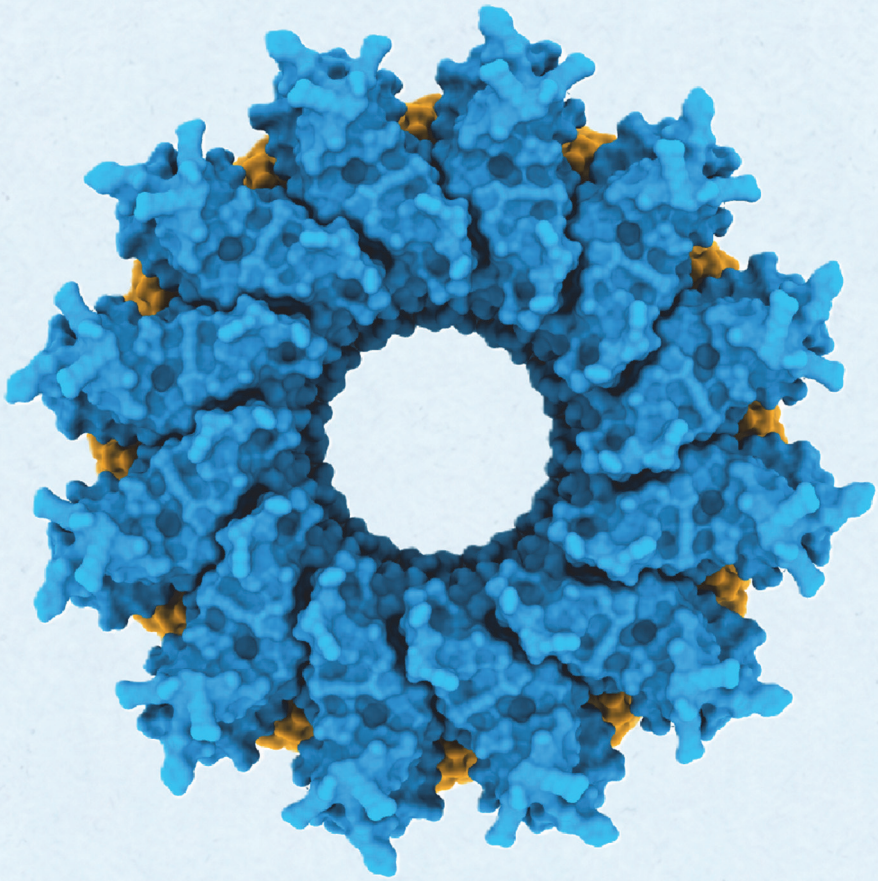
2026 KERN LIPID CONFERENCE

AUGUST 10-12 | BRECKENRIDGE, CO



Lipids and Lipoproteins in Cardiometabolic and Neurodegenerative Diseases

Organizers:
Kimberley Bruce, PhD & Clair Crewe, PhD

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2026 Kern Lipid Conference

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2026 Kern Lipid Conference

“Lipids and Lipoproteins in Cardiometabolic and Neurodegenerative Diseases”

August 10-12, 2026

Breckenridge, CO

Organizers: Kimberley Bruce, PhD & Clair Crewe, PhD

Cover caption: Cryo-EM reconstruction of the dodecameric mouse seipin/adipogenin complex, revealing the ring-shaped oligomeric 12-mer architecture that governs lipid droplet biogenesis. The structure provides new insights into the molecular mechanisms regulating cellular lipid storage.
Image of the seipin/adipogenin structure courtesy of Chao Li and Philipp E. Scherer.

Message from the President

Dear Colleagues and Friends in the Lipid and Bile Acid Research Community,

It is my distinct honor and pleasure to welcome you to another Kern Lipid Conference.

During my years at UT Southwestern in Dallas, I frequently heard about this meeting from Scott Grundy, Jay Horton, Mike Brown, Joe Goldstein, and especially Dave Mangelsdorf. Their enthusiasm for the Kern Conference made a lasting impression on me long before I had the opportunity to attend.

After returning to the University of Colorado in Denver in 2002, I attended my first Kern Meeting and was immediately captivated by its unique scientific atmosphere, intellectual rigor, and sense of community. It also helped that my friend and mentor, Franz Simon, was actively involved in the conference. In 2006, I succeeded Franz as Treasurer/Secretary, and in 2013, I had the privilege of succeeding Bob Eckel as President. Over the past two decades, the Kern Conference has become one of my foremost scientific and intellectual passions.

Our meeting would not be possible without the dedication and support of many individuals. I would like to express my sincere gratitude to our Board of Directors, our meeting chairs, and all of you whose participation and contributions make this conference so successful.

I would also like to extend special recognition to Susie Hayes and Dalan Jensen, who were integral members of the Kern team long before I became involved, and to Kaitlyn Murphy, who joined the team in 2022 shortly after becoming my Executive Assistant. Together, they devote countless hours to ensuring that every aspect of this meeting runs smoothly and successfully. Their commitment, professionalism, and attention to detail are invaluable. In fact, Kaitlyn and I discuss matters related to the Kern Conference at least weekly, and often more frequently, throughout the year.

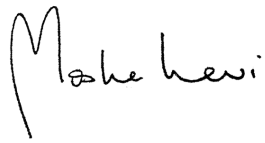
One of our most important accomplishments in recent years has been strengthening our collaboration with the Deuel Lipid Conference. Through ongoing discussions and mutual understanding, we have established a coordinated schedule in which the two conferences alternate annually, with meetings held in Colorado and California, respectively. This arrangement strengthens both organizations and benefits the broader lipid research community.

This year, we are especially pleased to inaugurate the **Scott Grundy Lecture**, honoring one of the founders of the Kern Conference and a transformative figure in our field. We are delighted that the inaugural lecture will be delivered by Philipp Scherer, with the introduction provided by Jay Horton. It is particularly fitting that both come from UT Southwestern, where Scott made so many enduring contributions and inspired generations of scientists.

Three years ago, I selected Jon Brestoff of Washington University in St. Louis to serve as Vice President of the Kern Conference. On Monday morning, immediately following the Kern Lecture, Jon will officially assume the presidency and begin a new chapter in the leadership of this organization. I am confident that the conference will continue to flourish under his guidance and vision.

Thank you for your participation, your scientific contributions, and your ongoing support of the Kern Lipid Conference. I wish all of you a productive, stimulating, and enjoyable meeting.

With best wishes,



Moshe Levi, MD
Kern Lipid Conference President

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Dr. Alessia Trimigno

+

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→ **"From Synapse to Systemic: The Expanding Reach of Lipidomics"**
Presented by Dr. Christian Klose, CTO at Lipotype

SESSION 6: "Emerging Technologies in Lipid Analysis and Imaging"

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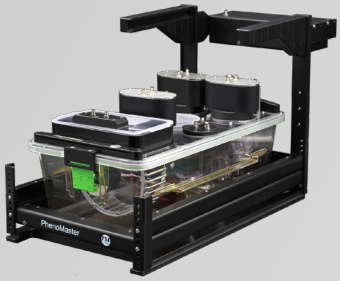

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Fred Kern, Jr., MD (1918-1997)

Fred Kern, Jr. was graduated from the University of Alabama in 1939 and from Columbia University, College of Physicians and Surgeons in 1943. After serving in the Medical Corps of the US Army, he became a fellow at Cornell Medical College. In 1952, Fred and his wife Bernie moved to Colorado where Fred served as a Professor of Medicine and Chief of Gastroenterology at the University of Colorado in Denver. Dr. Kern helped train generations of academic gastroenterologists who went on to teach at medical schools or research institutes in the United States, Canada, Australia, and Chile.

A distinguished researcher, Dr. Kern was known for his investigations in the areas of lipid metabolism, lactose intolerance, inflammatory bowel disease, the effects of estrogen and pregnancy on gallstone formation, and other areas of liver and digestive diseases. Dr. Kern was co-author of three books, 31 chapters in clinical textbooks, and more than 200 scientific articles. He received, among other honors, the 1988 University of Colorado Medal and the 1986 Friedenwald Medal, the highest award of the American Gastroenterological Association. And in 1986 he was named master of the American College of Physicians.

The Aspen Lipid Conference was organized by Fred Kern, Jr. and Rolla B. Hill, Jr. in 1977. Scott Grundy and Roger Davis joined with Fred Kern in 1985 to develop a regular schedule for the conference, which was incorporated in 1987. Fred's wife, Bernie, played a significant role in the development of the Aspen Lipid Conference as its coordinator for the first seventeen years. After Dr. Kern's death on May 2, 1997, the Board of Directors unanimously voted to rename this conference The Kern Aspen Lipid Conference to honor the legacy of Dr. Fred Kern, Jr. This tribute was continued when the conference moved to Vail and, later, Snowmass as The Kern Lipid Conference, its current name. Fred will always be remembered as a warm, intellectually challenging and wise person whose dedication to bridging significant scientific achievements and clinical practice served as the predominant basis for the development of this conference.

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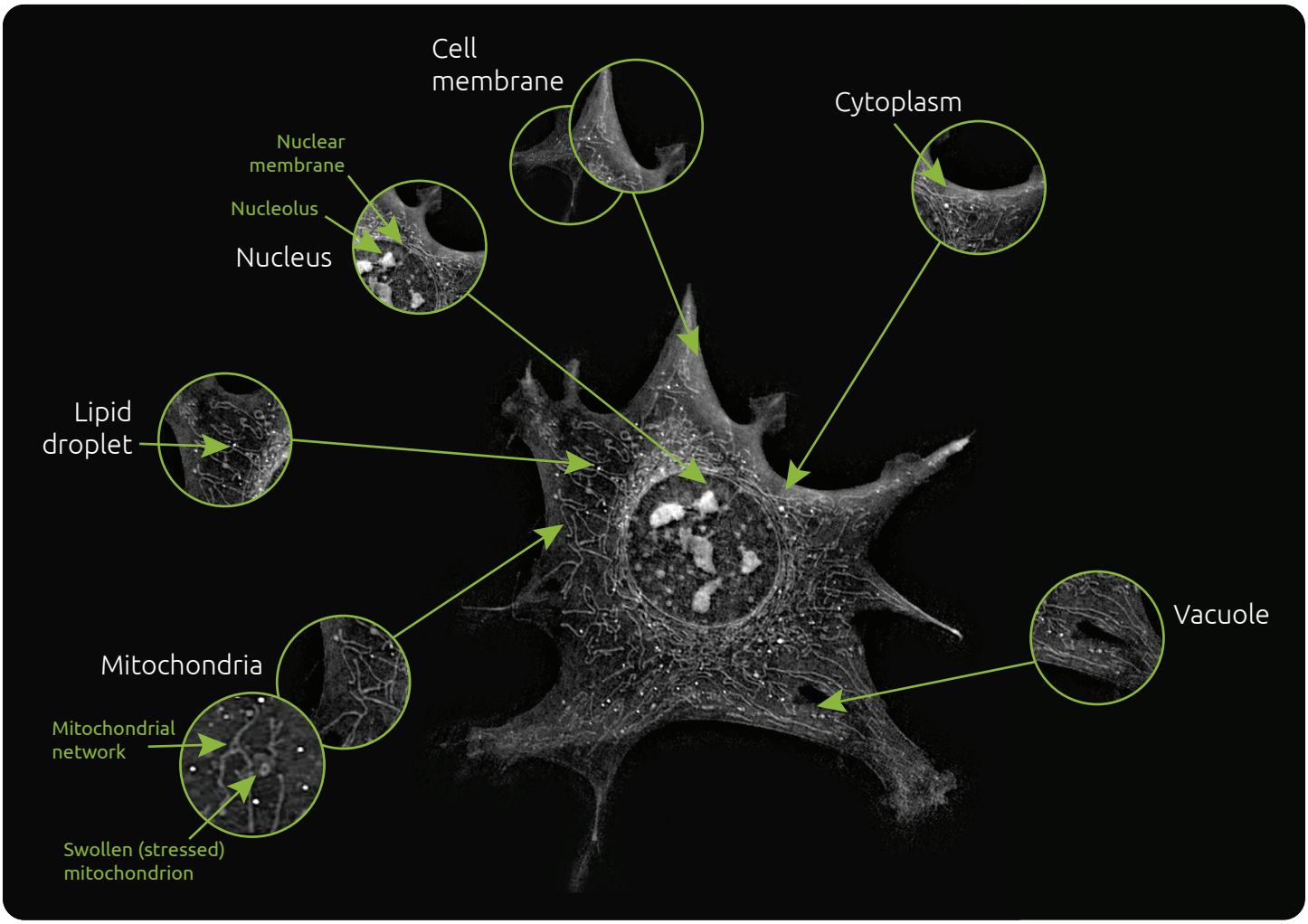

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Franz Simon, MD (1936 – 2012)

Franz Simon's essential passion was the world of scientific inquiry. He approached research with good humor and sportsmanship. His involvement with the Kern Lipid Conference stemmed from his primary commitment to young investigators, his belief in collaborative science, and his fascination with membrane physiology.

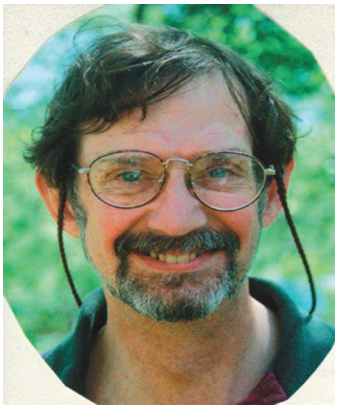
Dr. Simon was graduated from Pomona College in 1958 and from UC San Francisco Medical School in 1962. He completed his residency in Internal Medicine at the University of Colorado Denver and began a fellowship in Gastroenterology under Wade Volwiler and L. F. Fenster at the University of Washington Medical Center. After serving in the army at the Madigan U. S. Army Hospital in Tacoma, Franz entered a research fellowship with Dr. Irwin M. Arias at Albert Einstein College of Medicine, from 1967-1971. There he began his life-long investigation into the physiology of the liver, particularly the mechanics of bile secretion and hepatocellular membrane transporters.

In 1971, Dr. Simon returned to the University of Colorado Denver as Assistant Professor of Medicine, under the mentorship of Fred Kern, Jr. Franz continued at the University of Colorado for the rest of his career, rising to Professor of Medicine and Chief of the Division of Gastroenterology. He was pivotal at developing the V. A. Alcohol Research Center and the Hepatobiliary Center. He also worked diligently at the national level for the American Federation for Clinical Research, the American Association for the Study of Liver Diseases, the American Society for Clinical Investigation, and other organizations in the fields of hepatology and gastroenterology.

Dr. Simon was prescient in his early assessment that the phenomenon of cholestasis was often a disorder of bile secretion, rather than secondary to an obstructive etiology. At the time, this was a new way of thinking about the formation of bile and led him into the investigation of membrane protein turnover at the level of the hepatocellular canaliculus. Naturally, the entire phenomena of bile uptake, formation, composition, and secretion were of interest to him, and he became an enthusiastic supporter of the Kern Lipid Conference. He attended twenty-three meetings, became an officer and member of the Board of Directors, and was co-chairman for the 2001 conference.

Because of Dr. Simon's commitment to the training of young researchers in the field of lipid physiology and biochemistry, the Board of Directors has honored his memory by creating an award given to the scholar with the best poster presentation at each yearly Kern Lipid Conference.

David L. Williams, PhD (1946-2004)



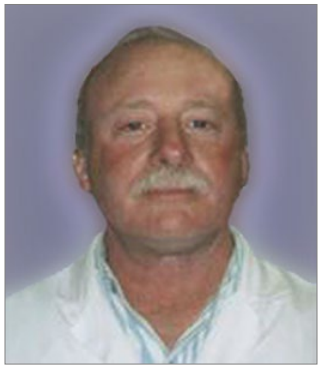
Born and raised in Pennsylvania, David Williams attended the University of California, Berkeley, and was graduated with a Bachelor of Arts degree in Zoology in 1967. He pursued further studies at Jack Gorski's laboratory at the University of Illinois and obtained his PhD with nine publications to his credit. His focus there was on the effects of ligand binding on the distribution of nuclear and cytosol estrogen receptors. He took a postdoctoral fellowship at the University of California, San Francisco, and then, in 1974, joined the new Department of Pharmaceutical Sciences at the State University of New York at Stony Brook. He remained on the faculty at SUNY Stony Brook for the next thirty years until his death in 2004 from the complications of Marfan Syndrome.

Dr. Williams' early research was in the field of regulation of avian yolk protein production by steroid hormones. He also investigated avian apolipoproteins, first characterizing avian ApoB and then finding that ApoA-I, in particular, was widely expressed in a variety of non-hepatic, or peripheral, tissues. He also found that human peripheral tissues synthesize apolipoproteins, particularly, ApoE. Thus in subsequent collaborations with many other laboratories, Dr. Williams' careful investigations over the years have added to the emerging understanding of ApoE and its metabolic role. His work also led to the discovery that ApoE could protect mice from atherosclerosis independently from its role as a ligand for lipoprotein receptors. He further looked at ApoE facilitation of the mammalian adrenal gland's uptake and storage of cholesterol for steroid hormone biosynthesis.

With numerous scientific achievements came peer recognition. Dr. Williams was granted the NIH MERIT Award in 1990. He had served on the editorial staffs of the Journal of Lipid Research and Molecular Endocrinology and was on many review committees for the National Science Foundation and the NIH. He was a member of the NICH Metabolism Study Section from 1991 to 1995. As a teacher and mentor he was active in training a generation of physicians and research scientists. Twenty-nine of his graduate students have pursued careers at universities or industry, including thirteen faculty members at ten academic institutions. Graduate students and physicians have benefited from his yearly series of lectures on "Principles of Medical Pharmacology," and he received an outstanding teaching award in 1997 from the Stony Brook University School of Medicine.

The memory of Dr. Williams is honored at the Kern Lipid Conference by a yearly conference lectureship and award for early career investigators.

Roger Davis, PhD (1945-2008)



Roger Davis was a major scholar in the fields of lipoprotein and bile salt metabolism and a founding member of the Kern Lipid Conference.

Dr. Davis was born in New York City, but moved to Delaware, where he attended high school in Wilmington and was graduated from the University of Delaware with a bachelor's degree in organic chemistry. He attributed his love of organic chemistry and his subsequent career in the biological sciences to inspiration from his acquaintance with Howard E. Simmons, Jr., a renowned chemist and later vice-president of research & development at Dupont. Dr. Davis obtained his PhD, also in organic chemistry, from Washington State University at Pullman.

His early post-doctorate years were spent first in the laboratory of Fred Kern, Jr., at the University of Colorado Denver, where he learned the basics of bile salt metabolism. Then he spent some time at the laboratory of Dan Steinberg, at UC San Diego, where he became fascinated with lipoprotein metabolism and the dynamics of ApoB synthesis and transport. These fields of inquiry became his lifelong passions. Subsequent tenured faculty appointments were held at Louisiana State University, at the University of Colorado Denver, and, from 1991 to his death in 2008, at San Diego State University. There, as a professor in the Department of Biology, he became the Director of Metabolic Research and helped design the new Bioscience Center, a building devoted solely to research on the campus.

Dr. Davis' scientific interests and achievements spanned many regions in the broad area of lipid metabolism. These included investigating the (lack of) inhibitory feedback effects of bile acids on bile acid synthesis; the secretion and degradation of ApoB; and, more recently, the discovery and therapeutic potential of specific genes. Although trained as an organic chemist, he readily pursued questions in a variety of biological areas and employed techniques and adapted strategies from those disciplines to find the answers. His projects had for over twenty-five years uninterrupted support from the NIH. He was an associate editor of the *Journal of Lipid Research* and a recipient of numerous awards and honors.

Dr. Davis was an effective and popular teacher. As a consequence many graduate students sought to have him as their mentor and have, themselves, gone on to rewarding careers in the biological sciences. He loved science and exuded what could be called a "contagious enthusiasm" for scientific inquiry. And he did this with wit and rigorous judgment.

Roger Davis was a loyal participant at the Kern Lipid Conference from its first meeting in 1977, with an attendance of twenty-two of its meetings. In 1985, he joined with Fred Kern, Jr., and Scott Grundy to reorganize the Kern Lipid Conference, which, beginning in 1987, was held on a yearly schedule. Dr. Davis was a conference chairman at three of the meetings and a faculty speaker at six, but his yearly active participation in the question and answer periods as well as in the informal gatherings between lectures enormously enriched the experience for all participants. In his honor the Board of Directors has established a conference lectureship each year for the rising scholar in transition between the early post-doctoral years and the beginning years of becoming an established investigator.

Scott Grundy, MD, PhD (1933–2025)

Scott Grundy, MD, PhD, was a pioneering clinical scientist whose work transformed the understanding of atherosclerotic cardiovascular disease, human nutrition, and lipid metabolism. His discoveries shaped modern approaches to cholesterol management and cardiovascular prevention, while his mentorship influenced generations of physician-scientists. He was also a founding member and a longtime participant in the Kern Lipid Conference.

Born in Memphis, Texas, Dr. Grundy attended Texas Technological College in Lubbock on a basketball scholarship. There he met Edith, his wife and partner of 68 years. After graduating with honors, he earned M.S. and M.D. degrees from Baylor College of Medicine before completing training in Internal Medicine and Pathology. He received his Ph.D. from Rockefeller University in 1968 and subsequently served as Chief of the Clinical Research Section of the National Institute of Arthritis and Metabolic Diseases in Phoenix, Arizona.

From 1973 to 1981, Dr. Grundy was a faculty member at the University of California, San Diego, and Director of the Metabolic Disease Laboratory at the Veterans Administration Hospital. His pioneering investigations into cholesterol metabolism and lipid disorders during this period laid the foundation for advances in cardiovascular prevention.

In 1981, Dr. Grundy joined UT Southwestern Medical Center as the founding Director of the Center for Human Nutrition, the first center of its kind at an American medical school. He later directed the Clinical and Translational Research Center and conducted decades of influential research on nutrition, obesity, lipid metabolism, and cardiovascular disease.

His colleagues recognized his enduring contributions in three areas: advancing the understanding of cholesterol metabolism and dietary effects on lipoproteins; guiding the development of clinical guidelines for the diagnosis and treatment of lipid disorders; and mentoring young investigators who became leaders in academic medicine.

Over his career, Dr. Grundy published nearly 500 scientific papers. He helped define the Metabolic Syndrome in 1997—now incorporated into the broader concept of Cardiovascular-Kidney-Metabolic (CKM) Syndrome—and advocated for its early recognition and treatment. He was also among the first investigators to demonstrate the effectiveness of statins in lowering cholesterol and reducing cardiovascular risk.

Dr. Grundy played a central role in establishing national and international standards for lipid management. He helped establish the National Cholesterol Education Program in 1985, served on its Adult Treatment Panel, and chaired or served on numerous American Heart Association (AHA) committees. He also served as President of the International Atherosclerosis Society (2004–2006) and led development of its 2014 Clinical Guidelines.

His accomplishments earned election to the National Academy of Medicine and numerous honors from the AHA, including the Discovery Award, designation as a Distinguished Scientist, and the Gold Heart Award. Dr. Grundy trained more than 100 research fellows and junior faculty members, leaving a legacy through those he mentored.

Dr. Grundy's association with the Kern Lipid Conference began at its inaugural meeting in Aspen in 1977. He helped reorganize the conference in 1985 with Fred Kern, Jr. and Roger Davis and served on its Board from 1987 until his death in 2025. Although declining mobility limited his attendance in later years, his enthusiasm and commitment never diminished. The Kern Lipid Conference, like UT Southwestern, owes much of its stature and success to Dr. Grundy's vision, leadership, and lifelong dedication to advancing the science of lipid metabolism and cardiovascular disease.

2026 Kern Lecturers

Kathryn Moore, PhD is the Jean and David Blechman Professor of Cardiology and Director of the Cardiovascular Research Center at NYU Grossman School of Medicine, where she is also a Professor of Medicine and Cell Biology. She is internationally recognized for defining molecular mechanisms that connect inflammation and metabolism to cardiovascular disease. Her research has uncovered fundamental roles for innate immune pathways and non-coding RNAs in cholesterol homeostasis and vascular inflammation. More recently, her work has revealed how cardiovascular injury can reprogram immune responses to influence cancer progression, helping establish new frameworks for understanding communication between seemingly distinct diseases.

Dr. Moore received her PhD from McGill University and completed postdoctoral training at Harvard Medical School. She began her faculty career at Harvard and Massachusetts General Hospital before joining NYU Langone Health.

A leader in the cardiovascular research community, Dr. Moore's honors include the NIH Outstanding Investigator Award, the AHA Distinguished Scientist Award, the Lefoulon-Delalande Grand Prix Scientifique, recognized by Clarivate as Highly Cited Researcher (top 1%) and election to the National Academy of Sciences.

Robert Farese, Jr., MD, is a Member of the Cell Biology Program at the Sloan Kettering Institute and founder and CEO of Kestrel Neuroscience.

Dr. Farese earned his BS in Chemistry from the University of Florida and his MD from Vanderbilt University. He completed training in internal medicine at the University of Colorado and in endocrinology and metabolism at UCSF and the Gladstone Institutes.

From 1994 to 2014, his laboratory at Gladstone/UCSF made seminal contributions to understanding triglyceride synthesis, lipid storage in lipid droplets, energy metabolism, and diseases of lipid storage. In 2014, he and Tobias Walther established the Farese & Walther Laboratory at Harvard, where Dr. Farese also chaired the Department of Molecular Metabolism. The laboratory moved to Memorial Sloan Kettering in 2022 and studies lipid-droplet formation, cellular lipid homeostasis, lysosomal lipid metabolism, and neurodegeneration.

His honors include the ASBMB Avanti Award in Lipids, the Endocrine Society's Roy Greep Award, the ASBMB–Merck Award, and election to the American Academy of Arts and Sciences. He also co-founded the Bluefield Project to Cure Frontotemporal Dementia.

Program Agenda

Monday, August 10, 2026

Time	Location	Event
06:30 AM – 09:00 AM	3rd Floor Foyer	**Badge Pickup**
07:00 AM – 08:30 AM	Coppertop	**Breakfast - *Sponsored as a Tribute to Dr. Steven H. Quarfordt and the Division of Gastroenterology at the Duke University Medical School***
08:00 AM – 08:10 AM	Peak 5	**Welcome Remarks & Opening Kern Lecturer Introduction** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University & Jonathan Brestoff, MD, PhD, President-Elect, Kern Lipid Conference, Washington University in St. Louis
08:10 AM – 08:55 AM	Peak 5	**Opening Kern Lecture** Kathryn Moore, PhD, NYU — *Reversing Atherosclerosis: Lipids, Immunity, and Cellular Fate*
		Session 1: Peripheral Lipids and Neurodegenerative Disease Chairs: Jonathan Brestoff, MD, PhD & Kate Townsend Creasy, PhD
08:55 AM – 09:25 AM	Peak 5	Cheryl Wellington, PhD, University of British Columbia — *The many ways peripheral lipoproteins affect the brain*
09:25 AM – 09:50 AM	Peak 5	Kimberley Bruce, PhD, University of Colorado — *Activating Lipoprotein Lipase with ApoC-II Mimetic Peptides*
09:50 AM – 10:15 AM	3rd Floor Foyer	Coffee Break
		Session 2: Causative Factors in Hyperlipidemia Chairs: Jay Horton, MD & Yu-Sheng Yeh, PhD, RD
10:15 AM – 10:20 AM	Peak 5	**Scott Grundy Lecture Introduction** Jay Horton, MD, University of Texas Southwestern Medical Center
10:20 AM – 10:50 AM	Peak 5	**Scott Grundy Lecture** Philipp Scherer, PhD, University of Texas Southwestern Medical Center — *Adipokines, Fibrosis, and the Future of Cardiorenal Metabolic Medicine*

Notes

10:50 AM – 11:20 AM	Peak 5	William Roell, PhD, Eli Lilly and Company - *GIPR agonism regulates adipocyte and whole body lipid metabolism in the context of GLP-1 and GCG*
11:20 AM – 11:30 AM	Peak 5	Nanolive-sponsored short talk Matthias Haeffner, Field Application Scientist, Nanolive - *From morphology to function: real-time label-free analysis of lipids and mitochondria in live cells*
11:30 AM – 11:35 AM	Peak 5	**Introduction and Presentation of the Roger Davis Award Lecture** Robert H. Eckel, MD, University of Colorado Anschutz Medical Campus
11:35 AM – 12:00 PM	Peak 5	**Roger Davis Award Lecture** Christy Gliniak, PhD, Rutgers University — *Elevated FGF21 from hepatic MetAP2 deletion is associated with selective ceramide reduction in visceral fat*
12:00 PM – 12:30 PM	Peak 5	**Lightning Talks – Round 1**
12:30 PM – 01:30 PM	Coppertop	**Lunch**
01:30 PM – 04:00 PM		**Afternoon Break**
		Session 3: Advances in Lipoproteins Chairs: Mary Sorci-Thomas, PhD & Bijoya Sen, PhD
04:00 PM – 04:30 PM	Peak 5	John Melchior, PhD, Pacific Northwest National Laboratory — *Decoding the Molecular Diversity of Brain Lipoproteins*
04:30 PM – 05:00 PM	Peak 5	Saskia Neher, PhD, University of North Carolina at Chapel Hill — *Emerging Technologies Provide New Insight into Lipoprotein Metabolism*
05:00 PM – 05:15 PM	Peak 5	Short talk Zhiwei Sun, MD, University of Colorado — *GPR182 is a lipoprotein receptor for dietary fat absorption*
05:15 PM – 05:45 PM	Peak 5	**Lightning Talks – Round 2**
06:15 PM – 08:00 PM	Peak 4	**Poster Session & Reception**

Notes

Tuesday, August 11, 2026

Time	Location	Event
07:00 AM – 08:30 AM	Coppertop	**Breakfast**
		Session 4: Lipid Signaling Chairs: Jacqueline Beaudry, PhD & Wentong Jia, PhD
08:00 AM – 08:30 AM	Peak 5	L. Ashley Cowart, PhD, Virginia Commonwealth University — *Sphingolipids as metabolic modulators in health and disease*
08:30 AM – 09:00 AM	Peak 5	Saranna Fanning, PhD, Harvard Medical School — *Approaching Parkinson's Disease as a Fatty Acid-opathy for Therapeutic Target Identification*
09:00 AM – 09:15 AM	Peak 5	Short talk Moshe Levi, MD, Georgetown University - *The Effects of NR and NAD Metabolism in Health and Disease*
09:15 AM – 09:30 AM	Peak 5	Short talk Sandip Mukherjee, PhD, Washington University School of Medicine — *Adipose Tissue Nicotinamide Phosphoribosyltransferase Regulates Systemic Metabolic Function Through Extracellular Vesicle Release*
09:30 AM – 09:35 AM	Peak 5	**Introduction and Presentation of the David L. Williams Lecture & Award** Mary Sorci-Thomas, PhD, Medical College of Wisconsin
09:35 AM – 10:05 AM	Peak 5	**David L. Williams Award Lecture** Kenichi Sakamoto, MD, PhD, Rutgers Robert Wood Johnson Medical School — *The Role of Increased Sympathetic Nervous System Activity in Metabolic Disease*
10:05 AM – 10:30 AM	3rd Floor Foyer	**Coffee Break**
		Session 5: Lipids and Immunometabolism Chairs: Robert Bauer, PhD & Ritsuko Nakai, MD, PhD
10:30 AM – 11:00 AM	Peak 5	Joseph Hill, MD, PhD, University of Texas Southwestern Medical Center — *HFpEF: Malady, Model, Meta-inflammatory Mechanisms*

Notes

11:00 AM – 11:30 AM	Peak 5	Priyanka Narayan, PhD, NIDDK — *APOE-Linked Lipid Perturbations Reshape Glial Function*
11:30 AM – 11:45 AM	Peak 5	Short talk Samantha Krysa, PhD, Washington University School of Medicine — *Neutrophils support brown adipose tissue thermogenesis*
11:45 AM – 12:00 PM	Peak 5	Short talk Kartik Rajagopalan, MD, PhD, University of Texas Southwestern Medical Center — *Leptin signaling to neurons increases tolerance to influenza infection*
12:00 PM – 12:15 PM	Peak 5	Short talk Wenceslao Martinez-Navarrete, PhD Candidate, University of Chicago — *Weight-cycling worsens obesity-induced inflammation through the reprogramming of myeloid cells and their progenitors*
12:15 PM – 01:15 PM	Coppertop	**Lunch**
01:15 PM – 03:00 PM		**Afternoon Break/Exhibition/Small Group Discussions**
		Session 6: Emerging Technologies in Lipid Analysis and Imaging Chairs: Alison Kohan, PhD & Clair Crewe, PhD
03:00 PM – 03:30 PM	Peak 5	Eric Potma, PhD, University of California, Irvine — *Differentiating lipids with hyperspectral stimulated Raman scattering microscopy*
03:30 PM – 04:00 PM	Peak 5	Lingyan Shi, PhD, University of California San Diego — *Imaging Metabolic Re-wiring in aging and diseases with SuMMIT-SRS*
04:00 PM – 04:15 PM	Peak 5	Lipotype-sponsored short talk Christian Klose, PhD, Lipotype - *From Synapse to Systemic: The Expanding Reach of Lipidomics*
04:15 PM – 04:20 PM	Peak 5	**JLR Lectureship Introduction** Kerry-Anne Rye, PhD, UNSW Sydney
04:20 PM – 04:50 PM	Peak 5	**JLR Lectureship** Kayla Sprenger, PhD, University of Colorado, Boulder — *Resolving*

Notes

		Apolipoprotein–Receptor Interactions in Neurodegeneration through Multiscale Molecular Dynamics
04:50 PM – 05:05 PM	Peak 5	Short talk David Saeb, PhD Candidate, University of Colorado, Boulder — *A Lipid Membrane Embedded Model of the Full TREM2–DAP12 Signaling Complex*
05:05 PM – 06:00 PM		**Pre-dinner break**
06:00 PM – 09:00 PM	Imperial Ballroom	**Dinner**

Wednesday, August 12, 2026

Time	Location	Event
07:00 AM – 08:30 AM	Coppertop	**Breakfast**
08:00 AM – 08:10 AM	Peak 5	**Presentation of the Franz Simon Poster Award** Jonathan Brestoff, MD, PhD, President, Kern Lipid Conference, Washington University in St. Louis
		Session 7: ApoE and Apolipoproteins Chairs: Robert (Nate) Helsley, PhD & Ainara Gonzalez Cabodevilla, PhD
08:10 AM – 08:40 AM	Peak 5	Lance Johnson, PhD, University of Kentucky — *APOE, PLIN2 and Lipid Droplet Dynamics in Alzheimer's Disease*
08:40 AM – 09:10 AM	Peak 5	Alice Chen-Plotkin, MD, University of Pennsylvania — *ApoA1 interacts with alpha-synuclein, modulating the development of Parkinson's disease pathology*
09:10 AM – 09:40 AM	Peak 5	Ali Javaheri, MD, PhD, Washington University in St. Louis — *Apolipoprotein M Mediates Interorgan Crosstalk in Aging and Metabolic Disease*

Notes

09:40 AM – 09:55 AM	Peak 5	Short talk Karthickeyan Chella Krishnan, PhD, University of Cincinnati — *Genetic Regulation of Hepatocyte Inter-Organelle Crosstalk through APOE Isoforms in MASLD*
09:55 AM – 10:20 AM	3rd Floor Foyer	**Coffee Break**
		Session 8: Lipid Droplets and Lipophagy Chairs: Kimberley Bruce, PhD & Saranna Fanning, PhD
10:20 AM – 10:50 AM	Peak 5	Zoltan Arany, MD, PhD, University of Pennsylvania — *Lipid droplets and lipid metabolism in cardiovascular disease*
10:50 AM – 11:20 AM	Peak 5	Michael Haney, PhD, University of Pennsylvania — *APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia*
11:20 AM – 11:35 AM	Peak 5	Short talk Anahita Ataran, MD, Washington University School of Medicine in St. Louis — *Lysosomal lipolysis is required for cardiomyocyte growth and lipid metabolism*
11:35 AM – 11:45 AM	Peak 5	**Closing Remarks & Closing Kern Lecturer Introduction** Jonathan Brestoff, MD, PhD, President, Kern Lipid Conference, Washington University in St. Louis
11:45 AM – 12:30 PM	Peak 5	**Closing Kern Lecture** Robert Farese, MD, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center — *The Phase of Fat: Formation, Regulation, and Functions of Lipid Droplets*

2026 Awards

David L. Williams Lecture and Scholarship Award Winner:
Kenichi Sakamoto, MD, PhD, Rutgers Robert Wood Johnson Medical School

Roger Davis Investigator Award for Transitional Faculty Winner:
Christy Gliniak, PhD, Rutgers University

Early Career Investigator Travel Stipend Award Winners:
Anahita Ataran, MD, Washington University in St. Louis
Juan Ávila Pagán, CU Anschutz
Julia Billups, PhD, Harvard Medical School
Sromona Das, PhD, University of Pennsylvania
Wentong Jia, PhD, Washington University in St. Louis
Md Saifur Khan, PhD, University of Pittsburgh
Samantha Krysa, PhD, Washington University School of Medicine in St. Louis
Wenceslao Martinez-Navarrete, University of Chicago
Preethi Parupalli, University of Texas at Dallas
Alexander Rocksvold, Medical College of Wisconsin
Mary Rouse, University of Colorado Anschutz
David Saeb, University of Colorado Boulder
Bijoya Sen, PhD, Buck Institute
Tsion Shiferaw, University of Colorado Anschutz
Isaiah Stephens, University of Kentucky
Jaclyn Whalen, Saint Louis University
Yu-Sheng Yeh, PhD, RD, University of Pittsburgh

Nutrition & Obesity Research Center (NORC) Travel Award Winners:
Marta Hita Hernandez, PhD, University of Colorado Anschutz
Sandip Mukherjee, PhD, Washington University in St. Louis
Suraj Patel, MD, PhD, University of Texas Southwestern Medical Center Kartik Rajagopalan, MD, PhD, University of Texas Southwestern Medical Center
Megan Schuetz, Washington University in St. Louis
Zhiwei Sun, MD, University of Colorado Anschutz

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2026 Kern Lipid Conference Co-Chairs:

Kimberley Bruce, PhD & Clair Crewe, PhD

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Ebru Erbay, MD, PhD, UCLA

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Jay Horton, MD, UT Southwestern Medical Center

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Samuel Klein, MD, Washington University in St. Louis

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Mary Sorci-Thomas, PhD, Medical College of Wisconsin

John Stafford, MD, PhD, The Ohio State University Wexner Medical Center

Gregory Steinberg, PhD, McMaster University

Conference Staff:

Fundraising Administrator and Event Planning:
Susan Hayes
UT Southwestern Medical Center
(214) 648-1636
Susan.Hayes@utsouthwestern.edu

IT Director & Assistant to the Treasurer:
Dalan Jensen
University of Colorado Anschutz Medical Campus
(303) 724-5371
Dalan.Jensen@cuanschutz.edu

Conference Coordinator:
Kaitlyn Murphy
Georgetown University
KM1566@georgetown.edu

Kern Lipid Conference Endowment Fund

In September 2007, the Board of Directors of the Kern Lipid Conference voted to create a conference Endowment Fund. The Endowment Fund is not meant to replace the current (and primary) means of conference support, which includes registration fees, solicitation of annual donations and grant submissions to various foundations, industry, and other scientific organizations. However, it is the intent and hope of the Board that an Endowment Fund will give individuals an opportunity to show support and also ensure the long term viability of this annual Conference. Annual income from the Endowment Fund will be used to supplement the operating budget.

Suggested Methods of Giving

Gifts are the voluntary transfer of property by donor without expectation or receipt of an economic benefit. Gifts are commonly made in the form of cash or marketable securities. Other planned gift options include retirement assets, life insurance, and provisions in a will or trust. The donor receives a tax deduction based on the value of the gift. By contributing to the Kern Lipid Conference Endowment Fund, you can be confident that the gift will continue to grow and join others whose gifts will help insure the conference has support far into the future.

Outright Gift

Outright gifts are a voluntary transfer of cash or marketable securities. They may be made anytime and make a lasting difference. Endowment giving can be established for many reasons, including:

- To honor a loved one, colleague, teacher, mentor, or friend;
- To celebrate personal accomplishments or business successes;
- To leave your own permanent legacy of perpetual support for the Kern Lipid Conference.

Donors may add to the fund at any time. The donor receives a tax deduction based on the value of the gift. A minimum gift donation of $500.00 is requested.

Pledge

A pledge is a promise to give. Gifts may be made over one or multiple years, up to a maximum of 5 years. Gifts are commonly made in the form of cash, marketable securities, life insurance, or planned gifts. To create your gift through a pledge, simply create a written promise, followed by appropriate gift payments. The donor receives no tax deduction until the gift is made.

Matching Gifts

Financial support is provided by companies through employee matching gift programs. These companies match their employees' donations to nonprofit organizations, enabling their employees to multiply their support by doubling or in some cases tripling employee gifts. To create a matching gift, contact your company's Human Resources office and follow the

company's procedure. Matching gifts create a tax deduction for both the company and the donor, for their portions only.

Wills and Trusts

Gifts are made through the donor's will or trust, effective upon the death of the donor. Donors wishing to utilize this method of giving should inform their attorney to include the gift in your will or trust. The donor's estate will receive a tax deduction for the value of the gift.

Life Insurance

A life insurance policy you currently own or purchase specifically for the gift. Also, employment-related policies can be good gifts. There are typically two options: a) make the conference the *owner* of the policy or b) the *beneficiary* of the policy. The donor should contact his/her insurance company to obtain the appropriate form.

Retirement Account Funds/IRAs

Any tax-deferred accounts created for retirement income purposes: IRAs, 401(k) accounts, 403(b) accounts, SEPs, profit-sharing plans, etc. which will be included in an estate (because they have not been annuitized) and which will be among the most highly taxed assets in the estate (both estate and income taxes may be applicable). To make your gift, request a change of beneficiary form from the plan's administrator.

Beneficiary Designation Information

To designate the Kern Lipid Conference as a recipient, the designation should be:

Kern Lipid Conference
(Tax identification #84-0978466)
Mailing Address:
PMB 328
16748 E. Smoky Hill Rd, STE 9C
Centennial, CO 80015

Professional Advice Disclaimer: *Donors are strongly encouraged to consult their own tax and estate planning professional. The information contained in this document is meant to serve as only as a guide and suggestions, and not meant to replace consultation with your own professional advisor(s).*

Conference Safety Plan

1R13AG099776-01 (PI Kimberley D Bruce; MPI Clair Crewe)

The Kern Lipid Conference is committed to providing a safe, inclusive, equitable, and respectful environment for all participants. The conference will provide an environment that is free from harassment, discrimination, and retaliation and will foster scientific exchange regardless of career stage, eminence in the field, or institutional affiliation.

All conference participants, including attendees, speakers, organizers, exhibitors, sponsors, vendors, and staff, are expected to conduct themselves professionally and respectfully throughout the meeting. The conference will not tolerate harassment or discrimination of any kind. Examples of prohibited behavior include, but are not limited to:

- Unwelcome comments or conduct, including verbal statements, written communications, social media posts, gestures, or visual displays related to an individual's protected characteristics.
- Unwelcome sexual advances or requests for sexual favors.
- Unwelcome teasing, joking, intimidation, or bullying based on actual or perceived gender identity, gender expression, or sexual orientation.
- Deliberate intimidation, stalking, sustained disruption of presentations or discussions, or inappropriate physical contact.
- Retaliation against any individual who reports or participates in the investigation of an incident.

Any participant who experiences or witnesses harassment or discrimination is encouraged to report the incident promptly. The Kern Lipid Conference has established multiple confidential avenues for reporting concerns. Reports may be submitted through the Kern Lipid Conference website (www.kernconference.org), directly to one of the Conference Co-Chairs (Drs. Kimberley D. Bruce at KIMBERLEY.BRUCE@cuanschutz.edu and/or Clair Crewe at clair.crewe@wustl.edu), or to conference leadership and administrative staff including Dr. Jonathan Brestoff (President of the Board of Directors at Brestoff@wustl.edu) or Kaitlyn Murphy (Conference Coordinator at km1566@georgetown.edu). Reports may be made at any time, including outside normal business hours.

All reports will be reviewed as promptly as possible by the Conference Co-Chairs together with designated members of the conference leadership. The review will seek to understand the concern, ensure participant safety, determine appropriate supportive measures, conduct an impartial review, and determine appropriate corrective actions. Any individual named in a complaint will not participate in the review or decision-making process. The conference leadership is committed to conducting prompt, fair, and equitable evaluations while maintaining confidentiality to the greatest extent possible. If a complaint is substantiated, appropriate corrective actions may include a verbal or written warning, removal from conference activities, immediate termination of conference participation without refund, prohibition from attending future Kern Lipid Conferences, loss of eligibility for NIH-supported travel awards or conference awards, and referral to the appropriate institutional officials or local law enforcement authorities when warranted. Any allegation involving criminal conduct, including sexual or physical assault, will be referred to the appropriate local law enforcement agency.

Participants are also encouraged to contact the U.S. Department of Health and Human Services Office for Civil Rights (HHS OCR) or the National Institutes of Health (NIH) regarding concerns of discrimination, harassment, or other inappropriate conduct. Filing a complaint with the Kern Lipid Conference is not required before filing with HHS OCR or NIH, and seeking assistance from conference organizers does not limit an individual's right to pursue external reporting mechanisms.

2026 Conference Participants

Last Name, First Name	Email Address	Organization/Institution
Aldrich, Emma	emal2471@colorado.edu	University of Colorado Boulder
Angelle, Conner	connerangelle@ufl.edu	University of Florida
Arany, Zoltan	zarany@pennmedicine.upenn.edu	University of Pennsylvania
Ataran, Anahita	attaran@wustl.edu	Washington University in St. Louis
Avila Pagan, Juan	juan.avilapagan@cuanschutz.edu	CU Anschutz
Bauer, Rob	rcb36@cumc.columbia.edu	Columbia University
Beaudry, Jacqueline	jacqueline.beaudry@utoronto.ca	University of Toronto
Bednarski, Tomasz	tomasz.k.bednarski@unl.edu	University of Nebraska-Lincoln
Billups, Julia	jbillups@bwh.harvard.edu	Harvard Medical School & Brigham and Women's Hospital
Brestoff, Jonathan	brestoff@wustl.edu	Washington University School of Medicine in St. Louis
Brookheart, Rita	rbrookheart@wustl.edu	WashU Medicine
Bruce, Kimberley	kimberley.bruce@cuanschutz.edu	University of Colorado Anschutz
Burchett, Jason	jason.burchett@vcuhealth.org	Virginia Commonwealth University
Byers, Crystal	crystal@curie.bio	Curie.Bio
Chella Krishnan, Karthickeyan	chellakn@ucmail.uc.edu	University of Cincinnati
Chen-Plotkin, Alice	chenplot@pennmedicine.upenn.edu	University of Pennsylvania
Coffey, Sarah	coffey@wustl.edu	Washington University School of Medicine in St. Louis
Cohen, Ann	cohenad@upmc.edu	University of Pittsburgh School of Medicine
Costa, Ana	ana.costa@colorado.edu	University of Colorado Boulder
Cowart, Lauren A.	lauren.cowart@vcuhealth.org	VCU
Creasy, Kate Townsend	kate.creasy@pennmedicine.upenn.edu	University of Pennsylvania
Crewe, Clair	clair.crewe@wustl.edu	Washington University in St. Louis
Cruz-Martin, Alberto	alberto.cruzmartin@cuanschutz.edu	CU Anschutz
Culkin, Patrick	pculkin@ionis.com	Ionis Therapeutics
Das, Sromona	sromona.das@pennmedicine.upenn.edu	University of Pennsylvania
Dedunupitiya, Disni	disni.dedunupitiya@ku.edu	Department of Chemistry, University of Kansas
Dombi, Mercedes	mdombi@ionis.com	Ionis
Dooling, Breanna	breanna.dooling@cuanschutz.edu	University of Colorado

Eckel, Robert	ROBERT.ECKEL@CUANSCHUTZ.EDU	University of Colorado Anschutz Medical Campus
Fanning, Saranna	sfanning2@bwh.harvard.edu	Harvard Medical School
Farese, Robert	rfarese@mskcc.org	Memorial Sloan Kettering Cancer Center
Finck, Brian	bfinck@wustl.edu	Washington University School of Medicine
Gliniak, Christy	christy.gliniak@rutgers.edu	Rutgers, New Brunswick
Gonzalez Cabodevilla, Ainara	Ainara.Gonzalezcabodevilla@nyulangone.org	New York University Grossman School of Medicine
Gorbe, Kelley	kelleygorbe@gmail.com	NewAmsterdam Pharma
Haeffner, Matthias	matthias.haeffner@nanolive.ch	Nanolive
Haeusler, Rebecca	rah2130@cumc.columbia.edu	Columbia University
Haney, Michael	Michael.Haney@pennmedicine.upenn.edu	University of Pennsylvania, Perelman School of Medicine, Department of Pathology
Hayes, Susie	susan.hayes@utsouthwestern.edu	UT Southwestern Medical Center
Helsley, Robert	robert.helsley@uky.edu	University of Kentucky
Hill, Joseph	joseph.hill@utsouthwestern.edu	UT Southwestern Medical Center
Hita Hernandez, Marta	hitamarta@yahoo.es	CU Anschutz, Colorado
Hokanson, John	john.hokanson@cuanschutz.edu	University of Colorado
Horton, Jay	Jay.Horton@UTSouthwestern.edu	UT Southwestern
Hossain, Md Arafat	m_hossain@u.pacific.edu	University of the Pacific
Hsieh, Joanne	joanne@gordian.bio	Gordian Biotechnology
Jang, In Hwa	jang0090@umn.edu	University of Minnesota
Javaheri, Ali	Ali.javaheri@wustl.edu	Washington University in St. Louis
Jensen, Dalan	Dalan.Jensen@cuanschutz.edu	University of Colorado Anschutz Medical Campus
Jia, Wentong	wjia@wustl.edu	Washington University School of Medicine in St. Louis
Johnson, Lance	Johnson.Lance@uky.edu	University of Kentucky
Kast, David	kast@wustl.edu	Washington University
Keller, Amy	amy.keller@cuanschutz.edu	University of Colorado Anschutz/RMR VA Medical Center
Kellison, Erik	erik.kellison@merck.com	Merck Research Laboratories
Khan, Md Saifur	khanmsr@pitt.edu	University of Pittsburgh
Kindle, Jason	jason.kindle@colinst.com	Columbus Instruments
Klose, Christian	klose@lipotype.com	Lipotype GmbH
Kohan, Alison	AKOHAN@pitt.edu	University of Pittsburgh, School of Medicine
Krysa, Samantha	krysa@wustl.edu	Washington University School of Medicine in St. Louis

Kurc, Gary	gary.kurc@tse-systems.com	TSE Systems
Lee, Nicola	Nlee7@jacksonville.edu	Baptist Medical Center
Levi, Moshe	moshe.levi@georgetown.edu	Georgetown University
Lim, Christina	k6lim@ucsd.edu	The Salk Institute
Ma, Jessica	Jessica.ma@gempharmatech.com	GemPharmatech
Martinez-Navarrete, Wenceslao	wenceslaom@uchicago.edu	University of Chicago
McNeil, Joshua	joshua.t.mcneil@gmail.com	NewAmsterdam
Melchior, John	john.melchior@pnnl.gov	Pacific Northwest National Laboratory
Moore, Kathryn	kathryn.moore@nyulangone.org	New York University
Mukherjee, Sandip	Sandip@wustl.edu	WashU, St. Louis
Murphy, Kaitlyn	km1566@georgetown.edu	Kern Lipid Conference / Georgetown University
Nakai, Ritsuko	nakair@wustl.edu	Washington University School of Medicine in St. Louis
Narayan, Priyanka	priyanka.narayan@nih.gov	NIH
Neher, Saskia	neher@email.unc.edu	UNC Chapel Hill
Nguyen, Melody	melody.n@wustl.edu	Washington Univ. in St. Louis
Niemeyer, Christy	christy.niemeyer@cuanschutz.edu	University of Colorado, Anschutz Medical Campus
Oettler, Daniela	daniela.oettler@tse-systems.com	TSE Systems
Orozco, Luz	orozcogl@gene.com	Genentech
Pao, Ping-Chieh	ping-chieh.pao@sanofi.com	Sanofi
Parupalli, Preethi	Preethi.Parupalli@UTDallas.edu	University Of Texas at Dallas
Patel, Suraj	suraj.patel@utsouthwestern.edu	UT Southwestern Medical Center
Peter, Angela	angela.k.peter@gmail.com	Edgewise Therapeutics
Potma, Eric	epotma@uci.edu	University of California, Irvine
Powell, Theresa	THERESA.POWELL@UCDenver.edu	University of Colorado
Radhakrishnan, Sridhar	sri@researchdiets.com	Research Diets, Inc
Rajagopalan, Kartik	kartik.rajagopalan@utsouthwestern.edu	UT Southwestern Medical Center
Rashan, Edrees	rashan@mit.edu	Massachusetts Institute of Technology
Revanna, Jasmin	jrevanna@salk.edu	Salk Institute for Biological Studies
Robinson, Stuart F.	drsfrobinson@gmail.com	St. Joseph Hospital, Orange, California
Rocksvold, Alexander	arocksvold@mcw.edu	Medical College of Wisconsin
Rodriguez-Agudo, Daniel	daniel.rodriguezagudo@vcuhealth.org	Virginia Commonwealth University
Roell, William	roell_william_c@lilly.com	Eli Lilly and Company

Rouse, Mary	mary.rouse@cuanschutz.edu	Anschutz Campus - Sch of Med - Endocrinology
Rye, Kerry-Anne	k.rye@unsw.edu.au	UNSW Sydney
Saeb, David	david.saeb@colorado.edu	University of Colorado Boulder
Sakamoto, Kenichi	ks1640@rwjms.rutgers.edu	Rutgers Robert Wood Johnson Medical School
Scherer, Philipp E	Philipp.Scherer@UTSouthwestern.edu	UT Southwestern Medical Center
Schuetz, Megan	harveym@wustl.edu	Washington University in St. Louis
Schwarz, Margrit	ms@blackwaybioscience.com	Spirochem
Sen, Bijoya	BSen@buckinstitute.org	Buck Institute for Research on Aging
Shi, Lingyan	l2shi@ucsd.edu	University of California San Diego
Shiferaw, Tsion	tsion.2.shiferaw@cuanschutz.edu	University of Colorado Anschutz Medical Campus
Soltanmohammadi, Elham	elham.soltanmohammadi@gempharmatech.com	GemPharmatech
Sorci-Thomas, Mary	msthomas@mcw.edu	Medical College of Wisconsin
Speliotes, Elizabeth	espeliot@med.umich.edu	University of Michigan
Sprenger, Kayla	kayla.sprenger@colorado.edu	Department of Chemical and Biological Engineering, University of Colorado Boulder
Srinivasan, Ashok	ashok@lipedema.org	Lipedema Foundation
Stafford, John	john.stafford@osumc.edu	Ohio State University
Stawikowski, Maciej	mstawikowski@fau.edu	Florida Atlantic University
Stephens, Isaiah	ist237@uky.edu	University of Kentucky
SUN, ZHIWEI	zhiwei.sun@cuanschutz.edu	University of Colorado Anschutz Medical Campus
Thyberg, Noah	noahthy@gmail.com	Nanolive
Torricelli, Richard	rtorrch@aol.com	Millennium Physician Group
Trimigno, Alessia	Trimigno@lipotype.com	Lipotype Inc.
Villani, Katelyn	kvillani@edgewisetx.com	Edgewise Therapeutics
Virostek, Megan	megan.virostek@utsouthwestern.edu	UT Southwestern Medical Center
Wang, Simeng	Simeng.Wang@UTSouthwestern.edu	UT Southwestern
Wellington, Cheryl	cheryl.wellington@ubc.ca	UBC Department of Pathology and Laboratory Medicine (UBC DPLM)
Whalen, Jaclyn	jaclyn.whalen@slu.edu	Saint Louis University
Yaspan, Brian	yaspan.brian@gene.com	Genentech
Yeh, Yu-Sheng	ysyeh@pitt.edu	University of Pittsburgh
Yrigoyen Rosas, Diana Ximena	dxy2@illinois.edu	University of Illinois Urbana-Champaign

Zhang, Xiangyu	xiz362@pitt.edu	University of Pittsburgh
Registrations received after 7/31/2026:		
Rice, Jordyn	jrice@arrowheadpharma.com	Arrowhead Pharmaceuticals
Morozova, Ksenia	kmorozova@rockefeller.edu	Rockefeller University

2026 Abstracts and Posters

Abstract #	Name -Last, First	Title	Institution	Poster #
Early Career Investigator Travel Award Winners & Applicants				
1	Ataran, Anahita	Lysosomal lipolysis is required for cardiomyocyte growth and lipid metabolism	Washington University in St. Louis	1
2	Avila Pagan, Juan	Sparse Complement C4 Dysregulation Induces Network-Wide Transcriptomic Alterations and Disrupted Cholesterol Biosynthesis in the Prefrontal Cortex	CU Anschutz	2
3	Billups, Julia	The GBA-Parkinson's Disease Fatty Acid-Ome as a Candidate Disease Biomarker	Harvard Medical School	3
4	Coffey, Sarah	Metabolically intact macrophages may restore tissue homeostasis and limit Leigh syndrome progression in Ndufs4—/— mice	Washington University	4
5	Costa, Ana	Mechanistic Insights into Apolipoprotein-Mediated Regulation of Lipoprotein Lipase: A Molecular Dynamics Simulation Study of Lipoprotein Metabolism	University of Colorado Boulder	5
6	Das, Sromona	ApolipoproteinA1 Modifies In Vivo Gut-to-Brain Alpha-Synuclein Pathological Transmission	University of Pennsylvania	6
7	Dedunupitiya, Disni	Immunoprecipitation of ApoE Lipoproteins from Mouse Brain Tissue for Downstream Lipidomic Analysis	University of Kansas	7
8	Dooling, Breanna	Apolipoprotein E contributes to Alzheimer's disease phenotypes in Down syndrome cerebral organoids	University of Colorado	8

9	Hossain, Md Arafat	Pharmacological Strategies to Enhance Adipose Thermogenesis in Lipedema Patients	University of the Pacific	9
10	Jia, Wentong	Human and mouse breastmilk contains respiration-competent extracellular mitochondria	Washington University	10
NA	Khan, Md Saifur	CERS2: A Central Regulatory Node Controlling Pancreatic β-Cell Failure and α-Cell Expansion in T2D	University of Pittsburgh	11
11	Krysa, Samantha	Neutrophils enhance defense of cold-induced hypothermia via mitochondria transfer to brown adipocytes	WASH U IN ST. LOUIS	12
12	Lim, Christina	Dysregulated Lipid Metabolism in APOE4 Pericytes and Its Impact on Neurovascular Function	The Salk Institute	13
13	Martinez-Navarrete, Wenceslao	Weight-cycling worsens obesity-induced inflammation through the reprogramming of myeloid cells and their progenitors	University of Chicago	14
14	Parupalli, Preethi	BAT specific FASN Inhibition as a Novel Strategy to Rescue Alcohol-Induced Hypertriglyceridemia and fatty liver disease by enhancing thermogenesis.	University of Texas at Dallas	15
~~15~~	~~Revanna, Jasmin~~	~~Impaired lipoprotein secretion by APOE4 leads to lysosomal and mitochondrial dysfunction in human microglia~~	~~Salk Institute~~	~~16~~
16	Rocksvold, Alexander	Pcpe2 Drives Adipose Dysfunction And Consequent Obesity Through TGFβ Signaling	Medical College of Wisconsin	17

17	Rouse, Mary	ApoE4 Inhibits Lipoprotein Lipase in a Lipidation and Cofactor Specific Manner	University of Colorado Anschutz	18
18	Saeb, David	A Lipid Membrane Embedded Model of the Full TREM2–DAP12 Signaling Complex	University of Colorado Boulder	19
19	Sen, Bijoya	Identifying novel lipophagy regulators necessary for proteostasis in neurodegenerative diseases	Buck Institute	20
20	Shiferaw, Tsion	ApoE Lipidation State Directs Immunometabolic Reprogramming of Human Microglia	University Colorado Anschutz	21
21	Stephens, Isaiah	Perilipin-2 Loss Reprograms Microglial Lipid Droplet Biology and Immunometabolic Responses	University of Kentucky	22
22	SUN, ZHIWEI	GPR182 is a lipoprotein receptor for dietary fat absorption	CU Anschutz Medical Campus	23
23	Whalen, Jaclyn	Age-Dependent Differences in Atherogenesis Revealed by Single-Cell Profiling of Murine Arteries	Saint Louis University	24
24	Yeh, Yu-Sheng	Beyond Neutral Lipases: The Adipocyte Lysosome as a Nexus for Lipid Mobilization and Systemic Metabolic Health	University of Pittsburgh	25
25	Yrigoyen Rosas, Diana Ximena	Adipose FXR Loss Impairs Angiogenic Gene Expression and Promotes Hepatic Steatosis in a murine model under a Western Diet.	UIUC	26
General Abstracts and Posters				
26	Aldrich, Emma	In Silico Sequence-to-Structure Analysis of Cancer-Associated TREM2 Variants to Inform Therapeutic Modulation of Macrophages	University of Colorado Boulder	27

27	Angelle, Conner	Concurrence of perilipin-2 and amyloid beta pathology in the brains of human and murine models of Alzheimer's disease	University of Florida	28
28	Bednarski, Tomasz	The role of hepatic cytosolic acyl-CoA metabolism in steatotic hepatocytes.	University of Nebraska-Lincoln	29
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Lysosomal lipolysis is required for cardiomyocyte growth and lipid metabolism

Abstract Number: 1
Poster Number: 1

Anahita Ataran (Washington University in St. Louis), Ali Javaheri (Washington University in St. Louis), Irfan Lodhi (Washington University in St. Louis), Kenneth Margulies (University of Pennsylvania), Jonathan Brestoff (Washington University School of Medicine in St. Louis), Clair Crewe (Washington University in St. Louis), Hongje Jang (University of California, San Diego), Lingyan Shi (University of California, San Diego)

The myocardium relies primarily on lipid metabolism to sustain energy demands, yet the contribution of lysosomal lipolysis to cardiac homeostasis remains unknown. Here, we define the role of lysosomal acid lipase (LAL), the lipase required for lysosomal lipolysis, in human myocardium, cultured cardiomyocytes, and in vivo models of stress. In failing human hearts, cardiomyocyte LAL expression was increased accompanied by reductions in lipid species and lipid droplet-associated proteins, consistent with enhanced lysosomal lipolysis. Genetic or pharmacologic inhibition of LAL impaired mitochondrial respiration and blunted cardiomyocyte growth in response to stress. Cardiomyocyte-specific LAL knockout mice also demonstrated reduced cell size and enhanced sensitivity to cardiotoxicity. Therapeutically, short-term dietary lipid supplementation improved survival and prevented cardiotoxicity in wild-type mice but failed to confer benefits in LAL-deficient animals. Together, these findings establish LAL-dependent lysosomal lipolysis as a key regulator of lipid-driven mitochondrial bioenergetics and adaptive cardiac growth and highlight lipid-based strategies as a potential therapeutic axis in heart failure.

Sparse Complement C4 Dysregulation Induces Network-Wide Transcriptomic Alterations and Disrupted Cholesterol Biosynthesis in the Prefrontal Cortex

Abstract Number: 2
Poster Number: 2

Juan Avila Pagan (CU Anschutz), Sonia Bolshakova (Broad Institute), Marta Sanchez Carbonell (CU Anschutz), Yaseer Sabir (CU Anschutz), Anna Hasche-Kluender (CU Anschutz), Clay Griffin-Derr (CU Anschutz), Paige Caley (CU Anschutz), Caroline Dias (CU Anschutz), Rhushikesh Phadke (Boston University), Alison Brack (Boston University), Alberto Cruz-Martin (CU Anschutz)

In the brain, the immune complement pathway (CP) is a molecular cascade that recruits microglia to tag and eliminate unwanted synapses, debris, and pathogens, thereby playing a vital role in maintaining brain homeostasis throughout our lifespan. The CP has also been shown to influence synaptic plasticity and circuit refinement in the brain. Although complement dysregulation has been linked to various neurological and psychiatric disorders, it remains unclear how localized increases in complement activity within a small group of cells affect gene regulation across larger cortical populations. To investigate this, we overexpressed the schizophrenia (SCZ) risk gene C4 in about 2% of prefrontal cortex neurons in mice through in utero electroporation. Bulk RNA sequencing of microdissected tissue revealed widespread transcriptional changes, predominantly in untransfected cells, indicating non–cell-autonomous effects of C4 overexpression (C4-OE). Sparse C4-OE led to increased expression of genes involved in cholesterol biosynthesis, axon guidance, synaptic plasticity, cytoprotection, and neurogenesis, suggesting compensatory remodeling or abnormal plasticity. Co-expression analysis identified a C4b-containing gene module rich in genes related to dendritic development and cell cycle regulation, indicating altered circuit maturation, while immune and inflammatory gene programs were broadly suppressed, reflecting homeostatic downregulation in response to sustained complement activity. We are currently testing whether the cholesterol biosynthesis signature induced by sparse C4 upregulation localizes to specific cortical cell populations and is accompanied by altered lipid droplet accumulation in the prefrontal cortex. Overall, this work suggests that sparse C4 dysregulation can reshape prefrontal cortical states at a network level and highlights altered cholesterol biosynthesis as a candidate mechanism linking complement-associated circuit remodeling to schizophrenia.

The GBA-Parkinson's Disease Fatty Acid-Ome as a Candidate Disease Biomarker

Abstract Number: 3
Poster Number: 3

Julia Billups (Harvard Medical School), Saranna Fanning (Harvard Medical School)

Background: Neurodegenerative diseases are increasingly being considered proteinopathies and lipidopathies. In Parkinson's Disease (PD) research, the proteinopathy+lipidopathy paradigm is being further refined to a fatty acid (FA)-opathy, centering FA metabolism dysregulation as fundamental to PD-associated lipid dysfunction. FA dyshomeostasis disrupts interactions of the PD-associated protein alpha-synuclein (αS) with lipid membranes, altering αS localization, conformation, and aggregation status. Correcting PD-associated FA dyshomeostasis rescues αS pathologies and represents a promising strategy for disease-modifying therapeutics. The most prevalent genetic mutations causing PD are in the GBA (Glucocerebrosidase) gene, affecting the lipid-regulating lysosomal enzyme glucocerebrosidase, and inducing αS and lipid dyshomeostasis. Studies elucidating FA alterations in GBA-Parkinson's Disease (GBA-PD) remain in their infancy. Understanding FA metabolism dysregulation in GBA-PD is critical to biomarker and therapeutic target identification. This study defines the GBA-PD fatty acid-ome (FA-ome).

Methods: Gas chromatography-mass spectrometry (GC-MS) with flame ionization detection was used to quantify a panel of 26 total (esterified + non-esterified) FAs in the plasma of a discovery cohort and 2 validation cohorts of males and females with and without GBA-PD. We analyzed saturated FA (SFA), monounsaturated FA (MUFA), and polyunsaturated FA (PUFA) abundance by disease status (non-PD, GBA-PD), sex, and age. We determined the impact of specific GBA mutations (E326K, N370S), and clinical outcomes (Unified Parkinson's Disease Rating Scale, Hoehn and Yahr scale, and Mini Mental State Examination scores) on the GBA-PD FA-ome.

Results (unpublished data): We identified GBA-PD as being associated with a dysregulated plasma FA-ome. Concentrations of plasma SFAs, MUFAs, and PUFAs were altered in participants with GBA-PD, with notable sex differences. Differential plasma FA profiles were identified for GBA-PD patients premised on GBA mutation type. Plasma FA concentrations in GBA-PD participants correlated with clinical outcomes. Premised on this study, we propose altered plasma FA concentration ratios to be candidate biomarkers for GBA-PD.

Conclusions: This research identifies distinct sex- and GBA mutation-dependent differences in the plasma FA-ome of individuals with GBA-PD that correspond with clinical measures of disease progression. Founded on disrupted GBA-PD FA profiles and significant correlations between FA concentrations and PD clinical outcomes, we posit that FA dysregulation in GBA-PD represents a novel target for the development of biomarkers and disease-modifying therapeutics.

Metabolically intact macrophages may restore tissue homeostasis and limit Leigh syndrome progression in Ndufs4—/— mice

Abstract Number: 4
Poster Number: 4

Sarah Coffey (Washington University), Stella Varnum (Washington Univ. in St. Louis), Wentong Jia (Washington University School of Medicine in St. Louis), Samantha Krysa (Washington University School of Medicine in St. Louis), Jacob S. Bedia (Washington Univ. in St. Louis), Rocky Giwa (Washington University School of Medicine in St. Louis), Melody Nguyen (Washington Univ. in St. Louis), Ritsuko Nakai (Washington University School of Medicine in St. Louis), Rachael Field (Washington University School of Medicine in St. Louis), Jonathan Brestoff (Washington University School of Medicine in St. Louis)

Leigh syndrome (LS) is a fatal pediatric neurodegenerative disease caused by mutations in genes that are required for mitochondrial oxidative phosphorylation. Patients with LS exhibit varied symptoms including ataxia, motor skill regression, seizures, and eventually impaired respiration, with death occurring by 3 years of age in most cases. Unfortunately, there are currently no effective therapies for LS, highlighting an urgent need to identify novel biological pathways that can be targeted to treat this and other inherited mitochondrial diseases. Emerging studies suggest that chronic inflammation drives LS progression, with macrophages implicated as a causal driver of disease. However, the mechanisms by which the immune system contributes to LS remain poorly understood. Using high-dimensional spectral flow cytometry to profile the composition of all major immune cell types in the peritoneal cavity of Ndufs4—/— mice, a well-established model of LS, we found that CD11b hi F4/80 hi macrophages are unexpectedly depleted compared to wildtype (WT) controls. Adoptive transfers of WT bone marrow-derived macrophages to replenish the macrophage pool in Ndufs4—/— mice appear to be associated with improvements in the morbidity and mortality of Ndufs4—/— mice. These findings suggest that macrophages with intact mitochondrial metabolism may limit the progression of LS, perhaps by contributing to the maintenance of tissue homeostasis. These studies also raise the possibility that cellular therapies that replenish healthy macrophages may be a novel therapeutic strategy to treat LS.

Mechanistic Insights into Apolipoprotein-Mediated Regulation of Lipoprotein Lipase: A Molecular Dynamics Simulation Study of Lipoprotein Metabolism

Abstract Number: 5
Poster Number: 5

Ana Costa (University of Colorado Boulder), Emma E. Lietzke (University of Colorado Anschutz, University of Colorado Boulder), Kayla Sprenger (Department of Chemical and Biological Engineering, University of Colorado Boulder), Kimberley Bruce (University of Colorado Anschutz)

Lipoprotein Lipase (LPL) serves as a key regulator of lipid metabolism by hydrolyzing triglycerides (TG) within triglyceride-rich lipoproteins and high-density lipoproteins. Given the strong correlation between elevated plasma TG levels and the risk of cardiovascular disease and hypertriglyceridemia, identifying the factors modulating LPL activity is critical. Apolipoproteins of the C-family (ApoC-I, II, and III) are amphipathic molecules bound to the surface of lipoproteins that facilitate the solubilization and transport of lipids, while simultaneously modulating metabolic enzymes such as LPL. ApoC-II is a known activator of LPL, whereas ApoC-I and ApoC-III act as potent inhibitors. Despite their structural similarities, the mechanistic drivers behind these contrasting roles are not yet fully understood.

Current research indicates that ApoC-III inhibits LPL activity by sterically hindering its access to the lipid-rich core of lipoproteins. However, conflicting mutational data suggests this inhibitory behavior is not exclusively tied to competitive lipoprotein binding between ApoC-III and LPL, raising the possibility of direct protein-protein interactions as a potential inhibitory pathway. Furthermore, ApoC-I has been shown to interact directly with other metabolic enzymes, such as lecithin cholesterol acetyltransferase, which contains structural similarities to LPL including an alpha/beta hydrolase core and a Serine-Aspartic Acid-Histidine catalytic triad responsible for its enzymatic activity. These observations, coupled with existing evidence that ApoC-II activates LPL by directly stabilizing its catalytic pocket, support a bimodal inhibitory mechanism theory where competitive lipoprotein binding and protein-protein interactions act concurrently.

To resolve these mechanisms, this work proposes using atomistic molecular dynamics simulations to characterize the interfacial behavior and interaction profiles of ApoC-I, II, and III. By simulating these apolipoproteins in both lipid-bound environments and in the presence of LPL, we aim to identify the key differences in protein-lipid dynamics and reveal potential LPL-ApoC binding interfaces. Capturing these protein dynamics at the atomic level will help determine the drivers of LPL activation and inhibition, providing a deeper understanding of the regulatory pathways governing lipoprotein metabolism, ultimately guiding therapeutic design that targets LPL across metabolic and cardiovascular diseases.

ApolipoproteinA1 Modifies In Vivo Gut-to-Brain Alpha-Synuclein Pathological Transmission

Abstract Number: 6
Poster Number: 6

Sromona Das (University of Pennsylvania), R. Tyler Skrinak (University of Pennsylvania), Charles Shen (University of Pennsylvania), Ava G. Ehrlich (University of Pennsylvania), Kelvin C. Luk (University of Pennsylvania), Alice Chen-Plotkin (University of Pennsylvania)

BACKGROUND: We previously showed that Apolipoprotein A1 (ApoA1) levels correlate with age at onset of Parkinson's disease (PD), PD disease severity, and dopaminergic system integrity in prodromal PD, with higher ApoA1 levels associated with better outcomes. Moreover, Mendelian randomization analysis using the ApoA1 protein quantitative trait locus rs670 as an instrumental variable supported a causal role for higher ApoA1 in protection from PD pathology. These human biomarker analyses are corroborated by work in the lab demonstrating an interaction between ApoA1 and alpha-synuclein (aSyn), the protein that misfolds and aggregates to form the characteristic pathological lesions of PD. Indeed, addition of ApoA1 rescues neurons from taking up fibrillar forms of aSyn and developing aSyn pathology.

METHODS: Our in vitro observations prompted us to investigate whether ApoA1 loss impacts in vivo spread of aSyn pathology in mice. Because ApoA1 is primarily synthesized in the liver and gut, we introduced pre-formed fibrils (PFFs) of aSyn by feeding wild-type (WT) vs. APOA1 knockout (KO) mice, testing whether they would seed pathological forms of aSyn (phosphorylated at Serine129, pSyn) in the gut and the brain. We fed aSyn monomer to mice as a negative control. Moreover, since gut inflammation plays a role in gut-to-brain transmission, assessments were performed in the presence vs. absence of dextran sodium sulfate (DSS) treatment to induce colitis. We assessed pSyn pathology by ELISA (detection antibody, EP1536Y) and by tissue staining 6 months post treatment.

RESULTS: Hematoxylin and eosin-stained gut tissues showed infiltration and induction of colitis in DSS-treated mice. In WT and KO animals fed with aSyn monomer control, we did not detect pSyn in gut, brainstem, or cerebrum lysates, as measured by ELISA. However, in WT and KO aSyn PFF fed animals, we detected pSyn in gut lysates by ELISA, with no impact of DSS-induced colitis. There was, however, a trend ($p=0.097$) towards increased pSyn in gut lysates in the APOA1 KO animals. In brainstem lysates of these WT and KO animals, we detected pSyn by ELISA, with more pSyn in DSS-treated mice. APOA1 genotype did not impact these brainstem pSyn measures. In cerebrum of WT and KO animals, we detected pSyn by ELISA, with similar amounts in WT vs. KO animals treated with DSS. However, in the absence of DSS-induced colitis, we detected significantly higher levels of pSyn in KO cerebrum lysates compared to WT ($p=0.0015$). Companion immunohistochemical studies of mouse brain tissue demonstrated pSyn staining in the gut myenteric layer, in the dorsal motor nucleus of the vagus, and in additional cortical areas.

CONCLUSIONS: We have developed an aSyn gut-to-brain transmission model of PD based on feeding aSyn PFFs to mice. APOA1 KO promotes gut-to-brain transmission in this model, with our data

suggesting that ApoA1 serves as a natural barrier to transmission that is lost under conditions of gut inflammation.

Immunoprecipitation of ApoE Lipoproteins from Mouse Brain Tissue for Downstream Lipidomic Analysis

Abstract Number: 7
Poster Number: 7

Disni Dedunupitiya (University of Kansas), Matt Zupan (University of Kansas), Jack Petersen (University of Kansas), Sophie Juliana (University of Kansas), Jennifer Amrein (University of Kansas), Meredith Hartley (University of Kansas)

Apolipoprotein E (apoE) in the brain redistributes lipids, including cholesterol between brain cells to maintain the myelin sheath, organelle biogenesis, synaptogenesis, and neuronal plasticity. In a genetic knock-out mouse model of myelin damage, we observed that myelin damage correlated with reduced free cholesterol and an accumulation of cholesterol esters in the brain. We hypothesized that apoE may be involved in transporting both cholesterol and cholesterol esters during myelin damage. However, limited information is available about the lipid contents of apoE lipoprotein particles in the brain due to the challenges of isolating native state lipoprotein particles. Prior studies focused on isolating lipoprotein particles from serum or plasma, with only a limited number of studies focused on isolating lipoproteins from tissues for downstream molecular analysis. In this study, we optimized immunoprecipitation of apoE lipoproteins from mouse brain tissue for downstream lipidomic analysis. We first reproduced the antibody-conjugated CNBr-activated sepharose bead immunoprecipitation protocol published in O'Leary et. al. for isolating apoE particles from primary rat astrocyte cell cultures. SDS-PAGE followed by Western blot analysis confirmed the presence of apoE protein. To assess the native apolipoprotein, we conducted Native-PAGE visualized under Coomassie blue staining and total protein blotting. Both analyses showed two distinct bands between 146 kDa and 200 kDa. The lighter lipoprotein band appears more abundant compared to the heavier lipoprotein, suggesting that the apoE in the rat astrocyte cell culture media is lipidated in two different compositions. Next, we were able to successfully perform the immunoprecipitation protocol on mouse brain tissue, and apoE particles were confirmed by Western blot. To separate the native state lipoproteins, size exclusion chromatography (SEC) was performed on samples from both rat astrocytes and mouse brain. These chromatograms showed protein complexes eluting at a similar size. We are currently optimizing the yield and performing additional analysis to confirm the identity of the apoE lipoproteins. Once optimized, the protocol will be applied to isolate apolipoprotein from demyelinating and healthy mouse brain tissues. Native lipoproteins will be separated using SEC and the lipid composition of lipoprotein particles will be analyzed using mass spectrometry. Our ultimate goal is to determine how apoE lipid transport mediates myelin damage, myelin debris clearance, and myelin repair.

Apolipoprotein E contributes to Alzheimer's disease phenotypes in Down syndrome cerebral organoids

Abstract Number: 8
Poster Number: 8

Breanna Dooling (University of Colorado), Anne Vielle (University of Colorado), Esteban Lucero (University of Colorado), Catherine Rydland (University of Colorado), Daphne Quang (University of Colorado), Rose Summers (University of Colorado), Hector Esquer (University of Colorado), Christina Coughlan (University of Colorado), Heidi Chial (University of Colorado), Aurélie Ledreux (University of Colorado), Huntington Potter (University of Colorado), Noah Johnson (University of Colorado)

Introduction: Adults with Down syndrome (DS) develop Alzheimer's disease (AD) brain pathology by age 40 due to triplication of the amyloid precursor protein gene (APP) on chromosome 21. Polymorphism of the apolipoprotein E gene (APOE) represents the strongest genetic contributor to AD in the typical population, yet its role in AD pathogenesis in individuals with DS (DS-AD) is unclear.

Methods: We developed human induced pluripotent stem cell-derived neurons, astrocytes, and cerebral organoids (COs) from donors with DS and from disomic controls. We used immunohistochemistry and immunoblotting to measure levels of AD-related proteins, and we performed RNA sequencing followed by differential gene and pathway analysis.

Results: Aged DS COs were smaller than disomic COs and formed robust amyloid-β neuropathology that was positively correlated with the levels of apoE. There were also significantly increased apoE levels in monoculture DS astrocytes compared to disomic controls. Transcriptomic profiling revealed distinct neuronal and astrocytic gene expression signatures in DS COs relative to disomic COs. We mapped these signatures to AD-specific ontologies and found broad commonalities in upregulated DEG pathways and deviations in downregulated DEG pathways between the three sample types. Lipid metabolism was a significantly altered pathway, associated with 18% of all upregulated genes and 16% of all downregulated genes that we identified. Lastly, we identified DEGs that have known interactions with APOE and APP, and we found that 9.4% of our DEGs had known interactions with APOE and 13.1% had known interactions with APP.

Conclusions: Taken together, our findings provide novel insights into the molecular mechanisms of DS-AD and indicate that apoE may contribute to the disease process.

Pharmacological Strategies to Enhance Adipose Thermogenesis in Lipedema Patients

Abstract Number: 9
Poster Number: 9

Md Arafat Hossain (University of the Pacific), Ankita Poojari (University of the Pacific), Atefeh Rabiee (University of the Pacific)

Lipedema, a frequently underrecognized chronic disorder of adipose tissue that predominantly affects women, is marked by the disproportionate accumulation of painful, nodular fat that is resistant to conventional interventions such as diet and physical activity. Although lipedema tissue is largely composed of subcutaneous white adipose tissue (SAT), it appears to preserve an inducible beige-like thermogenic capacity. However, in lipedema, this potential remains largely inactive, indicating underlying defects in metabolic signaling and energy expenditure. We propose that this resistance is driven by altered protein expression, mitochondrial dysfunction, and impaired thermogenic pathway activation. To explore these mechanisms, we conducted mass spectrometry–based proteomic and secretome analyses of patient-derived SAT to identify disease-associated protein signatures and secreted mediators contributing to lipid accumulation. Subsequent pathway enrichment analyses highlighted significant disruptions in signaling networks governing thermogenesis, mitochondrial integrity, and adipocyte plasticity.

To address this functional resistance, we evaluated a panel of pharmacological agents with established capacity to stimulate beige adipocyte thermogenesis, a recognized target in metabolic disease. The selection strategy incorporated both classical β-adrenergic–mediated pathways and alternative mechanisms involving other transmembrane receptor signaling, nuclear receptor signaling, and downstream cascades dependent or independent of β-adrenergic activation, covering both natural and synthetic compounds. The candidate compounds were selected for their reported ability to influence mitochondrial function and regulate thermogenic gene expression programs.

In vitro experiments using primary adipocytes derived from lipedema patients, as well as lean and obese controls, demonstrated that a few selected compounds markedly reduced lipid droplet size and accumulation after a 24-hour treatment period. These effects were initially visualized using Oil Red O staining and subsequently validated by real-time assessment of lipolytic activity using CellCyte X live-cell imaging. To refine candidate selection, ongoing multimodal analyses are being performed, including evaluation of gene and protein expression (qPCR, Western blot), cellular morphology (live cell imaging), mitochondrial dynamics (fission and fusion markers), mitochondrial membrane potential (live cell imaging), and mitochondrial function through oxygen consumption rate measurements (RESIPHER).

Together, these results provide important mechanistic insight into the metabolic disturbances underlying lipedema and highlight the potential of targeted, mechanism-driven pharmacological interventions to restore thermogenic function and improve metabolic flexibility in lipedema adipose tissue.

Human and mouse breastmilk contains respiration-competent extracellular mitochondria

Abstract Number: 10
Poster Number: 10

Wentong Jia (Washington University), Stella Varnum (Washington Univ. in St. Louis), Rocky Giwa (Washington University School of Medicine in St. Louis), Sarah Coffey (Washington University School of Medicine in St. Louis), Rachael Field (Washington University School of Medicine in St. Louis), Jasmine Wright (Washington University School of Medicine in St. Louis), Jacob S. Bedia (Washington Univ. in St. Louis), Melody Nguyen (Washington Univ. in St. Louis), Eva F. Cohen (Washington Univ. in St. Louis), Samantha Krysa (Washington University School of Medicine in St. Louis), Ritsuko Nakai (Washington University School of Medicine in St. Louis), Martin Picard (Columbia University), Drew Schwartz (Washington University), Clair Crewe (Washington University in St. Louis), Antonina Frolova (Washington University), Jonathan Brestoff (Washington University School of Medicine in St. Louis)

Breastmilk is an intricately balanced, complete source of nutrition for mammalian species. However, the composition of breastmilk has not been fully characterized. We demonstrate that human and mouse breastmilk contain large quantities of respiration-competent extracellular mitochondria (ex-Mito) that can be captured by wildtype or NDUFS4-deficient acceptor cells and enhance their capacity for aerobic respiration. Delayed weaning from lactating mothers significantly reduced the morbidity and mortality of the NDUFS4-deficient mouse model of Leigh syndrome, a severe primary mitochondrial disease. These observations suggest that breastmilk is an important source of ex-Mito and raise the possibility that prolonging breastmilk consumption might delay mitochondrial disease progression.

Neutrophils enhance defense of cold-induced hypothermia via mitochondria transfer to brown adipocytes

Abstract Number: 11
Poster Number: 12

Samantha Krysa (WASH U IN ST. LOUIS), VIKTORIA SZEIFERT (STANFORD), Jacob S. Bedia (Washington Univ. in St. Louis), FREDERIK DENORME (WASH U), AZUSA TERASAKI (STANFORD), Wentong Jia (Washington University School of Medicine in St. Louis), ROCKY GIWA (WASH U), Stella Varnum (Washington Univ. in St. Louis), Sarah Coffey (Washington University School of Medicine in St. Louis), Jasmine Wright (Washington University School of Medicine in St. Louis), JOHN .E MOLEY (WASH U), KESHAV BHATNAGAR (STANFORD), HAWA THIAM (STANFORD), THEODORE ROTH (STANFORD), CARA RADA (STANFORD), Rachael Field (Washington University School of Medicine in St. Louis), NICHOLAS BORCHERDING (WASH U), MONIKA BAMBOUSKOVA (WASH U), ROBERT CAMPBELL (WASH U), IRFAN LODHI (WASH U), CHRISTINA STALLINGS (WASH U), DERICK OKWAN-DUODU (STANFORD), Jonathan Brestoff (Washington University School of Medicine in St. Louis)

Brown adipose tissue (BAT) is a thermogenic fat depot in both mice and humans and is believed to maintain metabolic homeostasis by increasing energy expenditure and secreting hormones that regulate glucose homeostasis. BAT is activated primarily by sympathetic neurons that release catecholamines to induce expression of Uncoupling protein 1 (UCP1), and this sympathetic input is dampened by macrophages that import and degrade catecholamines. However, the functional roles of other innate immune cells in regulating BAT metabolism are poorly understood. Here, we made the unexpected observation that neutrophils are the most abundant immune cell population in BAT, where they undergo dramatic metabolic and transcriptional reprogramming to acquire a BAT-specific functional state and are required for optimal adaptive thermogenesis. As neutrophils infiltrate into BAT, they capture mitochondria released by thermogenically stressed brown adipocytes, a process that directly triggers neutrophils to transfer their own mitochondria to brown adipocytes in a bidirectional exchange. The transfer of neutrophil mitochondria to brown adipocytes is mediated by the formation of neutrophil extracellular traps (NETs). Disruption of neutrophil mitochondrial metabolism or inhibition of NET formation severely compromises adaptive thermogenesis in BAT and leads to cold-induced hypothermia. These findings reveal that neutrophils participate in bidirectional intercellular mitochondrial exchange with brown adipocytes to meet the metabolic demands of BAT and are critical for defending against changes in environmental temperature.

Dysregulated Lipid Metabolism in APOE4 Pericytes and Its Impact on Neurovascular Function

Abstract Number: 12
Poster Number: 13

Christina Lim (The Salk Institute), Fred Gage (Salk Institute)

Lipids are fundamental to brain biology, regulating membrane dynamics, mediating cell–cell interactions, and serving as key energy stores. Given the cellular heterogeneity of the brain, each cell type maintains a distinct lipid metabolic profile, and disruptions in lipid homeostasis within a single population can propagate system-wide dysfunction. As the primary lipid carrier in the brain, APOE is a critical regulator of lipid distribution across cell types, raising the possibility that APOE4 drives cell type–specific alterations in lipid metabolism that impact blood-brain barrier integrity.

Apolipoprotein E4 (APOE4) is the strongest genetic risk factor for Alzheimer's disease and is associated with early cerebrovascular dysfunction. While lipid dysregulation has been extensively studied in neurons and microglia, far less is known about how lipid metabolism is altered in pericytes and how this may influence neurovascular function.

To address this, we performed lipidomic and proteomic profiling of human iPSC-derived pericytes generated from four pairs of APOE isogenic lines. APOE4 pericytes exhibited distinct lipid signatures relative to APOE3 controls, including alterations in neutral lipid pools and enrichment of lipid classes. Notably, we identified changes in ganglioside (GM) abundance, a class of glycosphingolipids that regulate membrane organization and protein localization. Given prior evidence that gangliosides influence integrin localization and signaling, these findings suggest a potential mechanism by which APOE4-driven lipid remodeling may alter pericyte interactions with the extracellular matrix and neighboring cells.

Together, this work defines the lipid landscape of human pericytes and demonstrates that APOE4 reshapes their lipid composition. These findings provide a framework for understanding how altered lipid transport and metabolism in pericytes may contribute to blood–brain barrier dysfunction and broader neurovascular deficits in Alzheimer's disease.

Weight-cycling worsens obesity-induced inflammation through the reprogramming of myeloid cells and their progenitors

Abstract Number: 13
Poster Number: 14

Wenceslao Martinez-Navarrete (University of Chicago), Rotem Kalev-Altman (University of Chicago), Emilio Del Angel (University of Chicago), Aleepta Guha-Ray (University of Chicago), Lourdes Caceres (University of Chicago), Ada Weinstock (University of Chicago)

Weight loss improves obesity-related comorbidities and inflammation, however, subsequent weight regain has been linked to worsening of obesity-related diseases. Therefore, it is critical to understand how these body weight fluctuations (known as weight cycling; WC) impact inflammation. We hypothesize that WC leads to an altered inflammatory environment by the reprogramming of hematopoietic and progenitor stem cells (HSPCs) and their subsequent differentiation into highly inflammatory macrophages. To test this hypothesis, we first characterized how WC changes the immune cell composition in mouse circulation, bone marrow, and adipose. We found that WC reduced circulating immune cells and bone marrow HSPCs compared to non-WC obese controls, while adipose myeloid cells remained unchanged. Despite these reductions in immune cells, levels of plasma pro-inflammatory cytokines were equal to the non-WC group, suggesting heightened cytokine production per cell. To test if WC changes the inflammatory potential of macrophages, we differentiated bone-marrow derived macrophages (BMDMs) from WC and non-WC mice and stimulated them with lipopolysaccharide. We found that WC BMDMs secreted more pro-inflammatory and less anti-inflammatory cytokines. Additionally, WC BMDMs had a reduced ability to phagocytose bacteria. In vivo, normalized to their PBS-treated controls, lipopolysaccharide challenge resulted in increased circulating neutrophils, monocytes, and inflammatory cytokines in WC, compared to non-WC controls. To test whether WC influences the ability of HSPCs to produce mature immune cells, I performed a competitive bone marrow transplant in which HSPCs from donor WC mice are mixed 1:1 with lean competitor HSPCs and transferred to lean recipients. I tracked the contribution of donor cells to produce mature cells over 16 weeks using flow cytometry and found that WC HSPCs had a higher ability to repopulate the recipient immune system compared to non-WC HSPCs, and they produced more myeloid cells. Our findings highlight that WC is reprogramming HSPCs, leading to a shift in immune cell composition and heightened inflammatory response, despite reductions in overall cell numbers. Upon inflammatory challenge, WC mice mount a stronger inflammatory response, marked by increased myeloid cells and cytokines. Finally, WC enhances the propensity of HSPCs to produce inflammatory myeloid cells, all of which may explain the enhanced disease risk seen with WC.

BAT specific FASN Inhibition as a Novel Strategy to Rescue Alcohol-Induced Hypertriglyceridemia and fatty liver disease by enhancing thermogenesis.

Abstract Number: 14
Poster Number: 15

Preethi Parupalli (University of Texas at Dallas)

Alcohol consumption is a major contributor to global morbidity and mortality and is strongly linked to alcohol-associated liver disease (ALD). A key metabolic feature of ALD is hypertriglyceridemia (HT), driven by both increased hepatic triglyceride (TG) production and impaired peripheral clearance. Ethanol metabolism promotes TG accumulation by enhancing de novo lipogenesis, increasing very-low-density lipoprotein (VLDL) secretion, and reducing fatty acid oxidation. In addition, disruptions in TG clearance pathways are emerging as important contributors. Lipoprotein lipase (LPL) is central to hydrolyzing circulating TGs, but alcohol exposure can impair this process through mechanisms such as elevated apolipoprotein C-III, insulin resistance, and adipose tissue dysfunction. Notably, increased TG levels may occur even without changes in LPL activity, suggesting the involvement of alternative regulatory pathways. Brown adipose tissue (BAT), a thermogenic organ with a well-established capacity to clear circulating lipids upon activation a potential regulator of TG metabolism. Beyond LPL-mediated lipolysis, BAT can facilitate very-low-density lipoprotein receptor (VLDLR) mediated lipid uptake during cold-induced thermogenesis. However, the mechanistic basis of non-canonical thermogenic activation and its role in lipid metabolism during alcohol exposure remain poorly understood. In this study, we investigated whether targeting fatty acid synthase (FASN), a key enzyme in de novo lipogenesis, could modulate BAT function and TG clearance under ethanol exposure. Using a BAT-specific FASN knockout model, we show that inhibition of lipogenesis in BAT enhances thermogenesis and promotes the uptake of very-low-density lipoprotein (VLDL) particles, resulting in significantly improved plasma TG clearance during alcohol exposure. Consistent with these in vivo findings, our studies in primary brown adipocyte cultures confirm that pharmacological inhibition of FASN induces thermogenic activation, as evidenced by upregulation of key thermogenic genes, including UCP1, PRDM16, and PPARα, under both control and ethanol-treated conditions. Further, VLDLR transcript levels and VLDL-Dil uptake assays reveal that FASN inhibition enhances VLDL uptake via VLDLR, suggesting that BAT fuels thermogenesis through VLDL-derived lipid uptake. Collectively, these findings highlight a critical role for FASN inhibition in promoting non-canonical BAT activation and facilitating lipid clearance, particularly under alcohol exposure. Importantly, this metabolic adaptation improves hepatic lipid homeostasis through increased AMP-activated protein kinase (AMPK) activation and enhanced β-oxidation. Together, our results identify a role for BAT in mitigating alcohol-induced dyslipidemia through non-canonical thermogenic mechanisms. Targeting FASN in BAT may represent a promising therapeutic strategy for reducing HT and restoring systemic lipid balance in the context of alcohol exposure.

Impaired lipoprotein secretion by APOE4 leads to lysosomal and mitochondrial dysfunction in human microglia

Abstract Number: 15

~~**Poster Number: 16**~~

Jasmin Revanna (Salk Institute), Fred Gage (Salk Institute)

Microglia are specialized resident macrophages of the central nervous system that help to clear debris, pathogens, and neuronal synapses through phagocytosis. These cells play a crucial role in neuroinflammation and disease. However, their role in the onset or progression of disease, particularly in Alzheimer's disease (AD) remains unclear. Microglia express high levels of APOE, an important risk factor gene for AD. It has been shown that carriers of the APOE4 genotype have an increased risk for AD, while APOE2 carriers have protection to AD. Microglia are important in the clearance of pathology in disease, therefore we sought to understand the impact APOE4 has on microglial function. From 22 patient iPSC-derived microglia lines, we demonstrate that APOE4 suppresses the activated response state (ARMs), also known as disease associate microglia (DAMs), and promotes a senescent-like state. This supports ARMs having a neuroprotective role. We show that these senescent-like cells are G2 cell cycle arrested and contain an increase in cholesterol esters. We utilized isogenic APOE33 and APOE44 iPSCs to study their functional differences. APOE44 microglia have an overall increase of cholesterol esters, and specifically an accumulation in their lysosomes leading to impaired acidity and degradation capacity. We believe this causes stress at the endoplasmic reticulum (ER), as supported by proteomics data, which dysregulates lipid support to the mitochondria therefore causing mitochondrial stress as seen by an increase in reactive oxygen species (ROS) and a decrease in mitochondrial membrane potential. Microglia can shift between utilizing glycolysis, oxidative phosphorylation and fatty acid oxidation to generate energy, depending on their activation state, with proinflammatory microglia mostly utilizing glycolysis and anti-inflammatory microglia utilizing fatty acid oxidation and oxidative phosphorylation. We find that APOE4 contributes to a shift away from fatty acid oxidation and towards glycolysis, which then leads to an increase of lactate being secreted from the cells. Subsequently, these APOE44 microglia are more proinflammatory, secreting more cytokines like CCL2, IL-8 and IL-6. We show that neurons cultured with APOE44 microglia have significantly fewer lipids compared to those cultured with APOE33 microglia, suggesting APOE44 microglia may not provide neurons with appropriate lipid support. This leads to a decrease in synapse formation in the neurons cultured with APOE44 microglia. Lastly, APOE44 microglia secrete significantly less APOE and high-density lipoproteins compared to APOE33 microglia. These data indicate that microglia produce and export lipoproteins during normal function and that lipoprotein secretion is impaired in APOE44. Taken together, we show that this reduced lipoprotein secretion leads to cholesterol esters building up in cells, including in lysosomes, negatively impact the lysosome-endoplasmic reticulum-mitochondrial axis.

Pcpe2 Drives Adipose Dysfunction And Consequent Obesity Through TGFβ Signaling

Abstract Number: 16
Poster Number: 17

Alexander Rocksvold (Medical College of Wisconsin), Mirza Beg (Medical College of Wisconsin), Bilal Ahmad (Medical College of Wisconsin), Hao Xu (Medical College of Wisconsin), Rana Gupta (Duke University), Pablo Morales (Duke University), Mary Sorci-Thomas (Medical College of Wisconsin)

Obesity is a chronic health condition primarily affecting white adipose tissue (WAT) and is exacerbated by the consumption of a Western Diet (WD). Currently, it is estimated that >40% of the U.S. population is obese, and rising, dramatically increasing mortality by raising the prevalence of cardiovascular disease and cancer. It is well established that transforming growth factor beta (TGFβ) signaling is elevated in WAT and contributes to pathological adipose expansion and remodeling. Functionally, TGFβ signaling in WAT inhibits the master regulator of adipogenesis, peroxisome proliferator-activated receptor gamma (PPARγ). When PPARγ is attenuated, differentiation of new preadipocytes is impaired, leading to hypertrophy of existing adipocytes. WAT hypertrophy results in local inflammation and the downregulation of uncoupling protein 1 (UCP-1), a mitochondrial transporter associated with beiging of WAT. In WAT, mechanisms regulating TGFβ signaling are not fully understood, providing an opportunity to control healthy adipose expansion. We hypothesize that Procollagen C-endopeptidase Enhancer 2 (Pcpe2), an extracellular matrix glycoprotein expressed highly in WAT, promotes TGFβ signaling, which in turn inhibits PPARγ and UCP1 expression, attenuating healthy adipose beiging. Using an adipose-specific Pcpe2 knockout mouse model (Adipo+Pcpe2KO) we have shown the deletion of Pcpe2 protects against diet induced obesity (25% body weight reduction, $p<0.01$, $n=12$), reduces plasma glucose (23% reduction, $p<0.01$, $n=12$), and increases whole body energy expenditure ($p<0.03$, $n=8$), as measured by metabolic cage analyses, compared to control mice. Additionally, adipocytes lacking Pcpe2 show reduced TGFβ signaling, evidenced by a decrease in the phosphorylated-SMAD2/3 to total SMAD ratio. To further our investigations into Pcpe2's mechanism, we next examined PPARγ and UCP1 mRNA in adipocytes and found elevated PPARγ mRNA (8-fold, $p<0.01$) and UCP1 mRNA (6-fold, $p<0.0001$), in cells lacking Pcpe2 compared to controls. Overall, these data suggest that Pcpe2 acts as an extracellular enhancer of TGFβ signaling, which has the downstream effects of inhibiting PPARγ, and UCP1 and consequently attenuating healthy adipose expansion and remodeling.

ApoE4 Inhibits Lipoprotein Lipase in a Lipidation and Cofactor Specific Manner

Abstract Number: 17
Poster Number: 18

Mary Rouse (Univ of Colorado Anschutz), Emma E. Lietzke (University of Colorado Anschutz, University of Colorado Boulder), Dean Oldham (University of Colorado Anschutz), Hannah M. Binfet (University of Cincinnati, Oregon Health and Science University), Rowan S. Wooldridge (University of Cincinnati, Oregon Health and Science University), John Melchior (Pacific Northwest National Laboratory), Kimberley Bruce (University of Colorado Anschutz)

Apolipoprotein E (ApoE) is a critical regulator of lipoprotein transport in the central nervous system (CNS), and the ApoE4 isoform is the strongest genetic risk factor for Alzheimer's disease. Emerging evidence suggests that ApoE4 disrupts brain lipid metabolism; however, the molecular mechanisms underlying this dysfunction remain poorly defined. Lipoprotein lipase (LPL) is a key regulator of CNS lipoprotein metabolism and microglial function and has been implicated in neurodegenerative disease. Although ApoE4 has been proposed to inhibit LPL activity, the mechanisms governing this interaction have not been thoroughly investigated.

Using LPL activity assays, we examined the effects of astrocyte derived ApoE containing lipoproteins, purified unlipidated ApoE, and lipid bound ApoE incorporated into phospholipid rich recombinant HDL like particles on LPL function. We further assessed whether a mimetic peptide based on ApoC-II (ApoC-II-P), an endogenous activator of LPL, could modulate ApoE mediated inhibition. To define the molecular basis of ApoE dependent LPL inhibition, we performed high resolution molecular dynamics simulations.

We found that ApoE containing astrocyte derived lipoproteins potently inhibit LPL activity in cell free assays and that unlipidated ApoE4 similarly suppresses LPL when incorporated into triglyceride rich emulsions. In contrast, phospholipid bound ApoE did not inhibit LPL. Notably, ApoC II P attenuated ApoE mediated LPL inhibition. Molecular dynamics simulations revealed that ApoE4 preferentially associates with the LPL flexible "lid" domain, while ApoC II-P competes with and displaces this interaction.

Together, these findings demonstrate that the lipidation state of ApoE4 is a critical determinant of its ability to inhibit LPL and highlight ApoC-II-based mimetic peptides as a potential therapeutic strategy to restore lipid metabolism in ApoE4 associated neurodegenerative disease.

A Lipid Membrane Embedded Model of the Full TREM2–DAP12 Signaling Complex

Abstract Number: 18
Poster Number: 19

David Saeb (University of Colorado Boulder), Kayla Sprenger (Department of Chemical and Biological Engineering, University of Colorado Boulder)

Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is a transmembrane immune receptor expressed on microglia, the primary innate immune cells of the brain. TREM2 plays a central role in regulating brain lipid metabolism and microglial responses to lipid-rich debris, recognizing ligands, including phospholipids, and lipoproteins such as apolipoprotein E (ApoE). Dysregulation of these pathways has been strongly implicated in Alzheimer's disease (AD), and TREM2 has emerged as a promising therapeutic target with multiple drug candidates currently in development. TREM2 signals through its interaction with the adaptor protein DAP12 in the membrane, but the molecular mechanisms governing signal propagation remain poorly understood. Here, we apply multiscale molecular dynamics (MD) simulations to investigate the structural dynamics of the full TREM2–DAP12 signaling complex embedded in a lipid bilayer. Using a combination of coarse-grained and atomistic simulations, we perform the first-ever simulations of the complete receptor–adaptor complex within a membrane environment to examine how extracellular events may propagate through the lipid interface to initiate signaling. Our simulations reveal that the flexible stalk region of TREM2 enables the extracellular Ig-like domain to approach and interact directly with the membrane surface. These interactions create a coupling between the extracellular domain, the lipid bilayer, and the transmembrane signaling complex. This membrane engagement provides a mechanistic explanation for how ligand binding influences the orientation and dynamics of the receptor–DAP12 assembly, thereby modulating downstream signaling. Together, these results highlight an underappreciated role of membrane interactions in TREM2 signaling and provide molecular insight into how lipid–protein interactions may regulate microglial immune activation. More broadly, this work demonstrates how multiscale molecular simulations can reveal structural mechanisms of immune receptors within realistic membrane environments, informing therapeutic strategies targeting neuroinflammation and lipid metabolism in Alzheimer's disease.

Identifying novel lipophagy regulators necessary for proteostasis in neurodegenerative diseases

Abstract Number: 19
Poster Number: 20

Bijoya Sen (Buck Institute), Sophia Lehrman (Buck Institute), Malene Hansen (Buck Institute)

Disruption of lipid homeostasis is increasingly recognized as a feature of aging and neurodegenerative disease. Lipid droplets accumulate in neurons across multiple disease contexts, and recent work in mouse models demonstrate that decreased lipid turnover can directly impair cognitive function (Barnett AM et al., 2025). However, the mechanisms that regulate neuronal lipid clearance and how this process influences neuronal health remain poorly understood.

Using Caenorhabditis elegans as a genetically tractable model, we examined how impaired lysosomal lipid breakdown impacts organismal physiology and neurodegeneration-relevant phenotypes. Loss of the lysosomal lipase lipl-4, a close ortholog to human lysosomal acid lipase (LAL), display increased lipid accumulation. We previously reported that LIPL-4/LAL overexpression extends C. elegans lifespan in an autophagy-dependent fashion. In turn, we now found that impaired lipid clearance in lipl-4 mutants was accompanied by functional decline, including reduced motility and deficits in both short- and long-term associative learning. These observations link defective lipid turnover to behavioral phenotypes relevant to neurodegeneration. We next asked how lipid droplets could be selectively recognized and targeted for autophagic degradation in this context. To identify molecular components that mediate selective lipophagy, we implemented an unbiased candidate discovery pipeline. Lipid droplet–resident proteins were shortlisted from published mass spectrometry analyses of isolated C. elegans lipid droplets and subsequently screened in silico for the presence of LC3-interacting region (LIR) motifs, a defining feature of selective autophagy receptors that bind ATG8/LC3 family proteins. Functional screening of this group of ~300 candidate genes using RNAi revealed a short list of genes whose knockdown resulted in elevated lipid-droplet levels, consistent with a role in lipid clearance. Ongoing work is focused on further characterizing these candidates as potential lipophagy receptors and determining how they influence lipid turnover and neurodegeneration-associated phenotypes.

Together, this work moves beyond the observation that lipids accumulate in neurodegeneration by identifying candidate molecular components of the selective lipophagy machinery that may link lipid metabolism to neuronal dysfunction.

ApoE Lipidation State Directs Immunometabolic Reprogramming of Human Microglia

Abstract Number: 20
Poster Number: 21

Tsion Shiferaw (University Colorado Anschutz), Snigdha Sarkar (Biological Sciences Division, Earth and Biological Sciences Directorate, Pacific Northwest National), Katelyn Baker (Division of Endocrinology, Metabolism and Diabetes, University of Colorado Anschutz Medical Campus), Rowan S. Wooldridge (University of Cincinnati, Oregon Health and Science University), Hannah M. Binfet (University of Cincinnati, Oregon Health and Science University), Victoria Prozapas (Biological Sciences Division, Earth and Biological Sciences Directorate, Pacific Northwest National), Chinemerum Ogbu (Biological Sciences Division, Earth and Biological Sciences Directorate, Pacific Northwest National), Athena Schepmoes (Biological Sciences Division, Earth and Biological Sciences Directorate, Pacific Northwest National), Isaac Attah (Biological Sciences Division, Earth and Biological Sciences Directorate, Pacific Northwest National), Christy Niemeyer (University of Colorado, Anschutz Medical Campus), Kayla Sprenger (Department of Chemical and Biological Engineering, University of Colorado Boulder), James Hassell (Division of Endocrinology, Metabolism and Diabetes, University of Colorado Anschutz Medical Campus), Robert Eckel (University of Colorado Anschutz Medical Campus), John Melchior (Pacific Northwest National Laboratory), Kimberley Bruce (University of Colorado Anschutz)

The ε4 allele of apolipoprotein E (ApoE4) is the strongest genetic risk factor for Alzheimer's disease (AD) and has been linked to microglia dysfunction. Despite the growing interest in ApoEs role in microglial dysfunction, the degree to which its lipidation state shapes microglial biology remains unresolved. Thus, we examined isoform and lipidation-specific effects of ApoE on human microglia by supplementing cells with either lipid-free ApoE3 and ApoE4 or reconstituted high-density lipoprotein-like particles (rHDL) containing ApoE3 or ApoE4. Using label-free live cell holotomography and global proteomics, we were able to characterize microglial morphology, lipid droplet dynamics, mitochondrial abundance, and protein expression. We found ApoE4 treatment resulted in fewer but larger lipid droplets and increased mitochondrial fragmentation compared to ApoE3, effects that were augmented by rHDL-ApoE4. Proteomic analyses revealed a pronounced type I interferon response in cells exposed to lipid-free ApoE, which was exacerbated by lipid-free ApoE4. These findings highlight the importance of considering lipidation status when evaluating ApoE4-mediated microglial dysfunction underlying AD neuropathogenesis.

Perilipin-2 Loss Reprograms Microglial Lipid Droplet Biology and Immunometabolic Responses

Abstract Number: 21
Poster Number: 22

Isaiah Stephens (University of Kentucky), Lance Johnson (University of Kentucky)

Background: Lipid droplet accumulation is increasingly recognized as a feature of dysfunctional microglial states in neurodegeneration. In Alzheimer's disease (AD), lipid droplet-rich glia have been linked to impaired phagocytosis, inflammatory activation, and altered cellular metabolism. Perilipin-2 (Plin2), a lipid droplet-associated protein elevated in AD, may promote maladaptive lipid storage and impair microglial homeostasis. Thus, we sought to determine the role of Plin2 in microglial response to AD stimuli and whether the reduction of Plin2 would protect microglia from adopting a lipid-laden state.

Methods: We generated a Plin2 knockout (KO) BV2 microglial cell line to define how Plin2 regulates lipid droplet accumulation, lipid composition, phagocytic function, and transcriptional responses to AD-relevant stimuli. WT and Plin2 KO BV2 microglia were treated with oleic acid (250 uM), amyloid-beta (1.5 uM), myelin debris (15 ug/cm2), or dead neurons to model lipid loading and neurodegeneration-relevant stress. Lipid droplets were quantified by Lipi-Green staining and HALO analysis. Phagocytosis was assessed using pHrodo-zymosan particles under lipid-loading conditions. Lipidomics was performed by LC-MS after 24-hour treatment, and bulk RNA-seq was performed on identically treated samples. Complementary analyses were conducted in APOE3 and APOE4 iPSC-derived microglia following PLIN2 knockdown via siRNA transfection.

Results: Across treatment conditions, Plin2 KO microglia showed a consistent reduction in lipid droplet burden together with enhanced phagocytic capacity. Lipidomic profiling revealed depletion of triacylglycerols and diacylglycerols with increased cholesterol esters, indicating substantial remodeling of intracellular lipid storage. Transcriptomic analyses demonstrated increased oxidative phosphorylation and reduced inflammatory signaling, particularly following amyloid-beta exposure, consistent with a shift away from a lipid droplet-accumulating, dysfunctional state. We then extended these experiments into human APOE3 and APOE4 iPSC microglia. These effects were observed across both lipid-loading and disease-relevant challenge conditions in complementary experimental models.

Conclusion: Together, these findings identify Plin2 as a regulator of microglial lipid droplet biology, immunometabolism state, and functional responsiveness to AD-relevant stressors. Loss or reduction of Plin2 limits pathological lipid accumulation while promoting phagocytic and metabolic adaptation, supporting PLIN2 as a candidate therapeutic target in neurodegenerative disease.

GPR182 is a lipoprotein receptor for dietary fat absorption

Abstract Number: 22
Poster Number: 23

ZHIWEI SUN (CU Anschutz Medical Campus), Yuwen Zhu (University of Colorado Anschutz Medical Campus)

The lymphatic system plays a central role in lipid absorption by transporting triglyceride-rich particles called chylomicrons (CMs) from the small intestine to the systemic circulation. However, the molecular mechanism by which CMs get into the intestinal lymphatics is unknown. Here we demonstrated that GPR182, an atypical chemokine receptor in lymphatic endothelial cells, mediates dietary fat absorption. GPR182 knockout mice exhibit a selective increase in circulating high-density lipoproteins and are resistant to dietary-induced obesity. GPR182 ablation in mice leads to poor lipid absorption and thereby a delay in growth during development. GPR182 broadly interacts with and transports lipoproteins. Transmission electron microscopy analysis reveals that mechanistically, loss of GPR182 prevents CMs from entering the lacteal lumen of the small intestine. Consistent with this, GPR182 blockade with monoclonal antibodies protects mice from diet- induced obesity and treats existing obesity. Together, our study identifies GPR182 as a lipoprotein receptor that mediates dietary fat absorption and supports GPR182 blockade as a feasible approach to treat obesity and related disorders.

Age-Dependent Differences in Atherogenesis Revealed by Single-Cell Profiling of Murine Arteries

Abstract Number: 23
Poster Number: 24

Jaclyn Whalen (Saint Louis University), Ryan Allen (University of Arkansas for Medical Science), Emily Ebert (Saint Louis University), Michelle Brennan (Saint Louis University), Rajeev Aurora (Saint Louis University), Angel Baldan (Saint Louis University)

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of death and disability in Western societies. Most clinically relevant ASCVD disease occurs in older populations (typically aged 50+). However, the majority of previous atherosclerotic murine studies have consistently used young animals, usually 10–12 weeks at the beginning of intervention. To better understand how the aging of the artery may affect atherogenesis, we exposed young (3-month-old, corresponding to ~20-year-old human) and old (18-month-old, corresponding to ~55-year-old human) male mice to the same 4-month experimental dyslipidemia. We show that AAV-mPCSK9(D377Y) transduction followed by Western diet resulted in similar levels of hypercholesterolemia and hypertriglyceridemia in both groups. Despite this, morphometric analyses of serial sections of the aortic root revealed a significant reduction in lesion size and neutral lipid deposition in older mice compared to their young counterparts. We used single-cell RNA-seq to compare the cellular composition of plaques in young and old mice by creating pooled, single-cell suspensions of the proximal aorta (from the root to the left subclavian artery). Our analysis identified that subpopulations of contractile smooth muscle cells were enriched in old aortas while chondrocyte-like, synthetic cells were enriched in young aortas. A subpopulation of endothelial cells was exclusively found in old aortas; these were enriched in alpha-1 antitrypsin transcripts (Serpina1a/b/d), which are known to be anti-inflammatory and athero-protective. In addition to changes in relative abundance of functional cell subpopulations, many clusters (including smooth muscle cells, endothelial cells, and inflammatory cells) exhibited distinct age-dependent transcriptional profiles. These pathways, which are specific to aged arteries, are presumably more relevant to aged patients and may hold more relevant therapeutic potential. Overall, our data reveal distinct responses of young and aged arteries to identical proatherogenic conditions, emphasizing the importance and necessity of age-stratified experiments in future murine atherosclerosis studies.

Beyond Neutral Lipases: The Adipocyte Lysosome as a Nexus for Lipid Mobilization and Systemic Metabolic Health

Abstract Number: 24
Poster Number: 25

Yu-Sheng Yeh (University of Pittsburgh), Yu-Ling Chen (University of Pittsburgh), Jun Huang (University of Pittsburgh), Xiangyu Zhang (University of Pittsburgh), Md Saifur Khan (University of Pittsburgh), Ziyang Liu (University of Pittsburgh), Babak Razani (University of Pittsburgh)

Adipose tissue maintains systemic energy balance through the regulated mobilization of lipids. While cytosolic lipolysis via adipose triglyceride lipase (ATGL) is the canonical pathway, this system is frequently suppressed during obesity. Furthermore, ATGL-deficient models are still able to hydrolyze lipid droplets (LDs), suggesting alternative lipolytic pathways exist. Our recent publication (Yeh et al., Journal of Clinical Investigation, 2025) identified lysosomal acid lipase (LAL) as an essential, non-redundant mediator of such an alternative lipolytic route. However, the relative systemic significance of this pathway compared to canonical lipolysis remained undefined. The current study addresses critical gaps regarding the systemic significance of this pathway by defining the divergent roles of cytosolic and lysosomal lipolysis in maintaining metabolic flexibility.

Transcriptional profiling via snRNA-seq and qPCR reveals that in obese adipocytes, the lysosomal lipolysis pathway is robustly upregulated while the cytosolic pathway is suppressed, suggesting a functional redistribution of LD hydrolysis routes. To functionally dissect these distinct lipolytic routes, we utilized mouse models with adipocyte-specific deletion of LAL (A-LAL KO) or ATGL (A-ATGL KO), targeting the rate-limiting enzymes of the lysosomal and cytosolic pathways, respectively. Under normal diet baseline, both A-LAL KO and A-ATGL KO mice exhibit shared defects in stress-induced in vivo and ex vivo lipolysis alongside elevated respiratory exchange ratios compared to controls. While neither model showed significant differences in total body weight at baseline, both exhibited significantly higher fat mass. However, their metabolic profiles diverged sharply: A-LAL KO mice displayed markedly lower energy expenditure and impaired glucose/insulin tolerance tests, whereas A-ATGL KO mice maintained stable energy expenditure and showed improved glucose/insulin sensitivities. Upon high-fat diet challenge, these baseline divergences were amplified into opposite metabolic fates. A-LAL KO mice became significantly more obese, characterized by accelerated body weight gain and exacerbated fat mass accumulation, alongside worsened hepatic function. In contrast, ATGL deficiency remained notably protective against diet-induced obesity and hepatic steatosis.

Finally, ex vivo pharmacological cross-inhibition assays confirmed that these pathways function as independent metabolic axes for LD mobilization, as combining genetic deficiency with reciprocal pharmacological inhibition resulted in additive suppression of lipid mobilization. We conclude that the upregulation of adipocyte lysosomal lipolysis constitutes a distinct LD-trafficking axis essential for systemic metabolic regulation. Unlike the canonical pathway, this lysosomal axis represents a promising therapeutic target to restore adipose health and mitigate systemic metabolic complications in the obese population.

Adipose FXR Loss Impairs Angiogenic Gene Expression and Promotes Hepatic Steatosis in a murine model under a Western Diet.

Abstract Number: 25
Poster Number: 26

Diana Ximena Yrigoyen Rosas (UIUC)

Adipose tissue (AT) is a dynamic organ that expands or regresses in response to nutrient availability, requiring coordinated hormonal regulation and angiogenesis to support healthy remodeling. AT expansion occurs through hyperplasia or hypertrophy, both of which are linked to adipocyte differentiation and vascularization. The nuclear receptor Farnesoid X Receptor (FXR) functions as a nutrient sensor regulating lipid and glucose metabolism, and its role in adipose tissue has been associated with altered glucose homeostasis and angiogenic capacity. While obesity is a major driver of metabolic dysfunction-associated fatty liver disease (MAFLD), most studies rely on high-fat diets that don't reflect the excess carb intake seen in human studies. Here, we investigated the impact of adipose-specific FXR deletion (Ad-FxrKO) on systemic metabolic responses under a Western diet (WD; high-fat/high-sucrose). Male Ad-FxrKO and floxed control mice (C57BL/6J, 10–12 weeks, n=6–8/group) were fed chow or WD for 4 weeks. Metabolic phenotyping, histological analysis, and hepatic and adipose gene expression were performed to assess inter-organ crosstalk. Ad-FxrKO mice developed glucose intolerance, increased adipocyte hypertrophy, and presented increased hepatic steatosis under WD. Notably, the expression of genes involved in hepatic de novo lipogenesis was reduced in Ad-FxrKO mice despite increased lipid accumulation, suggesting a dissociation between hepatic lipid synthesis and storage. Concurrently, mesenteric AT exhibited reduced expression of angiogenesis-related genes, consistent with impaired tissue remodeling capacity. These findings support a model in which loss of adipose FXR disrupts angiogenic-dependent tissue expansion, promoting adipocyte hypertrophy. We are currently examining the delivery of adipose-derived fatty acids to the liver and whether it is driving steatosis independently of hepatic lipogenesis. We are also studying the contribution of hepatic insulin signaling to this phenotype. Overall, our data identifies adipose FXR as a key regulator of adipose–liver crosstalk under WD conditions and highlights its role in maintaining metabolic homeostasis and preventing further consequences, such as ectopic lipid deposition.

In Silico Sequence-to-Structure Analysis of Cancer-Associated TREM2 Variants to Inform Therapeutic Modulation of Macrophages

Abstract Number: 26
Poster Number: 27

Emma Aldrich (University of Colorado Boulder)

Tumor-associated macrophages drive immunosuppression in the tumor microenvironment, posing a major barrier to effective immunotherapy. A key regulator of this phenotype is Triggering receptor expressed on myeloid cells 2 (TREM2), a transmembrane receptor enriched in anti-inflammatory macrophages that integrates signals from lipid-rich environments. TREM2 binds a diverse range of lipid ligands, including lipoproteins and phospholipids, positioning it as a central mediator of macrophage lipid sensing and immunometabolic reprogramming. These lipid-dependent interactions influence macrophage proliferation, survival, phagocytosis, and inflammatory signaling, linking TREM2 activity to both tumor progression and systemic inflammatory disease. While TREM2 variants have been extensively studied in neurodegenerative contexts, particularly Alzheimer's disease, their role in cancer-associated lipid signaling and immunometabolism remains poorly understood. Here, we present an in silico framework to identify cancer risk-associated TREM2 variants and characterize their effects on the structure and energetics of the TREM2 immunoglobulin-like domain. By comparing cancer-associated variants with known Alzheimer’s disease variants, we identify divergent patterns of conformational sampling and energetic stabilization that suggest an inverse relationship between lipid-mediated signaling states in cancer and neurodegeneration. Importantly, these variant-induced structural shifts reshape the lipid-binding landscape of TREM2, altering its capacity to engage lipid ligands and modulate downstream immunometabolic pathways. Clustering of conformational states reveals pathogenicity-weighted ensembles predictive of distinct inflammatory phenotypes, highlighting how specific lipid-responsive conformations may bias macrophages toward immunosuppressive or immune-activating states. Together, this work establishes a mechanistic link between sequence variation, lipid recognition, and macrophage immunometabolism, providing a framework to target TREM2 conformations that selectively reprogram lipid-driven immune signaling in cancer and other inflammatory diseases.

Concurrence of perilipin-2 and amyloid beta pathology in the brains of human and murine models of Alzheimer's disease

Abstract Number: 27
Poster Number: 28

Conner Angelle (University of Florida), Guilian Xu (University of Florida), Stefan Prokop (University of Florida), Paramita Chakrabarty (University of Florida)

Introduction. Variations in Apolipoprotein E (APOE) confer the strongest genetic risk of Alzheimer's disease, (AD) with the APOE E4 isoform increasing AD risk while the E2 isoform protects against AD and increases human lifespan. Intracellular lipid droplet accumulation has emerged as a key feature of Alzheimer's disease pathogenesis, driven in part by dysfunction in glial metabolism. Compared to the neutral APOE E3 isoform, the E4 isoform inefficiently shuttles lipids released from stressed or damaged neurons, leading to their storage as perilipin-coated lipid droplets. This lipid droplet buildup marks a shift toward a dysfunctional glial phenotype associated with impaired amyloid clearance and heightened inflammatory signaling, suggesting that perilipin expression may serve as a marker of this pathological state.

Methods. We used immunohistochemistry with whole slide imaging and immunofluorescence with confocal imaging, followed by QuPath data analysis to identify perilipin-2 accumulation within Iba-1+ microglia and GFAP+ astrocytes on formalin-fixed paraffin embedded brain sections. We used rodent brains from the knock-in SAA-APP line expressing mutant human Aβ (n=19), the knock-in hAbeta line expressing wild type human Aβ (n=12), and the transgenic P301S PS19 tau line (n=13). Human brains, corresponding to Alzheimer's disease (n=20) or normal healthy individuals (n=4), were obtained from the University of Florida Human Brain & Tissue Bank.

Results. In microglia and astrocytes, humans and SAA-APP mice expressing APOE4 had significantly higher perilipin-2 staining indicative of high lipid droplet burden compared to other APOE alleles. Interestingly, correlation analysis of glial PLIN2 with cortical Aβ burden in SAA-APP mice showed strong positive relationship with both E4 and E2 isoforms. In hAbeta line that do not develop amyloid deposits in their lifetime, E4 isoform showed higher astrocyte perilipin-2, but microglial perilipin-2 was similar to E3 isoform.

Conclusions: We found increased perilipin staining in astrocytes and microglia in both mouse and human Alzheimer's disease tissue, correlating with extracellular Aβ pathology burden and APOE4 genotype, supporting a link between glial lipid droplet accumulation and increased disease risk in E4 individuals. Astrocytic induction of perilipin-2 in wild type Aβ mice indicates that these could be the first cells where E4 isoforms initiate lipid dysfunction in the prodromal phases of the disease. Accumulation of glial perilipin-2 in APOE2 mice with Aβ deposits indicate glial lipid dyshomeostasis still exists with APOE2 conferring neuroprotection from Alzheimer's disease through other mechanisms. Data from tauopathy cases will further inform the relationship of intracellular lipid dyshomeostasis with intracellular tau protein accumulation.

The role of hepatic cytosolic acyl-CoA metabolism in steatotic hepatocytes.

Abstract Number: 28
Poster Number: 29

Tomasz Bednarski (University of Nebraska-Lincoln), Sylwia Miekus (University of Bialystok), Anne Bader (University of Nebraska-Lincoln), Adam Tylicki (University of Bialystok)

Metabolic-associated steatotic liver disease (MASLD) is characterized by dysregulated lipid homeostasis and persistent metabolic stress. MASLD is the most prevalent liver disease, affecting ~35% of the U.S. population. Chronic liver inflammation and progressive fibrosis lead to the development of steatohepatitis, which may progress to cirrhosis and hepatocellular carcinoma. Despite clinical severity, only one FDA-approved therapy currently exists to prevent the progression of MASLD, creating an urgent need to identify novel molecular pathways that could serve as therapeutic targets. Cytosolic acyl-CoA thioesterases (ACOTs) and acyl-CoA synthetases (ACSs) regulate the balance between acyl-CoAs and free fatty acids; however, their transcriptional contributions to MASLD remain poorly defined. In this study, we investigated the effects of Acot1 and Acsf1 overexpression on lipid metabolism and hepatocyte stress-related gene expression.

AML12 mouse hepatocytes were transfected with plasmid vectors to induce overexpression of Acot1 or Acsf1, followed by steatosis induction using a physiologically relevant palmitic/oleic acid mixture (1:2 ratio). Gene expression related to lipid metabolism and cellular stress was quantified by qPCR. Steatosis was assessed by Oil Red O staining of lipid droplets and by measurement of triglyceride (TG) accumulation. Oxidative stress was evaluated by measuring the rate of reactive oxygen species (ROS) production.

Palmitate/oleate-induced steatosis markedly increased the expression of genes involved in lipid metabolism (Acc, Acsl1, Atgl, Cpt1/2, Dgat1/2, Fabp1/5, Fasn, Gpat1, Plin2, Srebp1), as well as markers of cellular metabolic stress (Atf4/6, Casp3, Ddit3, Ero1a, Grp78, Sod1, Xbp1), and elevated ROS levels in hepatocytes. Overexpression of Acot1 significantly attenuated this transcriptional response, restoring the expression of Acsl1, Atgl, Cpt1, Dgat1/2, Fabp1, Fasn, Gpat1 and Srebp1 toward baseline levels. This effect was accompanied by a significant reduction in lipid droplet formation and TG accumulation. Notably, Acsf1 modulation produced similar normalization of gene expression; however, in the case of Fabp1, Gpat1, and Srebp1, expression levels were even more reduced which resulted in improved mitigation of steatosis. Overexpression of either Acot1 or Acsf1 significantly decreased the expression of metabolic stress markers (Grp78, Atf4/6, Xbp1, Ero1a, Casp3) and reduced ROS production.

These findings suggest that cytosolic ACOT1 and ACSF1 play central roles in regulating the transcriptional response to lipid excess. Overexpression of either enzyme confers a protective effect by partially restoring normal expression patterns of lipogenic and stress-associated genes, with Acsf1 showing more pronounced anti-steatotic effects. Together, these results indicate that targeting ACOT and ACS pathways may help rebalance cellular metabolic homeostasis, positioning these enzymes as promising therapeutic targets for MASLD.

Adipose tissue dynamics after weight loss differ by intervention type

Abstract Number: 29
Poster Number: 30

Rita Brookheart (WashU Medicine), Terri A. Pietka (WashU Medicine), Rodrigo Suarez Lopez Gallo (WashU Medicine), Daniel Ferguson (WashU Medicine)

Introduction: For people with obesity, losing body weight to decrease adipose tissue mass can improve insulin sensitivity and decrease the risk for advanced metabolic diseases. Lifestyle modification, through sustained periods of negative energy balance, can reduce adiposity; however, surgical interventions provide alternative options for weight loss. Different types of weight loss interventions can result in various changes in the quantity and location of adipose tissue mass lost, suggesting that not all interventions impact adipose tissue biology similarly. The exact impact that distinct weight loss interventions have on adipose tissue and long-term human health is not well understood.

Results: Using publicly available bulk RNAseq data, we identified two lifestyle (low caloric diet) and two surgical (Roux-en-Y gastric bypass) intervention studies composed of people with obesity and type 2 diabetes that had 1) individualized demographic and anthropometric data pre- and post- weight loss and 2) bulk RNAseq data of abdominal subcutaneous adipose tissue obtained before and after weight loss. All study participants were from the same geographical region, met similar inclusion/exclusion criteria, had similar pre-weight loss demographic and anthropometric readouts and percentage of post-intervention weight lost (lifestyle 17.2 ± 4.6 %; surgery 20.0 ± 2.7 %; p=0.089), exhibited improvements in insulin sensitivity and metabolic health, and had RNA tissue samples processed and sequenced similarly. We performed secondary analysis of the RNAseq data and applied a standardized downstream analysis pipeline to transform and harmonize the data and determined differential expressed gene (DEG) analysis of each dataset. Gene set enrichment analysis was performed for each DEG list and revealed reductions in pathways for adipogenesis, inflammatory response, and mitochondrial metabolism (adj p <0.005) post-weight loss for both lifestyle and surgical intervention cohorts. To evaluate whether adipose cellular remodeling differed by intervention type, cell-type composition and proportions were determined by deconvolution using Bayesian methodology. Post-lifestyle intervention, adipose tissue exhibited immune cell remodeling, with a significantly reduced proportion of neutrophils and an increase in T cells (FDR <0.009). In contrast, post-surgical intervention revealed no differences in adipose tissue cell-type composition after multiple testing correction. Directional changes were observed for several immune populations, including increases in T cells and mast cells, but these effects were not statistically robust.

Conclusion: These data suggest that the type of weight loss intervention, surgical versus lifestyle modification, is associated with differences in adipose cellular remodeling. Future work will characterize T cell subtypes and adipocyte subpopulations following weight loss.

Ceramide Synthase 5 and Ceramide Synthase 2 Have Opposing Roles in Rodent Models of Diastolic Dysfunction

Abstract Number: 30
Poster Number: 31

Jason Burchett (Virginia Commonwealth Universi), Anna Kovilakath (Virginia Commonwealth University), Lauren A. Cowart (VCU)

Heart failure with preserved ejection fraction (HFpEF) accounts for over half of all heart failure cases and is driven by diastolic dysfunction (DD), yet the molecular mechanisms underlying DD remain poorly defined. Circulating sphingolipids are established biomarkers of heart failure, and preclinical studies link sphingolipids to cardiac dysfunction. However, prior approaches relied on nonspecific, systemic inhibition of sphingolipid synthesis, precluding identification of the specific lipids and enzymes driving cardiomyocyte-intrinsic disease. Here, we investigated the role of cardiomyocyte-specific ceramide synthase 2 (CerS2) and ceramide synthase 5 (CerS5), the enzymes that synthesize very long-chain and long-chain ceramides, respectively, in DD. Lipidomic analyses across five rodent models of DD revealed that common CerS5-derived sphingolipids were upregulated, whereas one common CerS2-derived sphingolipid was downregulated, suggesting opposing roles for these enzymes. Using inducible cardiomyocyte-specific deletion (ΔCM) models, we found that CerS5 loss preserved diastolic function, improved myocardial energetics, and protected against systemic metabolic dysfunction. In contrast, CerS2 loss did not protect against diastolic abnormalities or impaired AMPK signaling, and it promoted weight gain. Together, these findings identify a CerS5/CerS2 axis as a key player in DD in HFpEF and highlight CerS5 inhibition as a potential therapeutic approach for cardiometabolic disease.

Genetic Regulation of Hepatocyte Inter-Organelle Crosstalk through APOE Isoforms in MASLD

Abstract Number: 31

Karthickeyan Chella Krishnan (University of Cincinnati)

Background: Lipid droplets (LDs) are dynamic energy-storage organelles that interact with mitochondria to coordinate lipid metabolism, a process central to metabolic dysfunction-associated steatotic liver disease (MASLD) and its progression to steatohepatitis (MASH). LDs interact with two mitochondrial subtypes: LD-bound peridroplet mitochondria (PDM) and unbound cytoplasmic mitochondria (CM), which differ in localization and metabolic roles. CM primarily supports fatty acid oxidation (FAO), while PDM contributes to de novo lipogenesis (DNL). How these subpopulations respond during MASLD progression and how genetic factors regulate them remains poorly understood.

Aims: To isolate and characterize hepatic CM and PDM across MASLD stages and to identify and characterize LD-mitochondrial proteins that regulate their function and abundance.

Results: Using a diet-induced MASLD/MASH mouse model, we profiled CM and PDM across disease stages. CM and PDM exhibited an inverse relationship from healthy liver to steatosis and advanced MASH. PDM abundance and FAO capacity declined sharply as disease progressed, coinciding with mitochondrial fragmentation, lower MFN2, elevated DRP1, and increased CM abundance. In contrast, CM upregulated oxidative activity, suggesting compensatory adaptation to maintain energy homeostasis. Proteomic profiling revealed distinct compositions and pathway enrichments. Notably, APOE was enriched in CM and co-enriched with LAMP2, a marker of lysosome-associated lipid degradation.

The human APOE gene exists as three common alleles, ε2, ε3, and ε4, encoding APOE2, APOE3, and APOE4. Beyond lipoprotein clearance, APOE isoforms differentially influence susceptibility to metabolic and neurodegenerative diseases. APOE4 is a strong risk factor for Alzheimer's and cardiovascular disease but paradoxically associates with lower hepatic lipid burden. APOE3, the most common isoform, appears neutral in many contexts but promotes MASLD/MASH under metabolic stress. The mechanisms underlying these divergent hepatic effects remain unclear. Preliminary data from western diet-fed human APOE knock-in mice show APOE4 livers have smaller LDs and enhanced mitochondrial biogenesis, while APOE3 livers accumulate larger, inert LDs, a reversal of APOE4's pathogenic effects in astrocytes. APOE4 livers also show expanded oxidative CM, depleted lipogenic PDM, and reduced LRP1, a mitochondria-associated ER membrane (MAM) APOE receptor.

Conclusion: Our findings demonstrate that hepatic CM and PDM undergo distinct functional shifts during MASLD progression, and APOE isoforms differentially shape LD remodeling and mitochondrial adaptation. Specifically, APOE4 exerts hepatoprotective effects, highlighting isoform-specific regulation of inter-organelle crosstalk as a key determinant of MASLD susceptibility. Ongoing studies aim to define how APOE isoforms modulate mitochondrial subtypes to match hepatocyte energy demands during metabolic stress.

PPP1R3B Regulates Hepatic Lipid Partitioning with Implications for Cardiometabolic Disease and Alzheimer's Disease

Abstract Number: 32
Poster Number: 32

Kate Townsend Creasy (University of Pennsylvania), Varnitha Punnuru (University of Pennsylvania), Jaqueline Wu (University of Pennsylvania), Joseph A. Baur (University of Pennsylvania), Daniel J. Rader (University of Pennsylvania), Gregory Corder (University of Pennsylvania)

Genetic variation near the PPP1R3B locus has been associated with multiple cardiometabolic traits, including fasting glucose, plasma lipids, liver injury traits, and hepatic steatosis, yet the mechanisms linking this locus to lipid metabolism remain poorly defined.

In our 2025 Science Advances publication, we identified Ppp1r3b as a metabolic switch that shifts hepatic energy storage from lipid to glycogen. Using hepatocyte-specific mouse models, primary hepatocytes, and human genetic analyses, we showed that altered Ppp1r3b expression drives distinct metabolic states with important consequences for hepatic and systemic metabolism. Hepatocyte deletion of Ppp1r3b impaired glycogen storage resulting in glucose shunting toward de novo lipogenesis and increased hepatic triglyceride synthesis. Although young mice displayed compensatory increases in triglyceride secretion, lipid oxidation, and ketogenesis that limited steatosis, aging or high-sucrose diet challenge caused hepatic triglyceride accumulation, glucose intolerance, insulin resistance, and elevated ALT. Conversely, hepatocyte Ppp1r3b overexpression enhanced glycogen storage, reduced hepatic triglyceride content, improved glucose disposal, and lowered reliance on lipid oxidation, although excess glycogen storage was also associated with elevated ALT. In humans, common variants associated with increased PPP1R3B expression were linked to lower liver fat and reduced circulating lipids, whereas putative loss-of-function variants were associated with increased hepatic fat and elevated plasma lipids, reinforcing the findings from our experimental models. Together, these results establish PPP1R3B as a crucial regulator of hepatic substrate partitioning and systemic lipid metabolism, providing a mechanistic framework for understanding how this locus influences cardiometabolic disease risk.

Our ongoing studies further suggest that Ppp1r3b-mediated changes in liver metabolism alter whole-organism lipid metabolism, including the brain lipidome, and may influence neuroinflammation and cognitive function. Future work will define how hepatic Ppp1r3b-dependent metabolic remodeling affects brain lipid homeostasis and neurodegenerative phenotypes, with particular interest in mechanisms linking steatotic liver disease, circulating lipid species, and Alzheimer's disease risk.

Elevated FGF21 from hepatic MetAP2 deletion is associated with selective ceramide reduction in visceral fat

Abstract Number: 33

Christy Gliniak (Rutgers, New Brunswick), Ruth Gordillo (University of Texas Southwestern Medical Center), Andrew Lemoff (University of Texas Southwestern Medical Center), Philipp E Scherer (UT Southwestern Medical Center)

Methionine aminopeptidase 2 (MetAP2) inhibitors are anti-obesogenic and anti-carcinogenic, yet the mechanisms by which MetAP2 regulates major metabolic organs and systemic metabolism remain unclear. We previously reported that on a high-fat diet, hepatocyte-specific MetAP2 deletion (Liver-MetAP2 KO) protects against weight gain, markedly improves insulin sensitivity, and reduces basal insulin levels. These effects are driven by metabolic improvements in adipose tissue rather than by the liver or changes in energy expenditure. Mechanistically, hepatic MetAP2 loss upregulates the integrated stress response and circulating fibroblast growth factor 21 (FGF21). FGF21 acts directly on adipocytes via its receptors and is a potent regulator of lipid metabolism, lowering ceramide levels in adipose tissue. Since ceramides accumulate in visceral fat during obesity and are causal mediators of insulin resistance, we hypothesized that elevated FGF21 in Liver-MetAP2 KO mice may contribute to the reduction of ceramide burden in adipose tissue. We performed sphingolipidomic profiling of epididymal (eWAT) and subcutaneous (scWAT) adipose tissue from Liver-MetAP2 KO and control male mice after 16 weeks of high-fat diet, in both fed and fasted states. Interestingly, in control tissues, eWAT ceramide levels did not differ between fed and fasted conditions. In Liver-MetAP2 KO mice, ceramide species were broadly and significantly reduced in eWAT, and in both fed and fasted states. Reductions were further amplified by fasting, with ceramide 16:0 reduced by approximately 70%, ceramide 18:1 by 62%, and ceramide 24:1 by 68%. In the KO mice, lactosyl- and hexosyl-ceramides were reduced across nearly all species in eWAT. Sphingoid bases, including sphinganine and sphingosine, were also significantly lower. scWAT was less responsive to Liver-MetAP2 KO compared to eWAT. Ceramide 16:0 was modestly reduced, but the broad reductions observed in eWAT were absent. Notably, baseline comparisons of control depots revealed that hexosyl-ceramides were 5- to 10-fold more abundant in scWAT than in eWAT, highlighting fundamental differences in sphingolipid handling between visceral and subcutaneous fat. Serum adiponectin was unchanged in Liver-MetAP2 KO mice vs controls, indicating the ceramide reduction maybe independent of adiponectin receptor ceramidase activity and more dependent on the general improvement of adipose tissue quality or FGF21. This remains to be tested. These findings demonstrate that hepatocyte MetAP2 deletion selectively reduces ceramide species in visceral adipose tissue, independent of feeding state. Depot-specific ceramide lowering, potentially mediated by elevated FGF21, may contribute to the metabolic protection observed in these mice and identifies a novel mechanism by which hepatic MetAP2 inhibition improves systemic insulin sensitivity.

The N-terminus of Apolipoprotein B mediates the interaction of atherogenic lipoproteins with endothelial cells

Abstract Number: 34
Poster Number: 33

Ainara Gonzalez Cabodevilla (NYU Grossman SoM), Maria Concepcion Izquierdo (NYU Grossman SoM), Anna Tilp (University of Graz), Camila Calistru (NYU Grossman SoM), Waqas Younis (NYU Grossman SoM), Tobias Madl (University of Graz), Munichandra Tirumalasetty (NYU Grossman LI SoM), M. Mahmood Hussain (NYU Grossman LI SoM), Ira J. Goldberg (NYU Grossman SoM)

The development of atherosclerosis is triggered by the endothelial crossing and subendothelial retention of cholesterol-rich, apolipoprotein B (APOB)-containing LDL (which carries APOB100) and chylomicron remnants (which carry APOB48, the 48% N terminal sequence of apoB). In addition, multiple studies have established elevated postprandial triglyceride-rich lipoproteins (TRLs) as an independent risk factor for cardiovascular disease. However, the mechanisms whereby postprandial TRLs, which circulate mostly within chylomicrons, exert their atherogenic effects remain unknown. Two receptors - scavenger receptor-BI (SR-BI) and activin receptor-like kinase 1 (ALK1) – have been shown to mediate the atherogenic uptake and transcytosis of LDL across the endothelial cell (EC) barrier. We have shown that SR-BI (but not ALK1) also mediates EC uptake of nascent chylomicrons. RNAseq analysis revealed that chylomicron uptake led to EC inflammation and release of pro-inflammatory extracellular vesicles (EVs) with distinct microRNA signatures. In vitro, treatment with EVs derived from chylomicron-ladden ECs led to lipid accumulation and inflammatory gene expression in macrophages and naïve ECs. Consistently, hypetriglyceridemia due to lipoprotein lipase (LpL) deficiency exacerbated aortic inflammation and atherosclerosis in LDL receptor (LDLR) knockout mic. Using N-terminal fragments of APOB, molecular modeling, and site-directed mutagenesis, we identified the distinct sequences in APOB that mediate its atherogenic binding to ALK1 and SR-BI. Treatment with APOB18, a fragment of APOB comprising its 18% N-terminal sequence, reduced the uptake and transport of both chylomicrons and LDL by ECs, whereas a shorter fragment, APOB12, only blocked ALK1-mediated uptake of APOB100-containing lipoproteins. Importantly, treatment with an adeno-associated virus (AAV) to express APOB18 decreased atherosclerosis in LDLR knockout mice following 12 weeks of western diet. These findings identify the N-terminal region of APOB as the cause of atherosclerosis.

Together, our results support a mechanism whereby APOB-mediated receptor binding drives endothelial uptake of diverse atherogenic lipoproteins, while increased TRL burden amplifies lipid flux and EV-mediated inflammation. Targeting APOB–receptor interactions may therefore provide a broadly effective strategy to limit atherosclerotic disease.

Reduction in placental MFSD2a expression in mice causes microcephaly in the fetus and impairs neurobehavioral outcomes in adult offspring.

Abstract Number: 35
Poster Number: 34

Marta Hita Hernandez (University of Colorado Anschutz), Jamie Henry (University of Colorado Anschutz), Robert Dietz (University of Colorado Anschutz), Nicolas Busquet (University of Colorado Anschutz), Thomas Jansson (University of Colorado Anschutz), Theresa Powell (University of Colorado Anschutz)

Objective: Docosahexaenoic acid (DHA) is critical for fetal brain development and an inadequate supply during the perinatal period has been associated with impaired neurological and cognitive function in children. DHA is transported from the mother to the fetus via the placenta by the Major Facilitator Superfamily Domain Containing 2a (MFSD2a) transporter. Placental expression of MFSD2a is altered in common pregnancies complications such as maternal obesity and gestational diabetes. Moreover, these metabolic diseases during pregnancy have also been associated with neurobehavioral disorders such as anxiety, hyperactivity, and cognitive impairment in childhood. We tested the hypothesis that placenta-specific knockdown (KD) of MFSD2a in mice results in impaired neurobehavioral outcomes in adult offspring.

Methods: We generated placenta-specific KD of MFSD2a using a mouse model of trophectoderm lentivirus transfection with a shRNA construct targeting MFSD2a, followed by embryo transfer. Pups from placentas targeted with a scrambled, non-coding, sequence (SCR) served as controls. The brains of fetuses at E18.5 were collected and weighed. Fetal brain DHA content was measured by LC-MS/MS. Offspring behavior was tested at adult age. Cognition, memory, motor skills and anxiety-like behaviors were assessed using Contextual Fear Conditioning, Rotarod and Open field test. After the behavioral testing was completed, adult brains were collected and key markers for myelination, neuroinflammation and synaptic activity were assessed by simple western blot (JESS) in the cortex, hippocampus and cerebellum. Significance was determined by Student's t-test for comparisons between offspring from placental MFSD2a KD vs SCR groups and two-way ANOVA was used to assess significant sex differences.

Results: Fetuses with placental-specific MFSD2a KD demonstrated microcephaly with a 35% reduction in brain weight (n=24 SCR, n=23 MFSD2a KD, $p<0.0001$) and 14% lower brain DHA content (n=26 SCR, n=33 MFSD2a KD, $p<0.05$) compared to SCR. No change in body weight between both groups was observed. Adult mice from pregnancies with placental MFSD2a KD displayed a 45% increase in anxiety-like behavior (n=34 SCR and n=39 MFSD2a KD, $p<0.001$) and a reduction in motor skills (n=41 SCR, n=46 MFSD2a KD, $p<0.05$) and cognitive capacities both by 43% (n=20 SCR, n=20 MFSD2a KD, $p<0.05$). These differences were found predominantly in female adult offspring. Expression of brain function markers suggested that the adult female offspring of placental MFSD2a KD group had higher inflammation in the hippocampus and lower synaptic activity in the cerebellum while male brain demonstrated decreased myelination and synaptic activity in the cortex compared to the SCR group.

Conclusion: Placental specific reduction in the expression of the DHA transporter MFSD2a causes microcephaly in the fetus and disrupted neurobehavioral outcomes and brain function at adult age with the greatest impact in female offspring. This is the first report demonstrating a direct mechanistic link between placental DHA transport and offspring neurodevelopment. Our results suggest that placental DHA transfer by MFSD2a during pregnancy is critical for appropriate brain growth and long-term neurological development. Variation in MFSD2a expression previously demonstrated in placentas of obese and diabetic mothers may in part contribute to the known increase in neurological disorders in children who are exposed to these conditions in utero. Supported by NICHD R01 HD104644 and from the Colorado Clinical and Translational Science Institute CMH-M-25-46.

Functional Genomic In Vivo Screens in Visceral Adipocytes and Cardiomyocytes to Identify Novel Cardiometabolic Targets

Abstract Number: 36
Poster Number: 35

Joanne Hsieh (Gordian Biotechnology), Naoto Muraoka (Gordian Biotechnology), Vinay Kartha (Gordian Biotechnology), Shengping Wang (Gordian Biotechnology), Gavin Pharaoh (Gordian Biotechnology), Chris Carrico (Gordian Biotechnology), Daniel Fuentes (Gordian Biotechnology), Dimitry Popov (Gordian Biotechnology), Hikaru Miyazaki (Gordian Biotechnology), Linda Chio (Gordian Biotechnology), Lianna Fung (Gordian Biotechnology), Samuel Hayward (Gordian Biotechnology), Kelly Fagan (Gordian Biotechnology), Arnav Gupta (Gordian Biotechnology), Chase Bowman (Gordian Biotechnology), Amber Lim (Gordian Biotechnology), Tolga Berkman (Gordian Biotechnology), Smitha Shambhu (Gordian Biotechnology), Katie Doroschak (Gordian Biotechnology), Arthi Vaidyanathan (Gordian Biotechnology), Ying Yang (Gordian Biotechnology), Juana Cruz (Gordian Biotechnology), Sophia Ruiz (Gordian Biotechnology), Jesi Nonora (Gordian Biotechnology), Chris Towne (Gordian Biotechnology), Francisco LePort (Gordian Biotechnology), Martin Borch Jensen (Gordian Biotechnology)

Introduction: Adipose metabolism and cardiac function are governed by neuroendocrine systems poorly recapitulated ex vivo. Although patients with obesity, type 2 diabetes, and heart failure with preserved ejection fraction (HFpEF) benefit from incretin-based therapies and SGLT2 inhibitors, neither mature adipocytes nor cardiomyocytes express GLP-1R or SGLT2. Identifying novel, cell-autonomous therapeutic targets that complement or exceed current standards of care therefore necessitates an in vivo functional genomics approach.

Methods: AAV libraries containing >300 adipose and >200 cardiac genetic interventions were administered to semaglutide-treated, high-fat diet-fed Cas9-transgenic mice (obesity model) and obese ZSF1 rats (HFpEF model). AAV doses were titrated to optimize single-intervention delivery per cell, generating a mosaic tissue with internal inert controls. Transcriptomic responses in epididymal white adipose tissue and left ventricle were captured via snRNA-seq. Efficacy was evaluated using 'Disease Features'—curated, cell-type-specific, nonredundant, and unidirectional gene sets.

Results: In adipocytes, Ncor1, Pten, and Acvr1c knockouts yielded highly consistent responses across three independent screens. Ncor1 guides induced ‘Mitochondrial Biogenesis’, ‘Cholesterol Removal’ consistent with LXR activation, and ‘Angiogenic Adipokines’, indicating healthy adipose expansion. Pten guides upregulated ‘Cell Cycle-Associated’, ‘Basement ECM’, ‘Stiff ECM’, ‘Cholesterol Biosynthesis’, and Lep mRNA, indicating adipocyte hypertrophy. Conversely, Acvr1c guides decreased these features alongside ‘Lipid Droplet Structural Proteins’, suggesting lipolysis-mediated adipocyte shrinking. A novel target, "Augury1", upregulated lipolysis features and ‘Esterification’, suggesting active TG/FA futile cycling. Adipose-targeted "Augury1" knockdown alone drove 4.6% weight loss, and its co-administration potentiated semaglutide-induced weight loss from 9.3% to 12.9%, with insulin sensitization persisting post-semaglutide cessation. In cardiomyocytes, Pde5a/Pde9a dual knockdown upregulated the cellular stress-associated ‘NPPB-Correlated’ feature, whereas Nr3c2 knockdown downregulated it. Overexpression of target "Herald1" downregulated ‘NPPB-Correlated’ and upregulated ‘NPPB-

Anticorrelated’ signatures. Single-therapy validation of "Herald1" via AAV in obese ZSF1 rats significantly improved diastolic function, reducing E/e’ by 15.0% and isovolumetric relaxation time by 24.2%.

Conclusions: This scalable, in vivo platform enables high-throughput interrogation of hundreds of therapeutic targets directly within the native disease milieu. Within-animal comparisons eliminate systemic confounding variables like food intake, identifying novel, cell-autonomous interventions that provide robust additive benefits even alongside agents like GLP-1R agonists.

Perivascular adipose tissue remodeling modulates mitochondrial metabolism

Abstract Number: 37
Poster Number: 36

Amy Keller (RMR VA Medical Center/CU), Garrett Potter (RMR VA Medical Center/CU), Melissa Henckel (RMR VA Medical Center/CU), Leslie Knaub (RMR VA Medical Center/CU)

Perivascular adipose tissue (PVAT) regulates vascular function via paracrine signaling. We have reported that housing rats at thermoneutral (30°C, TN) conditions alters PVAT phenotype from brown adipose (BAT) to white adipose (WAT). We also have shown sex-dependent abnormalities in vasoreactivity and mitochondrial function. To further this work, we hypothesized that TN-mediated PVAT phenotypic transformation alters BAT regulator PRDM16, fatty acid composition, fatty acid (FA) transporter FATP1, mitochondrial dynamics, and lipid oxidation in a sex-dependent manner. Male and female Wistar rats were housed at room temperature (24°C, RT) or TN for 16 weeks. Endpoints included PVAT fatty acid composition, RNAseq analysis, and PVAT mitochondrial respiration and complex expression. Palmitoleic and arachidonic acid were significantly lower in TN-housed females (48.5% and 15.5%, respectively, $p<0.05$) and males (63.0% and 40.1%, respectively, $p<0.05$) housed at RT. PVAT of all animals housed at TN showed mitochondrial respiration significantly diminished in lipid substrate experiments for states 3, 4, and uncoupled ($p<0.05$ for all). RNAseq analysis showed that expression of FATP1 was lower in all animals housed at TN, more prominently in females. KEGG pathway analysis highlighted down enrichment of central metabolic pathways (carbon metabolism, pentose phosphate, fructose and mannose, and glycolysis and gluconeogenesis pathways) in TN-housed rats of both sexes, exhibiting a broad shift towards lower metabolic demand. Differential gene expression showed convergent upregulation of mitochondrial compensation and detoxification genes (e.g., CYP2E1, PRODH, SQRDL) in TN-housed rats of both sexes, consistent with temperature-induced impairment of fatty acid oxidation and increased oxidative stress. Female PVAT displayed selective upregulation of pro-lipid storage and anti-adipose browning genes WISP2 and LHFP, alongside muted fatty acid desaturation capacity (SCD1 downregulation, PLA2G16 upregulation), suggesting amplified lipid accumulation and metabolic-derived inflammation. These transcriptomic shifts align with observed loss of BAT markers and diminished lipid-substrate mitochondrial respiration and support a model wherein housing temperature-altered PVAT phenotype, fatty acid composition and metabolic flux impacts lipid transport more prominently in females. Future directions include continuing investigation into PVAT's metabolic phenotype, and how alterations may contribute to vascular crosstalk and regulation differently between the sexes.

MALDI imaging analysis of diabetes-induced disruptions in the spatial organization of kidney lipid metabolism in genetic mouse models

Abstract Number: 38
Poster Number: 37

Moshe Levi (Georgetown University), Dalton Brown (JHU), Caitlin Tressler (JHU), Avi Rosenberg (JHU), Xiaoxin Wang (Georgetown University), Komuraiah Myakala (Georgetown University), Kristine Glunde (JHU)

Introduction: Diabetes mellitus is characterized by increased levels of serum glucose and lipids, specifically triglycerides and cholesterol. Chronic hyperglycemia in type 2 diabetes drives diabetic nephropathy, causing early renal hyperfiltration, proteinuria, glomerular hypertrophy, mesangial expansion, renal macrophage accumulation, and inflammation. It is currently not known how diabetes alters the spatial distribution of lipids in the kidney. In this study, we determined the lipid distribution in the kidneys of diabetic db/db mice which have a leptin receptor mutation and develop severe obesity and type 2 diabetes, in comparison to nondiabetic db/m mice. We utilized matrix-assisted laser desorption/ionization (MALDI) imaging to analyze the spatial lipid distribution in the kidneys of db/db mice compared to those from db/m mice as controls.

Methods: Db/db and db/m mice (n=4 each) were sacrificed, and kidneys frozen in liquid nitrogen vapors. Frozen kidneys were faced with a central coronal cut, cryo-sectioned at 10-micron thickness, and thaw-mounted onto indium-tin-oxide slides. All kidney sections were placed on the same slide. Following vacuum desiccation, 2,5-dihydroxybenzoic acid (DHB) matrix was deposited using an optimized spraying protocol of 40 mg/mL DHB in 70% acetonitrile and 0.2% trifluoroacetic acid on an HTX M5 sprayer. All kidney tissue sections were imaged in the same experiment on a Bruker timsTOF fleX MALD-2 instrument in positive ion mode using 50-micron raster, 50-micron imaging laser, 250 laser shots per pixel, and a mass range of m/z 300 to 2,000 Dalton. Data were analyzed in SCiLS Lab.

Preliminary Data: MALDI imaging data were normalized to total ion count (TIC) and unsupervised k-means clustering segmentation was performed to generate regions of interest (ROIs) of the renal cortex and medulla for spatial lipidomic discovery analysis. This MALDI imaging analysis revealed major differences in lipid composition and distribution in diabetic db/db versus nondiabetic db/m kidneys in the cortex and the medulla. The comparison between db/db versus db/m medulla revealed 31 significantly different lipids, while comparing db/db cortex with db/m cortex resulted in 92 significantly different lipids. Specifically, we observed that ceramide 36:3;O3, which was detected as [M+H]+ ion at m/z 578.5242, was significantly increased in the medulla of diabetic versus control kidneys. Lactosylceramide d18:1/12:0 was detected as [M+H]+ ion at m/z 806.5689 and significantly increased in the cortex and medulla of diabetic versus control kidneys. In contrast, phosphatidylcholine O-38:7 levels, which were detected as [M+Na]+ ion at m/z 812.5575, were significantly decreased in the cortex of diabetic mice compared to controls. Ongoing studies are currently determining glomerular versus tubular lipid distributions by pathology-guided analyses following Periodic Acid-Schiff (PAS) staining of the same kidney sections which underwent MALDI imaging analysis. On-tissue tandem mass spectrometry is also ongoing to identify all significantly different m/z features detected in db/db versus db/m medulla and cortex of the kidney. Taken together, our study of diabetic kidneys compared to

controls in genetic mouse models of diabetes revealed several new findings in ceramide and phospholipid metabolism. Our initial findings point toward profound and spatially distinct metabolic lipid differences in diabetic kidneys.

Novel Aspects: MALDI imaging revealed that diabetic mouse kidneys display spatially distinct differences in ceramide and phospholipid metabolism compared to nondiabetic controls.

Ceramide and Glucosylceramide in Kidney Disease

Abstract Number: 39
Poster Number: 38

Moshe Levi (Georgetown University), Xiaoxin Wang (Georgetown University), Komuraiah Myakala (Georgetown University), Ewa Krawczyk (Georgetown University), Lauren A. Cowart (VCU), Avi Rosenberg (JHU), Kristine Glunde (JHU)

Altered lipid metabolism is increasingly recognized as key mediators of renal lipid accumulation, inflammation, oxidative stress, and fibrosis. Ceramide and glucosylceramide levels are increased in the kidneys of aged mice. Treatment of these mice with a pan ERRα/ERRγ agonist decreases C:20 Ceramide and C24:0 and C24:1 Glucosylceramide levels, and decrease inflammation and age-related kidney disease. Glucosylceramide synthase which mediates glucosylceramide synthesis is expressed in human podocytes and tubular cells, and in mouse podocytes and proximal tubular cells. Glucosylceramide levels are also increased in the kidneys of diabetic db-db mice. To determine a role for glucosylceramide in diabetic kidney disease we treated diabetic mice with Eliglustat, an inhibitor of glucosylceramide synthase. The decrease in glucosylceramide levels were associated with a significant decrease in albuminuria, increase in nephrin expression, and decreases in fibronectin and collagen IV. There was also a decrease in CD45 expression. To further determine a role for glucosylceramide we overexpressed UGCG (glucosylceramide synthase) in mouse proximal tubule cells. We found this resulted in significant increases in TNF alpha and MCP-1, whereas there were significant decreases in mitochondrial membrane potential, PGC-1a, an important mediator of mitochondrial biogenesis, and Cpt1a, a mediator of mitochondrial fatty acid oxidation. Our results therefore indicate an important role for glucosylceramide in the pathogenesis of age- and diabetes-related kidney disease.

Adipose Tissue Nicotinamide Phosphoribosyltransferase Regulates Systemic Metabolic Function Through Extracellular Vesicle Release

Abstract Number: 40
Poster Number: 39

Sandip Mukherjee (WashU, St. Louis), Daniel Ferguson (WashU Medicine), Elise I. Gadson (WashU, St. louis), Kathleen R. Markan (WashU, St. Louis), Jun Yoshino (WashU, St. louis), Maxwell Lin (WashU, St. Louis), Mohammad Habibi (WashU, St. Louis), Snigdha Tiash (WashU, ST. Louis), Hector Palacios (WashU, St. Louis), Xiaoxia Cui (WashU, St. louis), Evguenia Kouranova (WashU, ST. Louis), Edziu Franczak (Wake Forest University), Qiuyuan Guo (WashU, St. Louis), Jill Kealing (WashU, ST. louis), Terri A. Pietka (WashU Medicine), Kim H. H. Liss (WashU), John P. Thyfault (WashU), Gary J. Patti (WashU), Brian Finck (Washington University School of Medicine), Clair Crewe (Washington University in St. Louis)

Nicotinamide adenine dinucleotide (NAD+) is a vital coenzyme in energy metabolism. Nicotinamide phosphoribosyltransferase (NAMPT) maintains the cellular NAD+ pool by synthesizing the NAD+ precursor, nicotinamide mononucleotide (NMN), and diminished adipocyte NAMPT activity has been implicated in aging- and obesity-related metabolic dysfunction. However, the mechanisms by which adipose tissue NAMPT/NMN produces systemic metabolic benefits are still unclear. We generated adipocyte-specific NAMPT overexpressing (ANOV) mice and examined their metabolic phenotype at baseline and in the context of diet-induced obesity. Male ANOV mice are protected from diet-induced metabolic dysfunction including the development of adipose tissue inflammation, glucose intolerance, and insulin resistance. In contrast female ANOV mice were less protected from metabolic dysfunction, possibly due to higher endogenous expression of NAMPT in WT female mice. Livers of ANOV mice showed improved insulin signaling, increased NAD content, and reduced steatosis, suggesting that NAMPT regulates interorgan communication between adipocytes and hepatocytes. Extracellular vesicles (EV) isolated from ANOV mice enhanced insulin signaling in HepG2 cells and improved glucose tolerance in obese WT mice. In contrast, EV from adipocyte-specific NAMPT KO (ANKO) mice suppressed HepG2 insulin signaling. Prior work has suggested that enzymatically-active NAMPT circulates in AT-EV. AT-EV from ANOV mice were directly taken up by the liver and increased NAMPT abundance in recipient cells. Moreover, NAD content was increased in ANOV AT-EVs and blocking NAMPT activity in hepatocytes blunted the enhanced insulin stimulated AKT-phosphorylation after ANOV-EV treatment. Furthermore, AT-EV lipidomic analyses demonstrated that several sphingomyelin and ceramide species were decreased in ANOV-AT EVs compared to WT-EVs. In contrast, ANKO AT-EVs showed a higher ceramide species content compared to WT controls. Collectively, these data suggest that altered EV cargo composition in NAMPT gain or loss of function mouse models is a crucial factor for regulating systemic glucose homeostasis and highlight novel mechanisms by which adipocyte NAD+ metabolism regulates systemic metabolic dysfunction via EVs.

Development of the NIB50 Strategy for High-Efficiency Mitochondria Transplantation Reveals Mitophagy-Dependent Metabolic Integration in Leigh Syndrome

Abstract Number: 41
Poster Number: 40

Ritsuko Nakai (Washington Univ. in St. Louis), Sarah Coffey (Washington University School of Medicine in St. Louis), Stella Varnum (Washington Univ. in St. Louis), Wentong Jia (Washington University School of Medicine in St. Louis), Jacob S. Bedia (Washington Univ. in St. Louis), Eva F. Cohen (Washington Univ. in St. Louis), Rachael Field (Washington University School of Medicine in St. Louis), Rocky Giwa (Washington University School of Medicine in St. Louis), Melody Nguyen (Washington Univ. in St. Louis), Jasmine Wright (Washington University School of Medicine in St. Louis), Samantha Krysa (Washington University School of Medicine in St. Louis), Jonathan Brestoff (Washington University School of Medicine in St. Louis)

Background: Leigh syndrome (LS) is a devastating inherited mitochondrial disorder characterized by progressive neurodegeneration and high mortality, with no current cures. While we recently developed mitochondria transfer-based therapies for LS (Nakai/Varnum et al., Nat Metab, 2024), their clinical efficacy is limited by variable cellular uptake and a poor understanding of how transplanted mitochondria integrate into host metabolic networks.

Objective: To develop a high-efficiency in vitro mitochondria transplantation platform, "NIB50," and elucidate the molecular mechanisms required for functional integration of exogenous mitochondria into LS patient-derived fibroblasts.

Methods: We systematically evaluated existing respiration buffers, identifying that ionic buffers maximize mitochondrial uptake. Based on this, we developed the highly optimized Nakai Ionic Buffer (NIB) to establish the "NIB50 strategy." Intact mitochondria, isolated from healthy donor fibroblasts, were transplanted into LS fibroblasts harboring distinct pathogenic mutations (FBXL4, ECHS1, SURF1, MT-ATP6). Metabolic integration was longitudinally assessed using the Resipher system for continuous 144-hour oxygen consumption rate (OCR) monitoring, alongside evaluations of mitochondrial biomass, polarization, cellular ATP, mtDNA copy number, and Complex I/Cytochrome C oxidase activities. To evaluate mitophagy's role, we compared five groups: healthy fibroblasts, mutant fibroblasts, and mutants treated with mitochondria, the mitophagy inhibitor Bafilomycin A1 (BafA1), or both.

Results: The NIB50 strategy achieved robust mitochondrial uptake efficiency with no evidence of degradation for at least 96 hours. In FBXL4-mutant fibroblasts, mitochondria transplantation induced a significant OCR rescue, yielding a nearly two-fold increase over untreated mutants, with effects sustained for at least 6 days. This metabolic recovery was driven by improved mitochondrial polarization and OXPHOS-dependent ATP production without a concurrent increase in host mitochondrial biomass or mtDNA copy number, suggesting qualitative functional integration rather than mere quantitative expansion. Crucially, BafA1 co-treatment completely abrogated the transplant-induced OCR rescue,

indicating host mitophagy is a prerequisite for functional efficacy. Preliminary studies are expanding these findings to SURF1, ECHS1, and MT-ATP6 mutations to confirm mechanistic universality.

Conclusions: We establish NIB50 as a highly effective platform for robust metabolic rescue in patient-derived LS models. Crucially, we show that the functional success of exogenous mitochondria depends on active host mitophagy, identifying innate quality-control pathways as critical therapeutic targets for optimizing mitochondria transfer in neurodegenerative disorders.

Rubicon Deficiency Unmasks a Microbiome-Driven Mitophagy Circuit That Promotes Age-Associated Obesity

Abstract Number: 42
Poster Number: 41

Melody Nguyen (WUSTL), John Moley (Washington University School of Medicine in St. Louis), Sarah Coffey (Washington University School of Medicine in St. Louis), Wentong Jia (Washington University School of Medicine in St. Louis), Jasmine Wright (Washington University School of Medicine in St. Louis), Rachael Field (Washington University School of Medicine in St. Louis), Alexander Lewis (Washington University School of Medicine in St. Louis), Rocky Giwa (Washington University School of Medicine in St. Louis), Xinya Zhang (Washington University School of Medicine in St. Louis), Samantha Krysa (Washington University School of Medicine in St. Louis), Nicholas Borcherding (Washington University School of Medicine in St. Louis), Andrew Gelman (Washington University School of Medicine in St. Louis), Mike White (Washington University School of Medicine in St. Louis), Jonathan Brestoff (Washington University School of Medicine in St. Louis)

Obesity is associated with mitochondrial dysfunction in adipocytes and the induction of mitophagy to recycle damaged mitochondria via lysosomal degradation. Recent studies indicate that mitophagy is restrained by a protein called Rubicon, which is downregulated in white adipose tissue (WAT) with aging. However, the role of Rubicon in regulating obesity pathogenesis is not well understood. We demonstrate that Rubicon-deficient mice develop spontaneous obesity, macrophage accumulation in white adipose tissue, and lower whole-body energy expenditure by middle age (~1 year) when separately housed. Co-housing with wildtype (WT) mice transferred the dominant WT microbiome and prevented these obesity-associated phenotypes in Rubicon-deficient mice. Microbiome analyses revealed that the obesity phenotype in separately housed Rubicon-deficient mice was preceded by the emergence of a gut microbiome that produces cis-vaccenic acid (cVA). cVA levels in serum were positively correlated with adiposity in mice, and this fatty acid promotes mitophagy in primary adipocytes in an Interleukin (IL)-1-dependent manner. Consistent with this finding, deletion of the IL-1 receptor prevented age-associated obesity in Rubicon-deficient mice. Furthermore, deletion of the crucial mitophagy protein Parkin in Rubicon-deficient mice also prevented aging-associated obesity. To assess the cell-type-specific effects of Rubicon deficiency, we generated new Rubicon conditional knockout mice and found that Rubicon expression in adipocytes but not macrophages was required to limit high-fat diet (HFD)-induced obesity. Together, these findings suggest that Rubicon restrains a cVA/IL-1/mitophagy circuit in adipocytes that contributes to obesity pathogenesis. These results challenge the prevailing view that mitophagy is uniformly beneficial and raise the possibility that excessive, unchecked mitophagy in adipocytes has deleterious metabolic consequences.

Herpes Simplex Virus Type 1 (HSV-1) infection induces APOE4-dependent astrocyte lipid droplet accumulation and AD-related pathology

Abstract Number: 43
Poster Number: 42

Christy Niemeyer (University of Colorado, AMC)

Herpes simplex virus type 1 (HSV-1) has increasingly been linked to chronic neuroinflammation and Alzheimer's disease (AD), particularly in individuals carrying the APOE4 allele. Astrocytes are critical regulators of lipid metabolism and immune homeostasis in the CNS and are preferentially infected during HSV-1 CNS invasion. However, how APOE isotype influences astrocyte metabolic responses to HSV-1 infection remains unclear. We hypothesized that HSV-1 infection induces APOE-dependent disruptions in astrocyte lipid metabolism, promoting lipid droplet accumulation and glial dysfunction.

To investigate this, we utilized primary mouse astrocytes expressing humanized APOE2, APOE3, or APOE4 alleles. Cells were mock infected or infected with HSV-1 and assessed for intracellular lipid droplet accumulation following infection. HSV-1 induced a distinct APOE isotype-dependent response. APOE2 and APOE3 astrocytes showed minimal changes in lipid droplet accumulation following infection, whereas APOE4 astrocytes demonstrated a significant increase in intracellular lipid droplets after HSV-1 exposure.

To further examine glial metabolic responses in vivo, we isolated ACSA1+ astrocytes from HSV-1-infected wild-type (C57BL/6) and AD-model (5xFAD) mice. Glial populations from infected animals exhibited evidence of immunometabolic dysregulation, including increased lipid droplet accumulation and inflammatory polarization. Together, these findings suggest that HSV-1 infection disrupts glial lipid homeostasis in an APOE-dependent manner and may synergize with AD-associated genetic risk factors to promote neuroinflammatory and neurodegenerative vulnerability.

Human APOE4 astrocytes display lipid droplet accumulation, increased IL 6 secretion, and adversely affect myelin protein levels in iPSC derived oligodendrocytes

Abstract Number: 44
Poster Number: 43

Ping-Chieh Pao (Sanofi), Iqra Pervaiz (Sanofi), Julia Maeve Bonner (Sanofi), Janina Schwarte (Sanofi), Kelly Bales (Sanofi), James Dodge (Sanofi)

Apolipoprotein E (ApoE) mediates lipid transport between cells and is essential for proper brain function. The APOE genotype represents the strongest genetic risk factor for sporadic Alzheimer's disease (AD), with the E4 allelic variant (APOE4) carrying the highest risk and prevalence. APOE4 astrocytes exhibit lipid accumulation due to impaired lipid efflux, contributing to dysregulated lipid storage, stress responses, and inflammation. Here, we characterized human induced pluripotent stem cell (iPSC)-derived astrocytes harboring APOE3 (neutral) or APOE4 (risk) genotypes. Despite comparable astrocyte maturation, APOE4 astrocytes displayed enlarged lipid droplets and elevated IL-6 secretion. Additionally, conditioned media from APOE4 astrocytes impaired myelin protein production in iPSC-derived oligodendrocytes. We next determined whether liver X receptor (LXR) agonism could modulate lipid and inflammatory phenotypes in APOE4 astrocytes. In a six-point dose-response assay, the LXR agonist GW3965 significantly reduced lipid droplet size in APOE4 astrocytes, whereas IL-6 secretion was unexpectedly elevated at lower agonist concentrations. In summary, iPSC-derived APOE4 astrocytes recapitulate key AD pathological features associated with APOE4 and represent a valuable platform for evaluating therapeutic agents targeting dysfunction in APOE4 carriers.

Disclosures: This study was funded by Sanofi. All authors are Sanofi employees and may hold shares and/or stock options in the company.

Adipose Tissue Lipolysis Establishes Metabolic Tolerance to Infection

Abstract Number: 45

Suraj Patel (UT Southwestern Medical Center), Kartik Rajagopalan (UT Southwestern Medical Center), Ankita Sarkar (UT Southwestern Medical Center)

Host defense against infection requires not only pathogen clearance (resistance) but also the ability to maintain physiologic stability despite ongoing inflammation (tolerance). While infection is known to induce profound metabolic remodeling, the contribution of lipid mobilization to disease tolerance remains incompletely defined.

Here, we demonstrate that infection robustly activates adipose tissue lipolysis in both humans and mice, resulting in increased circulating non-esterified fatty acids (NEFAs). In murine models of endotoxemia and polymicrobial sepsis, this lipolytic response is characterized by activation of canonical signaling pathways in white adipose tissue, including hormone-sensitive lipase phosphorylation and downstream PKA signaling. Genetic disruption of adipose triglyceride lipase (ATGL) specifically in adipose tissue abolishes infection-induced NEFA release and results in worsened hypothermia, bradycardia, and mortality, indicating a critical role for adipose lipolysis in promoting tolerance to infection. In contrast, disruption of brown adipose tissue lipolysis does not recapitulate this phenotype, highlighting a specific role for white adipose tissue.

Mechanistically, supplementation with NEFAs rescues the impaired tolerance observed in lipolysis-deficient mice, whereas glycerol does not, supporting a model in which lipid substrates, not gluconeogenic intermediates, mediate this adaptive response. Conversely, pharmacologic inhibition of fatty acid utilization exacerbates physiologic decline during infection, further reinforcing the importance of lipid metabolism in host tolerance. Notably, disruption of hepatic fatty acid oxidation alone is insufficient to impair tolerance, suggesting that extrahepatic or systemic lipid utilization pathways are critical.

Together, these findings identify adipose tissue lipolysis as a central metabolic adaptation to infection that promotes host tolerance through mobilization of lipid substrates. These results establish a direct link between lipid metabolism and immunometabolic resilience, with potential therapeutic implications for sepsis and other inflammatory diseases.

Leptin signaling to neurons increases tolerance to influenza infection

Abstract Number: 46

Kartik Rajagopalan (UT Southwestern Medical Center), Soumya Kamath (UT Southwestern Medical Center), David Bautista (UT Southwestern Medical Center), Tadiwanashe Gwatiringa (UT Southwestern Medical Center), Han Ngo (UT Southwestern Medical Center)

Severe infection can result in hypotension, bradycardia, and hypothermia each of which increases mortality risk. While catecholamine infusion is used to treat dangerously low blood pressure and heart rate, how the sympathetic nervous system is regulated during infection is unclear.

Leptin is an adipokine that maintains energy homeostasis by signaling to the hypothalamus to regulate different physiological processes. It also stimulates pro-inflammatory responses in immune cells, and both mice and humans with leptin deficiency show increased infection susceptibility that is corrected with leptin supplementation. However, due to the pleiotropic function of leptin, a mechanistic understanding about how leptin deficiency leads to poor infection outcomes is unclear.

Our previous work demonstrated that leptin supplementation at physiologic doses prior to infection prevented autonomic failure and resulted in complete survival after influenza infection. Notably, viral titers from lung and serum were equivalent between groups, as leptin deficient ob/ob mice were able to clear the virus as effectively as leptin supplemented ob/ob mice. This implicated a non-immune mechanism underlying the survival difference between the groups.

We now show that leptin signaling to neurons, not the immune cell compartment, is critical for preventing autonomic failure and subsequent mortality after influenza infection. Interestingly, obese, metabolically dysregulated mice with defective leptin signaling to GABAergic neurons are not susceptible to influenza, indicating that leptin deficiency-driven metabolic dysregulation is not the driver of poor outcomes. Instead, leptin signaling to a discrete non-GABAergic neuronal population is necessary for survival. Mechanistically, leptin supplementation in ob/ob mice increased levels of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, in brown and white adipose tissue, activating thermogenic and lipolytic gene expression programs respectively through increased sympathetic output.

Together, these findings identify a neuronal leptin signaling axis that regulates sympathetic tone during infection, with important implications for improving outcomes in severe infections.

Overnutrition and Estrogen Deficiency Drive Insulin Resistance and Adipose Tissue Dysfunction via Sympathetic Nervous System Overdrive

Abstract Number: 47

Kenichi Sakamoto (Rutgers University)

Obesity causes metabolic disease and type 2 diabetes, principally through the induction of insulin resistance. Insulin resistance is a pivotal contributor to adipose tissue dysfunction, which is characterized by unrestrained lipolysis, reduced lipogenic capacity, increased adipose tissue inflammation, fibrosis, and senescence. This adipose tissue dysfunction in turn drives systemic glucose intolerance and metabolic disease including hepatic steatosis.

The mechanisms that account for overnutrition-induced insulin resistance remain poorly understood as impaired cellular insulin signaling, long considered central to insulin resistance, does not always parallel impaired whole-body insulin action. Emerging evidence instead suggests an important role for heightened sympathetic nervous system (SNS) activity, as overnutrition rapidly increases plasma norepinephrine (NE). However, the causal contribution of elevated SNS tone to metabolic dysfunction has remained unclear.

Here, we utilize a mouse model of inducible, peripherally restricted deletion of tyrosine hydroxylase (THΔper), which abrogates catecholamine release from sympathetic nerves without affecting catecholaminergic neurons in the CNS. High-fat diet (HFD) similarly increased body weight in THΔper and their WT littermate controls. Plasma levels of NE, epinephrine, and glucagon were elevated only in WT controls, but not in the THΔper mice. HFD feeding-induced glucose intolerance was markedly improved in the THΔper mice. Hyperinsulinemic-euglycemic clamp studies demonstrated that overnutrition-induced hepatic insulin resistance was markedly ameliorated in the THΔper mice, even though cellular insulin signaling in the liver was comparable. THΔper mice are protected from HFD-induced adipose tissue dysfunction and liver steatosis, possibly due to decreased non-esterified fatty acid flux from adipose tissue to the liver. Both pharmacological inhibition of lipolysis using an adipose triglyceride lipase (ATGL) inhibitor and genetic deletion of ATGL improved HFD-induced insulin resistance.

We are currently extending this framework to estrogen deficiency, an important driver of adipose tissue dysfunction and insulin resistance in aging women. We find that enhanced sympathetic drive similarly promotes lipid mobilization and metabolic dysfunction. Using an ovariectomy (OVX) model of estrogen deficiency, we further demonstrate that loss of estrogen increases sympathetic tone, reflected by elevated plasma NE and increased adipose SNS activity. Suppressing NE release in OVX mice, either through sympatholytic treatment or in THΔper mice, reduces lipolysis and markedly ameliorates estrogen-deficiency–induced insulin resistance, adipose tissue dysfunction, and hepatic steatosis.

Together, these findings establish that increased SNS activity to adipose tissue and the resulting lipolysis are key drivers of insulin resistance and adipose tissue dysfunction induced by both overnutrition and estrogen deficiency.

Elucidating DFCP1's Role in Metabolism During Skeletal Muscle Myogenesis

Abstract Number: 48
Poster Number: 44

Megan Schuetz (Washington University), Victoria Ismail (Washington University)

Skeletal muscle myogenesis relies on the differentiation of muscle precursor cells into multi-nucleated myofibers and dysfunction can lead to a host of myopathies including muscular dystrophy and cachexia. This intricate process involves a metabolic shift from glycolytic myoblasts to oxidative myotubes and requires extensive remodeling of the mitochondrial network. The existing network must be degraded first through mitophagy, a form of selective autophagy. Cells can then undergo extensive mitochondrial biogenesis to replenish the cell with a mature mitochondrial network that is primed for fatty acid oxidation, a key metabolic process for differentiation. However, due to their cytotoxicity, fatty acids must be stored within lipid droplets (LDs) and their catabolism must be tightly regulated. Recently, the early autophagy marker, Double FYVE Domain Containing Protein 1 (DFCP1), has been implicated in the regulation of mitophagy by mediating the constriction of the omegasome to release autophagosomes. Additionally, our lab identified DFCP1 as a regulator of lipolysis by revealing its ability to sequester the rate-limiting enzyme, ATGL. However, these studies were done in glycolytic U2OS cells and little is known about DFCP1's role in an oxidative environment such as skeletal muscle. To address this, we created a DFCP1 KO C2C12 line and found that differentiation was inhibited. DFCP1 KO cells are unable to fuse and fail to accumulate any late-stage myogenic regulatory factors. Furthermore, we identified that DFCP1 KO cells had significantly reduced mitochondrial content at late-stage differentiation. To gain better insight on these defects, we performed bulk RNAseq on WT and DFCP1 KO cells during early-stage differentiation. We found that WT cells upregulated numerous metabolism and muscle-specific genes during early-stage differentiation. Interestingly, DFCP1 KO cells upregulated less than 60% of the metabolism genes and less than 20% of the muscle-specific genes compared to WT. Taken together, this implicates DFCP1 as a key regulator of skeletal muscle myogenesis, likely as a driver of metabolism and fatty acid availability.

Multi-ethnic GWAS meta-analysis identifies 17 loci associated with metabolic Dysfunction Associated Liver Disease (MASLD) that define new disease subtypes, mechanisms, and predict advanced liver disease

Abstract Number: 49
Poster Number: 45

Elizabeth Speliotes (University of Michigan), Xiaomeng Du (University of Michigan), Yanhua Chen (University of Michigan), Nichole Palmer (Wake Forest University)

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a heritable condition that is now the most common cause of chronic liver disease in the United States. Its prevalence varies by ancestry. Some genetic variants have been linked to MASLD but many remain to be identified.

Methods: We conducted the largest cross ancestry genome-wide association meta-analysis of imaging and ICD based NAFLD in five cohorts: (1) Genetics of Obesity-related Liver Disease (GOLD) Consortium, consisting of 9 United States and European cohorts with computed tomography (CT)-measured hepatic steatosis; UK Biobank participants with hepatic steatosis defined by magnetic resonance imaging (2) or diagnosis codes (3); (4) eMERGE; and (5) FinnGen. Our meta analysis included 66,814 individuals with hepatic steatosis defined by imaging and 3,584 cases (vs. 621,081 controls) of MASLD defined by diagnosis codes.

Results: We identified 17 genetic variants associated with hepatic steatosis at genome-wide significance ($p< 5$ E-8). PheWAS identified 7 clusters of genes that identify subtypes many of which affect lipid biology. The include genes that play a role in liver lipid export (PNPLA3, TM6SF2,PTPRD) lipid import (APOE), lipid burning (FTO/IRX3/5), insulin biology(INSR, PNPLA2), lipid absorption(MTTP), glucose to fatty acid formation(GCKR, TRIB1), and lipid diversion of triglycerides to phospholipids and other membrane lipids (MARC1, MBOAT7, GPAM, ADH1B. TOR1B) as important causes of MASLD. Mendelian randomization analyses showed causal effects of hepatic steatosis on cirrhosis and esophageal varices and BMI and waist circumference on hepatic steatosis. Across ancestries in GOLD we found >10% absolute difference in effect allele frequencies (EAF) for MASLD-increasing variants in PNPLA3, GCKR, TRIB1, and ADH1B but there was not heterogeneity of effect size. The top 10%, 5% and 1% of a polygenic score of these hits identified individuals that will develop MASLD, cirrhosis and hepatocellular carcinoma (HCC) at an odds of 2,3,4 respectively creating new ways to identify high risk individuals for earlier care.

Conclusions: We identified genetic variants that define new subtypes of MASLD, their mechanism, and show that they can identify individuals at risk of advanced liver disease. This advances our understanding of MASLD and opens up new possibilities for diagnosis and treatment.

Solvatochromic Probes Reveal Lipid Trafficking Microenvironments

Abstract Number: 50
Poster Number: 46

Maciej Stawikowski (Florida Atlantic University), Nicholas McInchak (Florida Atlantic University), Vicente Rubio (Florida Atlantic University), Christopher Gomez (Florida Atlantic University), Qi Zhang (Florida Atlantic University)

Neutral lipid trafficking is central to organelle communication and metabolic regulation, yet direct visualization of lipid microenvironments in living cells remains a major challenge. To address this, we have developed a library of solvatochromic fluorescent lipid analogs based on the substituted 1,8-naphthalimide scaffold. These probes fluoresce in a polarity-dependent manner, enabling real-time visualization of neutral lipid dynamics within a subcellular context. Together, these lipid-based probes cover three major neutral lipid analogs-cholesterol, DAG, and TAG-providing a unified platform for environment-sensitive imaging of lipid composition, distribution, and remodeling. By integrating computational design with cellular validation, our solvatochromic lipid probes provide a modular platform for dissecting lipid behavior in diverse physiological contexts. Using these probes, we observe that cholesterol-based CND analogs partition among endosomal vesicles, lipid droplets, and lysosomes, in contrast to BODIPY-cholesterol conjugate. Notably, these probes exhibit similar Lo/Ld partitioning ratios, highlighting differences in trafficking rather than membrane phase preference. One of the DAG-like analogs was unexpectedly found to accumulate rapidly (within minutes) in lipid droplets, similar to BODIPY, but unlike TAG-based analogs. In contrast to BODIPY, however, the DAG analog does not diffuse away from lipid droplets and persists for at least 24 h after incubation, revealing distinct retention behavior among neutral lipid species. The probes are synthetically accessible, photostable, and compatible with live-cell imaging, and their emission shifts correlate with changes in the in-situ microenvironment. This approach enables direct examination of lipid phase behavior, lipid transport to and from lipid droplets, and lipid exchange with other organelles.

Label-free, dynamic cell painting: A comprehensive method for high content screening at the population and organelle levels

Abstract Number: 51
Poster Number: 47

Noah Thyberg (Nanolive), Matthias Haeffner (Nanolive)

High content phenotypic screening has re-emerged as a powerful approach for identifying and characterizing drug candidates, especially in an era where target-based screening often overlooks complex biological responses. Yet, conventional cell painting methods rely on fluorescent staining and endpoint imaging to assess phenotype, which introduces variability, limits biological relevance, and complicates data analysis.

To demonstrate label-free phenotypic screening in action, one 96-well plate was used to investigate six drugs at four concentrations each, plus controls (three replicates). Wells were imaged each hour using the 3D Cell Explorer 96focus (Nanolive). The high resolution (200nm) of the interferometric holotomography system produces quantitative images of cellular structures without labelling; cells and their organelles can then be segmented and analyzed automatically by AI-powered digital assays.

At the population level, cell count, confluency, and morphology were used to assess each drug's effect on viability over time. Lack of cell growth was identified as stable cell count over time in some conditions, indicating cell cycle arrest. Where cell death was detected, the mechanism (apoptosis or necrosis) was assigned automatically.

At the organelle level, changes in mitochondrial population, dry mass, and morphology were monitored, alongside lipid droplet population, dry mass, and morphology. Observed drug-induced effects included mitochondrial biogenesis and increased lipid droplet dry mass, indicating changes to cellular metabolism.

Together, these capabilities form a comprehensive, label-free phenotypic screening workflow, enabling researchers to extract quantitative, time-resolved data across many diverse cellular features, accelerating discovery and improving the predictive value of in vitro drug screening.

Endonectin Defines an Intracellular Adiponectin Pathway Governing PPARγ Transcriptional Control

Abstract Number: 52
Poster Number: 48

Megan Virostek (UT Southwestern Medical Center), Toshiharu Onodera (UT Southwestern Medical Center), Jan-Bernd Funcke (UT Southwestern Medical Center), Garrett Kimble (UT Southwestern Medical Center), Evelyn A Bates (University of Kentucky College of Medicine), Shiuhwei Chen (UT Southwestern Medical Center), Terry D Hinds Jr (University of Kentucky College of Medicine), Michael Buszcza (UT Southwestern Medical Center), Samuel Klein (Washington University School of Medicine), Philipp E Scherer (UT Southwestern Medical Center)

Adiponectin is a secretory adipokine with insulin-sensitizing, anti-inflammatory, and anti-fibrotic properties. Four adiponectin knockout (AKO) mouse models exist, all of which effectively ablate circulating adiponectin. However, there are significant phenotypic differences across AKO models, raising questions regarding the origin of these discrepancies. Here we identified a new adiponectin isoform, hereinafter referred to as endonectin. Differential endonectin expression between AKO models primarily accounts for their phenotypic variability. Endonectin arises from alternative splicing of exon 1 and 3. Notably, endonectin retains the critical globular bioactive domain and lacks the extracellular export signal. Consequently, unlike canonical adiponectin, endonectin functions intracellularly. Surprisingly, endonectin is a naturally occurring and expressed in humans and wild-type mice.

Differential retention of endonectin explains the phenotypic divergence among AKO strains. Houston and Osaka AKO mice lack exon 2 but retain exons 1 and 3. These mice lack adiponectin but maintain endonectin, we designate these models as endonectin-dominant. In contrast, Dallas AKO mice lack the entire adiponectin gene spanning from exon 1 to 3, representing a complete AKO model which lacks both adiponectin and endonectin. Dallas AKO mice are characterized by lower body weight, reduced adipose tissue weight and lower PPARγ activity. Remarkably, reconstitution of endonectin's globular domain leads to an increase in body weight and a partial recapitulation of the Osaka AKO model transcriptome signature.

Mechanistically, endonectin's globular domain enhances PPARγ activity by modulating the interaction of coregulators with PPARγ thereby promoting PPARγ transcription. Specifically, endonectin recruits NCOA1 and NCOA4, while dissociating TF65 and PPRC from the PPARγ transcriptional complex. Consistent with a metabolically protective role, we demonstrate metabolically healthy obese and lean individuals have higher endonectin expression compared to metabolically unhealthy obese individuals. Collectively, these findings establish endonectin as a functional intracellular adiponectin isoform that regulates PPARγ activity, reconciles phenotypic divergence among AKO models and highlights human relevance.

Integrated spatial and traditional single-cell RNA expression profiles of livers from fasted and refed mice

Abstract Number: 53
Poster Number: 49

Simeng Wang (UT Southwestern), Jay Horton (UT Southwestern)

Hepatocytes carry out distinct functions based on their anatomic location in hepatic acinus. The hepatic lobule is divided into periportal, midzonal, and pericentral zones. Periportal hepatocytes are exposed to highly oxygenated nutrient-rich blood, whereas pericentral hepatocytes are exposed to relatively deoxygenated and nutrient-poor blood. Midzonal cells exist in an intermediate environment and may serve as progenitor cells. A detailed characterization of liver cell subgroups within each zone in response to nutrient changes has not been described. Here, we used spatial transcriptomics of liver sections together with a recently developed cellular isolation method that permits single-cell sequencing (scRNA-seq) of hepatocytes and nonparenchymal cells (NPCs) to characterize metabolic regulatory networks in response to fasting/refeeding.

Spatial transcriptomics was performed using fresh frozen liver sections from mice subjected to fasting and refeeding. Liver cells were also isolated from mice fasted 24 hr (n=3) and mice refed a fat-free diet for 6 hr (n=3) or 12 hr (n=3) for traditional scRNA-seq. Computational analysis utilized Seurat, RNA velocity, and Cellrank to integrate data from isolated cells and liver sections.

For hepatocytes, 4 distinct periportal, 3 midzonal, and pericentral subpopulations of hepatocytes were identified. In response to refeeding, midzonal hepatocytes displayed the greatest gene expression changes. Periportal cells and midzonal cells closest to the portal triad had the highest expression of genes involved in lipogenesis, lipid transport, and cholesterol synthesis; following the expression of transcription factors SREBPs, ChREBP, RXRa, and LXRb. Expression of genes involved in glycolysis and fructolysis were restricted to periportal cells in refed livers. Midzonal cells closest to pericentral region expressed genes involved in bile acid metabolism and detoxification as did the pericentral cells, which also expressed genes involved in glutathione metabolism, cholesterol biosynthesis, and cytochrome P450 enzymes. In the fasted state, expression of genes involved in fatty acid oxidation were highest in the pericentral and midzonal cells but increased the most in subpopulations of periportal hepatocytes closest to the portal triad. Expression of genes involved in gluconeogenesis were highest in the periportal cells, but expression expanded to midzonal and pericentral cells with fasting. Pericentral cells expressed genes enriched in monocarboxylic acid, glycerolipid metabolism, and detoxification, which are largely regulated by Pparα and Nfe2l2.

Fasting induced genes involved in tubular morphogenesis and migration in stellate cells, hepatic progenitor cells, and macrophages. Refeeding induced the expression of genes involved in retinoid metabolism and transport, plasma lipoprotein remodeling and assembly, and metabolism of fat-soluble vitamins.

In summary, our data provide the first transcriptome landscape at the single cell resolution of the distinct cellular subsets and their spatial location in response to fasting/refeeding.

Dietary cholesterol is a novel nutritional driver of macrophage mTOR signaling in atherosclerosis

Abstract Number: 54
Poster Number: 50

Xiangyu Zhang (University of Pittsburgh), ali ajam (University of Pittsburgh), Babak Razani (University of Pittsburgh)

Hypercholesterolemia is a major risk factor for immune cell activation and atherosclerosis although our understanding of cholesterol's pathogenic signaling roles is rudimentary. Recent links between cholesterol and mammalian target of rapamycin (mTOR) signaling in cell lines opens the possibility of novel effects for elevated cholesterol in pro-atherogenic signaling. Here, we show that elevated LDL-c in humans correlates with mTORC1 activation and reciprocal autophagy suppression in circulating monocytes. Diet-induced elevations in plasma cholesterol in mouse models similarly show graded activation of mTORC1 with concomitant reductions in autophagy in atherosclerotic plaque macrophages resulting in exacerbation of lesion size and complexity. LDL cholesterol (LDL-c) and cholesterol-containing atherogenic lipids are potent mTORC1 inducers in macrophages on par with classical activators such as leucine. Cholesterol and leucine combine to dampen autophagy/mitophagy, resulting in mitochondrial dysfunction and apoptosis in an mTOR-dependent manner. The cholesterol sensor LYCHOS is upregulated in macrophages of both human and mouse plaque transcriptomic datasets and targeting its expression blunts cholesterol-mTORC1 activation and deleterious downstream signaling. Our work defines a novel atherogenic signaling role for cholesterol in macrophages that is therapeutically relevant and highlights mechanisms by which dietary nutrients such as lipids and amino acids can cooperate to drive atherosclerosis.

Beyond Mitochondria: A Calcium-Dependent Peroxisome-Lipid Droplet Signalling Axis Regulates Adipocyte Lipolysis.

Abstract Number: 55
Poster Number: 51

Morozova, K[1], Hadley, CK[1,2] , Diedrich, JK[3], Pinto, AFM[3], Banerjee, P[4], Saghatelian, A[5], Zalckvar, E[6], Klemm, R[7], Cohen, P.

[1]Laboratory of Molecular Metabolism, The Rockefeller University, New York, NY, USA
[2]Weill-Cornell/Rockefeller/Sloan Kettering Tri-Institutional MD-PhD Program, New York, NY, USA
[3]Department of Molecular Medicine, The Scripps Research Institute, La Jolla, CA, USA
[4]Frits and Rita Markus Bio-Imaging Resource Center, The Rockefeller University, New York, NY, USA
[5]Clayton Foundation Laboratories for Peptide Biology, The Salk Institute for Biological Sciences, La Jolla, CA, USA
[6]Department of Physiology, Anatomy, and Genetics, University of Oxford, Oxford, UK
[7]Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat-Gan, Israel

Adipocyte lipolysis requires coordinated subcellular reorganization to efficiently mobilize stored fatty acids from lipid droplets (LDs) while mitigating lipotoxicity. Peroxisomes are functionally required for this catabolic process and dynamically redistribute to the surface of LDs following lipolytic stimulation. However, the molecular machinery regulating peroxisome engagement remains unknown. Here, we show that peroxisome-LD interactions during lipolysis are calcium-dependent and identify candidate mediators of this organelle crosstalk.

To address this, we used whole-organelle immunopurification coupled with tandem mass tag (TMT) proteomics (PEROXO-IP) in 3T3-L1 adipocytes under basal and forskolin-stimulated conditions. PEROXO-IP selectively enriched intact peroxisomes, capturing both resident and transiently associated proteins with a 94% coverage of the annotated peroxisomal proteome. Quantitative proteomics revealed dynamic remodeling of the peroxisome-LD interface during lipolysis, with recruitment of lipid droplet coat proteins (PLIN1, PLIN2) and lipid hydrolases (ATGL, HSL) to the peroxisome surface. Unbiased GO analysis identified calcium-dependent protein and phospholipid binding as top enriched molecular functions, implicating Ca^{2+} signaling in peroxisome-LD contact regulation.

Pharmacological Ca^{2+} chelation with BAPTA-AM impaired forskolin-stimulated free fatty acid release without affecting PKA-mediated PLIN1 and HSL phosphorylation, indicating a specific requirement for Ca^{2+} downstream of adrenergic signaling. Of the proteins identified by PEROXO-IP, annexin A6 (ANXA6) - a calcium-dependent phospholipid binding protein and known LD proteome component - emerged as a top functional candidate. ANXA6 loss-of-function impaired stimulated lipolysis in 3T3-L1 adipocytes, as well as mouse primary adipocytes, phenocopying Ca^{2+} chelation.

Together, these findings establish Ca^{2+} as a regulator of peroxisome-LD contact dynamics during lipolysis and implicate ANXA6 as a mediator. Understanding the molecular basis of this organelle crosstalk may open new avenues for targeting dysregulated lipid mobilization in obesity and type 2 diabetes.