to advance compounds that target these proteins as a potential new approach for precise OC therapies.

Funding acknowledgements: Gynecological Oncology Pilot Award, NIH NIAID R01 (R01AI154274 (Burgett PI), Oklahoma Center for Advancement of Science and Technology (OCAST) Health Award (HR17-116), Oklahoma Shared Clinical and Translational Resources Pilot Award, Presbyterian Health Foundation Bridge Grant

DELIVERY TECHNOLOGIES FOR CYTOKINE IMMUNOTHERAPY OF NEURO-INFLAMMATORY DISEASES

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Abstract: Our interdisciplinary team develops drug delivery technologies for treatment of inflammatory brain injury, with a focus on brain-infiltrating monocytes, brain-resident macrophages, and microglia. We hypothesize that targeted immunotherapy to brain-resident and brain-infiltrating macrophages will mitigate the neurological consequences of injury or disease-associated inflammatory brain damage in rodents. We will describe two distinct routes of delivery and associated technologies for macrophage immunotherapy in the central nervous system. The first delivery system is a cytokine-stabilizing nanocomposite gel based on photopolymerized blend of natural and synthetic polymers with entrapped biodegradable nanoparticles. We optimized this dosage form for its ability to mimic native brain tissue rheology and sustain the delivery of multiple to the surrounding tissue. Intracerebral gel injections were well tolerated in both healthy and diseased rats, and local cytokine delivery at tested doses did not lead to cytokine accumulation or immunogenicity to either blood or peripheral organs. Further, our preliminary data indicated potential effectiveness of intracerebral cytokine delivery to mitigate neurological consequences of inflammatory brain damage in a rat model of hemorrhagic stroke. Our second technology is a nanogel-cytokine conjugate, which exhibits excellent targeting properties for adherent macrophages, indistinguishable colocalization with whole blood components, and retained cytokine bioactivity. We are presently evaluating the extent to which administration route influences the ability of these cytokine bioconjugates to modulate distinct tissue-resident macrophage subsets (including those in the brain parenchyma) in mice. Taken together, we have developed two promising delivery systems for modulating brain-resident and brain-infiltrating macrophages, with future application in the treatment of not only brain injury but also diverse inflammatory diseases.

Acknowledgement: Funding for this research is gratefully acknowledged from the OUHSC-IBEST Collaborative Research Program (to AB, JRC), American Cancer Society IRG2023-1 (to JB, JRC), Harold Hamm foundation (to JRC), and the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health under award number 1R35GM150970 (to JRC).

PROSTATE CANCER INDUCES COGNITIVE IMPAIRMENT VIA DELIVERING SPECIFIC MICRORNA CARGO LOADED IN SMALLER EXTRACELLULAR VESICLES

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Hormone therapy in prostate cancer patients is associated with high-risk for cognitive impairment but the role of cancer cells in inducing distant neurodegeneration remains unknown. Here, using a transgenic mouse model of prostate cancer (TRAMP mice), we focused on the role of small extracellular vesicles (sEV) released by PCa in mediating this long-distance communication. We observed that TRAMP mice, PCa was accompanied with decreased hippocampal long-term potentiation (LTP), a surrogate for memory, high Aβ1-42 deposition in brain (PiB, PET), and impaired spatial learning. The molecular changes in the brain of TRAMP mice were further confirmed by spatial profiling. The treatment of wild-type C57BL6 mice with sEV from TRAMPc1 cells (sEVTRAMPc1) also showed a significant decrease in LTP suggesting the key role of PCa-secreted in sEV in the induction of neurocognitive deficits. Moreover, sEVTRAMPc1 disrupted blood brain barrier and showed propensity to localize to the brain. Cargo analysis of sEVTRAMPc1 revealed the enrichment of specific miRNAs (miRNA125b-2-3p, miRNA128-3p, miRNA146a-5p and miRNA222-3p) associated with neurodegenerative diseases. Importantly, we observed significantly higher expression of these miRNAs in the hippocampus region of the brain, associated with memory and learning but not in other brain regions as well as other vital organs. Mechanistic studies revealed a strong pro-inflammatory effect of sEVTRAMPc1 in monocytes that was largely reversed in the presence of anti-miRs against miRNA125b-2-3p, miRNA128-3p, miRNA146a-5p and miRNA222-3p. Further, sEVTRAMPc1 treatment induced a pro-inflammatory M1-phenotype in microglia cell lines. Overall, these results have identified a potential mechanism of PCa-induced cognitive impairment.

THE PROTECTIVE ROLE OF 17ALPHAE2 IN HEPATOCELLULAR CARCINOMA (HCC) DRIVEN BY NON-ALCOHOLIC STEATOHEPATITIS (NASH) IN MALE MICE

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Nonalcoholic steatohepatitis (NASH) is an advanced form of nonalcoholic fatty liver disease that affects around 6.5% of adults in the United States. NASH can progress to cirrhosis and hepatocellular carcinoma (HCC). Men and postmenopausal women are at higher risk of developing NASH compared to premenopausal women. Multiple findings suggest that endogenous estrogens play a role in mitigating these diseases. An ongoing clinical trial is evaluating the efficacy of 17-β estradiol (17βE2) as a treatment for postmenopausal women with NASH. Men are excluded from this trial due to concerns related to feminization. We have recently reported that 17α-estradiol (17α-E2), a nonfeminizing diastereomer of 17βE2, can mitigate hepatic steatosis and fibrosis.

This study aims to determine if 17αE2 can attenuate NASH-driven HCC without inducing overt feminization in male mice.

To induce NASH or HCC, mice were treated with low doses of CCL4 combined with western diet for respectively 12- or 24 weeks. We evaluated untreated low-fat diet controls and treatment groups receiving dietary 17αE2 or 17βE2. We divided each treatment group into preventive (long-term estrogen administration) and therapeutic groups (short-term estrogen administration). Throughout the experiment, we measured body mass, body composition, fasting glucose, and fasting insulin. We observed beneficial effects of 17αE2 and 17βE2 on body mass and composition, although the magnitude of the effect was more significant in the 17αE2 preventive group.

At 24 weeks, mice receiving 17αE2 in the preventive fashion also presented significantly less tumor burden than other groups. We also observed a significant reduction in hepatic lipid accumulation by the 24 weeks in the 17αE2 preventive group. We are currently evaluating tumor-suppressor, fibrosis, and immune-modulatory pathways to unravel the mechanisms that underline our findings. In summary, our study demonstrates that 17αE2 might be a promising therapeutic compound for NASH-related diseases, and our studies are ongoing.

Funding: NIH [R01 AG070035].

MOLECULAR MECHANISMS OF DESENSITIZATION AND INTERNALIZATION OF OXYTOCIN RECEPTOR IN NEURONS

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Social deficits are a prominent feature of autism spectrum disorder and many other neuropsychiatric diseases. Since there are currently no drugs available to treat these debilitating symptoms, it is critical to decipher the neuronal mechanisms underlying social behavior and their impairments in mental illnesses. Oxytocin, first discovered as a hormone that strengthens contractions during labor and facilitates lactation, has subsequently been found to have a critical role as a neuromodulator regulating social behavior. Recent work has begun to clarify how oxytocin acts on neuronal circuits to modify inter-neuronal communication and circuit properties. However, there is a large gap in the understanding of the intracellular signaling pathways that are activated by oxytocin acting on its receptor in neurons. In particular, the regulatory mechanisms that control oxytocin receptor (OXTR) signaling in neurons remain unexplored. We have identified robust and rapid-onset desensitization of OXTR response in multiple regions of the mouse brain. Sequential application of OXTR agonists reveals that spiking of neurons in acute brain slices in response to the second application of the agonist is smaller than the first response, indicating OXTR desensitization. Both postsynaptic spiking responses and presynaptic activation undergo similar desensitization. Using novel Bioluminescence Resonance Energy Transfer (BRET) assays applied for the first time in primary neuronal cultures, we define the molecular locus of desensitization. We identify that GRK2, GRK3, and GRK6 are the GRK isoforms that are recruited to the activated OXTR in neurons followed by the recruitment of β-arrestin-1 and -2. Interestingly, recordings in β-arrestin-1 and -2 knockout mice and in CRISPR/Cas9-based β-arrestin double knockout reveal that β-arrestins are redundant for neuronal OXTR desensitization. In contrast, inhibition of GRK2, GRK3 and GRK6 kinase activity leads to suppression of the desensitization of OXTR response and receptor internalization. This work provides insights into the regulatory mechanisms governing an important G protein-coupled receptor in the brain, which may lead to future development of therapeutic agents that alleviate social deficits in neuropsychiatric disorders.

Funding Sources: NIH/NIMH, Whitehall Foundation, Presbyterian Health Foundation.

STUDIES OF DGLA EFFECTS ON PLATELET AND OVARIAN CANCER INTERATIONS

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Increasing evidence implicates the role of platelets in the development and progression of ovarian cancer, a highly lethal disease that can arise from the fallopian tube (FT). Thrombosis is a major cause of mortality in patients with ovarian cancer, suggesting that cancer alters platelet behavior. The objective of this study was to develop a cell culture model of the pathological interactions of human platelets and ovarian cancer cells, using normal FT epithelial cells as a healthy control, and to test the effects of antiplatelet dihomo-gamma-linolenic acid (DGLA) in the model. Both healthy and cancer cells caused platelet aggregation; however, platelets only affected spheroid formation by cancer cells and had no effect on spheroid formation by healthy cells. When naturally formed spheroids of epithelial cells were exposed to platelets in transwell inserts that did not allow direct interactions between the two cell types, platelets caused an increase in the size of the spheroids formed by cancer cells but not healthy cells. When cancer cell spheroids formed using magnetic nanoshuttles technology were placed in direct physical contact with platelets, the platelets caused spheroid condensation. In ovarian cancer cells, DGLA promoted epithelial-to-mesenchymal (EMT) transition at doses as low as 100 μM, inhibited metabolic viability, and induced apoptosis at doses of ≥175 μM. DGLA doses ≤175 μM, used to avoid direct DGLA effects on cancer cells, had no effect on the pathological interactions between platelets and ovarian cancer cells in our models. These results demonstrate that the pathological interactions between platelets and ovarian cancer cells can be modeled in cell culture and that DGLA has no effect on these interactions, suggesting that targeting platelets is a rational approach for reducing cancer aggressiveness and thrombosis risk in ovarian cancer patients; however, DGLA is not an appropriate candidate for this strategy.

Acknowledgements: This work was supported by the US National Cancer Institute grants R01 CA196200 awarded to Dr. Doris Benbrook, and P30CA225520 awarded to the University of Oklahoma Stephenson Cancer Center and used the Stephenson Cancer Center Clinical Trials Office and the Molecular Biology and Cytometry Research Shared Resource.

UNDERSTANDING THE LINK BETWEEN INFLAMMATION, NECROPTOSIS, AND AGING LIVER: IMPLICATIONS FOR NONALCOHOLIC FATTY LIVER DISEASE AND HEPATOCELLULAR CARCINOMA

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Chronic inflammation significantly contributes to both the initiation and advancement of hepatocellular carcinoma (HCC) and plays a pivotal role in the development of non-alcoholic fatty liver disease (NAFLD) linked to obesity—a prominent risk factor for HCC in the United States. HCC exhibits heightened prevalence in the elderly, predisposing them to increased mortality. Despite the well-established connection between inflammation, aging, and HCC, the precise molecular processes governing inflammation and its role in age-related HCC remain unclear. We hypothesized that necroptosis, an inflammatory mode of cell death, plays a contributory role in age-related hepatic inflammation and the development of HCC associated with NAFLD in mice. Our studies in *Sod1*$^{-/-}$ mice, a model of accelerated aging and spontaneous HCC development, show the pharmacological inhibition of necroptosis attenuated necroptosis, inflammation, and fibrosis in the liver. Similarly, genetic (*Ripk3*$^{-/-}$ and *Mlkl*$^{-/-}$ mice) and pharmacological (Necrostatin-1s) blocking of necroptosis resulted in reduced hepatic inflammation (TNFα, IL6, IL1β, CCL2), pro-inflammatory M1 macrophages, senescence markers (p16, p21) and features of NAFLD (fibrosis, steatosis). In a direct investigation of necroptosis in NAFLD-induced HCC, both control (WT) mice and those lacking *Ripk3* or *Mlkl* were given an HCC-inducing diet. Compared to control mice, *Ripk3*$^{-/-}$ and *Mlkl*$^{-/-}$ mice showed decreased hepatic inflammation, pro-inflammatory macrophages, tumor incidence, and expression of oncogenic proteins. Additionally, *in vitro* experiments revealed inhibition of necroptosis, achieved through either necrosulfonamide treatment or siRNA, resulted in reduced cell proliferation and colony formation ability in human liver cancer cells. In conclusion, our findings indicate the critical involvement of necroptosis as an inflammatory mediator in both aging and HCC. This implies that targeting of necroptosis could serve as a potential approach to prevent HCC development in the elderly.

Funding: R01AG059718, R03CA262044, Geroncology pilot grant, VA Merit grant, OCAST Postdoctoral grant (HF21-009)

MATERNALLY SUPPLEMENTED PQQ TARGETS CERAMIDE METABOLISM IN OFFSPRING TO BLUNT DEVELOPMENTAL PROGRAMMING OF NAFLD

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Maternal obesity is a key risk factor for pediatric nonalcoholic fatty liver disease (NAFLD). Using a mouse model of Western-style diet (WD)-induced maternal obesity, we studied effects of supplementing dams with pyrroloquinoline quinone (PQQ; a potent dietary antioxidant) during gestation and lactation on hepatic lipid metabolism and fibrosis in offspring at postnatal day (PND) 14 and at 16 wks after a 4-wk WD challenge. Maternal PQQ (mWDPQQ) altered bioactive sphingolipids in adult offspring compared with those exposed to maternal WD (mWD), and protected offspring from WD-induced weight gain. mWDPQQ increased very long-chain ceramides (VLCer; 219%, P=0.0002), associated with protection from fibrosis, concomitant with decreased expression of genes promoting ceramide degradation (*Asah2,* P=0.0014 and *Acer3,* P=0.02). Expression of *Scd1*, a desaturase regulating triglyceride biosynthesis, was attenuated in mWDPQQ offspring at PND14 (P=0.0009) and at 16 wks (P=0.0012), while expression of *Elovl3*, an enzyme promoting elongation of saturated fatty acids and ceramide production, was increased (P=0.0026). Comparative pathway analysis of RNASeq data showed enrichment of pathways in fatty acid metabolism, hepatic fibrosis, and, unexpectedly, signaling through the aryl hydrocarbon receptor (AHR; a ligand-activated transcription factor regulating immune function and hepatotoxicity). Chromatin IP in mWDPQQ liver showed increased AHR binding to the *Cyp1a1* promoter, its canonical target, compared with mWD, suggesting AHR signaling is activated by mWDPQQ. AHR binding to the *Scd1* promoter, a known AHR target, was increased, as was binding to *Asah2* and *Acer3*, putative new AHR targets regulating long-chain ceramide degradation. These findings suggest that maternal PQQ has both short- and long-term effects on blunting steatosis/fibrosis and promoting VLCer increase through novel AHR targets, protecting offspring from NAFLD.

Acknowledgments: This research was funded by NIDDK R01DK121951 to JEF and KRJ. We thank the Stephenson Cancer Tissue Pathology Core, supported partly by NIGMS P20GM103639 and NCI P30CA225520. We thank Rohan Varshney and Michael Rudolph at OUHSC for help with GC-MS analyses and Karin Zemski Berry and Bryan Bergman of the NORC Lipidomics Core at CU Anschutz for the ceramide analyses.

ALLEVIATION OF TUMOR-INDUCED CACHEXIA BY RET-SELECTIVE INHIBITOR SELPERCATINIB

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Background and Objectives: Cancer-associated cachexia is a devastating syndrome characterized by body weight loss, particularly skeletal muscle atrophy. Currently, there is no effective therapy for cancer-associated cachexia. Glial cell derived neurotrophic factor (GDF15) is known to regulate body weight. Recently, GDF15 was found to activate RET protein tyrosine kinase via binding of its co-receptor, GDNF family receptor α-like(GFRAL). In clinical trials of RET-targeted therapy, a side effect of RET-selective protein kinase inhibitors selpercatinib and pralsetinib was body weight gain. Thus, we hypothesize that a RET-selective kinase inhibitor may be used to treat cancer-associated cachexia. In this study, we investigated whether selpercatinib could alleviate cachexia in a tumor model in animals.

Methods: Human Fibrosarcoma (HT-1080) cells were subcutaneously injected into the right flank of ICRSC-F mice to induce cachexia. Mice were divided into three groups, tumor bearing mice treated with vehicle and selpercatinib (30 mg/kg, qd) by oral gavage, and tumor free mice treated with vehicle. Food intake, grip strength, body weight, and tumor size were measured for each group. Endpoint was determined by 20% reduction from primary body weight. Hindlimb muscles, (tibialis anterior (TA), quadriceps (QA) and gastrocnemius (GA)), subcutaneous fat and brown fat were collected, weighed and snap-frozen in liquid nitrogen. Terminal blood was collected by cardiac puncture, and plasma was extracted to measure GDF-15 level in circulation.

Results: HT1080 cells caused significant body weight loss and reduced food intake in both groups compared to the tumor free mice. Human GDF15 based ELISA showed an increased GDF-15 level in circulation of both tumor-bearing mice groups. Both fat loss and muscle loss were observed in the cachectic phenotypes while selpercatinib-treated group showed a significant rescue of fat and muscle loss, improved grip strength and food intake.

Conclusions: The rapidly growing HT1080 tumors caused cachexia in the host mice, characterized by body weight loss, muscle loss, and fat loss, and loss of food consumption. Plasma GDF15 was elevated in mice bearing HT1080 tumors. Selpercatinib at 30 mg/kg/day significantly improved the food consumption, body temperature, grip strength, skeletal muscle weight, and white fat weight of the tumor bearing cachectic animals. These results show that selpercatinib partially alleviated cachexia at the testing dose.

Funding: The study was supported in part by NIH grant R01CA273168 and by a PHF grant.

INHIBITION OF IRHOM BY CD44-TARGETING NANOCARRIER FOR IMPROVED CANCER IMMUNOCHEMOTHERAPY

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The multifaceted chemo-immune resistance is the principal barrier to achieving cure in cancer patients. Identifying a target that is critically involved in chemo-immune-resistance represents an attractive strategy to improve cancer treatment. IRhom1(RHBDF1) plays a role in cancer cell proliferation and its expression is negatively correlated with immune cell infiltration. Here we showed that iRhom1 decreased chemotherapy sensitivity by regulating the MAPK14-pHSP27 axis. In addition, iRhom1 inhibited the cytotoxic T-cell response by reducing the stability of ERAP1 protein and the ERAP1-mediated antigen processing and presentation. To facilitate the therapeutic translation of these novel findings, we developed a biodegradable nanocarrier that was effective in codelivery of iRhom pre-siRNA (pre-siiRhom) and chemotherapeutic drugs. Importantly, this nanocarrier was highly effective in tumor targeting and penetration through both EPR and CD44-mediated transcytosis in tumor endothelial cells as well as tumor cells. Inhibition of iRhom1 further facilitated tumor targeting and uptake through inhibition of CD44 cleavage. Co-delivery of pre-siiRhom and a chemotherapy agent (DOX or CPT-SAHA) led to significantly enhanced antitumor efficacy and activated tumor immune microenvironment in multiple cancer models. Targeting iRhom1 together with chemotherapy represents a novel strategy to overcome chemo-immune resistance in cancer treatment.

Acknowledgement of Funding:

This work was supported by the fund from National Institute of Health grants R01CA219399, R01CA223788, RO1CA278608, RO1CA270623 (to SL), RO1CA239716 (to BL & SL), and The David and Betty Brenneman Scholar Fund (to SL).

EFFEROCYTOSIS OF CANCER CELLS PERFORMED BY HUMAN MONOCYTE-DERIVED MACROPHAGES IS DIMINISHED UNDER HYPOXIA

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One of the characteristics of solid tumors is the presence of areas experiencing severe hypoxia that are highly necrotic. Macrophages tend to accumulate in hypoxic regions within the tumor microenvironment and exhibit their various functions. However, it remains unclear how lower oxygen levels affect macrophages' ability to perform efferocytosis. This process involves the uptake and lysosomal degradation of apoptotic cells, leading to an anti-inflammatory response that could potentially result in a pro-tumorigenic effect. Currently, there are no published data on efferocytosis that would simultaneously take into account the following three components: human macrophages, cancer cells, and various oxygen levels. To address this gap, we performed *in vitro* studies on human monocyte-derived macrophages (hMDMs), which were initially incubated in either normoxia (21% O_2) or hypoxia (0.5% O_2). Three different cancer cell lines (DU145, A375, and A549) were killed by pellet culture and stained with two dyes: pH-sensitive pHrodo Red and pH-insensitive CellTrace Violet. pHrodo Red becomes increasingly fluorescent in an acidic microenvironment, constituting a suitable indicator of engulfed cells localized in phagolysosomes. hMDMs were co-incubated with cancer cells and subsequently analyzed with confocal fluorescence microscopy and flow cytometry. The use of two fluorescent dyes allowed us to distinguish two populations of macrophages that were able to engulf cancer cells. The first population (hMDMs CellTrace+pHrodo+) directed the phagocyted cells to the lysosomes, whereas the second (hMDMs CellTrace+pHrodo-) did not perform phagosome acidification. Moreover, for hypoxia, the number of CellTrace+pHrodo+ macrophages and the mean fluorescence of pHrodo Red were significantly lower when compared to normoxia. These findings were consistent across all examined tumor cell lines. Hence, our data indicate that cancer cell efferocytosis by human monocyte-derived macrophages appears to be diminished under hypoxic conditions. Further studies are needed to assess its consequences on cytokine release and the mechanism of this phenomenon.

Acknowledgment of Funding: This work has been supported by Statutory Activity from the Ministry of Education and Science (Warsaw, Poland).

FGF1 REGULATES GLYCOLYSIS THROUGH ETV4 IN OBESITY-ASSOCIATED BREAST CANCER CELLS

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Obesity is associated with resistance to breast cancer endocrine therapies and excess patient mortality, particularly for estrogen receptor-positive (ER+) tumors that represent 70% of all cases. Adult weight gain in women with obesity, characterized by adipose tissue expansion, is an independent prognostic factor for breast cancer. In a preclinical model, we found that weight gain promoted ER+ tumor growth after endocrine therapy through adipose-derived FGF1. To determine the underlying mechanisms, we used tamoxifen-resistant MCF7 cells (TAMR) treated with FGF1 *in vitro*, combined with gene expression profiling and metabolic analysis. ETS variant 4 (ETV4), which regulates ER activity and breast cancer cell glycolysis, was the top gene induced by FGF1 in multiple ER+ lines, including TAMR cells. ETV4 was also upregulated in human PDX tumors grown in obese versus lean mice. In invasive human breast cancer specimens, high versus low ETV4 expression predicted a shorter recurrence-free survival regardless of tumor subtype. In TAMR cells, FGF1 increased glycolysis but not mitochondrial respiration in the presence of glucose and glutamine, accompanied by elevated glycolytic gene expression and cell proliferation.

We hypothesized that ETV4 induction by FGF1 mediates altered ER activity and glycolytic metabolic reprogramming in obesity-associated breast cancer cells. ETV4-knockout TAMR cells failed to induce glycolytic genes and activity after FGF1 treatment compared to wild-type cells, and this associated with lower cell proliferation. Additionally, ETV4 loss led to a decrease in glucose substrate oxidation in the endocrine-resistant cells. Taken together, our data suggest that FGF1 supports breast cancer endocrine therapy resistance in the context of obesity through ETV4 induction and metabolic reprogramming. The ability to preferentially use a variety of metabolic substrates may provide an advantage to cancer cells growing in a nutrient-rich environment, and ETV4 may serve as a biomarker for patients at high risk for progression.

Funding This work was supported by NIH R01CA241156

PROGNOSTIC SIGNIFICANCE OF THE ACQUIRED LOSS OF RETINAL DEGENERATION PROTEIN 3 (RD3) IN CANCER STEM CELLS IN ENDOMETRIAL CANCER

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Endometrial cancer (EC) is the most common gynecological cancer in women with about 20% of patients developing a locoregional recurrence. The prognosis for recurrent tumors is weak and the overall survival rate is about 15%. This is attributed to high clonal heterogenicity within EC, specifically the selection and enrichment of cancer stem cells (CSC). Although the precise mechanisms involved in cancer cells plasticity, conferring stem-like properties are not completely understood. Our studies in other tumor systems indicated RD3 plays a pivotal role in regulating such plasticity. Our recent research in a cohort of (n=232) EC patients indicated that RD3 could serve as a novel prognostic and predictive biomarker. Furthermore, we have sequentially unveiled that RD3 is constitutively expressed across all human adult and fetal tissues beyond the retina; tumor cells acquire denovo RD3-loss with therapy pressure and RD3-loss dictates tumor evolution. Here we investigated whether acquired loss of RD3 in CSCs could serve as a prognostic marker for disease evolution and a predictive marker for patient survival. The spatiotemporal modification in RD3 transcription specifically in EC-CSCs and adjacent tumor cells was examined in a cohort of 62 patients using RNAScope, a cutting-edge ISH technology. EC-CSCs were precisely annotated with the expression of CSC markers CD44 and CD133 with automated multiplex immunofluorescence. For equitable quantification ISH and IF were performed in our custom archived TMA. RD3 transcription in EC-CSCs were quantified using Halo analysis ISH v 3.0.4 (by Indica Labs). The results revealed a significant loss of RD3 in EC-CSCs when compared to that of tumor cells, indicating the crucial role of RD3 in regulating EC progression through CSC. Compared to the clinically favorable disease, we observed a profound RD3-loss in the CSCs in the invasive stages indicating that RD3-loss in EC-CSCs could correspond and/or dictate EC evolution with metastasis. Furthermore, the loss of RD3 in the EC-CSCs was significant in patients presented with progressive disease defying current clinical therapy recognizing its relevance in acquired therapy resistance. Taken together, the outcomes of this study uniquely define that the selective RD3-loss in EC-CSCs could serve as a prognostic and predictive indicator for EC progression, therapy resistance, and tumor evolution.

Funding: This work was partially or in full, funded by Department of Defense CA-210339; OCAST-HR19-04; NIH-P20GM103639 and NIH-NCI-Cancer center support Grant

THE ROLE OF SENESCENCE AND INFLAMMATION IN MATERNAL OBESITY

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The worldwide prevalence of obesity has dramatically increased over the past two decades resulting in a rise in maternal obesity (MO). It is well established that a mother's poor nutrition both before and during pregnancy can have a negative impact on the health of her offspring. Therefore, it is important to understand the potential life-long effects of MO on the offspring as well as to develop interventions that can protect the offspring born to obese mothers. As MO studies are difficult to conduct in humans long-term, animals, primarily mice, have been indispensable in elucidating the potential causative mechanisms underlying the effects of MO on the progeny. Studies from mice have also shown that offspring born to obese dams show a variety of negative effects including obesity, inflammation, and diabetes. These changes not only persist into adulthood (i.e., 3 to 6 months of age), but tend to become more pronounced with maturation in a sex-specific manner. *However, the long-term consequences and underlying mechanisms of MO on lifespan and diseases of aging are unknown*. Preliminary data from our lab show that offspring born to obese dams demonstrate accelerated deterioration in age-related health measures by 18-months of age. Additionally, our data shows increased senescence, inflammatory macrophages, and inflammation in the liver and bone marrow MNCs obtained from the offspring of MO mice, implicating cellular senescence and inflammation, hallmarks of aging, as potential mechanisms behind the deleterious long-term effects of MO in the offspring. Whether inflammation from cellular senescence is responsible for decline in heath measures and the aging phenotype in MO is unclear. Our study focuses on directly testing the role of senescence in MO related deleterious effects, paving the way for new therapeutic approaches to treat MO related disease pathologies.

The research was supported by the following grants: KO1AG 056655-01A1 (NIH), OCASCAR, American Federation of Aging Research 17132, PHF-Harold Hamm Diabetes Center.

NON-NECROPTOTIC ROLES OF MLKL IN DIET-INDUCED OBESITY, LIVER PATHOLOGY, AND INSULIN SENSITIVITY

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Metabolic disorders such as obesity and type 2 diabetes are major risk factors for metabolic dysfunction-associated fatty liver disease (MAFLD) that impacts 20-30% of the US population. Nearly 25% of individuals with MAFLD develop metabolic dysfunction-associated steatohepatitis (MASH), a condition linked to considerable morbidity and mortality. Chronic inflammation has been identified as a key player in MAFLD and its progression to liver cirrhosis and liver cancer. Necroptosis, an inflammatory cell death pathway, is elevated in MAFLD patients and mouse models, yet the role of necroptosis in MAFLD is unclear due to diverse mouse models and inhibition strategies. In our study, we inhibited necroptosis by targeting mixed lineage kinase domain like pseudokinase (MLKL), the terminal effector of necroptosis, in a high-fat, high-fructose, high-cholesterol (HFHFrHC) mouse model of MAFLD. Despite HFHFrHC diet upregulating MLKL (2.5-fold), WT mice livers showed no increase in necroptosis markers or associated proinflammatory cytokines. Surprisingly, *Mlkl*$^{-/-}$ mice experienced exacerbated liver inflammation without protection from diet-induced liver damage, steatosis, or fibrosis. In contrast, *Mlkl*$^{+/-}$ mice showed significant reduction in these parameters that was associated with elevated Pparα and Pparγ levels. Both *Mlkl*$^{-/-}$ and *Mlkl*$^{+/-}$ mice on HFHFrHC diet resisted diet-induced obesity, attributed to increased beiging, enhanced oxygen consumption and energy expenditure due to adipose tissue, and exhibited improved insulin sensitivity. These findings highlight the tissue specific, non-necroptotic effects of MLKL on the liver and adipose tissue, and suggest a dose-dependent effect of MLKL on liver pathology.

Funding: NIH/NIA grant R01AG059718, NIH/NCI grant R03 CA262044, Geroncology pilot grant

CINNABARINIC ACID PROTECTS AGAINST METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE VIA ARYL HYDROCARBON RECEPTOR- DEPENDENT ACTIVATION OF NQO1 SIGNALING

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Cinnabarinic acid (CA), a tryptophan catabolite and a bona fide Aryl hydrocarbon Receptor (AhR) agonist has demonstrated protective effects against metabolic dysfunction-associated steatotic liver disease (MASLD). However, the significance of AhR in CA-mediated protection against MASLD is largely unknown. This study aims to elucidate the role of AhR signaling in CA-induced hepatoprotection and identify the downstream signaling pathways mitigating MASLD. In this study, AhR floxed (control), and hepatocyte-specific AhR knock-out (AhR-hKO) mice were subjected to control and high-fat, high-fructose, high-cholesterol diet for 20 weeks to induce metabolic dysfunction associated steatohepatitis (MASH). A prophylactic CA treatment via intraperitoneal injections was performed. CA administration reduced body weight gain and adiposity in AhR-floxed mice but not in AhR-hKO mice subjected to obesogenic diet. Moreover, CA mediated protection against steatosis, inflammation, and fibrosis in MASH diet-fed mice was dependent on hepatic AhR. CA regimen attenuated hepatic lipid uptake and fatty acid synthesis by downregulating expression of genes involved in fatty acid uptake, and de novo lipogenesis. RNA-sequencing and subsequent pathway enrichment analysis performed on the differentially expressed genes identified NRF2/NQO1 mediated oxidative stress response signaling as one of the critical pathway involved in CA-mediated protection. Chromatin immunoprecipitation analysis confirmed interaction of AhR to xenobiotic response element (XRE) present within the promoter region of NQO1 in response to CA treatment. Furthermore, knocking NQO1 in primary hepatocytes failed to provide CA-mediated protection against steatosis in an in vitro MASLD model. In conclusion, this study confirmed the significant role of hepatic AhR in CA-mediated protection against MASH. Moreover, this study identified that the hepatoprotective effects of CA are absolutely dependent on AhR-mediated NQO1 signaling. The characterization of AhR-NQO1 pathway will be critical to highlight CA as a potential pre-clinical therapeutic against MASLD. This work is supported by NIH R01 DK121951 to JEF, and R01 DK122028 to ADJ.

DNA DAMAGE WITH CANCER AND AGING ALTER DNA METHYLATION READOUTS AND "EPIGENETIC AGE"

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DNA methylation data has been used to make "epigenetic clocks" which attempt to measure chronological and biological aging. These models rely on data derived from bisulfite-based measurements, which exploit a semi-selective deamination and a genomic reference to determine methylation states. Here, we demonstrate how another hallmark of cancer and aging, genomic instability, influences methylation measurements in both bisulfite sequencing and methylation arrays. In *in* vitro transformed cells, we demonstrate that somatic mutations detected by whole genome shotgun sequencing alter the detected methylation levels. Next, using DNA samples taken from aging mouse hippocampi, we assayed DNA methylation using the Illumina Mouse Methylation Microarray with bisulfite-converted and unconverted DNA. We found that non-methylation factors lead to "pseudomethylation" signals that are both confounding of epigenetic clocks and uniquely age predictive. Quantifying these covariates in studies of cancer and aging will be critical to understanding which physiological changes are driven by *bona fide* epigenetic alterations from those arising from other common genomic damage events.

Acknowledgements: This work was funded by NIH grants #P30AG050911 (JDW, WMF), #P30GM149376 (JDW), and #R01-CA230641 (MMH). This project was also supported by a Longevity Impetus Grant to JDW and WMF.

IDENTIFYING HOW ENDOTHELIAL PROTEASE-ACTIVATED RECEPTORS CONTROL INSULIN SIGNALING: IMPLICATIONS FOR DIABETES

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Thrombin, a circulating serine protease with increased activity in diabetics, signals through protease-activated receptors 1 and 4 (PAR1/4). To determine endothelial cell (EC)-specific roles of PARs in diabetes, we generated *Par1*$^{fl/fl}$;*Par4*$^{fl/fl}$;*Cdh5(PAC)-Cre*^{ERT2} (*Par1/4*^{ECko}) mice and induced diabetes using streptozotocin.

Diabetic *Par1/4*^{ECko} mice had reduced hyperglycemia, increased body mass, and no significant difference in insulin levels from diabetic littermate controls. Insulin/glucose tolerance testing revealed that *Par1/4*^{ECko} mice had increased insulin sensitivity; however, *Par1*^{ECko} and *Par4*^{ECko} mice did not phenocopy *Par1/4*^{ECko} mutants.

Cultured PAR1/4-depleted ECs showed increased basal insulin receptor (IR/*INSR*) activity even without insulin treatment. They also had increased expression of the IR Type A (*INSR*-A) spliceform, which is reported to have high insulin-independent activity. Treatment of cultured ECs with a PAR1 ligand increased expression of the insulin-dependent IR Type B (*INSR*-B) spliceform. These data indicate that endothelial PAR1/4 can modulate IR splicing, potentially by regulating the *INSR* splicing enzymes CUGBP1 and MBNL1, which are present in ECs. Importantly, we found that cultured PAR1/4-depleted ECs grown in a monolayer on a transwell displayed an increased capacity for insulin transcytosis across the transwell than did control cells. Therefore, we hypothesize that altered splicing toward the *INSR*-A spliceform facilitates insulin transcytosis across PAR1/4-depleted ECs.

Since we found that ECs in many wildtype mouse organs predominately express IR-B *in vivo*, a switch to endothelial IR-A expression in *Par1/4*^{ECko} mice may increase IR activity and insulin transcytosis out of the bloodstream and into tissues that require it for glucose uptake. Altogether, we propose that loss of endothelial PAR1/4 enhances IR activity via splicing and elevates whole-body insulin sensitivity by increasing insulin transport to parenchymal tissues.

Support or Funding Information: This work was supported by a grant from the National Institutes of Health (R35HL144605) an American Heart Association Predoctoral Fellowship (23PRE1414240) and an OMRF Predoctoral Fellowship.

TIME-RESTRICTED FEEDING INDUCES BEIGING AND REJUVENATES ADIPOSE TISSUE WITH BENEFICIAL EFFECTS ON CEREBRAL FUNCTION IN AGED MICE

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Adipose tissue, traditionally viewed as purely an energy reserve, has recently been unveiled as a critical endocrine organ. Through the secretion of adipokines, adipose tissue plays a role in inter-organ communication, most notably with the brain to maintain metabolic homeostasis and cognitive function. Aberrant adipokine signaling, often exacerbated with aging, has emerged as a characteristic of dysfunctional adipose tissue. This dysregulation can lead to inflammatory conditions, potentially disrupting neural homeostasis and heightening the vulnerability of older individuals to cognitive impairments. This study investigated the capacity of time-restricted feeding (TRF) to promote beiging (induction of brown adipocytes positive for uncoupling protein 1(UCP1) within white adipose tissue depots) in aged mice, exploring its potential in modulating adipokine profiles, attenuating inflammation, and mitigating age-associated cognitive decline. To test this hypothesis, we collected adipose tissue samples from 24-month-old mice that underwent 6 months of TRF and compared their profiles to young and age-matched controls on an unrestricted (ad-lib) diet. Immunohistochemical analyses of brown adipose tissue (BAT), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT) revealed a reduction in pro-inflammatory markers CD80 and F4/80^{hi} across all adipose tissues. A shift towards an anti-inflammatory state was indicated by an increase in CD163 levels in SAT and VAT. Additionally, the increased expression of UCP1 pointed towards enhanced thermogenic capacity, suggesting a potential metabolic advantage. This was reinforced by an increase in electron transport chain activity in all adipose tissues. These findings have powerful implications given the links between systemic inflammation, disrupted adipokine signaling, and neurodegenerative conditions. Serum studies and transcriptomics are currently being used to further understand the influence TRF has on adipose tissue and how these changes affect brain health in aged mice. Such insights pave the way for future research exploring dietary strategies to combat age-related cognitive decline.

Funding: Stephenson Cancer Center, National Institute on Aging R03 AG070479, American Heart Association

UNRAVELING THE ROLE OF NEURON-SPECIFIC ERA IN 17A-ESTRADIOL-MEDIATED BENEFITS ON SYSTEMIC METABOLISM IN MALE MICE

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Male and female mammals often age at disparate rates. This promotes divergent incidences of chronic diseases between the sexes. Unraveling the mechanisms underlying sexually divergent aging and chronic disease burden could aid in the development of sex-specific therapies for treating disease. 17α-estradiol (17α-E2), which elicits benefits in male but not female mice, is a naturally occurring diastereomer of 17β-estradiol (17β-E2) that is generally nonfeminizing. Our previous work has determined that 17α-E2 administration decreases food intake, reduces adiposity, and dramatically improves metabolic homeostasis in male mice. We recently reported that the global deletion of ERα abolishes the beneficial metabolic effects of 17α-E2 in male mice. We also showed that intracerebroventricular delivery of 17α-E2 into the brain of male rats significantly improved hepatic insulin sensitivity, thereby suggesting that a primary site of 17α-E2 action is the hypothalamus due to its role in modulating peripheral metabolism. Therefore, we hypothesized that ERα-expressing neurons in the hypothalamus mediate the majority of beneficial metabolic effects of 17α-E2 in male mice. To test this, we generated mice lacking ERα receptors in hypothalamic neurons and evaluated the metabolic effects of 17α-E2 treatment. All mice were high-fat fed for 9 months prior to study initiation. Metabolic parameters were evaluated at baseline and throughout the 14-week intervention. We found that 17α-E2 treatment decreased food intake, body mass, and fat mass while improving glucose tolerance, insulin sensitivity, and hepatic steatosis in wild-type males. Conversely, these benefits were absent in male hypothalamic ERαKO mice, indicating that 17α-E2 improves systemic metabolism through the hypothalamus. In addition to suggesting hypothalamic ERα may be a ‘druggable’ target in males, our studies also provide critical insights into how male and female mammals age in divergent fashions. Future studies are needed to determine specific hypothalamic neuronal populations that mediate the beneficial effect of 17α-E2 in male mice.

This work was supported by the NIH [R00 AG051661; R01 AG070035].

EXPLORING THE ROLE OF THE 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. The lack of relevant *in vitro* models hinders a mechanistic understanding of obesity's impact on early disease stages when cancer cells invade the local environment. In a retrospective study on human breast specimens, we analyzed gene expression in DCIS and IDC from women with varying BMI. IDC from women with low BMI resembled DCIS from women with high BMI, suggesting tumor-intrinsic effects of obesity on cancer stage. Gene expression profiles highlighted extracellular matrix (ECM) remodeling and epithelial-to-mesenchymal transition pathways in obesity associated DCIS compared to other specimens. We hypothesize that tumor extrinsic mechanisms, particularly ECM alterations, promote DCIS progression in obesity. We developed a novel 3D in vitro model by isolating adipose ECM from lean and obese environments. Human breast cancer cells were cultured in this ECM, and spheroid size, growth rates and number of spheroids were analyzed. We performed untargeted mass spectrometry to define the matrix proteome and pathway analysis of enriched networks in lean and obese conditions. Immunoblot assessed cellular changes in cancer associated signaling molecules. Preliminary findings showed significantly increased number of spheroids and greater breast cancer sphere size in obese ECM after three days, indicating an obesity-driven ECM shift that fosters proliferation. Cancer cells in obese, but not lean ECM displayed morphological features of invasion. Our study highlights a crucial role for obesity-induced ECM remodeling in DCIS to IDC transition and in the growth of aggressive breast cancer cells, suggesting therapeutic potential for targeting ECM in obese breast cancer patients with obesity.

Supported by R01 CA241156

THE ROLE OF NECROPTOSIS-ASSOCIATED CHRONIC INFLAMMATION IN THE DEVELOPMENT OF LIVER CANCER IN NOVEL KNOCK-IN MOUSE MODELS FED A WESTERN DIET

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Chronic inflammation is a major contributor to aging as well as the etiology of many age-related diseases, including cancer. Necroptosis is a regulated necrosis involving Ripk3 and Mlkl genes and plays a role in inflammation. The goal of this research is to use two novel-knock-in mouse models (*Ripk3-KI* and *Mlkl-KI*) to directly test the role of hepatic necroptosis induced inflammation in mice fed a western diet (WD). Mice that overexpress Ripk3 and Mlkl specifically in hepatocytes are generated when crossed albumin-cre, i.e., *hRipk3-KI* and *hMlkl-KI* mice. We hypothesize that overexpressing Ripk3 or Mlkl in hepatocytes will increase necroptosis and inflammation in the liver, promoting fibrosis, and liver cancer in mice fed WD. To test our hypothesis, we subjected control, *hRipk3-KI*, and *hMlkl-KI* mice to WD feeding for 3-, 6-, and 12-months. Importantly, we found increased necroptosis in hepatic KI mice models fed a WD compared to control mice on the same diet. We also found elevated levels of pro-inflammatory macrophage marker (CD68), inflammatory cytokine (TNFα), increased fibrosis (picrosirius red staining) in hepatic KI mice models fed a WD after 3, 6, and 12 months of feeding. There is no evidence of tumor in the control or hepatic KI mice fed a chow diet. However, 20-30% of control and ~60% hepatic KI mice on the WD showed liver tumors. Further, >5mm sized tumor nodules also noticed in hepatic KI mice. In conclusion, our study demonstrates that necroptosis specifically in liver tissue can lead to the development of fibrosis and liver cancer in mice fed a WD.

Funding: NIHR01AG057424, VA1IK6BX005238.

NOVEL, ENGINEERED FUSOGENIC LIPOSOME-BASED ANTI-OXIDANT DELIVERY SYSTEM IMPROVES THE BLOOD-BRAIN BARRIER INTEGRITY IN AGING

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Vascular dysfunction plays a pivotal role in age-related cognitive decline and neurodegeneration. The aging process often leads to a loss of integrity in the blood-brain barrier (BBB), initiating neuroinflammation and contributing to a decline in cognitive function. In previous research, we demonstrated the potential of resveratrol (RSV), a natural polyphenol, to target cerebromicrovascular endothelial cells (CMVECs), effectively countering age-related oxidative stress and improving vascular function, both in vitro and in vivo. However, the limited bioavailability of resveratrol raised questions about its effectiveness concerning the BBB and neuroinflammation.

Our study aimed to address this challenge by introducing a novel drug delivery system designed to enhance the efficiency of polyphenol delivery. This innovative approach involved the use of fusogenic liposomes (FL) integrated with a bioengineered protein corona (PC) featuring specific apolipoprotein E (ApoE). Our central hypothesis posited that PC formation could be harnessed to directly target CMVECs and enhance liposomal uptake, with the ultimate objective of effectively delivering RSV to the brain's microvessels in aging subjects (ApoE-FL-RSV).

Our investigation encompassed the characterization of ApoE-FL uptake by CMVECs, along with an analysis of its biodistribution and pharmacokinetics in vivo. Remarkably, our findings revealed a significant increase in ApoE-FL-RSV accumulation within CMVECs in vivo, compared to control FL uptake. We employed advanced in vivo multiphoton imaging to longitudinally monitor the effects of ApoE-FL-RSV on the BBB, which demonstrated a significant rejuvenation of the endothelial barrier function in aged mice treated with ApoE-FL-RSV.

In light of these results, we concluded that the fusogenic liposomal delivery system holds promise as a viable pharmacological intervention for addressing age-related vascular cognitive impairment.

Funding: AHA834339, RF1AG072295, R01AG055395, R01AG068295; R01AG070915, K01AG073614, R01NS100782, R01CA255840, and Presbyterian Health Foundation.

CARDIOVASCULAR DISEASE RISK IS INCREASED IN ADOLESCENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Metabolic dysfunction-associated steatotic liver disease (MASLD) in adults increases cardiovascular disease (CVD) risk, but less is known about those risks in adolescents. We hypothesized that MASLD raises CVD risk in adolescents beyond what could be attributed to obesity and low aerobic fitness. We compared 4 groups of boys and girls, ages 11-20y, across a continuum of body size, fitness, and liver health: 1) the healthiest were normal weight with adequate aerobic fitness based on reported thresholds (NW-Fit, n=22), followed by; 2) NW with low fitness (NW-LoFit, n=53); 3) obese with low fitness and without MAFLD (Ob, n=47); and 4) obese with low fitness and biopsy-confirmed MASLD (n=60). MASLD patients had moderate to severe liver steatosis and 87% had ≥ stage 1 liver fibrosis. MASLD and Ob had similar body fat (45±7%), and were higher (p<0.01) than NW-LoFit (29±7%) or NW-Fit (22±7%). VO_2peak was ~10% lower in MASLD (1.76±0.38 l/min adjusted for lean mass) than either Ob (1.95±0.33, p=0.03) or NW-LoFit (1.94±0.25, p=0.03), which were all lower (p<0.01) than NW-Fit (2.48±0.31). MASLD had higher triglycerides (p<0.01) than all other groups, while Ob was intermediate (64±28, 80±38, 107±50, & 195±114 mg/dl for groups 1-4, respectively). Likewise, MASLD had the lowest HDL-C, while Ob was intermediate (57±14, 57±14, 47±13, & 39±9 mg/dl for groups 1-4, respectively). Insulin resistance (iHOMA2-IR) differed among all groups (all p<0.01), increasing from group 1 to 4. Systolic and diastolic blood pressures for MASLD were 6% higher than Ob and 9-12% higher than either of the NW groups (all p<0.01). Carotid-femoral pulsewave velocity did not differ between NW-Fit and NW-LoFit (4.6±0.6 & 4.8±0.6 m/s, respectively) but was higher (p<0.01) in Ob (5.2±0.7 m/s) and higher still in MASLD (5.6±0.7 m/s, p<0.01). Augmentation index, increased from NW-Fit (-11±10%) to NW-LoFit (-2±10%) to Ob (7±11%) to MASLD (13±13%, all p<0.01). All of these CVD risk factors progressed in severity from the NW-Fit to the MASLD groups. Similar to adults, adolescents with MASLD have added CVD risk compared to NW and Ob peers without MASLD.
Funded by NIH R01DK129656, Oklahoma Shared Center for Translational Resources, Harold Hamm Diabetes Center, Presbyterian Health Foundation, and Children's Health Foundation.

EXPLOITING METABOLIC VULNERABILITIES OF OVARIAN CANCER WITH UPREGULATED SUCCINATE DEHYDROGENASE

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Ovarian cancer remains the deadliest of all gynecologic malignancies due to limited therapeutic options and chemoresistance. The response to chemotherapy is affected by the high metabolic flexibility of ovarian cancer cells, which allows the cells to reprogram their metabolism and survive the treatment. Better understanding mechanisms regulating ovarian tumor metabolism could be exploited to develop new improved therapies. Our work demonstrated that the upregulation of mitochondrial enzyme succinate dehydrogenase (SDHA) is particularly prevalent (~20% of patients) in ovarian carcinoma and contributes to high energy tumor metabolism and cell survival. We observed that SDHA overexpressing cancer cells showed improved ability to survive and generate colonies in anchorage-independent conditions, which is an important feature of ovarian tumor cells surviving and spreading in peritoneal fluid (ascites). We also demonstrated that the overexpression of SDHA is associated with a significant increase of OXPHOS and ATP production. Further, we performed a drug screening and identified an anti-metabolic compound shikonin known to disrupt glucose and glutamine metabolism. In *in vitro* studies, shikonin exhibited a profound anti-tumor efficacy and selectivity towards SDHA overexpressing tumor cells superior to that observed with chemotherapy. Importantly, our *in vivo* studies showed that shikonin is highly effective in suppressing SDHA-high tumor growth in patient-derived and mouse ovarian cancer models. In summary, the unique metabolic state of ovarian cancer associated with SDHA amplification could be successfully targetable offering a potential new treatment strategy for ovarian cancer patients.

Acknowledgement of Funding: The NIH Centers of Biomedical Research Excellence (COBRE) Grant (1 P20 GM139763-01) awarded to Dr. Bieniasz.

METABOLIC CROSSROADS OF ESTROGEN RECEPTOR SIGNALING: ADIPOCYTE PROGENITORS AND DIABETES RISK IN BREAST CANCER SURVIVORS

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Breast cancer survivors who have undergone endocrine therapy face a 30% higher risk of developing type 2 diabetes (T2D) compared to individuals with breast cancer who did not undergo endocrine therapy. Furthermore, their risk is 19% higher compared to matched individuals without cancer, suggesting a potential association between endocrine therapy and the risk of type 2 diabetes in breast cancer survivors. Our recent research determined that in female obese mice, endocrine therapy disrupted metabolic homeostasis causing glucose intolerance and ectopic fat deposition associated with adipocyte hypertrophy and depletion of adipocyte progenitor cells. We hypothesize that estrogen receptor (ER) signaling maintains the self-renewal of adipocyte progenitors during weight gain to promote healthy adipose expansion and this is disrupted with endocrine therapy. Single-cell RNA sequencing revealed a loss of the Wnt1-inducible signaling protein 2 (Wisp2), which promotes stromal cell proliferation, in progenitor populations of adipose tissue after endocrine therapy. In mouse APCs, we found that Esr1 and Wisp2 were co-expressed in undifferentiated cells, and estrogen treatment induced Wisp2 expression, which was dependent upon ERα. Flow cytometry analysis showed that progenitors were greater with estrogen and/or Wisp2 treatment and lower after ER antagonism. Endocrine therapies increased markers of fibrosis, inflammation, and senescence in adipocyte progenitors *in vitro* and *in vivo*, and these effects were reversed by Wisp2 treatment. In summary, estrogen receptor signaling regulates the balance between adipocyte hypertrophy and hyperplasia, potentially through Wisp2. The results of this study may help us better understand and prevent the risk for diabetes in breast cancer survivors.

Funding Acknowledgement: R01 CA241156 (EAW); HHDC/SCC Postdoctoral fellowship (NST); CCSG P30 CA225520; Human Environmental Sciences Institute (HESI) THRIVE grant; Komen Foundation

TARGETING THE "ACHILLES HEEL" OF ANDROGEN RECEPTOR ACTIVITY IN CASTRATION-RESISTANT PROSTATE CANCER

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Background

Each year, millions of men are diagnosed with prostate cancer. The unchecked activation of the Androgen Receptor (AR) spurs prostate cancer (CaP) development and progression. Mutations or the presence of AR splice variants can add complexity to tumor ecology, leading to chemoresistance. The study aims to develop novel inhibitors targeting the "Achilles Heel" of AR activity: the N-terminal domain. This would circumvent the limitations of LBD (Ligand Binding Domain) therapies and offer a superior treatment option for patients. Though the AR-NTD is an intrinsically disordered protein with few α-helices and β-sheets, which complicates structure-based drug design, we have developed a unique small molecule inhibitor, ASR600, which specifically targets AR-NTD and promotes AR and AR- variants degradation by ubiquitination at previously unknown sites. Here we report a novel ubiquitination site in the AR-NTD, which can be efficiently targeted to inhibit AR signaling in chemoresistant and Castration-Resistant Prostate Cancer (CRPC). Furthermore, spatiotemporal analysis of PDX prostate tumors underscores the biological and clinical importance of the AR-NTD inhibitor as a CRPC treatment.

ASR-600/603 targets unique ubiquitination sites in AR-NTD

It has been identified four AR ubiquitination sites: K845, K847, and K913 in the C-terminal LBD and one N-terminal ubiquitination site at lysine 311 of AR. Interestingly, ASR600 continued to inhibit AR expression even when we mutated all the ubiquitin sites of AR. This suggests that ASR600's AR ubiquitination targets different NTD sites. Mass spectrometry analysis of ASRs-mediated mono-ubiquitinated N-terminal AR identified K16 as an ASR600 ubiquitin acceptor. Altering these ubiquitination sites rescues AR expression from ASR600-mediated degradation, emphasizing the AR N-terminus as an ASR600 target. To discern the role of the K16 ubiquitination site in AR protein turnover, we evaluated AR protein stability in LNCaP cells that stably expressed ARWT or AR-K16R constructs. Our data indicates the pivotal importance of K16 for AR transcriptional activity. ASR600, when used as a sole agent, exhibited inhibitory responses in PDX of clinically aggressive, AR-expressing tumors. Spatial gene expression analysis (CytAssist Visium) organized cells in the prostate tissue into 12 clusters. The study revealed marked expression differences in AR signature genes between control and ASR600-treated samples. Crucially, AR signaling, and related markers mainly aligned with epithelial markers rather than stromal ones. This suggests a decrease in stromal AR in the control, pointing to prostate cancer progression. In contrast, the ASR600-treated PDX tumor showcased reduced AR signaling within epithelial cells.

Conclusion

Current therapies targeting the LBD of AR have their drawbacks. Over time, prostate cancer patients develop resistance to these treatments. There is a significant focus on targeting AR-NTD, but success has been limited due to its inherent disordered structure. ASR600, derived from the natural metabolite UroA, uniquely targets AR-NTD by ubiquitinating the protein at a new site, K16. Our ongoing in vivo studies, combined with the current research, lay a strong foundation for initiating IND-enabling TOX studies, followed by a phase-I clinical trial for ASR-600 in CRPC patients.

HYPERINSULINEMIA BREAST CANCER RISK AND PROGRESSION: DISTINCT EFFECTS ON NORMAL VERSUS TRANSFORMED CELLS

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Prediabetes (elevated blood glucose) affects more than 33% of adults. Up to 70% of breast cancers are caused by lifestyle factors, including obesity, prediabetes, and diabetes. Hyperinsulinemia precedes prediabetes but is not routinely measured. Insulin promotes the growth of established breast cancers, but its function at early stages is less clear. We found that a high fat/high sucrose diet accelerated mammary tumor formation in transgenic mice, accompanied by elevated insulin and glucose. Insulin receptor loss delayed mammary tumor latency and reduced multiplicity but did not impact tumor growth or metastasis in mouse models of breast cancer. We developed 3D models to study the effects of insulin on three cell lines: non-transformed breast M10A, premalignant M10A-T1 and malignant M10A ductal carcinoma in situ (DCIS). Sphere number, size, circularity, and cell viability were measured. Sphere area directly correlated with circularity in M10A cells (larger spheres, regular shape) but this relationship was inverted in M10A-DCIS cells (larger spheres, irregular). Physiologic insulin levels (0.2nM) stimulated growth of M10A-DCIS spheres. In contrast, hyperinsulinemia (20-200nM) was required to increase M10A and -T1 sphere size. The number of spheres was directly correlated to insulin in M10A cells but inverted in M10A-T1 and M10A-DCIS cells. Cell viability was directly correlated with insulin levels for M10A and M10A-T1 cells, but not M10A-DCIS. Insulin primarily stimulated Akt phosphorylation in M10A cells and Erk phosphorylation in M10A-DCIS cells. Expression of insulin receptors (IR-A, IR-B) and insulin-like growth factor (IGF1R) was influenced by cell line and insulin concentration. Overall, hyperinsulinemia affects features of aggressiveness in breast epithelial cells depending on whether they are normal or malignant, suggesting a distinct role for elevated insulin in breast cancer risk versus progression.

THE ROLE OF SENESCENCE AND ENDOTHELIAL TO MESENCHYMAL TRANSITION IN THE AGING CEREBRAL VASCULATURE

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Age-related vascular cognitive impairment and dementia (VCID) is a growing concern for the aging population and refers to cognitive decline resulting from underlying cerebrovascular pathologies (such as impaired neurovascular coupling (NVC), disrupted blood-brain barrier (BBB) function, and cerebral microhemorrhage formation). Senescent cells accumulate with age and acquire a senescence-associated secretory phenotype (SASP) consisting of pro-inflammatory cytokines. Senescent cell accumulation exacerbates the cerebrovascular pathologies associated with VCID; however, the molecular mechanisms underlying how senescent cells and SASP, promote vascular dysfunction are not understood. During endothelial to mesenchymal transition (EndMT) endothelial cells (ECs) lose their characteristic endothelial phenotype and transition to a mesenchymal-like phenotype in response to a variety of triggers, including some SASP components. Thus, I hypothesize that increases in senescent brain cells with age result in increased SASP driving EndMT in ECs of brain microvasculature. We compared outcomes in three groups of EC lineage tracing mice (*Cdh5-Cre^{ERT2} ROSA$^{f/f\ tdT}$*): 1) young control mice, 2) aged control mice, and 3) aged mice treated with senolytic (ABT-263). Brain endothelial cells from each group were enriched using fluorescence-activated cell sorting. Cells were analyzed via scRNAseq and clustering analysis. As expected, expression of senescence core genes increased in aged mice and was ameliorated after depletion of senescent cells by senolytic treatment. Notably, we observed age-related increases in transcription of select EndMT-associated transcription factors in endothelial cells which decreased in response to senolytic treatment. Our data suggests a connection between the presence of senescent cells and the promotion of EndMT in brain ECs with age.

Funding: This work was supported by grants from the Presbyterian Health Foundation, the National Institute on Aging (R01AG070915, R01AG068295, R01CA255840), the Oklahoma Nathan Shock Center (P30AG050911), and the Cellular and Molecular GeroScience CoBRE (1P20GM125528)

DEVELOPMENT OF MULTITARGET DRUGS FOR SYNERGISTIC INHIBITION OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disease with a complex pathogenesis, leading to the progressive loss of cognitive functions and ultimately death. Existing treatments targeting Aβ are limited in their ability to slow down neurodegeneration. Our lab has produced several peptide candidates that exhibit multitarget activity not only against Aβ, but also against 3 additional specific targets involved in AD pathogenesis. In this study, we compared the in vitro activities of two peptide candidates, ALZ100 and ALZ300. We evaluated the effect of peptide candidates on Aβ fibrilization using a Thioflavin T fluorescence assay to quantify fibrils. We evaluated the effect on Aβ oligomerization using Enzyme Linked Immunosorbent Assay (ELISA) to quantify oligomers. By adding peptide to the reaction before or after Aβ oligomerization, we tested each candidate's ability to inhibit and reverse oligomerization respectively. Finally, we evaluated the binding of peptide candidates to their other specific targets; the receptor for advanced glycation end-products (RAGE), the toll-like receptor TLR4 and the S100 calcium-binding protein S100A9, using ELISA. Both ALZ100 and ALZ300 inhibit the fibrilization of Aβ with IC50 values of 3.7 μM and 11.6 μM, respectively. Both candidates also inhibit and reverse oligomerization of Aβ with similar IC50 values. ALZ100 and ALZ300 bind RAGE with the highest affinity (apparent Kd of 0.4-0.6 nM), then S100A9 (4.4-5.1 nM), and finally TLR4 (94-185 nM). Small aggregates of Aβ, like fibrils and oligomers, are major drivers of AD onset and progression. Inhibiting and reversing their formation is thus a promising strategy for the mitigation of AD. The ability of ALZ100 and ALZ300 to bind additional targets involved in AD pathogenesis (RAGE, S100A9, and TLR4) gives them the potential for enhanced inhibition of AD progression. Together, these characteristics offer an innovative solution to an unmet clinical need.

Funding: The OUHSC College of Pharmacy Seed Grant; The Midwest Biomedical Accelerator Consortium (MBArC), NIH/N
The OU Office of Technology Commercialization, Growth Fund; The OCAST-Oklahoma Applied Research Support

GAS6-TARGETING MULTI-FUNCTIONAL NANOPARTICLES FOR ENHANCED CANCER THERAPY

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Introduction

Growth arrest-specific 6 (Gas6) belongs to the Vitamin-K dependent protein family. It binds receptor tyrosine kinases of the TAM family and then activates downstream signaling. Activation of TAM receptors promote oncogenic functions and drug resistance in cancer cells, while suppressing immune response in macrophages via interaction with phosphatidylserine and Gas6. Warfarin, a traditional Vitamin-K agonist, has been shown to interfere the generation of Gas6 and thus reduce the activation of TAM receptors.

Hypothesis

We hypothesize that co-delivery of warfarin and doxorubicin to tumors using a warfarin-conjugated nanoparticle will significantly inhibit tumor growth through sensitizing cancer cells to chemotherapy and enhancing anti-tumor immune response while avoiding the severe side effect associated with both drugs.

Results and Conclusion

In vitro, warfarin treatment led to sensitization of cultured CT26 and 4T1 cells to doxorubicin (DOX) treatment. In consistent with literature, we found that more phosphatidylserine (PS) was exposed on the cell surface following DOX treatment, which caused enhanced phagocytosis and suppressed immune response in co-culture with macrophages. Co-treatment with warfarin partially decreased PS exposure and attenuated the PS-mediated immune suppression in macrophages. Taken together, warfarin significantly enhanced the cytotoxicity of DOX and reversed immune suppression in vitro.

To simultaneously deliver warfarin and doxorubicin to tumor site, we designed a warfarin-conjugated polymer (pWa) which can co-load warfarin and DOX together for a two-staged release. The synthesized pWa formed micellar nanoparticles (NPs) of around 140 nm with considerable warfarin and DOX loading capacity of 14.7% and 9.5%, respectively. Delivery of DOX and warfarin via pWa nanocarrier led to improved drug retention in blood and enhanced drug accumulation at tumor site. The combination treatment of DOX and warfarin resulted in enhanced antitumor activity comparing to treatment with either single drug. However, codelivery of the two drugs via the pWa NPs led to further improvement in therapeutic efficacy. In addition, this treatment led to increased numbers of NK cells and activated macrophages, and decreased numbers of M2 macrophages, indicating an enhanced immune response in tumor microenvironment.

Acknowledgement of Funding

RO1 CA239716
RO1 AI145034

CO-DELIVERY OF NEBL SIRNA VIA A TUMOR-TARGETING HYBRID NANOPARTICLE TO IMPROVE THE THERAPEUTIC EFFICACY OF AZACITIDINE TREATMENT IN NON-SMALL CELL LUNG CANCER

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Epigenetic aberrations, especially DNA hypermethylation, play a crucial role in tumor progression by silencing tumor suppressor genes and immune-related genes. The DNA demethylation agent Azacitidine (Aza) is capable of reversing the hypermethylation and has attracted growing interest. However, the activity of Aza in solid tumors has been disappointing, partly due to its poor stability in the aqueous environment and the challenge in delivery of sufficient amounts of drug to tumors without causing significant systemic toxicity.
We have recently developed an Aza-conjugated pro-drug nanocarrier (PAza) that is highly effective in tumor-selective delivery. To further understand the mechanism of PAza in solid tumors, we performed RNA seq for PAza-treated 3LL tumors. Aza significantly induced the upregulation of Nebl, a gene encoding the focal adhesion component Lasp2.

The GSCA database indicates that Nebl expression is negatively correlated to the infiltrated CD8+ T cell population in lung cancer. Consistent with the GSCA data, Nebl knockdown led to a ~100-fold increase in the mRNA level of CXCL10, a chemokine critically involved in T cell recruitment. In addition, the combination of Aza and siNebl can potently decrease the gene expression of dipeptidylpetidase IV (DPP4), the enzyme that cleaves CXCL10 and thus impedes the recruitment of CD8+ T cells to tumor tissue. We modified PAza into an iRGD-PEG-DOPA coated hybrid nanoparticle to render it effective in the selective codelivery of Aza and siNebl to tumors. The combination of azacitidine and siNebl dramatically increased the numbers of both total and granzyme B-positive CD8+ T cells in tumors, leading to significantly improved antitumor activity in the 3LL non-small cell lung cancer (NSCLC) model.

NUTRITIONAL KETOSIS AMELIORATES PATHOLOGIES IN A MOUSE MODEL OF MULTIPLE SCLEROSIS BY MODULATING TRYPTOPHAN, SEROTONIN, AND MELATONIN PATHWAYS ALONG THE GUT-CNS AXIS

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Background: Multiple sclerosis (MS) is an autoimmune disease characterized by inflammation, demyelination, and axonal damage. 50% of individuals with MS (pwMS) suffer from painful episodes of optic neuritis (ON) during their disease course. ON damages the axons of the optic nerve and kills retinal ganglion cells (RGCs), potentially leading to irreversible vision loss. Current immune modulatory therapies reduce new episodes of ON, but have limitations related to tolerability, safety, and their inability to halt disability accumulation, even in the absence of new relapses.
Objective: To overcome these limitations, we investigated the therapeutic efficacy of nutritional ketosis using a ketogenic diet (KD) enriched in medium chain triglycerides and fiber that was formulated to be non-obesogenic. We tested this diet in the mouse model of MS called experimental autoimmune encephalomyelitis (EAE).
Methods: EAE was induced in C57BL/6J male and female mice by immunization with the myelin oligodendrocyte glycoprotein (MOG_{35-55}) peptide antigen. KD or control diet feeding began after symptom onset and continued until 28 days post immunization. Mice were scored daily for motor deficits and visual acuity followed by post-mortem tissue analyses to count RGCs and quantify myelination and inflammatory infiltrates on optic nerves. RNA extracted from optic nerves was subjected to bulk RNA sequencing. Complementary untargeted metabolomic profiling of plasma and cecal content was performed to correlate changes in circulating metabolites with transcriptional responses on optic nerves.
Results: KD feeding restored motor and visual functions, and preserved RGCs as well as myelination of the optic nerve, concomitant with restricting lymphocyte and microglial infiltration. RNA sequencing and metabolomic analysis revealed that the KD increased tryptophan metabolites in the gut and plasma concordant with transcriptionally activating the serotonergic and melatonin pathways within optic nerves.
Conclusions: This study presents evidence that a dietary strategy for mitigating autoimmune demyelinating optic neuritis works in part by reducing inflammation on optic nerves via tryptophan metabolism in the gut. Our data support a model in which circulating tryptophan and its derivatives promote the localized biosynthesis of serotonin and melatonin, hormones with potent anti-inflammatory activity, at anatomical sites susceptible to MS pathology.