2024 KERN LIPID CONFERENCE

“Lipids and Mitochondria in Metabolic Disease"

August 12-14, 2024
Viceroy Snowmass

ORGANIZERS:
Jonathan Brestoff, MD, PhD
Nada Abumrad, PhD
Gregory Steinberg, PhD

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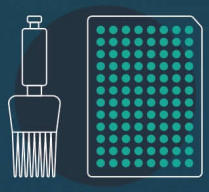

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Message from the President

It is my pleasure to welcome you to the 47th Kern Lipid Conference.

The Kern Lipid Conference began in 1977 in Aspen, Colorado. When the University of Colorado sold the Given Institute, we relocated the meeting to Vail, Colorado. This year marks our return to Snowmass/Aspen for the first time since 2010.

This year's topic centers on the diverse facets of mitochondrial metabolism. I'd like to extend my heartfelt gratitude to Jonathan Brestoff, Nada Abumrad, and Gregory Steinberg for curating an engaging and insightful program that promises to captivate us all.

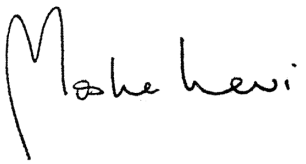
A special thank you goes to Kaitlyn Murphy, Susan Hayes, and Dalan Jensen for their dedicated efforts in making this conference a reality.

We are also deeply appreciative of the NIH for their conference grant support, as well as our sponsors and the Kern Lipid Board Members, whose contributions make this gathering possible.

Please note that we have implemented an NIH Conference Safety Plan, details of which are included in this program and available on the Kern Lipid Conference website.

Additionally, starting this year, the conference will alternate annually with the Deuel Lipid Conference. This means the Deuel Lipid Conference will be held in 2025, followed by the Kern Lipid Conference in 2026, and so forth.

Thank you for joining us, and we look forward to a productive and inspiring conference!



Moshe Levi, MD
Kern Lipid Conference President

Cover caption: “Pictorial representation of tumor necrosis factor alpha interacting with lipid droplets and mitochondria in muscle” – Drawn by: Glen Oomen
Provided by: Gregory Steinberg, PhD, McMaster University

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*Funding for this conference was made possible (in part) by 1R13HL176131 from the National Heart Lung and Blood Institute (NHLBI). The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.
**This activity is supported by an educational grant from Lilly.

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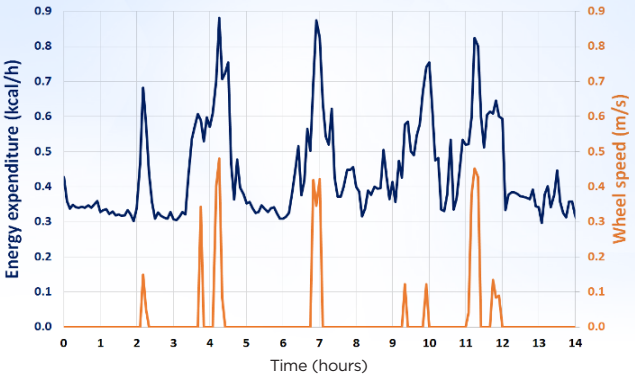

Competitor's System

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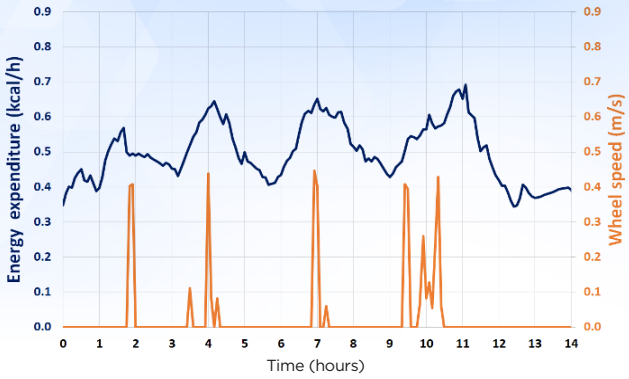

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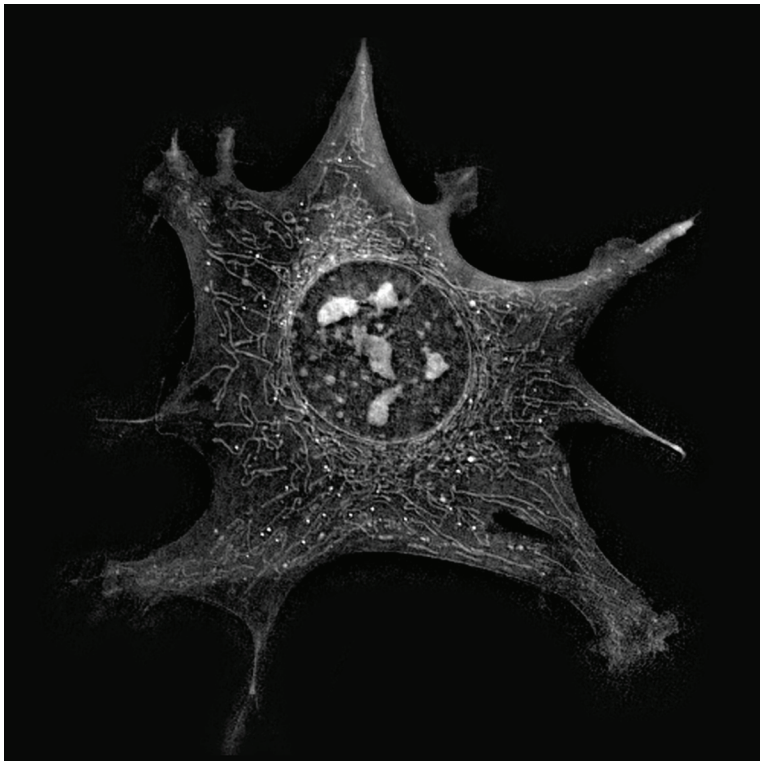

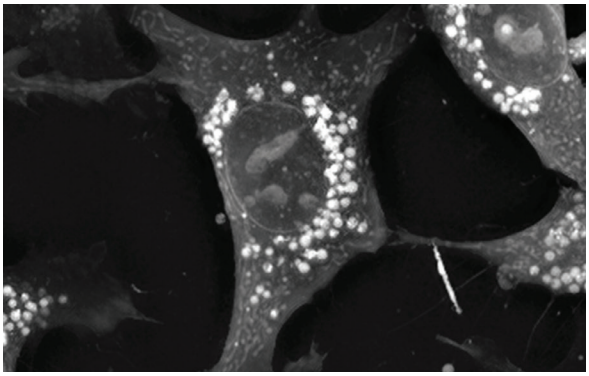

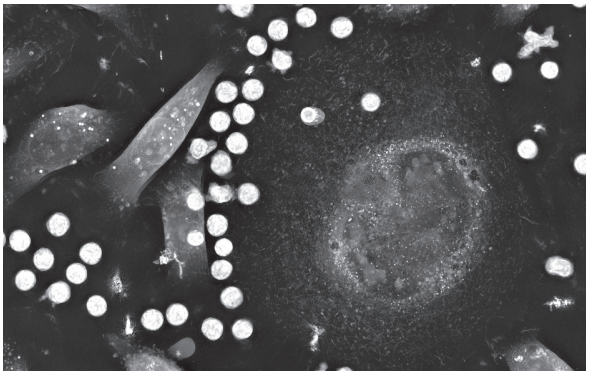

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Fred Kern, Jr., MD (1918-1997)

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.

Lipedema is an adipose disorder with unknown etiology and poorly characterized pathophysiology.

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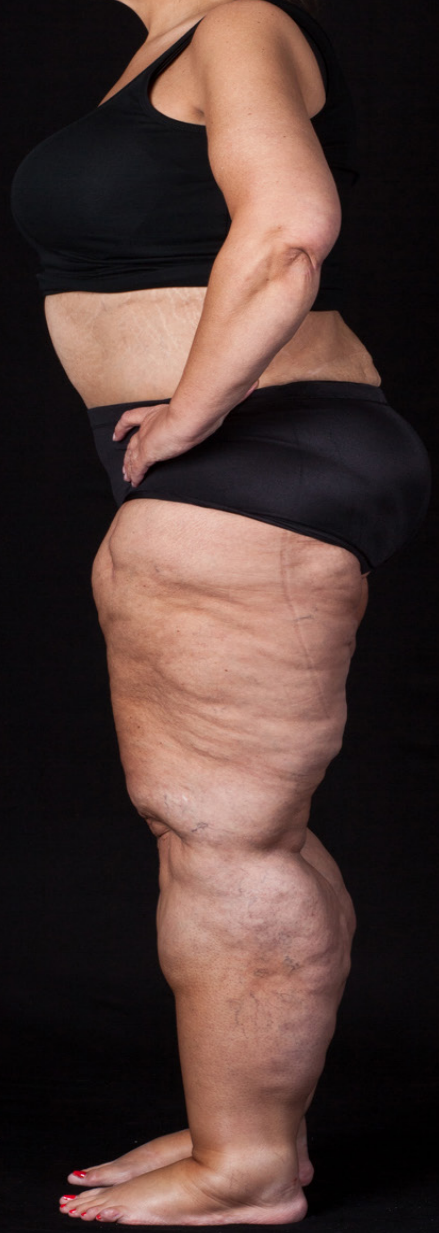
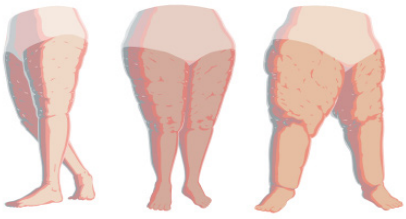


We are investing in research to **define, diagnose,** and **develop treatments for Lipedema**.
Learn more about LF, our research, and funding opportunities.

Lipedema.org/research-grants



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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.

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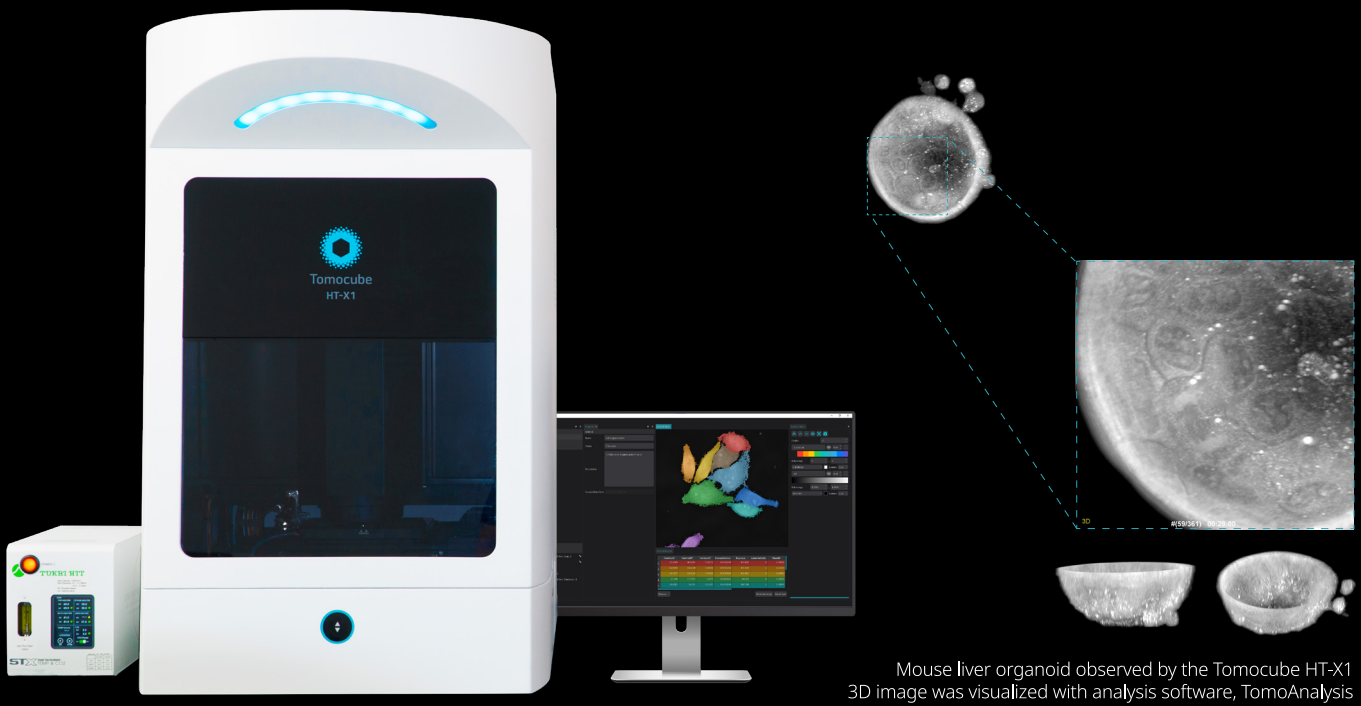

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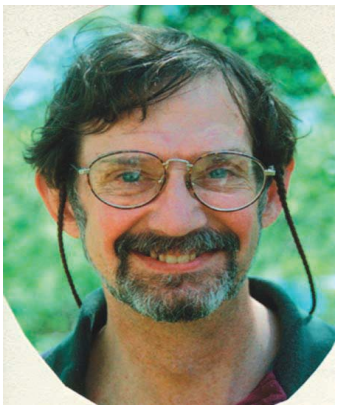


David L. Williams, PhD (1946-2004)

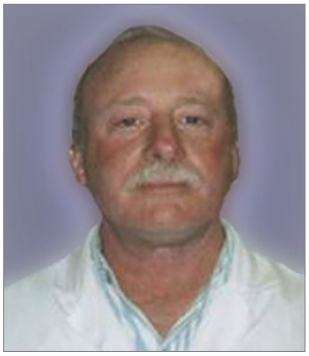
Born and raised in Pennsylvania, David Williams attended the University of California, Berkeley, and was graduated with a Bachelor of Arts degree in Zoology in 1967. He pursued further studies at Jack Gorski's laboratory at the University of Illinois and obtained his PhD with nine publications to his 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.

2024 Kern Lecturers

Shingo Kajimura, PhD is a Professor at Harvard Medical School & Beth Israel Deaconess Medical Center and a Howard Hughes Medical Institute Investigator.
He is a molecular biologist who aims to understand the molecular basis for bioenergetics in health and disease. The overarching goal of his research is to provide a blueprint for rewiring the molecular circuitry of bioenergetics by defined factors to improve metabolic health. His lab explores diverse biological materials to understand metabolism at the molecular, cellular, and organismal levels. His work has led to the now widely accepted notion that the role of brown/beige fat in energy balance extends beyond UCP1-mediated thermogenesis. His awards include the 2024 Sable Award, the 2022 Richard E. Weitzman Outstanding Early Career Investigator Award and the 2020 Catalyst Award in Diabetes, Endocrinology and Metabolic Diseases. He obtained his BS, MS and PhD from the University of Tokyo, Japan and did his postdoctoral training at the Dana-Farber Cancer Institute.

Kathryn Wellen, PhD is a Professor in the Department of Cancer Biology at the University of Pennsylvania Perelman School of Medicine. She earned her PhD from Harvard School of Public Health, working with Gökhan Hotamisligil, studying the role of adipose tissue inflammation in metabolic diseases. She performed postdoctoral work with Craig Thompson at the University of Pennsylvania, focusing on cancer cell metabolism and metabolic signaling mechanisms. Her work there played an important role in establishing the concept that epigenome is sensitive to metabolism, with the demonstration that histone acetylation is responsive to acetyl-CoA production by the enzyme ATP-citrate lyase in mammalian cells. Her lab continues to be broadly interested in links between cellular metabolism, signaling, and gene regulation in metabolic diseases and cancer. She has been recognized by honors including the 2023 AACR Award for Outstanding Achievement in Basic Cancer Research and the 2023 Sable Award for Outstanding Contribution to Metabolic Physiology.

2024 Kern Lipid Conference

"Lipids and Mitochondria in Metabolic Disease"

Monday, August 12 - Wednesday, August 14, 2024

Viceroy Snowmass - Snowmass, Colorado

Organizers:

Jonathan Brestoff, MD, PhD, Washington University in St. Louis

Nada Abumrad, PhD, Washington University in St. Louis

Gregory Steinberg, PhD, McMaster University

All talks held in Grand Ballroom, Level 1

Monday, August 12, 2024	
Conference Check-In	
7:00-8:00am	**Conference Check-In** *Foyer of the Grand Ballroom Salons 2-4, Level 1*
Opening Kern Lecture	
8:05am	**Welcome Remarks & Opening Kern Lecturer Introduction** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University
8:15am	**Opening Kern Lecture: "How do cells make heat?"** Shingo Kajimura, PhD, Beth Israel Deaconess Medical Center/Harvard Medical School & HHMI
Session 1: Lipids and Mitochondrial Metabolism in the Brain Session Chair: Clair Crewe, PhD, Washington University in St. Louis Co-chairs: Saranna Fanning, PhD, Harvard Medical School and Brigham & Women's Hospital & Simeng Wang, MD, PhD, UT Southwestern Medical Center 9am-12:15pm	
9am	**"Lipid metabolism defects in Alzheimer's and Parkinson's disease models"** Hugo Bellen, DVM, PhD, Baylor College of Medicine
9:30am	**"Analysis of Altered NAD Metabolism in Citrin Deficiency Resolves the FGF21 Paradox and Reveals Glycerol-3-Phosphate/ChREBP Signaling as a Key Molecular Driver of Lipogenesis"** Charles Brenner, PhD, City of Hope
10am	**"Mitochondria, energy constraints, and cellular aging"** Martin Picard, PhD, Columbia University
10:30-10:45am	**Morning Break** *Salon 1 & Ballroom Terrace, Level 1*
10:45am	**"Importance of Hippocampus Lipid Remodeling in Behavior"** Nada Abumrad, PhD, Washington University in St. Louis
11:15am	*Nanolive-sponsored short talk:* **"AI-enabled, label-free monitoring of mitochondria in health and diseases"** Mathieu Frechin, PhD, Nanolive - Switzerland

Notes

11:30am	*Short talk:* **"Metabolic imaging of brain lipid metabolism during aging and diseases"** Yajuan Li, PhD, University of California-San Diego
11:45am	**Introduction and Presentation of the Roger Davis Award Lecture** Robert H. Eckel, MD, University of Colorado Anschutz Medical Campus
11:50am	**Roger Davis Award Lecture: "Desmosterol regulates liver myeloid cell identity controlling immunometabolic functions in MAFLD/MASH"** Pablo Fernandez-Tussy, PhD, Yale University
12:15-1:15pm	**Lunch** *Salon 1 & Ballroom Terrace, Level 1*
1:15-4pm	**Afternoon Break**
Session 2: Immune Cells and Lipids in Metabolic Disease Session Chair: L. Ashley Cowart, PhD, Virginia Commonwealth University Co-chairs: Emily Goldberg, PhD, University of California, San Francisco 4-6pm	
4pm	**"Targeting Microglial Lipid and Lipoprotein Metabolism in Neurodegenerative Disease"** Kimberley Bruce, PhD, University of Colorado Anschutz Medical Campus (rescheduled from session 1)
4:30pm	**"Immunometabolic crosstalk between energy and nutrient sensing pathways"** Morgan Fullerton, PhD, University of Ottawa
5pm	**"Unconventional role of T cells and the skin in controlling systemic lipid metabolism"** Taku Kambayashi, MD, PhD, University of Pennsylvania
5:30pm	*Short talk:* **"Induction of TFEB promotes Kupffer cell survival and reduces liver pathology in MASLD"** Mandy Chan, PhD Candidate, Washington University in St. Louis
5:45pm	*Short talk:* **"Targeting hepatic oxalate overproduction to treat MASH by modulation of fatty acid β-oxidation and monocyte chemotaxis"** Oren Rom, PhD, LSU Health Shreveport
Poster Session & Reception 6:15-8:15pm Nest Patio & Deck, Level 3 (In the event of bad weather, the poster session & reception will be held in Summit Meeting Rooms 1&2, Level 3) Colorado evenings tend to be cool after sunset, please plan appropriately	
Tuesday, August 13, 2024	
Session 3: Mitochondria Transfer in Metabolic Disease Session Chair: Zoltan Arany, MD PhD, University of Pennsylvania Co-chairs: Tomasz Bednarski, PhD, University of Nebraska – Lincoln & Catherine Poholek, MD, PhD, University of Pittsburgh 8am-12:10pm	
8am	**"Regulated Extracellular Vesicle Secretion by Adipocytes"** David Bernlohr, PhD, University of Minnesota

Notes

8:30am	**"Adipocyte extracellular vesicles in metabolic regulation"** Clair Crewe, PhD, Washington University in St. Louis
9am	**"Innate immune cell regulation of brown fat thermogenesis"** Jonathan Brestoff, MD, PhD, Washington University in St. Louis
9:30am	*Tomocube-sponsored short talk:* **"How do various techniques (holotomography and ptychography) contribute to discovery and research?"** YongKeun Park, PhD, Korea Advanced Institute of Science and Technology
9:45-10:05am	**Morning Break** *Salon 1 & Ballroom Terrace, Level 1*
10:05am	**"Biophysical Characterization of Cancer Metabolism: Multiparametric Imaging and Phenotypic Tracking in Mitochondrial Dynamics"** Michelle Digman, PhD, University of California Irvine
10:35am	**"Macrophages, keepers of mitochondrial health"** Andres Hidalgo, PhD, Yale
11:05am	**Introduction and Presentation of the David L. Williams Lecture & Award** Mary Sorci-Thomas, PhD, Medical College of Wisconsin
11:10am	**David L. Williams Award Lecture & Award: "Regulation of postprandial lipid handling and fuel selection with long-acting glucose-dependent insulinotropic peptide"** Jacqueline Beaudry, PhD, University of Toronto
11:40am	*Short talk:* **"Brown adipocytes transfer mitochondria to neutrophils to promote adaptive thermogenesis"** Samantha Krysa, PhD, Washington University in St. Louis
11:55am	*Short talk:* **"A Role for Macrophages in Tissue Mitochondrial Homeostasis Via Heterophagy"** Jose Angel Nicolas Avila, PhD, University of California - San Francisco
12:10-1:10pm	**Lunch** *Salon 1 & Ballroom Terrace, Level 1*
1:10pm	**Afternoon Break**

Exhibitor Hall Open

1-4pm

Grand Ballroom Foyer

List of exhibitors:

- Columbus Instruments
- Lucid Scientific
- Nanolive
- Sable Systems International, Inc.

Small Group Discussions

1-2pm

Salon 1 & Ballroom Terrace, Level 1

	Academic Career Success: Some of the logistics of succeeding in a scientific career.

Notes

	Academic-Industry Partnership: How to navigate collaborations in academia with industry partners.
	Diversity, Equity & Inclusion (DEI) in Academic Labs: How to build a lab culture that maximizes success and opportunity for all lab members.
	The Faculty Job Search: For those who are starting to search for faculty jobs, how to prepare and navigate the job search process.

Wednesday, August 14, 2024

Session 4: Lipids and Mitochondrial Metabolism in Metabolic Disease

Session Chair: Jay Horton, MD, UT Southwestern

Co-chairs: Xiangyu Zhang, PhD, University of Pittsburgh & Robert Helsley, PhD, University of Kentucky

8:30-11:30am

8:30am	**Presentation of the Franz Simon Poster Award – Recipient To be Announced** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University
8:35am	**Presentation of the Most Innovative Poster and Most Impactful Poster Awards *sponsored by Lipotype GmbH* - Recipients To be Announced** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University
8:40am	**"Adapting to Metabolic Stress"** Alan Saltiel, PhD, University of California, San Diego
9:10am	**"Regulation of lipid metabolism and mitochondrial function in obesity, diabetes, and aging"** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University
9:40am	**"Skeletal muscle metabolic (re)programming in obesity and weight loss"** Mary-Ellen Harper, PhD, University of Ottawa
10:10-10:30am	**Morning Break** *Salon 1 & Ballroom Terrace, Level 1*
10:30am	**"Mitochondria Lipid Droplet Interaction"** Orian Shirihai, MD, PhD, UCLA
11am	*Short talk:* **"Peroxisomal Regulation of Adipose Tissue Thermogenesis"** Irfan Lodhi, PhD, Washington University in St. Louis
11:15am	*Short talk:* **"Brown adipose tissue CoQ deficiency activates the ISR and triggers an FGF21- dependent mitohormetic response"** Amanda Gunawan, PhD Candidate, University of California, Berkeley
11:30am-1pm	**Lunch** *Salon 1 & Ballroom Terrace, Level 1*

Session 5: Lipids in Cancer

Session Chair: Kimberley Bruce, PhD, University of Colorado Anschutz Medical Campus

Session Co-chair: Karthickeyan Chella Krishnan, PhD, University of Cincinnati College of Medicine

1-2:45pm

1pm	**"Modulation of fatty acid metabolism enhances tumor immunogenicity"** Gregory Steinberg, PhD, McMaster University
1:30pm	**"Metabolic co-option of immune cells in cancer"** Sue Kaech, PhD, The Salk Institute for Biological Studies

Notes

2pm	*Short talk:* **"Gene Expression and Fatty Acid Profiling of Metabolically-driven Human Hepatocellular Carcinoma"** Garrett Anspach, MD, PhD Student, University of Kentucky
2:15pm	**"Mitochondrial Stress Signaling in Aging, Disease and Immunity"** Gerald Shadel, PhD, The Salk Institute for Biological Studies
Closing Kern Lecture	
2:45pm	**Closing Remarks & Closing Kern Lecturer Introduction** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University
2:55pm	**Closing Kern Lecture: "At the crossroads of lipids and mitochondria: acetyl-CoA in health and disease"** Kathryn Wellen, PhD, University of Pennsylvania
3:40-6pm	**Afternoon Break**
Final Night Dinner & Dancing	
6-8pm	**Cocktail Reception & Dinner** *Salon 1 & Ballroom Terrace, Level 1*
8-10pm	**Music & Dancing** *Salon 1 & Ballroom Terrace, Level 1*

2024 Awards

David L. Williams Lecture and Scholarship Award - Winner

Jacqueline Beaudry, PhD, University of Toronto

David L. Williams Lecture and Scholarship Award – First Runner Up

Oren Rom, PhD, LSU Health Shreveport

Roger Davis Investigator Award for Transitional Faculty - Winner

Pablo Fernandez-Tussy, PhD, Yale University

Roger Davis Investigator Award for Transitional Faculty - First Runner Up

Jose Angel Nicolas Avila, PhD, University of California - San Francisco

Early Career Investigator Travel Stipend Award Winners

Garrett Anspach, University of Kentucky
Mandy Chan, Washington University in St. Louis
Joseph Choi, Johns Hopkins University
Liujuan Cui, PhD, UCLA
Yajing Gao, PhD, University of California, Los Angeles
Rocky Giwa, Washington University St Louis
Amanda Gunawan, B.S., University of California, Berkeley
Eleni Hughes, PhD, Georgetown University Medical Center
Maryam Jamil, PhD, Virginia Commonwealth University
Wentong Jia, PhD, Washington University in St. Louis
Samantha Krysa, PhD, Washington University in Saint Louis
Yajuan Li, University of California, San Diego
Xuejing Liu, Washington University in Saint Louis
Ziyang Liu, University of Pittsburgh
Jiameng Sun, B.S., Washington University in St. Louis
Xuenan Sun, PhD, UT Southwestern Medical Center
Trace Thome, PhD, University of Pennsylvania
Yu-Sheng Yeh, PhD, RD, University of Pittsburgh

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Immunometabolic Impact of TREM2 Variants on ApoE Binding in Cancer: Insights for Therapeutic Development

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Properly regulated lipid metabolism is critical for the function of macrophages across various tissue types. Dysregulation in lipid metabolism can lead to alterations in macrophage activation patterns, contributing to the pathogenesis of numerous diseases, including cancer. Reprogramming of lipid metabolism in tumor-associated macrophages induces immunosuppression within the tumor microenvironment, presenting a significant challenge for therapeutic development.

An emerging target for immunometabolic regulation of immunosuppression mediated by tumor-associated macrophages is Triggering receptor expressed on myeloid cells 2 (TREM2), which serves as a pro-tumorigenic immunosuppressive marker in cancer. TREM2 is a surface receptor that promotes macrophage proliferation and regulates inflammation and lipid metabolism through diverse ligand binding. This promiscuous binding implicates TREM2 in various disease states, and its interactions with Apolipoprotein E (ApoE), a critical regulator of lipid homeostasis, have been extensively studied, particularly in the context of neurodegenerative diseases.

The R47H variant of TREM2 impairs interactions with ApoE, increasing the risk of Alzheimer's disease. Conversely, three gene polymorphisms of ApoE—E2, E3, and E4—alter interactions with TREM2, serving as protective, neutral, and pathogenic variants associated with Alzheimer's disease, respectively. Intriguingly, evidence suggests protective interactions between wildtype TREM2 and ApoE4 in cancer. This indicates that the same conformation of the complex that is deleterious in pro-inflammatory, neurodegenerative disease states may promote inflammatory pathways and counteract immunosuppression in cancer. However, the effects of TREM2 cancer-associated variants on ApoE binding and ensuing regulation of lipid metabolism are unexplored.

In this study, we utilized an *in silico* approach based on long-timescale molecular dynamics simulations to analyze TREM2 dynamics in the presence of cancer-associated mutations, probing changes in ApoE binding and informing future *de novo* drug design. Understanding how TREM2 variants interact with ApoE isoforms and deviate from protective conformations can guide the design of variant-specific TREM2 allosteric regulators. These regulators would modulate the conformation of TREM2 without competing with the ApoE binding site, aiming to restore the protective conformation of the wildtype TREM2-ApoE4 complex and potentially restore lipid homeostasis. Overall, this work provides novel insights into therapeutic design to target the TREM2-ApoE pathway in macrophage dysfunction in cancer, with applications to other inflammatory disease states.

Gene Expression and Fatty Acid Profiling of Metabolically-driven Human Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma (HCC) is the most common form of liver cancer and the third leading cause of cancer death worldwide. As hepatitis B remains the foremost risk factor for HCC, metabolic dysfunction-associated steatotic liver disease (MASLD) is the fastest-growing etiology of HCC. The focus of this work is to identify novel gene and fatty acid associations in human MASLD-driven HCC that may be exploited for therapeutic benefit.

Methods: Human HCC tumor (n=8) and adjacent non-tumor samples (n=8) were obtained from the Biospecimen Procurement and Translational Pathology Shared Resource Facility at the University of Kentucky Markey Cancer Center. All patients met cardiometabolic MASLD criteria and were negative for viral hepatitis. Hematoxylin and eosin (H&E) staining was used for pathological determination of tumor and adjacent nontumor tissue. Lipids were extracted using a methyl-tert-butyl ether extraction method and subjected to lipidomics by the West Coast Metabolomics Center. RNA was isolated, purified, and used for bulk sequencing. Data were analyzed using paired nonparametric analyses via a Wilcoxon or Mann-Whitney test, where appropriate.

Results: Histological analysis by H&E showed significant lipid vacuole accumulation in HCC tumors relative to nontumor tissue. Lipidomics analyses revealed significant increases in long-chain nonesterified monounsaturated fatty acids (MUFAs; C16:1, C18:1, C20:1) and MUFA-enriched phospholipids (PC30:1, PC32:1, PE32:1, and PC36:1) in tumors relative to nontumor tissue. No significant differences were observed in nonesterified polyunsaturated fatty acids (PUFAs; C18:2, C20:4, and C22:6), PUFA-enriched phospholipids (C36:4, C38:4, C38:6, C40:6), or in fatty acid esters of hydroxy fatty acids (FAHFAs; C38:2, C38:4, C38:6). However, both MUFA- (C14:1, C18:1) and PUFA-enriched acylcarnitines (C18:2, C18:3) were collectively reduced in human tumors. Differential analysis of RNA sequencing revealed 854 genes down regulated and 850 genes upregulated in tumors versus nontumor tissue. Consistently, fatty acid oxidation genes (*CPT1A*, *CPT2*, *ACADL*, *ACADM*, *ACADS, HADHA*) were significantly lower in tumor versus nontumor tissue. Genes involved in *de novo* lipogenesis were largely dysregulated (e.g. no differences in *SREBF1* or *FASN*; increases in *ACLY, ACACA,* and *SCD1*; decreases in *ACSL1*) in tumor versus nontumor tissue.

Conclusions: These results suggest HCC tumors exhibit a reduced capacity to undergo mitochondrial β-oxidation resulting in accumulation of free- and esterified-MUFAs with a concomitant reduction in MUFA-carnitines. Current studies are underway to determine mechanisms by which MUFAs and the impairment of hepatic MUFA catabolism through FAO promotes the development of HCC and tumor growth in mice.

Alpha-synuclein alters the neuronal lipidome in synucleinopathies and regulates phosphatidylserine synthesis at the Mitochondria-Associated ER Membranes (MAM)

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In synucleinopathies such as Parkinson's disease (PD) and multiple system atrophy (MSA), alpha-synuclein (αSyn) plays a crucial role in the pathogenesis of disease. Furthermore, there is mounting evidence to suggest lipid dyshomeostasis is also associated with these diseases. In this study, we analyzed the lipid composition of post-mortem human samples, including the substantia nigra pars compacta (SNc) of PD donors and striatum of MSA donors, identifying lipid species to discriminate PD cases from MSA and control samples.

Our analyses also found that the PD nigral samples displayed higher levels of phosphatidylcholine (PtdCho) and phosphatidylserine (PtdSer) species bound to long chain and unsaturated fatty acids. Since PD is associated with increased expression of αSyn via multiplications of the αSyn-encoding *SNCA* gene, we generated patient-derived, induced pluripotent stem cell (iPSC)-derived dopaminergic neurons carrying different dosages of αSyn from: no αSyn (SNCA-Knockout) to normal (SNCA-wild-type) to 1.5x endogenous level (SNCA-Duplication). Largely recapitulating the same analyses on the PD brain, we found a striking association between αSyn dosage and PtdSer. Since previous work had found that αSyn localizes to the mitochondria-associated endoplasmic reticulum (ER) membranes (MAM), we performed subcellular fractionation experiments using our simplified iPSC-derived neuronal model to investigate the effect of αSyn dosage at MAM, finding that αSyn level regulates PtdSer synthesis by feedback-control regulation of PtdSer synthase 2 (PSS2). Our results reveal αSyn-driven changes in MAM activity alter the neuronal lipidome, and increased alpha-synuclein expression impairs the regulation of PtdSer in cellular membranes from affected cells.

Our study offers mechanistic insight linking αSyn pathology to dysregulation of the neuronal lipidome as seminal factors in synucleinopathies, which have pathogenic implications and can be traced back to alterations at MAM. Approaches rescuing MAM should thus be considered in the development of much needed new therapeutic strategies for the treatment of these dreadful disorders.

Enhancing lysosomal lipid metabolism in Kupffer Cells prevents cell death and reduces pathology in metabolic dysfunction-associated steatotic liver disease

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During the development of metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as non-alcoholic fatty liver diseases or NAFLD), liver resident macrophages/Kupffer cells (KCs) decrease in number, and monocyte-derived macrophages (MdMs) infiltrate the liver. However, the mechanism(s) and consequences of KC loss remains unclear. Using a mouse model of MASLD, we discovered that as liver disease progresses KCs develop perturbed phagolysosomal function and fail to store fatty acids in neutral lipid droplets.

To devise a strategy for KCs to counter these cellular abnormalities, we generated an *in vivo* model in which TFEB, a master transcriptional regulator of lysosomal biogenesis and lipid metabolism, is overexpressed selectively in KCs ($KC^{Cre}TFEB^{Tg}$). Both $KC^{Cre}TFEB^{Tg}$ and their Cre-only littermates (KC^{Cre}) had similar weight gain when fed a MASLD-inducing diet. However, KC number was preserved and inflammatory MdM recruitment was reduced in $KC^{Cre}TFEB^{Tg}$ mice. This was not a consequence of increased proliferation as BrdU and Ki67 assays revealed similar rates of proliferation in WT and $TFEB^{Tg}$ KCs. Furthermore, using an inducible overexpression system of TFEB in MdMs, we confirm that overexpressing TFEB itself does not induce rapid upregulation of KC markers *in vivo*. Therefore, TFEB-overexpression in KCs promotes the survival of *bona fide* KCs during MASLD. TFEB can increase fatty acid oxidation and induce the release of GDF-15 both of which could protect KCs from lipotoxicity; however, we found these factors were dispensable for the protection of KCs by TFEB. Instead, we discovered that overexpression of TFEB in bone marrow-derived macrophages led to protection from necroptotic, lipotoxic, and ferroptotic cell death. KCs isolated from $TFEB^{Tg}$ mice also had reduced levels of oxidized lipids, which are known to promote ferroptosis.

In terms of liver pathology, overexpression of TFEB in KCs reduced liver steatosis and injury. Electron microscopy of macrophages revealed that $TFEB^{Tg}$ KCs contained large lipid droplets in vacuoles. RNA sequencing of KCs from $KC^{Cre}TFEB^{Tg}$ and KC^{Cre} animals confirmed the induction of several lysosomal lipid metabolic genes in the transgenic KCs after diet feeding. Utilizing labeled fatty acids to track lipids *in vivo* and *in vitro* functional studies, we showed that TFEB-overexpressing macrophages have enhanced uptake of exogenous free fatty acid and lipoproteins compared to WT macrophages. Taken together, TFEB-overexpression contributes to KC survival in MASLD and reduces hepatic lipid load by re-programming lysosomal handling of lipids in KCs.

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Carnitine Palmitoyltransferase 1 facilitates fatty acid oxidation in a noncell autonomous manner

Joseph Choi

Starvation initiates a series of metabolic adaptations to enable continuous production and delivery of nutrients to critical organs, tissues and cells. This response is coordinated in large part by the liver that responds by liberating glucose to the circulation initially from glycogen stores followed by *de novo* glucose production (i.e. gluconeogenesis). Ketones are also produced and provide an alternative energy source to glucose for highly oxidative tissues such as the brain. Fatty acid oxidation is critical for these processes as it provides the carbon substrate for ketogenesis (acetyl-CoA) and mitochondrial bioenergetics (ATP, NADH) to facilitate gluconeogenesis. Two sister enzymes carnitine palmitoyltransferase 1 (Cpt1) and carnitine palmitoyltransferase 2 (Cpt2) are required for fatty acid import into the intermembrane space for β-oxidation. Our lab has previously shown that mice lacking hepatic Cpt2 ($Cpt2^{L-/-}$) have a whole-body catabolic response. $Cpt2^{L-/-}$ mice also exhibit increased long-chain acylcarnitines in the liver and in circulation. To understand the contribution of acylcarnitines to the hepatic transcriptional and the whole-body fasting response, we generated mice lacking Cpt1a in the liver ($Cpt1a^{L-/-}$) and compared them to $Cpt2^{L-/-}$ mice. Surprisingly, the $Cpt1a^{L-/-}$ mice have an extremely stunted transcriptional response compared to the $Cpt2^{L-/-}$ mice although both livers become equally lipid-laden. We also show that much of this transcriptional response is driven by Pparα, a major transcription factor involved in the fasting response. While Cpt1a is the major hepatic isoform, there is an increase in the other isoform, Cpt1b. To stringently delete acylcarnitine generation, we then generated a double-knockout of both Cpt1a and Cpt1b ($Cpt1a1b^{L-/-}$). Surprisingly, Cpt1b appears to have minimal contribution to the hepatic physiological and transcriptional response during the fasted state. In order to understand the contribution of acylcarnitines to the incredible transcriptional response seen in $Cpt2^{L-/-}$ mice, we then also generated a hepatic **triple-**knockout of Cpt1a, Cpt1b, and Cpt2 ($TKO^{L-/-}$). We see a reversal of circulating free fatty acids and triglycerides as well as a reversal of some transcriptional targets such as Fgf21 and Cd68, suggesting a non-metabolic signaling role of long-chain acylcarnitines. We have developed an incredibly stringent line of mouse models to understand the non-metabolic roles of long-chain acylcarnitines and have indeed found direct and novel roles of long-chain acylcarnitines to the fasting response.

Bile Acids in Mitochondrial Dysfunction and Neurodegenerative Disease

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University of Reading*, NZP UK Ltd (an ICE Pharma Company+

Mitochondrial dysfunction and disruption of mitochondrial dynamics act as underlying features in most neurodegenerative diseases, and therefore stand as a potential target for therapy. Over the last few years, bile acids (BAs), such as ursodeoxycholic acid (UDCA), have emerged as potential treatment for various neurodegenerative diseases, owing to their neuroprotective and non-toxic properties.

Using *C. elegans* as a model, we studied the effect of UDCA treatment on healthy ageing, investigating lifespan and mitochondrial function in aged worms. Additionally, we used rotenone, a complex I inhibitor, to impair mitochondrial function, leading to a reduction in ATP, increased production of ROS and a decrease in mitochondrial membrane potential. The mitochondrial dye, TMRE, was used as an indicator of mitochondrial dysfunction owing to its membrane permeability and cationic fluorescence. UDCA was tested for rescue effects on mitochondrial dysfunction in this wild-type *C. elegans* model.

Treatment with BAs restores mitochondrial function in rotenone treated *C. elegans*. Rotenone-induced developmental delays, reduction in body size and impaired motility was rescued by the presence of the UDCA. The cytoprotective properties of UDCA, in rescuing mitochondrial function, support its use as a therapeutic option for the treatment of neurodegenerative disease.

Clstn3b Mediates Contact of Endoplasmic Reticulum-Lipid Droplet-Mitochondria

Liujuan Cui, Peter Tontonoz

Department of Pathology and Laboratory Medicine

Brown adipose tissue (BAT) plays an important role in energy homeostasis. Endoplasmic reticulum (ER), lipid droplets (LDs), and mitochondria (MT) are essential organelles involved in lipid synthesis, storage, and utilization in brown adipocytes. How the interactions of these three organelles contribute cellular lipid metabolism and energy homeostasis are incompletely understood. Here, we show that the integral ER membrane protein Clstn3b facilitates the efficient use of fatty acids by regulating LD-mitochondria interactions. In oleic acid (OA)-treated brown preadipocytes, Clstn3b stimulated binding of LDs to MT. Clstn3b translocated from LDs after isoproterenol treatment in differentiated brown adipocytes, allowing LD-MT contact. In addition, Clstn3b enhanced isoproterenol-stimulated reduction of LD size. Comparative proteomics analysis of isolated LDs revealed more active lipid metabolic processes in Clstn3b overexpressed brown adipocytes after isoproterenol stimulation. *In vivo,* mice lacking Clstn3b had reduced LD-MT contacts in BAT. These findings shed light on molecular mechanisms by which Clstn3b regulates ER-LD-MT crosstalk to facilitate lipid utilization in thermogenic adipocytes.

T cell cholesterol transport is a metabolic checkpoint that links intestinal immune responses to dietary lipid absorption

Yajing Gao, John P. Kennelly, Xu Xiao, Emily Whang, Alessandra Ferrari, Alexander H. Bedard, Julia J. Mack, Alexander H. Nguyen, Thomas Weston, Lauren F. Uchiyama, Min Sub Lee, Stephen G. Young, Steven J. Bensinger, Peter Tontonoz

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The intrinsic pathways that control membrane organization in immune cells and the impact of such pathways on cellular function are not well defined. Here we report that the non-vesicular cholesterol transporter Aster-A links plasma membrane (PM) cholesterol availability in T cells to immune signaling and systemic metabolism. Aster-A is recruited to the PM during T-cell receptor (TCR) activation, where it facilitates the removal of newly generated "accessible" membrane cholesterol. Loss of Aster-A leads to excess PM cholesterol accumulation, resulting in enhanced TCR nano-clustering and signaling, and Th17 cytokine production. Finally, we show that the mucosal Th17 response is restrained by PM cholesterol remodeling. Ablation of Aster-A in T cells leads to enhanced IL-22 production, reduced intestinal fatty acid absorption, and resistance to diet-induced obesity. These findings delineate a multi-tiered regulatory scheme linking immune cell lipid flux to nutrient absorption and systemic physiology.

UCP1 regulates immunometabolic reprogramming of macrophages in response to IL-4 and parasitic helminth infection.

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Uncoupling protein 1 (UCP1) is a thermogenic protein that contributes to core body temperature defense and regulates systemic metabolic homeostasis. Recent studies indicate that UCP1 can also be expressed by macrophages in response to type 2 cytokines, such as Interleukin (IL-4), which are strongly induced by parasitic helminth infections and allergic diseases. However, the function of UCP1 in macrophages is unknown. In this work, we demonstrate that UCP1 expression by macrophage is neither necessary nor sufficient for defense of core body temperature in mice exposed to cold environmental temperatures. Rather, UPC1 is required for IL-4 to elicit metabolic reprogramming of macrophages by increasing their oxygen consumption rates and inducing proton leak to generate heat locally. Mice lacking UCP1 in macrophages have lower fecal parasite egg burdens, indicating that UCP1 expression during helminth infection is detrimental to the anti-helminth immune response. These findings suggest that UCP1 metabolically rewires macrophages to brake type 2 cytokine-associated inflammation and that parasitic worms elicit this UCP1-dependent immunometabolic checkpoint to dampen anti-helminth immunity and enhance their fitness during infection.

Abstract

Brown adipose tissue CoQ deficiency activates the ISR and triggers an FGF21-dependent mitohormetic response

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Coenzyme Q (CoQ, aka ubiquinone) is an essential component of the mitochondrial electron transport chain (ETC) as well as a membrane-incorporated antioxidant. We are interested in how altered CoQ levels affect the function of CoQ and mitochondria-rich tissue, particularly brown adipose tissue (BAT). Primary CoQ deficiencies can be caused by hereditary mutations in the biosynthesis pathway while secondary CoQ deficiencies are associated with the pharmacological use of HMG-CoA Reductase inhibitors, statins, which are widely used to treat hypercholesterolemia and prevent cardiovascular disease. It remains unclear how cells sense and compensate for CoQ deficiencies and how CoQ deficiencies affect BAT activity. Using 4-chlorobenzoic acid (4CBA) to pharmacologically inhibit CoQ biosynthesis in brown adipocyte cells and a UCP1-cre driven deletion of the CoQ biosynthetic enzyme PDSS2 ($PDSS2^{BKO}$) in mice, we can induce primary CoQ deficiency. Using these CoQ deficiency models we find that CoQ deficiency causes mitochondrial dysfunction including the suppression of UCP1 expression, decreased brown adipocyte oxygen consumption rate (OCR), alterations to mitochondrial morphology and accumulation of mitochondrial RNAs in the cytosol. RNAseq analysis revealed induction of the mitochondrial unfolded protein response (UPR^{mt}) and integrated stress response (ISR) resulting from CoQ deficiency. Despite BAT dysfunction and decreased BAT UCP1 expression, $PDSS2^{BKO}$ animals surprisingly display increased whole-body respiration rates at room temperature and thermoneutrality and resistance to diet induced obesity. In line with the enhanced metabolic rates, BAT to inguinal white adipose tissue (iWAT) interorgan crosstalk caused significant browning of iWAT in $PDSS2^{BKO}$ animals. This mitohormesis-like compensatory effect depends on the ATF4-FGF21 axis and BAT secreted FGF21, revealing an unexpected role for CoQ in the modulation of whole-body energy expenditure with wide-ranging implications for primary and secondary CoQ deficiencies. Future studies aim to elucidate if statin induced secondary CoQ deficiency in brown adipocytes elicits a similar phenotype and mechanism in vitro and in vivo.

Estrogen-related receptors (ERRs) activation regulates mitochondrial function and inflammation in diabetic kidneys

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Diabetes mellitus is a major cause of death and disability worldwide and continue to be the leading cause of kidney disease in the U.S. and around the world. The exact pathogenesis of diabetic kidney disease remains uncertain and is likely multifactorial. Recent evidence indicates that altered lipid metabolism are increasingly recognized as key mediators of renal lipid accumulation, inflammation, oxidative stress, and fibrosis. Lipid metabolism entails the oxidation of fatty acids to either generate energy or synthesize new lipids. In our previous study we have found the decreased fatty acid oxidation in diabetic kidneys. As a main regulator for fatty acid oxidation, estrogen-related receptor (ERR) has decreased expression as well. To explore whether the activation of ERR pathway can improve the fatty acid oxidation and ensuing lipid metabolism, we employed a novel pan-ERR agonist SLU-PP-915 to treat the db/db mice of type 2 diabetes. After 12-week treatment, we observed a significant improvement in urinary albumin excretion, a hallmark of diabetic kidney disease. Furthermore, we have performed detailed electron microscopy analysis. Our data have shown that the ERR activation decreased glomerular basement membrane width and mesangial expansion, and improved podocyte foot processes. The pathological change in the kidney has been associated with significant improvement in mitochondrial structure as shown from electron microscopy data, in both podocytes and proximal tubules. In an in vitro model using mouse proximal tubule cells, we treated the cells cultured under high glucose media with ERR agonist and found that SLU-PP-915 reduced high glucose induced expression of pro-inflammatory cytokines, and increased the expression of master mitochondrial regulator PGC-1a and key fatty acid oxidation enzymes CPT-1 and MCAD. These data suggest that the activation of ERR, a new approach to target the lipid metabolism and fatty acid oxidation, can improve the diabetic kidney disease by regulating the mitochondrial function and inflammation.

Uncovering a Novel Role of Serine Palmitoyltransferase 3 (SPTLC3) in Maintaining Mitochondrial Ceramide Levels and Hepatocyte Mitochondrial Function

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Sphingolipids play critical roles in various cellular functions and metabolic disorders, including Non-alcoholic Fatty Liver Disease (NAFLD), Non-alcoholic Steatohepatitis (NASH), and Hepatocellular Carcinoma (HCC). The Serine Palmitoyltransferase (SPT) complex, comprising subunits SPTLC1 and SPTLC2, is responsible for generating the most prevalent canonical sphingolipids. Intriguingly, SPTLC1 can also form complexes with SPTLC3, leading to the production of less explored non-canonical sphingolipids. Despite increased expression of SPTLC3 observed in liver disorders such as NAFLD and HCC, its specific molecular mechanism remains elusive. Therefore, our study aimed to elucidate the role of SPTLC3 and its downstream non-canonical sphingolipids in liver function. We utilized a novel mouse model lacking SPTLC3 in hepatocytes (SPT3-hKO), revealing a significant impact on mitochondrial biology. SPT3-hKO mice exhibited a notable reduction in oxygen consumption rate, predominantly affecting mitochondrial complex I. This deficiency was accompanied by decreased complex I-derived parameters, including the NAD+/NADH ratio and ATP production in SPTLC3-hKO mice, indicating compromised complex I function. Interestingly, primary hepatocytes from SPTLC3-hKO mice showed an increased reliance on glycolysis for energy production. Furthermore, suppression of SPTLC3 in a human hepatocyte cell line (HC-3716) mirrored the findings observed in murine data. Our study highlights the crucial role of non-canonical sphingolipids in maintaining mitochondrial membrane integrity. Remarkably, we observed significant alterations in the sphingolipid profile within the mitochondrial membrane, particularly reduced levels of non-canonical d17 ceramides. These changes likely contribute to the observed dysfunction in complex I and decreased membrane potential in SPT3-hKO livers. Additionally, we noted an overall abundance of atypical ceramides within the mitochondrial fraction, suggesting that alterations in the mitochondrial ceramide pool, rather than the entire cellular pool, play a pivotal role in driving mitochondrial dysfunction. These findings provide valuable insights into the intricate interplay among SPTLC3, mitochondrial membrane composition, complex I function, and energy metabolism in liver pathophysiology.

MXRA8 impairs a vascular-thermogenic circuit to drive obesity

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Matrix-remodeling associated 8 (MXRA8) is a cell surface protein implicated in cancer, inflammation, and arthritogenic alphavirus infection. MXRA8 is most highly expressed in adipose tissue, however its molecular functions and role in metabolic disease pathogenesis are unknown. We demonstrate that MXRA8 is increased in adipose tissue in obese mice and humans and exacerbates obesity by impairing Uncoupling protein 1-dependent thermogenesis. Mechanistically, MXRA8 is expressed by adipocyte progenitors and binds the anti-angiogenic protein Thrombospondin 1 (TSP1) to deplete the vascular bed that sustains thermogenic beige/brown adipocytes. A novel therapeutic targeting MXRA8 preserves the adipose vascular bed and increases beige/brown adipocytes to ameliorate obesity. These studies reveal that MXRA8 impairs a vascular-thermogenic circuit to drive obesity and is a previously unappreciated target to treat this metabolic disease.

Brown adipose tissue neutrophils capture mitochondria from adipocytes to maintain metabolic homeostasis

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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. Neutrophils accumulate in BAT in response to cold environmental temperatures and are required for mice to optimally defend their core body temperature, maintain appropriate energy expenditure, and sustain their BAT mass. Mechanistically, brown adipocytes transfer mitochondria to neutrophils upon entry into the BAT to stimulate the formation and release of neutrophil extracellular traps (NET), which are required for the defense of core body temperature and BAT thermogenesis. These findings suggest that neutrophils acquire mitochondria from brown adipocytes to evoke a tissue-specific immunometabolic functional program that sustains BAT homeostasis and supports mammalian adaption to cold environments.

Lipid metabolic imaging of brain during aging and diseases

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Abstract
Understanding the dynamics of lipid metabolism in brain is essential to unravelling the mechanistic basis of brain aging and neurodegeneration. Traditional imaging methods such as MRI, PET, Fluorescence, and Mass Spectrometry have fundamental limitations including low chemical specificity and low spatial resolution. As an emerging non-linear vibrational imaging technique, stimulated Raman scattering (SRS) imaging offers high chemical specificity, high resolution, deep penetration, and quantitative capability. We apply a multimodal imaging platform that integrates deuterium isotope probed SRS microscopy (DO-SRS), multiphoton fluorescence (MPF), and second harmonic generation (SHG) together to visualize lipid metabolic dynamics in animal brains. The enzymatic incorporation of deuterium (D) will generate carbon-deuterium (C-D) bonds in newly-synthesized lipids. The vibrational signals of these C-D bonds can be detected by SRS in the spectral cell-silence region (wavenumber 1800 – 2800 cm^{-1}). By leveraging this cutting-edge imaging technique, we first reveal that lipid metabolic activity in *Drosophila* brain decreased during aging and tauopathy. We further found deuterium labelled lipids were transferred from tauopathy iPSC-neurons to microglia and induced LD accumulation, oxidative stress, inflammation, and impaired phagocytosis in microglia. Dietary restriction (DR), downregulation of insulin/IGF-1 signaling (IIS) pathway, and overexpression of AMPK signalling pathway all lead to significant enhancements of brain lipid turnover and reduction of lipid accumulation. Moreover, combined with our advanced deconvolution method (Adam optimization-based Pointillism Deconvolution) and penalized reference matching (PRM) algorithm, this non-invasive, universally applicable technology platform enables the detection of macromolecular with high fidelity in the subcellular resolution We are now diving into understanding the mechanism of various organelle metabolic changes underlying the neuronal degeneration.

Keywords: metabolic imaging, SRS, deuterium, brain, aging, tauopathy, neurodegeneration

The R47H mutation inhibits flexible dynamics in the CDR2 of TREM2 that underlie variable binding interactions with the ligand ApoE

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Alzheimer's disease (AD) is a progressive and ultimately fatal neurodegenerative disorder that affects millions of Americans each year. One of the hallmarks of AD is dysregulated lipid metabolism, specifically in microglia and its proteins that mediate the endocytosis of lipoproteins. Certain genetic variations, such as specific isoforms of apolipoprotein E (ApoE) and mutations in the microglial surface protein known as Triggering receptor expressed on myeloid cells 2 (TREM2), have been linked disrupted lipid metabolism and thus an increased risk of AD. Notably, ApoE4 and TREM2^{R47H} are considered the most significant genetic risk factors for late-onset AD, respectively. It is believed that these two variants interact directly, exacerbating their effect on dysfunctional lipid and cholesterol metabolism in the brain. However, the precise molecular mechanisms underlying the interaction between TREM2 and ApoE, as well as how this interaction is affected by AD-associated mutations, remain unclear. In this study, we utilized molecular docking and molecular dynamics simulations to investigate the direct binding interactions between TREM2 and monomeric ApoE. Our simulations reveal the impact of AD-associated mutations in TREM2 (R47H) and ApoE isoforms (ApoE2/3/4) on ligand binding. We observed dynamic conformations and differences in secondary structures within the TREM2 complementarity-determining region 2 (CDR2) across TREM2 variants. Furthermore, our findings suggest that these structural differences in wild-type TREM2 and TREM2^{R47H} lead to contrasting interactions with ApoE residues. Interestingly, our simulations also showed increased binding between TREM2 and ApoE4, which was dependent on the microenvironment and positioning of ApoE4's hinge. Overall, this study provides new insights into how multiple mutations may affect antagonistic protein-protein interactions. These findings have broader implications, suggesting potential alterations in downstream microglial signaling pathways that control lipid metabolism, which could impact the onset and progression of AD.

Futile metabolism of branched chain fatty acids controls energy homeostasis

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Brown and beige adipocytes express uncoupling protein 1 (UCP1), a mitochondrial protein that disassociates respiration from ATP synthesis and promotes heat production and energy expenditure. However, UCP1$^{-/-}$ mice are not obese unless housed at thermoneutrality, consistent with the existence of alternative mechanisms of thermogenesis. Here, we describe a UCP1-independent mechanism of thermogenesis involving futile metabolism of monomethyl branched chain fatty acids (mmBCFA) in peroxisomes. These fatty acids are synthesized by fatty acid synthase (FASN) using a precursor derived from catabolism of branched chain amino acids and our results indicate that β-oxidation of mmBCFAs is mediated by the peroxisomal protein ACOX2. Notably, cold exposure upregulated proteins involved in both biosynthesis and β-oxidation of mmBCFA in thermogenic fat. Acute thermogenic stimuli promoted translocation of FASN to peroxisomes, the site of BCFA β-oxidation. Adipose-specific knockout of ACOX2 impaired cold tolerance and increased diet-induced obesity and insulin resistance. Conversely, forced expression of ACOX2 in adipose tissue promoted adipose thermogenesis in a UCP1-independent manner and improved metabolic homeostasis. Use of a peroxisome-localized temperature sensor called Pexo-TEMP revealed that ACOX2-mediated β-oxidation of mmBCFA increases the intracellular temperature in wild-type and UCP1$^{-/-}$ brown adipocytes. Together, these results identify a previously unrecognized role for peroxisomes in adipose tissue thermogenesis, characterized by a futile cycle of mmBCFA synthesis and catabolism.

Galectin-3 plays a critical intracellular role in macrophages by promoting the repair, removal, and replacement of damaged lysosomes and protecting against atherosclerosis

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Galectin-3 (Gal3) is a β-galactoside-binding lectin predominantly known as a secreted inflammatory biomarker in cardiovascular disease, with significantly elevated circulating levels in patients with atherosclerosis and myocardial infarction. However, the molecular mechanisms of Galectin-3 action and whether its intracellular role contributes to atherogenesis remain unclear. Using several databases of bulk and single cell RNAseq, we first show that Gal3 transcripts are upregulated during plaque progression with particular abundance in the myeloid/macrophage lineage and foamy macrophages. Furthermore, Gal3 transcripts correlate significantly with increases in a network of lysosomal genes, suggesting a possible link between macrophage Gal3 and lysosomal function. Indeed, instigation of lysosome membrane damage in primary macrophages via cholesterol crystals and LLOMe triggers robust recruitment of Gal3 to lysosomes by sensing exposed carbohydrate moieties of proteins including Lamp1. Gal3 recruitment initiates a two-pronged lysosomal recovery program composed of either lysosomal repair involving the ESCRT complex or lysosomal removal and replacement involving autophagy/lysophagy and TFEB-mediated lysosomal biogenesis. Gal3-KO macrophages corroborate these findings displaying blunted ESCRT recruitment, diminished autophagy and TFEB activation, and resultant accumulation of damaged lysosomes. Gal3-deficiency also results in enhanced apoptosis and inflammasome/IL-1β activation upon triggering of lysosomal stress in macrophages. These findings are recapitulated in vivo, where Gal3-null bone marrow transplanted in atherogenic LDLR-null mice yields increased lesion size as well as altered plaque composition with macrophage accumulation, apoptosis, and necrotic core formation, characteristic features of the advanced plaque. Taken together, our data implicate unique and previously unrecognized protective function for intracellular Galectin-3 in macrophages and atherosclerosis which are distinct from its traditional role as an inflammatory biomarker in cardiovascular disease.

Glucosylceramide regulates mitochondria function and inflammation in diabetic kidneys

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Altered lipid metabolism is increasingly recognized as key mediators of renal lipid accumulation, inflammation, oxidative stress, and fibrosis. Recent studies also indicate a role for ceramides and sphingolipids in the pathogenesis and progression of kidney disease in diabetes and in obesity.

Glycosphingolipids are formed by the addition of sugars to ceramide. Glucosylceramide synthesis from ceramide is mediated by glucosylceramide synthase (Ugcg). Further glycosylation pathways result in the formation of over 300 glycosphingolipids including lactosylceramide, GM1 and GM3.

To address whether glucosylceramide plays a role in the pathogenesis of diabetic kidney disease, we used type 2 diabetes model of db/db mice to examine whether glucosylceramide level could change in diabetic kidneys. Using lipidomics, we have found increased glucosylceramide levels in the kidneys of diabetic db/db mice compared to nondiabetic db/m mice. We further looked into the glucosylceramide synthase UGCG. UGCG is expressed in podocytes and tubular cells of human and mouse kidney, as determined by single nuclei RNA-seq and IHC and IF. We then overexpressed UGCG in mouse proximal tubule cells. The overexpression of UGCG caused significantly increased inflammation and decreased mitochondrial gene expression. To test whether the inhibition of glucosylceramide synthase could mediate the beneficial effects of reduced glucosylceramide level in the kidney, we treated the diabetic mice with UGCG inhibitor eliglustat and found that the short-term treatment of eligludtat successfully decreased the overall glucosylceramide level in the diabetic kidneys.

In this study, we explored the potential impact of UGCG-mediated glucosylceramide synthesis in the diabetic kidneys and provided evidence to support a novel treatment avenue to use UGCG inhibitor eliglustat.

Running on empty: Succinyl CoA depletion in heart failure due to coincident upregulation of ketone oxidation and heme synthesis

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To identify molecular signatures associated with the progression of cardiac hypertrophy to heart failure (HF), we conducted metabolomics and proteomics on heart mitochondria and cardiac tissue from two established models of hypertrophic heart disease: spontaneously hypertensive rats and mice subjected to transaortic constriction (TAC). Our results identified succinylcarnitine, a marker of succinyl-CoA, as the best predictor of cardiac function. Succinylcarnitine decreased in a stepwise manner with fractional shortening in both models. Likewise, we observed an inverse correlation between succinylcarnitine, fractional shortening, and succinyl-CoA consuming pathways, ketolysis and heme synthesis. In the healthy heart, ketone oxidation occurs during fasting and/or carbohydrate restriction, but the failing heart increases ketolysis irrespective of nutritional status. Cardiac heme is generated locally to support oxygen transport via myoglobin, mitochondrial biogenesis, and as a cofactor for hemoproteins, including electron transport system members and nitric oxide synthase. Additionally, the succinyl-CoA-dependent enzyme that catalyzes the first committed step in heme synthesis, delta-aminolevulinate synthase 1 (ALAS1), emerged as the most down-regulated protein in a proteomics analysis of hearts from overnight fasted as compared with fed mice. Diminished ALAS1 flux during fasting is presumed to preserve succinyl-CoA for use as an obligatory cofactor for the ketolytic enzyme, succinyl-CoA-3-oxaloacid CoA transferase (SCOT). Using myocyte-specific SCOT knockout animals, we determined that fasting regulation of cardiac ALAS1 requires the ketolytic pull on succinyl-CoA. These data support a model where the healthy heart senses and prioritizes a limited pool of succinyl-CoA for either ketolysis or heme synthesis, depending on nutritional status. By contrast, HF appears to present a dilemma wherein hypertrophied hearts require coincident increases in ketone oxidation and heme synthesis, thereby imposing a drain on succinyl-CoA. To test this hypothesis, we are supplementing aminolevulinic acid (ALA), the ALAS1 reaction product, in the drinking water of C57BL6NJ mice. ALA supplementation increases blood and urine heme metabolites without consuming succinyl-CoA. Ongoing studies combining ALA supplementation with TAC induced HF will determine whether a) succinyl-CoA is limiting to heme synthesis and/or ketone oxidation, b) releasing the ALAS1 pull on succinyl-CoA prevents its depletion, c) increased heme synthesis capacity improves mitochondrial quality and number, and d) if alleviating the succinyl-CoA dilemma in TAC hearts impacts cardiac remodeling and function. In conclusion, our studies highlight a nutrient-sensitive metabolic node crucial in both normal cardiac physiology and HF pathogenesis. Understanding the intricate balance between ketone oxidation and heme synthesis may offer insight into the metabolic underpinnings of HF.

The flexible stalk domain of sTREM2 modulates its interactions with phospholipids in the brain

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The microglial surface protein Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) plays a critical role in mediating brain homeostasis and inflammatory responses in Alzheimer's disease (AD). The soluble form of TREM2 (sTREM2) exhibits neuroprotective effects in AD, though the underlying mechanisms remain elusive. Moreover, differences in ligand binding between TREM2 and sTREM2, which have major implications for their roles in AD pathology, remain unexplained. To address these knowledge gaps, we conducted the most computationally intensive molecular dynamics simulations to date of (s)TREM2, exploring their interactions with key damage- and lipoprotein-associated phospholipids and the impact of the AD-risk mutation R47H. Our results demonstrate that the flexible stalk domain of sTREM2 serves as the molecular basis for differential ligand binding between sTREM2 and TREM2, facilitated by its role in stabilizing the Ig-like domain and altering the accessibility of canonical ligand binding sites. We identified a novel ligand binding site on sTREM2, termed the 'Expanded Surface 2', which emerges due to competitive binding of the stalk with the Ig-like domain. Additionally, we observed that the stalk domain itself functions as a site for ligand binding, with increased binding in the presence of R47H. This suggests that sTREM2's neuroprotective role in AD may, at least in part, arise from the stalk domain's ability to rescue dysfunctional ligand binding caused by AD-risk mutations. Lastly, our findings indicate that R47H-induced dysfunction in membrane-bound TREM2 may result from both diminished ligand binding due to restricted complementarity-determining region 2 loop motions and an impaired ability to differentiate between ligands, proposing a novel mechanism for loss-of-function. In summary, these results provide valuable insights into the role of sTREM2 in AD pathology, laying the groundwork for the design of new therapeutic approaches targeting (s)TREM2 in AD.

** This work is currently under review for publication at *eLife.*

RNA processing as a potential mediator of Mitochondrial Metabolism

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Caloric restriction (CR) delays aging and the incidence of age-related diseases, and substantial evidence suggests that metabolic reprogramming is a key mechanism. The factors that regulate the connection between metabolism and longevity, however, are not known.

Prior work in non-human primates revealed one potential regulatory mechanism - altered exon usage, a form of RNA processing, was widely observed across the metabolic network engaged by short-term CR. Parallel datasets measuring proteomic profiles and lysine acetylation marks from the same tissues revealed CR-responsive acetylation events on several RNA helicases, which are RNA processing enzymes.

To examine these phenomena, we used two parallel approaches. For the first, we performed a reanalysis of previously collected data that compared CR treatment in mice to treatment with pharmacological treatments mediating metabolism – bezafibrate, lithium, and resveratrol. We examine adipose transcriptional profiles and circulating lipid profiles in parallel with phenotypic data to identify connections between metabolic changes and RNA processing. Bezafibrate treatment led to statistically significant changes in the expression of more than 10 RNA helicase enzymes, while lithium induced a dramatic increase in exon usage changes over and above that of either bezafibrate or CR. This suggests that these drugs, which phenocopy many of the physiological effects of CR, also engage RNA processing as a mechanism and thus may be useful as tools to probe this mechanism.

For the second, more mechanistic approach, we generated lysine to glutamine (KQ) and lysine to arginine (KR) acetylation-mimic mutants of lysine 162 (K162) on the endogenous helicase DDX39B, one of the sites identified in the non-human primate work. Analysis of oxygen consumption in these mutant cell lines revealed significant changes in both basal and maximal respiration. KQ mutant cells showed a strong and statistically significant increase in maximal respiration, while KR mutants showed a dampening of both basal and maximal respiration. We also observed significantly increased mitochondrial membrane potential in both mutant lines, as well as altered

mitochondrial respiration complex stoichiometry, suggesting changes to mito-nuclear crosstalk. These data implicate DDX39B and the TRanscription-EXport (TREX) complex as a regulator of metabolic adaptation, and indicate a potential signaling axis that connects production of acetyl-CoA, nuclear RNA processing, and mitochondrial output.

Overall, these data and approaches highlight the potential of targeting RNA processing mechanisms for modulating metabolism and warrant further investigation of their regulatory role.

Hepatocyte *Period 1* regulates liver glucose and lipid metabolism independent of the core circadian clock

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Abstract:

The liver coordinates metabolic and circadian inputs to optimize substrate utilization, and both overnutrition and disruption of circadian feeding patterns render deleterious consequences to the host. However, precise mechanisms of interaction between core circadian genes and hepatic glucose and lipid metabolism during normal fasting and overnutrition are incompletely understood.

Here, we show that hepatocyte *Period 1* (*Per1*) is uniquely upregulated during fasting independent of other core circadian genes. Mice lacking hepatocyte *Per1* ($Per1^{LKO}$) exhibit impaired peripheral lipolysis, ketogenesis, hepatic triglyceride (TG) accumulation, and glucose oxidation termination during fasting. Starved hepatocyte cells experience dysregulated mitochondrial function. Mechanistically, we define a downstream pathway which *Per1* is required for fasting-induced pyruvate dehydrogenase kinase 4 (*Pdk4*) through reorganizing the chromatin structure at enhancer and promoter regions of fibroblast growth factor 21 (*Fgf21*). *Fgf21* mediates *Pdk4* activation during fasting, and *Pdk4* phosphorylates and directly inhibits pyruvate dehydrogenase localized at mitochondria to terminate glucose oxidation.

In contrast, when challenged with a Western diet (WD), $Per1^{LKO}$ mice exhibit increased body weight gain and hepatic steatosis, enhanced hepatic *de novo* lipogenesis (DNL) gene expression, and elevated nuclear translocation of transcription factor carbohydrate response element binding protein (ChREBP). Mechanistically, to assess the extent to which forced hepatocyte *Per1* expression attenuates WD-induced metabolic disease, and the interaction between *Per1* and the core clock, we generated a *Per1* mutant construct lacking a key circadian functional domain - the CRY-binding domain ($Per1^{\Delta CBD}$). Strikingly, both full-length *Per1* and $Per1^{\Delta CBD}$ overexpression attenuate serum and hepatic TG accumulation and hepatic DNL gene expression in wildtype mice and mice with hepatocyte-specific *Bmal1*-deletion ($Bmal1^{LKO}$ mice). Immunoprecipitation and mass spectrometry reveal the ChREBP-regulatory enzyme protein phosphatase, PP2A, as a common interacting protein between full-length and *Per1* mutant construct. *In vivo*, pharmacologic PP2A blockade through LB-100 administration reverse the increased weight gain observed in WD-fed $Per1^{LKO}$ mice. Taken together, we conclude that *Per1* suppresses hepatic lipogenesis and TG accumulation by binding to and inhibiting PP2A, independent of its core clock function. The data define a novel function of *Per1* as a potential mechanism by which the hepatocyte links circadian and metabolic inputs to optimize fuel utilization.

Disruption of AdipoR1 and AdipoR2 in adipocyte causes adiponectin-independent metabolic actions through reducing LPCAT3 activity

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Adiponectin derived from adipose tissue plays an important role in obesity and diabetes. AdipoR1 and AdipoR2 serve as the principal receptors for adiponectin and correlate with adiponectin sensitivity. To explore the function of adiponectin receptors AdipoR1 and AdipoR2 in adipose tissue, we generated adiponectin receptor double Knockout (DKO) mice. Here, we unexpectedly found that DKO mice improved glucose tolerance and insulin sensitivity, which may be through adiponectin-independent manner. Using lipidomics and unbiased phospho-proteomics, we identified lower LPCAT3 activity as the major factor to influence membrane lipid rafts, which reduced polyunsaturated PCs in adipocyte plasma membrane and surprisingly attenuated diet-induced glucose intolerance and insulin resistance. Thus, our data suggested that there is a new downstream signaling of Adiponectin receptors R1/R2, which can manipulate membrane phospholipid saturation through targeting LPCAT3.

Chronic Transcriptional Activity of the Aryl Hydrocarbon Receptor Promotes Skeletal Muscle Mitochondriopathy in Chronic Kidney Disease

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Introduction: Chronic kidney disease (CKD) causes a progressive myopathic disease with symptoms of skeletal muscle (SkM) wasting, weakness, and fatigue. As renal function declines, the accumulation of uremic metabolites (UMs) negatively impacts SkM health and function. Interestingly, several UMs in CKD are ligands to the ubiquitously expressed ligand-activated transcription factor, the aryl hydrocarbon receptor (AHR). Chronic activation of the AHR is associated with metabolic alterations in several tissue types and has been proven toxic in some cases. **Purpose**: The purpose of this study was to investigate whether chronic activation of the AHR plays a causal role in the development of myopathic symptoms in CKD. **Methods**: Muscle biopsies from CKD patients and adult controls with normal renal function were used to examine AHR signaling and mitochondrial respiratory function. The mechanistic role of the AHR was explored using SkM-specific AHR knockout mice (AHR^{mKO}) and SkM-specific AHR knockdown via adeno-associated virus in mice with adenine-induced CKD, as well as ectopic expression of a constitutively active AHR (CAAHR) in mice with normal kidney function. Additional mechanistic experiments were carried out in cultured muscle cells. Outcome measures included gene and protein expression, mitochondrial bioenergetic testing, and robust muscle functional phenotyping. **Results**: Compared to controls with normal renal function, AHR-dependent gene expression (*CYP1A1* and *CYP1B1*) was significantly upregulated in gastrocnemius SkM of CKD patients (P=0.032) and the magnitude of AHR activation was inversely associated with mitochondrial respiration (P<0.001). In mice with CKD, SkM mitochondrial oxidative phosphorylation (OXPHOS) was significantly impaired and strongly correlated with both the level of tryptophan-derived UMs and AHR activation. AHR^{mKO} significantly improved mitochondrial OXPHOS in mice with CKD (~28% increase, P=0.045) and abolished the relationship between UMs and OXPHOS. This uremic metabolite-AHR-mitochondrial axis in SkM was further confirmed using SkM-specific AHR knockdown in C57BL6J that express a high-affinity AHR allele, as well as ectopic viral expression of CAAHR in mice with normal renal function. AHR activation led to impairments in pyruvate dehydrogenase (PDH) enzyme function (~29% decrease, P<0.05), significant increases in *Pdk4* expression (P<0.05) and phosphorylation of PDH enzyme (P<0.05), mechanistically contributing to impaired pyruvate-supported OXPHOS function. **Conclusion**: Using a combination of genetic and chemical techniques in cell culture and animal models, these findings establish a uremic metabolite-AHR-Pdk4 axis in SkM that governs mitochondrial deficits in CKD.

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Targeting phospholipid metabolism via *Pla2g15/plag-15* results in reduced senescence in murine kidneys and promotes longevity in *C. elegans*

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Aging was long considered an irreversible and passive process. However, genetic and pharmacological interventions have shown that aging can be actively regulated and influenced to reduce the burden of age-related diseases on society. Dysregulated lipid metabolism plays a vital role in aging and age-related diseases, while the mechanisms are still not well understood. We previously found an accumulation of phospholipid bis(monoacylglycero)phosphates (BMP) in aged mice and humans, compared to young controls. BMP, primarily found in lysosomes and endosomes, is synthesized from phospholipid LPG, a reaction involving lysophospholipase *PLA2G15* in humans *(Pla2g15* in mice*)*. First, we used the worm *C. elegans* to elucidate if the *PLA2G15* orthologue, *plag-15,* is involved in aging regulation*.* Next, we used a kidney aging model to investigate the role of *Pla2g15* metabolism in cellular senescence.

Knockdown of *plag-15* shows increased lifespan and healthspan in *C. elegans.* The lipidomic analysis revealed that *plag-15* RNAi worms exhibited a decrease in lysophosphatidic acid (LPA), lysophosphatidylcholine (LPC) and lysophosphatidylethanolamine (LPE) abundance, however, no changes in BMP were found, suggesting a distinct role of *plag-15* in the regulation of lipid metabolism in worms. To find the mechanism behind the lifespan extension of *plag-15* worms, we selected and prioritized several candidate genes from RNAseq profiles of *plag-15* RNAi worms and validated them with lifespan measurement. We found that lysosome-regulating genes *hlh*-30/TFEB, *elt-3/GATA* and *pmp-5/*ABCD4 were required for longevity induced by *plag-15* RNAi.

Next, we aimed to explore the role of *Pla2g15* in aging and kidney disease using mouse kidney proximal tubular epithelial cells. Transcript expression of *PLA2G15/Pla2g15* was significantly increased in human and murine kidneys during aging, as well as in senescent TECs. Global deletion of *Pla2g15* by CRISPR/Cas9 showed reduced *Pla2g15* enzyme activity and reduced senescent features such as decreased p21 gene expression and G2/M arrest. Although the lipidome of *Pla2g15* KO cells showed no difference in BMP abundance compared to the controls, hydroxy dihexosylceramide (hex2cer) and trihexosylceramide (hex3cer) were significantly decreased in the *Pla2g15* KO cells.

Taken together, targeting nematode *plag-15* and mouse *Pla2g15* results in increased lifespan and reduced senescence, respectively. We also showed that BMP is not changed in both worm and mouse cell models. Overall, our data suggest that *plag-15/Pla2g15* might be a potential therapeutic target for healthy (renal) aging.

Mitochondria transfer reduces the morbidity and mortality of Leigh Syndrome

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Mitochondria transfer is a recently described phenomenon in which donor cells deliver their mitochondria to recipient cells. One function of mitochondria transfer is to provide energetic support to neighboring cells, a concept reinforced by studies demonstrating that exogenous healthy mitochondria can rescue cell-intrinsic defects in mitochondrial metabolism in *Ndufs4*$^{-/-}$ macrophages. Exposing hematopoietic stem cells (HSC) to purified mitochondria before autologous HSC transplantation was used to treat Pearson Syndrome-associated anemia, and direct administration of purified mitochondria minimizes ischemic damage to the heart and brain. However, the therapeutic potential of using mitochondria transfer for inherited mitochondrial diseases is unclear. Here, we show that wildtype bone marrow transplantation improves the morbidity and mortality of the *Ndufs4*$^{-/-}$ mouse model of Leigh Syndrome (LS), effects associated with release of hematopoietic cell-derived mitochondria into circulation and mitochondria transfer to host cells in multiple organs. Administering isolated WT mitochondria also extended lifespan, improved neurologic function, and increased energy expenditure of *Ndufs4*$^{-/-}$ mice. Furthermore, cross-species administration of human mitochondria into *Ndufs4*$^{-/-}$ mice recapitulated the ameliorative effects on lifespan and neurologic function. These data suggest that mitochondria transfer-related pathways can be harnessed to treat mitochondrial diseases such as LS.

Lysosomal Acid Lipase is a Non-canonical Mediator of Adipocyte Lipolysis

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Adipose tissue is a primary storage site for neutral lipids which are broken down via lipolysis, a metabolic process that occurs in the cytoplasm. Cytoplasmic lipolysis is initiated by adipose triglyceride lipase (ATGL), widely considered the predominant mechanism of liberating free fatty acids (FFAs) and glycerol from triglycerides during fasting or cold-induced non-shivering thermogenesis. However, lipolysis is still observed in mice deficient in cytosolic lipases implying that complementary pathways can promote lipid degradation. An alternative pathway that could be involved is lysosomal lipolysis, mediated by the enzyme lysosomal acid lipase (LAL). We found that LAL expression increases in the adipose tissue of mice in response to fasting, cold exposure, and treatment with CL316,243 (CL), a mimic of cold-induced lipolysis. To investigate the physiological role of LAL in adipocyte lipolysis, LAL was targeted genetically or pharmacologically using adipose-specific LAL knockout (A-LAL KO) mice or the LAL-specific inhibitor, Lalistat, respectively. Mice with suppressed lysosomal lipolysis exhibited impaired thermogenesis, as evidenced by blunted FFA and glycerol release during lipolytic stimuli including cold exposure or CL treatment. Similar results were obtained in stimulated fresh adipose tissue *ex vivo*. Importantly, these findings were independent of cytosolic lipolysis as LAL deficiency did not suppress expression of ATGL or its cofactors. Moreover, LAL inhibition of adipose tissues from ATGL-deficient mice showed additive suppression of lipolysis. Overall, our data suggest a previously unrecognized and significant role for lysosomes in adipocyte lipid metabolism beyond classical cytosolic lipolysis.

Ambiguous outcomes of LXR activation as a potential treatment for MASH pathogenesis

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While metabolic dysfunction-associated steatotic liver disease (MASLD) affects 30% of the US population, there is currently no approved pharmaceutical treatment to inhibit the progression of MASLD to its more severe stage of metabolic dysfunction-associated steatohepatitis (MASH). Even though liver X receptor (LXR) is a key hepatic lipogenic factor, the effect of LXR activation on MASLD progression is not well understood. We hypothesize that LXR activation might reduce MASH pathogenesis by alleviating metabolic stress in hepatocytes.

To test this hypothesis, 8-week-old male wild type (WT) or obese, melanocortin-4 receptor knockout ($Mc4^{r-/-}$) mice were placed on either chow or Western diet (WD) for 8 weeks. Half of the WD-fed mice were given WD supplemented with GW3965 (100mg/kg), a selective, orally active agonist for the LXR. Sodium [$^{13}C_3$]lactate was infused intravenously into conscious, unrestrained mice for 2 hours and ^{13}C-enrichments of plasma glucose and liver metabolites were measured by GC-MS, then used to regress liver metabolic fluxes using the INCA 2.0 modeling platform.

LXR activation significantly decreased body mass, which was correlated with reduction of subcutaneous fat, and greatly improved glucose homeostasis of $Mc4r^{-/-}$ mice which corresponded with activation of AMPK and PI3K pathways. On the other hand, histological analysis revealed that GW3965 supplementation failed to improve liver steatosis, lobular inflammation, hepatocyte ballooning or fibrosis. On the molecular level, however, LXR activation proportionally increased the expression of genes of key metabolic pathways: amino acid synthesis and transport, fatty acid synthesis and oxidation, pentose phosphate pathway, glycolysis, and mitochondrial respiration. Additionally, pyruvate cycling fluxes (V_{PC}, V_{PK+ME}, V_{PEPCK}) were elevated in $Mc4r^{-/-}$ fed diet supplemented with GW3965. Furthermore, pathways involved in stress response such as MAPK and NFκB together with TLR cytokine and chemokine signaling were decreased after GW3965 treatment. Finally, p53 and KEAP1-NRF2 pathways, autophagy, endocytosis, lysosomal degradation, DNA damage repair, nucleotide synthesis and salvage, and reactive oxygen response were increased by LXR activation.

Taken together, these data suggest that LXR activation reduces metabolic stress in hepatocytes of genetically obese WD-fed animals but fails to resolve MASH phenotype.

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Desmosterol regulates liver myeloid identity controlling immunometabolic functions in MAFLD/MASH

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Obesity and overnutrition are fueling the rise of cardiometabolic diseases like atherosclerosis, diabetes, and fatty liver, where lipid accumulation plays a critical role. Cholesterol and other sterols accumulate in these lipid-loaded conditions, impacting immune cell function and inflammation. Our group and others have previously identified desmosterol, a precursor of cholesterol biosynthesis, as an activator of the LXR transcription factor family, that regulates inflammation in myeloid cells, affecting atherosclerosis. However, the role of desmosterol in other metabolic diseases such as MALFD/MASH has not been fully studied.

Recently, it has been described that LXRs play a key role in the acquisition of the phenotype of liver resident macrophages (Kupffer cells – KC). Moreover, in MAFLD/MASH, KCs are progressively lost in the liver and replenished by infiltrating myeloid cells, a process in which LXR influence the genetic reprogramming of circulating myeloid cells recruited to the liver. Based on the role of desmosterol in activating LXR, we hypothesize that liver desmosterol may regulate the genetic reprogramming of recruited myeloid cells, affecting their inflammatory function and the progression of the disease. We have developed conditional knock-in and knock-out models of DHCR24 (the enzyme that converts desmosterol into cholesterol) to regulate desmosterol in the liver. Using these models to target DHCR24 in hepatocytes and macrophages, we have been able to discriminate between the origin of desmosterol in the liver and studied its role in myeloid cell reprogramming and disease progression.

We have found that depletion of desmosterol in hepatocytes aggravates liver inflammation and fibrosis in MAFLD, increasing immune cells recruitment to the liver, particularly affecting the inflammatory phenotype of recruited macrophages. scRNA-seq analysis showed increased number of macrophages in the liver, and increased percentage of recruited macrophages compared to KCs in desmosterol deficient livers. Gene expression and pathway analysis revealed more inflammatory macrophages and reduced LXR activation and mitochondrial function in desmosterol-deficient livers. These results suggest that hepatocyte-derived desmosterol is crucial for LXR activation in newly recruited macrophages, promoting a KC-like phenotype, and that desmosterol depletion aggravates the inflammatory phenotype of liver macrophages and the progression of the disease.

In summary, we describe that desmosterol derived from hepatocytes is essential for KC reprogramming of liver recruited macrophages. These results are of particular interest for the development of therapeutic approaches using GalNAc-ASOs against DHCR24 to increase desmosterol content in the liver and reduce inflammation and progression of the disease, an approach that is being tested in our laboratory.

Hepatic Inactivation of CPT1a Reduces ApoB-containing Lipoproteins in Plasma of Mice

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects almost 1 billion people worldwide and increases risk stratification for cardiovascular disease resulting in excess morbidity and mortality. Genome- and epigenome-wide association studies have associated variants and methylation status of carnitine palmitoyltransferase 1a (CPT1a) to reductions in very low-density lipoprotein (VLDL) cholesterol and triglyceride levels. Thus, the primary goal of this project is to determine the mechanism by which CPT1a-dependent mitochondrial fatty acid oxidation alters hepatic and lipoprotein metabolism.

Methods: Eight-week-old *Cpt1a* floxed mice expressing the human APOB100 transgene (*Cpt1a*$^{fl/fl}$/B100^{Tg}) were administered control adenoassociated virus (AAV) or AAV encoding Cre-recombinase under control of a liver specific promoter (TBG-Cre). Control and LKO mice were placed on low-fat control or western-type diet (WTD; 42% kcal fat, 0.2% cholesterol) for 16 weeks. Livers were collected and used for histological and lipid analysis, while gene and protein expression were measured by RNA sequencing (bulk, single cell) and immunoblotting, respectively. Lipoprotein composition in plasma was determined by size exclusion chromatography and nuclear magnetic resonance (NMR). Rates of VLDL-triglyceride secretion were quantified after lipase inhibition with poloxamer 407. Liquid and gas chromatography-mass spectrometry were employed to measure bile acid species and fecal neutral sterols, respectively.

Results: Mice with liver-specific deletion of *Cpt1a* (LKO) displayed lower circulating APOB levels consistent with reduced triglyceride rich lipoproteins and LDL particle number. No changes in biliary flow rate, cholesterol secretion rate, bile acid secretion rate, total bile acids, or fecal cholesterol levels were observed in control or LKO mice. Despite a reduction in steady-state plasma lipids, VLDL-triglyceride secretion rates were enhanced in LKO mice, suggesting accelerated clearance of apoB-containing lipoproteins. In addition, western diet feeding elevated hepatic triglycerides in LKO mice across both sexes, while cholesterol (free and esterified) increased by ~2.5-fold specifically in females. Greater accumulation of free cholesterol coincided with an increase in inflammation and fibrosis of the liver in female LKO mice.

Conclusions: Liver-specific deletion of *Cpt1a* reduces plasma LDL-cholesterol and triglycerides, despite having accelerated VLDL-secretion. Increases in hepatic free cholesterol levels were observed only in female LKO mice, which associates with a pro-inflammatory gene signature and overall fibrosis of the liver. These studies provide mechanistic insight into why genetic variants and hypermethylation of Cpt1a associates with reductions in circulating apoB-containing lipoproteins in humans. Current studies are ongoing to assess rates of lipoprotein clearance in WT and LKO mice.

Mitochondria promote their own removal by expanding the macrophage pool:

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The emergence of multicellular life required high level tissue specialization, and indeed organs contain dedicated parenchymal cells that perform the primary function of the tissue (e.g. contraction or heat generation), as illustrated by myocytes in heart and different skeletal muscles or adipocytes in brown adipose tissue. However, because of their high level of specialization, differentiated parenchymal cells lose autonomy in processes which are not directly linked to their primary function, such as mobility, access to nutrients or elimination of their damaged components. Thus, the specialization of parenchymal cells demands external support for long-term fitness and optimal tissue function. In the heart, this support is illustrated by the transfer of spent mitochondria from cardiomyocytes to surrounding macrophages for silent disposal, but how this fundamental process is regulated is unknown. We performed an organismal-wide screening and found that the transfer of mitochondria is prominent in organs that heavily rely on mitochondrial respiration for their function, including heart, skeletal muscles, and brown adipose tissue (BAT). Supporting the relevance of this process in tissue biology, depletion of macrophages or interference with their phagocytic capacity using knockout mice for Mertk, a molecule involved in the capture of parenchymal-cell-derived mitochondria by macrophages, reduced the mitochondrial activity of these tissues and compromised their mechanical and thermogenic performance. Interestingly, by comparing muscles with varying workloads and metabolic demands, we found that the abundance of parenchymal-derived material (including mitochondria) disposed through macrophages exquisitely aligned with the mitochondrial activity of the myofibers and density of macrophage population network in these tissues. Genetic enhancement of mitochondrial activity in myocytes was sufficient to increase macrophage content and their capacity to eliminate parenchymal material, while surgically induced reduction of muscle workload caused mitochondrial activity decay and attrition of the macrophage pool. Muscles regulated macrophage numbers by coupling the mitochondrial content of myocytes with the number of fibroblasts producing CSF1, a growth factor that controls macrophage survival and proliferation. Consistently, inhibition of CSF1 or its receptor (CSF1R) collapsed macrophage numbers in different muscles and the mitochondrial activity of these tissues. Thus, by regulating the abundance of macrophages, tissues with highly specialized parenchymal cells enact an adaptive mechanism that copes with mitochondrial turnover and supports their function.

Expression of Apolipoprotein E by Lymph Node Stromal Cells Finetunes the Immune Response to Intestinal Infection

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Autoimmune disease is caused by the disruption of the intricate balance between protective and pathogenic immune activation. Patients with chronic autoimmunity also have major disruptions in plasma lipids, which lead to increased and earlier cardiovascular disease. Options for treating autoimmune disease and preventing cardiovascular disease are limited, highlighting *the gap in our understanding of the mechanistic link between lipid metabolism and immune regulation*. Lymph nodes (LN) play an important role in immune homeostasis, surveilling for pathogens while maintaining tolerance to innocuous and self-antigens. Lymph node (LN) stromal cells, including T-cell zone fibroblastic reticular cells (TRCs), have essential architectural and immunoregulatory functions and are critical for the balance between protective immunity and pathogenic inflammation. During infection, TRCs facilitate T-cell activation and in response, activated T-cells promote suppressive functions by TRCs. The ability of LN TRCs to both promote and restrain inflammation is critical for maintaining the balance between functional and excessive immune responses; however, *our understanding of what regulates these opposing TRC functions is limited*.

Using RNA-sequencing from cultured TRCs, we show that TRCs unexpectedly upregulate lipid metabolism transcriptional programs after stimulation with activated lymphocytes. Surprisingly, we find that TRCs express high levels of apolipoprotein E (apoE), a fat-binding protein that regulates plasma lipoproteins and cellular cholesterol metabolism. ApoE is most notably produced by the liver and intestine, with expression in some immune cells such as macrophages, but expression in stromal cells has not previously been shown. Intestinal infection with *Citrobacter rodentium* leads to increased expansion of apoE+ TRCs in gut-draining LNs compared to apoE- TRCs. We generated a TRC-specific Apoe knock-out mouse ($CCL19^{\Delta Apoe}$) and demonstrate that absence of apoE in TRCs leads to increased intestinal inflammation after *C. rodentium* infection. $CCL19^{\Delta Apoe}$ mice have abrogated CD4 T-cell activation and decreased generation of T follicular helper cells and germinal center B cells in gut-draining LNs compared to $CCL19^{Ctrl}$ mice. Using a TRC/T-cell co-culture system we show that the loss of apoE from TRCs augments the capacity for TRCs to suppress T-cell activation. In addition, there is a significant increase in the accumulation of neutral lipids in T-cell zones of LNs from $CCL19^{\Delta Apoe}$ mice compared to $CCL19^{Ctrl}$ mice, suggesting that apoE in TRCs regulates local LN lipid metabolism. *Together, our data indicate that apoE is a novel regulator of TRC function and LN lipid metabolism.* Future studies are aimed at understanding the mechanisms by which apoE regulates these processes.

Cholesterol and amino acids derived from dietary sources drive atherosclerosis via synergistic activation of macrophage mTORC1 signaling

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The pathogenic role for lipids, especially cholesterol, in atherosclerosis is well established although relevant mechanisms of action continue to be uncovered. Recent studies linking cholesterol, cholesterol sensing, and the induction of proatherogenic mammalian target of rapamycin (mTOR) signaling is one area with significant therapeutic potential. Our previous studies demonstrated a critical role for amino acids, especially leucine, derived from dietary protein in promoting plaque progression through activation of macrophage mTORC1. We thus aimed to understand the role of cholesterol in macrophage mTOR signaling, its relation to amino acid-mediated effects, and cooperation between dietary lipids and protein in plaque mTOR activation and atherosclerosis. Here, we show LDL cholesterol as well as atherogenic lipids containing modified cholesterol (7-Ketocholesterol and oxLDL) are potent inducers of macrophage mTORC1 especially inconcert with leucine. Importantly, cholesterol and leucine synergistically dampen autophagy/mitophagy, resulting in mitochondrial dysfunction and apoptosis, a process which is completely mTORC1-dependent. In vivo, we find lesional macrophage mTORC1 is stimulated by elevation of plasma cholesterol in ApoE-null mice (n=8-10 per group) fed a Western Diet, while increases in circulating amino acids and cholesterol as a result of diets enriched in protein and lipids lead to mTORC1 hyperactivation and concomitant reduction in autophagy. In conclusion, our study identifies a previously unrecognized signaling role for cholesterol in macrophages and highlights a unique and therapeutically relevant mechanism by which dietary nutrients such as lipids and amino acids can cooperate to drive atherosclerosis.

Presenter: Dr. Jacqueline Beaudry, PhD

Title: Lowering postprandial lipid levels with long-acting glucose-dependent insulinotropic peptide in obese high-fat fed mice.

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Abstract:

Glucose-dependent insulinotropic peptide (GIP) has become an important gut-released hormone, that when combined with glucagon-like peptide-1 (GLP-1), increases weight loss and lowers glucose and lipid profiles better than the leading GLP-1 agonist in humans and rodents. GIP is known to augment pancreatic beta cell release of insulin secretion after the oral ingestion of nutrients. GIP has receptors that are present in similar tissues to GLP-1 but unlike GLP-1, GIP receptor (GIPR) is expressed in whole adipose tissue. These receptors in adipose tissue have been suggested to regulate body weight and insulin sensitivity, but their role in energy metabolism is not well established. Evidence suggests that GIPRs in the brain are responsible for regulating food intake that leads to weight loss. Interestingly, GIPR agonism does not seem to play a role in whole-body energy expenditure but does appear to increase fatty acid utilization; however, the tissue responsible for regulating these effects is not yet fully defined. Brown adipose tissue (BAT) is an organ known to increase the dissipation of energy through non-shivering thermogenesis primarily through fatty acid oxidation. We have set out to determine if BAT contributes to GIPR-induced whole-body fatty acid oxidation and lipid metabolism. In previous work, we were the first to demonstrate that the removal of GIPR in BAT (GIPR BAT KO) led to higher postprandial lipid excursions in diet-induced obese (DIO) male mice. Currently, we demonstrate that acute (single dose) and chronic (14 days; daily injections) GIP (Acyl-GIP; 1 nmol/kg) treatment did not change energy expenditure but did increase whole-body fatty acid oxidation in male DIO mice. However, this increase in whole-body fatty acid oxidation is abolished in DIO GIPR BAT KO mice. Notably, these effects were all found to be independent of changes in body weight, body composition, food intake, gastric emptying, and hormone secretion, such as insulin. Next, we studied the role of GIPR agonism on postprandial lipid excursions. We found that in male DIO mice exhibiting intact BAT GIPR had lower lipid levels, but in GIPR BAT KO mice this effect was abolished. Interestingly, the effect of GIPR agonism on postprandial lipid excursions were found to not occur in female control or BAT GIPR KO mice. Together, our studies suggest that the BAT may play a role in regulating whole-body fatty acid oxidation and lipid clearance in the postprandial state after fat administration in DIO mice. Our findings may indicate a role for GIPR agonism on regulating lipid levels independently to changes in weight and food intake and that these effects may be sex dependent.

Functional Compartmentalization of Hepatic Mitochondrial Subpopulations During MASH Progression

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Lipid droplets (LDs) are highly dynamic energy storage organelles that play an important role in metabolic dysfunction-associated steatotic liver disease (MASLD) development. LDs interact with mitochondria that are essential for both de novo lipogenesis (DNL), fatty acid esterification as well as fatty acid oxidation (FAO). These seemingly contradictory findings have prompted researchers to suggest the existence of multiple subpopulations of mitochondria, which can compartmentalize DNL, fatty acid esterification and FAO, within the same cell. Indeed, investigators have identified and characterized two different mitochondrial subpopulations from brown and white adipose tissues. The mitochondria surrounding the LDs are referred to as LD-associated peridroplet mitochondria (PDM) and unassociated cytoplasmic mitochondria (CM). Currently, there are limited evidence on the role of PDM in healthy liver metabolism both during fed and overnight fasted conditions. Nevertheless, the role of PDM function in diseased liver such as during metabolic dysfunction-associated steatohepatitis (MASH) progression remains unknown. Here we isolated both hepatic CM and PDM from a mouse model of diet-induced MASLD/MASH to characterize their relative function during simple steatosis to advanced MASH. As a healthy control, we isolated both hepatic CM and PDM from chow-fed mice. We demonstrated an inverse relationship between them during MASLD progression. Hepatic PDM content increased with early steatosis reaching its peak at late steatosis, and then significantly decreased with later stages of the disease i.e., advanced MASH. In strong contrast, the hepatic CM content initially decreased with early steatosis reaching its lowest at late steatosis and then appeared to increase with MASH. Proteomics of the two mitochondrial populations isolated from different stages of the disease revealed that they are compositionally and functionally distinct. We next found that, compared to CM, hepatic PDM are bioenergetically active with higher pyruvate oxidation and TCA cycle flux capacities in both healthy and diseased liver, thus playing an anabolic role. On the contrary, hepatic CM had higher FAO capacity with MASH progression, thus playing a catabolic role. Additionally, we found that higher respiration capacity of PDM was associated with higher levels of OXPHOS protein complexes. Transmission electron microscopy (TEM) examinations of the liver revealed larger and elongated mitochondria during healthy and early steatosis, while they appear small and fragmented with MASH progression. Our TEM observations coincided with higher MFN2 protein levels in hepatic PDM. Altogether, the high degree of differences between hepatic CM and PDM subpopulations during MASLD highlights their distinct role in disease progression towards MASH.

Hepatic Oxalate Overproduction Impairs Mitochondrial Fatty Acid β-Oxidation and Induces Monocyte Chemotaxis: A Novel Target for Concurrent Treatment of MASH and Atherosclerosis

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Affecting one third of the global population, with limited pharmacotherapy available, metabolic dysfunction-associated steatotic liver disease (MASLD) has become the leading cause of chronic liver disease. Surprisingly, the major cause of death in patients with MASLD, particularly in those with the more severe metabolic dysfunction-associated steatohepatitis (MASH), is atherosclerotic cardiovascular disease (ASCVD). This highlights a critical need to identify targetable pathways for concurrent treatment, which has been hampered by limited understanding of the pathophysiology and metabolic pathways linking these two diseases. Recently, we and others uncovered oxalate metabolism commonly dysregulated in MASLD and ASCVD. While oxalate effects in the kidneys are well known, they have not been systematically studied in hepatocytes, the primary cells responsible for its formation. Moreover, in MASH and associated atherosclerosis, a causative role of oxalate, its underlying mechanisms and the therapeutic potential of targeting oxalate overproduction are unknown. Through comprehensive studies in multiple cohorts of patients and mice with MASLD/MASH or ASCVD, we identified the suppression of enzymes that limit hepatic oxalate production and activation of enzymes that drive oxalate formation. Particularly, alanine-glyoxylate aminotransferase (AGXT), a liver-specific enzyme that detoxifies glyoxylate, the oxalate precursor, was suppressed due to promoter hypermethylation, and oxalate was markedly increased in correlation with disease severity. Using CRIPSR/Cas9, we generated *Agxt*$^{-/-}$ and *Agxt*$^{-/-}$ / *Apoe*$^{-/-}$ mice that demonstrated hepatic oxalate overproduction, accelerated MASH and atherosclerosis with suppressed hepatic fatty acid β-oxidation (FAO) and induced proinflammatory pathways. In hepatocytes, oxalate overload caused mitochondrial dysfunction and lipid accumulation by inhibiting the transcription of peroxisome proliferator-activated receptor α (PPARα) and blocking mitochondrial FAO. Oxalate overload also upregulated C-C motif chemokine ligand 2 (CCL2) and CCL5 to induce monocyte infiltration to the liver and atherosclerotic plaque. Importantly, limiting oxalate production via hepatocyte-specific AGXT overexpression (AAV8-TBG-AGXT) or using a novel dual inhibitor (MDMG-935P) of glycolate oxidase (GO) and lactate dehydrogenase A (LDHA), which catalyze glyoxylate and oxalate formation respectively, ameliorated MASH and atherosclerosis by enhancing hepatic FAO and lowering monocyte chemotaxis. These findings uncover hepatic oxalate overproduction as a driver of both MASH and atherosclerosis, highlighting the potential of targeting this newly identified dysregulated metabolic pathway for concurrent treatment of these two prominent diseases.

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Related References: (*Equal contribution; #Corresponding author)

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High-Fat Diet Causes Rapid Loss of Intestinal Group 3 Innate Lymphoid Cells Through Microbiota-Driven Inflammation

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Summary

Innate lymphoid cells (ILCs) are increasingly appreciated to play a critical role in tissue homeostasis, immunity, and tolerance. At steady state, intestinal ILC3 are the main source of IL-22, ensuring epithelial barrier integrity, containing the microbiota, and protecting against pathogenic bacteria. In addition, ILC3 support intestinal tolerance to commensal bacteria and dietary antigens. ILC3 can also sense changes in dietary nutrients, such as vitamin A and aryl hydrocarbon receptor ligands (AHR-L) that affect their development, function and ultimately intestinal health. ILC3 have been described to be able to acquire high amounts of extracellular fat but the effect of dietary fat on ILC3 homeostasis is unknown. Here we show that ILC3 are severely depleted from the small and large intestine of obese mice fed high-fat diet (HFD) but not in leptin deficient obese mice. Notably, consumption of HFD for only 24 hours is sufficient to trigger ILC3 cell death. Total loss of ILC3 is reached after one week of HFD without significant weight gain or impaired glucose tolerance. However, we found that this short-term consumption of HFD increases intestinal permeability and host susceptibility to *Citrobacter rodentium* infection. Unexpectedly, we found that ILC3 were maintained in germ-free (GF) mice fed HFD. However, ILC3 were depleted when HFD-fed GF mice were inoculated with either living, heat-killed bacteria or with lipopolysaccharides, which associated with intestinal permeability and inflammation. Gene expression profiling of ILC3 from short term HFD-fed mice revealed that LPS phenocopied the differential effect of microbiota on dampening peroxisome proliferator-activated receptor (PPAR) signaling, and activating TNFα target genes involved in cell activation, exhaustion, oxidative stress and lipotoxicity. In vitro, lipid laden ILC3 are susceptible to TNFα induced cytotoxicity in a dose dependent manner. In vivo, TNFα blockade, the use of antioxidant, or TLR4 deficiency was sufficient to protect ILC3 from HFD-induced lipotoxicity. Specifically, restricted depletion of TLR4 on $Cx3cr1^{+}$ mononuclear phagocytes curtailed their HFD-induced early expansion, TNFα production and protected from ILC3 loss. Collectively, our findings reveal differential regulation of ILC3 homeostasis by the crosstalk of dietary fat with microbiota-mediated inflammation, ranging from activation to cell death, preventing early repair of intestinal permeability, and increasing susceptibility to opportunistic pathogens independently of obesity and metabolic syndrome.

Biophysical Characterization of Cancer Metabolism: Multiparametric Imaging and Phenotypic Tracking in Mitochondrial Dynamics

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The reorganization and distribution of mitochondria have been extensively examined within neuronal cells, evidencing their critical role in meeting localized bioenergetic needs and facilitating the removal of impaired or malfunctioning mitochondria[1,2]. The influence of mitochondrial spatial dynamics within cancer cells, however, remains largely uncharted territory. To investigate these complex and nuanced interactions and their impact on cellular functions, we developed and applied advanced imaging techniques to monitor mitochondrial movement, assess their functionality, and understand their contribution to the overall metabolic state of the cell. We have created a user input-independent mitochondria tracker capable of analyzing mitochondrial dynamics at sub-pixel resolutions. Our software, called "Mitometer" (available at GitHub)[3], is capable of tracking individual mitochondria in timelapse fluorescence images, and can furthermore detect fission and fusion dynamics between adjacent mitochondria[4]. Moreover, our research involves the multiplexing of various imaging techniques, including the phasor approach to fluorescence lifetime Imaging microscopy (FLIM) measurements of NADH, spectral phasors, and second harmonic generation (SHG) with Phasor analysis of Local Image Correlation Spectroscopy (PLICS). These advanced imaging approaches offer a comprehensive understanding of mitochondrial behavior and metabolic signatures, providing insights into how cancer cells exploit unique mitochondrial populations to facilitate their metastatic dissemination. By further evaluating the spheroids-extracellular matrix interaction using SHG with PLICS, our research aims to characterize the cellular microenvironment and collagen remodeling in breast cancer spheroids. These comprehensive methods not only enhance our understanding of cancer cell behavior but also hold the potential to identify novel therapeutic targets for disrupting the metastatic process. Overall, our work aims to unravel the intricate relationship between mitochondrial dynamics and cancer progression, potentially paving the way for targeted therapeutic interventions to impede metastatic spread.

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Approaching Neurodegenerative Diseases as Lipidopathies: How Lipid Metabolism Dyshomeostasis Defines a Rational Membrane Remodeling Therapeutic Strategy for Parkinson's Disease and Dementia

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Parkinson's disease (PD), dementia and other synucleinopathies have long been regarded as proteinopathies. Our lab investigates these diseases as proteinopathies and **lipidopathies**. PD patients vs. controls lipidomic analyses converge on lipid metabolism as altered in PD; increasing numbers of synucleinopathy risk loci are in lipid pathways; Lewy Body hallmarks of disease are lipid-rich; the disease-associated protein α-synuclein (αS) has physiologic and pathogenic interactions with phospholipids and fatty acids; and αS alters lipid metabolism. Collectively, these strongly support an αS/lipid interplay and a major role for lipid metabolism in modulating PD phenotypes in the brain. Hence, approaching these diseases as proteinopathies and **lipid metabolism disorders** is a new strategy for mechanistic understanding and therapeutic target identification for brain diseases.

Increased wt/familial αS mutations increase monounsaturated fatty acids, inducing lipidome dysregulation. Our group defined this dyshomeostasis and identified candidate therapeutic targets (stearoyl CoA-desaturase [SCD] and hormone sensitive lipase [LIPE]) that reverse disease-relevant phenotypes in patient-derived neurons and preclinical *in vivo* models with an SCD inhibitor entering clinical trials. These findings were presented at the Kern Conference, 2023.

Kern Lipids and Mitochondria in Metabolic Disease Conference, 2024: The key question driving our latest research is: Can the distinct properties of αS-associated membrane dyshomeostasis pinpoint **new therapeutic strategies for brain aging diseases**? We will present unpublished data on a distinct approach to **lipid metabolism remodeling** to regulate membrane composition as a therapeutic.

Phospholipid membrane composition is fundamental to protein:membrane interactions and regulating health and disease dynamics, particularly in aging. This is principally important in metabolism in the lipid-rich brain. Deeming lipid metabolism homeostasis as a disease informant aids in pinpointing therapeutic strategies for neurodegeneration.

A key PD determinant is αS interactions with membranes, ultimately defining αS conformation, and disease phenotypes. We sought to correct disease-associated aberrant αS:membrane interactions by re-balancing metabolism using strategic targeted fatty acid treatment, premised on correcting dysregulated membrane fatty acid composition. Using ^{13}C-labeled fatty acid tracing we determined the composition of remodeled lipid membranes associated with PD phenotype rescue. Tracing defined the mechanism of rescue as correcting of shorter chain saturated: longer chain unsaturated lipid equilibrium in patient-derived neurons. This stands in mechanistic agreement with our SCD and LIPE findings, augmenting the relevance of therapeutic targeting of fatty acid metabolism. Metabolism is a key indicator of health and disease and aided in generating this new candidate therapeutic strategy, the ultimate use of lipid metabolism to generate therapeutics for neurodegenerative diseases.

AI-enabled, label-free monitoring of mitochondria in health and diseases

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Our study focuses on the effects of SARS-CoV-2 on cells and their organelles, specifically lipid droplets and mitochondria. Dynamic changes during viral infection were captured over a 30 to 42-hour imaging period using advanced label-free holotomographic microscopy. Utilizing Artificial Intelligence (AI), we quantified phenotypic changes in hundreds of single cells from the start of infection to cell death and compared them to non-infected cells.

Key Findings:

- SARS-CoV-2 leads to perinuclear lipid droplet accumulation.
- The virus alters both the shape and dry mass of mitochondria.
- Infection causes lipid droplets and mitochondria to move away from each other, indicating an altered energy metabolism.
- Our high-content imaging approach distinguished the effects of different SARS-CoV-2 strains.
- Foundation models for dynamic analysis of organelle biology are within reach, laying the groundwork for future research.

We used AI to analyse these changes and applied Bayesian network modelling to understand how organelle cross-regulation (OCR) is altered by the virus. This study led to the establishment of an AI-driven platform for real-time, label-free analysis of organelle and cellular changes.

Join us to discuss these findings and the methodologies developed by Nanolive and Institut Pasteur in Paris.

Metabolic regulation of protein modification by short-chain fatty acids

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The dynamic modification of proteins by many metabolites suggests an intimate link between energy metabolism and post-translational modifications (PTM). For instance, starvation and low carbohydrate diets lead to the accumulation of the ketone body, β-hydroxybutyrate (BHB), whose blood concentrations increase more than 10-fold into the millimolar range, concomitant with the accumulation of lysine β-hydroxybutyrylation (an adduct known as Kbhb) of proteins. As with other lysine acylation events, Kbhb marks can be removed by histone deacetylases (HDACs). Here, we report that class I HDACs unexpectedly catalyze a reverse reaction, condensation of a free amine group on lysine residues with β-hydroxybutyrate (BHB), thereby forming Kbhb. Mutational analyses of the HDAC2 active site reveal a shared reliance on key amino acids for classical deacetylation and non-canonical HDAC-catalyzed β-hydroxybutyrylation. We observe similar requirements for the lactylation of lysine (Kla) by lactate. Also consistent with reversible HDAC activity, Kbhb and Kla formation are driven by mass action and substrate availability due to wide physiological dynamic ranges of particular short-chain fatty acids. Our data uncover a novel mechanism of PTM deposition relevant to metabolically-sensitive proteome modifications.

Advancing a Lipedema Research Roadmap: Recommendations to characterize adipose tissue and biology of a complex disease

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Lipedema is a type of adipose tissue disorder characterized by cuffing at the hands and feet, and pain and bruising of the limbs following an accumulation of subcutaneous adipose tissue. The lipedema field is nascent, and, despite recent advancements, approximately 50% of research papers have been published in the past 5 years. Given the recent growth of the field, the Lipedema research operates within a resource-constrained environment. To map out next steps within the field as a whole, the Lipedema Foundation took a unique collaborative approach with a multi-stakeholder and multi–disciplinary Research Roadmap. In this poster, we have indicated which next steps are a priority for characterizing disease biology. Several recommendations regarding adipose tissue and adipocytes are highlighted in this research roadmap, and will be discussed. This roadmap serves as a compilation of critical priorities that must be addressed to realize a compelling vision for the future of Lipedema research that can build an environment for high-quality clinical trials and advance diagnosis and treatment.

Lipid Droplet-associated Noncoding RNA-coded Proteins

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Lipid droplet (LD) is a cellular organelle with a neutral lipid core covered by a monolayer phospholipid membrane and some proteins. LDs have been found in almost all organisms from bacteria to humans. Recent study reveals that LDs are conserved and might be originated 3.19 billion years ago. Over storage of neutral lipids in LDs is a causative factor for many metabolic disorders, such as obesity, fatty liver, and atherosclerosis. Therefore, understanding LD dynamics will pave the way to overcome ectopic lipid storage-induced metabolic syndromes. The proteomes and lipidomes of isolated LDs have been accumulated, and several disease-related key proteins have been identified in LDs. One of them, HSD17B13 has recently been found to play essential role for the development of nonalcoholic fatty liver disease (NAFLD). Decreasing its expression using siRNA reduces nonalcoholic steatohepatitics (NASH), which is under clinic trial. Therefore, studying LD proteins, especially compared nondisease model to disease model, can be useful and critical to identify key regulators of the disease.

Although we and others have identified more than 100 resident and dynamic proteins in LDs by isolation- proteomics-verification, the regulation of LD size, movement, and interaction with other organelles remains largely unknown. Thus, we proposed there must be some new proteins on LDs. To do so, we focus on noncoding RNA-coded proteins in LDs and identified more than 20 small peptides using our new ORF database. Those proteins cannot be identified using conventional proteomics. To confirm our finding, knocking in a tag is applied to detect endogenous expressed noncoding RNA coded proteins. Furthermore, one of these new LD proteins, termed LD-associated noncoding RNA-coded protein 1 (LDANP1) is examined for its function. We found that LDANP1 is engaged in regulating the storage of neutral lipids in LDs and insulin signaling processes within myoblasts. In addition, deletion of one amino acid drives the LD targeting sequence of LDANP2 to mitochondria, suggesting the tight connection between LDs, organelle with monolayer phospholipid membrane and mitochondria, organelle with bilayer phospholipid membrane. Identification of LDANPs and their functions initiates a new direction to study roles of LDs in metabolic diseases with those new LD proteins.

1-deoxysphingosine Activation of Nuclear Receptor 2 Family Member 2, NR2F2, Reactivates Fatty Acid Oxidation in Adipocytes

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Background. The prevalence of childhood obesity in the United States is approaching 20%, and approximately 40% of U.S. children are either overweight or obese. Evidence in humans indicates that perinatal exposure to the high levels of omega-6 (n6-) fatty acids (FA), relative to omega-3 (n3-FA), prevalent in the U.S. maternal diet establishes greater risk for obesity in childhood.

Methods. Specialized maternal diets, either high n6-FA (safflower oil) or control-FA (soybean oil) were provided at the time of mating, dams underwent normal gestation and lactation, and litters were sacrificed on postnatal day 12 (PND12). Inguinal subcutaneous adipose was processed and Adipocyte Stem-like Cells (ASCs) were isolated by flow cytometry. Adipocyte metabolism was measured by Seahorse and molecular signatures by qPCR, immunoblotting, and mitochondrial proteomics. Whole body energetics was measured by indirect calorimetry and fuel utilization by ^{13}C-palimitate tracer.

Results. Early-life n6-FA exposure led to PND12 pups with inguinal adipocyte hypertrophy, 9% greater body fat, metabolic fuel preference shifted away from lipids (higher VCO_2/VO_2), and diminished whole-body ^{13}C-palmitate oxidation. ASCs from PND12 pups had reduced metabolic regulator NR2F2 protein, correlating with lower PPARγ, PGC1α, and UCP1 levels in downstream adipocytes. The n6-FA exposure programed ASCs with 50% lower basal, maximal, and ATP-coupled respiration. Mitochondrial proteomics pathway analyses of n6-FA relative to control-FA exposed adipocytes revealed downregulation of Oxidative Phosphorylation (OXPHOS) and Electron Transport Chain (ETC) proteins ATP5F1A, ATP5MG, ACOX, ACADS, COX6C, and UQCRC1. Remarkably, transient ligand activation of NR2F2 with 1-deoxysphingosine (1-DSO, 300 nM) in ASCs, before adipogenic differentiation, increased PPARγ, PGC1α, and CPT1A, reigniting cellular FAO after adipogenesis. Although NR2F2 activation in ASCs was transient, the mitochondrial proteomics revealed persistently increased mitochondrial complex I, OXPHOS, and ETC components. The 1-DSO activation was specific to NR2F2 in ASCs, because transient 1-DSO treatment failed to boost FAO following *in vitro* deletion of the gene in ASCs from NR2F2$^{f/f}$ pups.

Conclusions. Cumulatively, our findings support a model in which ASCs, exposed to disproportionately high n6-FA relative to n3-FA, suppress NR2F2, leading to less robust expression of beige adipocyte regulators. The n6-FA exposed ASCs give rise to adipocytes with diminished ETC and OXPHOS enzymes, and a blunted FAO capacity, while retaining an enhanced lipogenic gene expression and triacylglyceride accumulation. Understanding mechanisms that activate adipocyte metabolism in response to dietary FA, or their signaling lipid derivatives, could pave the way for promising interventions that might protect against childhood obesity.

FGF21 Distinctly Reduces Ceramide Levels in Visceral Fat of Obese Mice

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Fibroblast growth factor-21 (FGF21), primarily secreted by the liver, plays a crucial role in energy balance and glucose and lipid metabolism. Adipocytes also secrete FGF21 and are key targets for its anti-diabetic effects. Our previous research showed that inducible, adipocyte-specific FGF21 expression mitigated diet-induced obesity and extended lifespan. We found that increased FGF21 significantly reduced proteins involved in immune responses in the visceral epididymal fat depot (eWAT) but not in the subcutaneous fat depot (scWAT). Both adipose tissues overexpressed FGF21 and its co-receptors *B-klotho* and *Fgfr-1c* at similar levels, prompting us to investigate the differential effects of FGF21 activity in eWAT versus scWAT.

Tissues were collected from high-fat diet-fed male mice with doxycycline-inducible, adipocyte-specific FGF21 overexpression and their control littermates. The mammalian target of rapamycin complex 1 (mTORC1) is a crucial regulatory node in the FGF21 signaling network in adipocytes, mediated by the mitogen-activated protein kinase pathway. While basal ERK phosphorylation was unaffected by FGF21 overexpression in both eWAT and scWAT, FGF21 overexpression promoted the phosphorylation of two key mTORC1 effectors, p70S6 Kinase 1 and eIF4E binding protein (4E-BP), in eWAT but not in scWAT. mTORC1 activity mediates insulin signaling via phosphorylation of protein kinase B (AKT), which increased in eWAT but not in scWAT.

mTORC1 deficiency in adipocytes promotes inflammation and the synthesis of ceramides, lipids that stimulate inflammation and systemic insulin resistance. FGF21 overexpression significantly decreased five ceramide species and ten sphingomyelin species in eWAT compared to control samples, while ceramides C24 and C25 increased in scWAT. Additionally, six species of hexosyl- and lactosyl-ceramides were reduced in eWAT of transgenic mice compared to control mice, with fewer reductions observed in scWAT. Lipids generated from ceramide degradation, such as sphinganine and sphingosine, were significantly lower in eWAT of transgenic mice compared to control mice and remained unchanged in scWAT.

Our findings highlight the significant impact of FGF21 on adipose tissue, particularly its ability to reduce ceramide species in eWAT. We are investigating the underlying mechanisms, focusing on the potential role of mTORC1 signaling, which was notably upregulated in eWAT but not in scWAT. We are now determining whether the ceramide-lowering effect is dependent on adiponectin, an adipokine increased by FGF21, which counteracts the detrimental effects of elevated ceramides. This is largely through stimulation of adiponectin receptor ceramidase activity. Overall, this study illustrates a novel aspect of FGF21's function in systemic metabolism, by regulating inflammation prominently in visceral adipose tissue.

Myelination and lipid metabolism in the adolescent HIV-1 transgenic rat brain

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Human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND) affect 30-50% of people with HIV (PWH) and are associated with persistent white matter pathologies. New HIV infection rates are climbing among adolescents, who may be particularly vulnerable to white matter disruption during the critical window of adolescent myelination. The HIV-1 transgenic (Tg) rat model is a noninfectious model of HIV neuropathology which exhibits an altered transcriptome suggestive of deficient myelination, but no studies have directly examined oligodendroglial myelination and potential mechanisms of white matter disruption in this model. Myelin is highly enriched in lipids, which are critical for appropriate myelin structure and function. Interestingly, transcriptome analyses indicate reduced lipid metabolism and myelin proteins in PWH; disrupted brain lipid metabolism results in myelin abnormalities and is predictive of cognitive decline in HIV. We therefore hypothesized that glial lipid metabolism is disrupted by HIV-1 and impairs adolescent myelination. To address this, we are analyzing oligodendroglial populations and myelination of the HIV-1 Tg rat brain at 3 and 9 weeks of age. Western blot analyses of myelin protein expression in control and HIV-1 Tg rat microdissected caudate, cortex, hippocampus, and corpus callosa indicate no significant changes in myelin basic protein (MBP), 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CNPase), myelin oligodendrocyte glycoprotein (MOG), or myelin associated glycoprotein (MAG), despite strong trends toward increased MBP in the caudate and decreased MBP in the callosum at 9 weeks. However, expression of fatty acid synthase (FASN) was significantly decreased in the HIV-1 Tg rat cortex and caudate, and acetyl-CoA carboxylase (ACC) was significantly altered in callosum at 3 weeks and cortex at 9 weeks. To determine whether changes in lipid biosynthesis enzymes affect myelin lipid composition, we performed an assay for total cholesterol on purified whole brain myelin at 9 weeks and discovered a strong trend toward increased total cholesterol. We are continuing our lipid analysis with assays for phospholipids and free fatty acids. If observed changes in myelin lipids result in impaired adolescent myelination, lipid metabolism may be a promising therapeutic target to improve white matter integrity and ameliorate associated HAND pathology in people living with HIV.

Mechanobiological regulation of beige adipocyte differentiation and metabolism

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Obesity is a major healthcare challenge and is associated with a higher risk for cancer. A better understanding of adipose tissue homeostasis could yield new strategies to treat obesity and obesity-related illnesses. White fat cells generally serve as a lipid reservoir whereas brown and beige fat can dissipate heat via mitochondrial protein uncoupling protein 1 (UCP1). We have previously shown a novel mechanism in which thermogenic and metabolic activation of brown adipose fat can be modulated via a myosin 7 and YAP/TAZ-dependent mechanotransductive signaling network. Whether similar mechanisms exist for beige fat activation remains unclear. Our preliminary data shows that there is a significant increase in the tissue stiffness following beigeing, suggesting that external biomechanical forces from adipose tissues may be associated with beige differentiation decisions. We also screened for myosin expression in beige adipocytes using qPCR and discovered that myosin IIA (NMII-A, or MYH9) is highly expressed. We observed that beige adipocytes from an inducible MYH9 knock down (KD) cell line exhibited a significantly reduced cellular storage modulus, UCP-1 expression, and respiration. This suggests that beige adipocyte differentiation and metabolic activation do indeed require internal force generation by MYH9. Interestingly, MYH9 mainly localized around peripheral actomyosin bundles and in the vicinity of lipid droplets (LD) and mitochondrial contact sites. Transmission electron microscopy (TEM) revealed that mitochondria were significantly smaller and more fragmented in MYH9 KD cells compared to vehicle (VEH) control cells. Those alterations in organelle structures are also associated with mitochondria dysfunctions such as increased redox and decreased membrane potential. These studies will help provide new insights into the functional connections between MYH9-mediated contractile force and beige adipocyte metabolism and differentiation.

Hepato-cardiac interorgan communication controls cardiac hypertrophy via combined endocrine-autocrine FGF21 signaling

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FGF21 is a hormone expressed mainly in the liver but also in other organs including the heart. Despite the protective action of FGF21 in patients and mice with metabolic syndrome and some cardiac disease models, elevated plasma and cardiac FGF21 levels were found in patients with end-stage heart failure (HF). Thus, it remains unknown whether FGF21 elevation is part of HF pathophysiology or a protective response.

To address this, we measured serum and myocardial FGF21 levels in humans with left ventricular hypertrophy (LVH) or hypertension and found that they are significantly elevated. To investigate the contribution of cardiac and extracardiac FGF21 in HF, we assessed the temporal profile of hepatic, plasma and cardiac FGF21 levels in mice with transverse aortic constriction (TAC). Hepatic FGF21 expression and plasma FGF21 levels were elevated 3 days post-TAC and prior to the onset of cardiac complications. Two weeks post-TAC, when pathologic LVH begins to develop, cardiac FGF21 expression was also elevated and coincided with myocardial fibrosis, metabolic derangement, and accumulation of toxic lipid species. To test the involvement of FGF21 in the pathophysiology of LVH, we applied TAC on two mouse models with hepatocyte-(HEP-FGF21-/-) or cardiomyocyte-(CM-FGF21-/-)-specific FGF21 deletion that we generated. Surprisingly, the pro-hypertrophic role of TAC was abolished in both HEP-FGF21-/- and CM-FGF21-/- mice. Inhibition of FGF21 signaling either via hepatocyte- or cardiomyocyte-specific FGF21 deletion reversed the pro-hypertrophic myocardial transcriptome, metabolome and lipidome profiles. The observed changes indicated improvement in cardiac energetics. The aggravating effect of cardiomyocyte FGF21 per se was confirmed with reconstitution of FGF21 expression in the cardiomyocytes of HEP-FGF21-/- mice via administration of a cardiotropic Myo-AAV91A that encodes for mouse FGF21. Constitutive cardiomyocyte FGF21 expression negated the cardioprotective effects of hepatic FGF21 ablation and caused systolic and diastolic dysfunction, associated with cardiac fibrosis, increased expression of HF markers, and cardiomyocyte enlargement. To explore the translational perspective of the therapeutic effects of FGF21 inhibition, we developed anti-sense oligonucleotides that target FGF21

(ASO-FGF21) and administered them in wild type mice with TAC after the onset of pathologic hypertrophy. This treatment reversed LVH, fibrosis, inflammation, and cardiac dysfunction.

Our research shows that in response to increased cardiac afterload, cardiomyocyte FGF21 upregulation is a critical event that is stimulated by liver-derived FGF21 and drives pathologic cardiac hypertrophy in an autocrine fashion. Conclusively, a hepato-cardiac endocrine-autocrine FGF21 signaling axis governs pathologic cardiac hypertrophy, which can be treated via FGF21 inhibition.

Desmosterol regulates microglia and astrocyte identity controlling pruning in brain development

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Cholesterol plays a critical role in the brain, serving as an essential component of cell membranes and myelin sheaths. Due to the blood-brain barrier, the brain relies solely on local de novo synthesis for cholesterol, independent of peripheral sources. Desmosterol, a cholesterol precursor and an activator of the LXR transcription factor family, significantly impacts immune function and inflammation, however, its role in the brain remains unclear. Notably, desmosterol levels peak around day 3.5 post-birth, a critical period for brain development and maturation, while Dhcr24, the enzyme that converts desmosterol to cholesterol, is inversely regulated, suggesting the importance of a tight regulation of desmosterol levels during developmental stage.

Understanding the unique mechanisms and pathways involved in the maintenance of cholesterol homeostasis in the brain is crucial, considering that perturbations to these processes are implicated in numerous neurodegenerative diseases. Thus, any injuries to the immature brain that affect cholesterol homeostasis may have long-term adverse neurological consequences. Dhcr24 has been implicated in neuroprotection, oxidative stress, inflammation, and other conditions. Our project explores brain cholesterol biosynthesis and metabolism, focusing on cholesterol trafficking and related biological processes during brain maturation. Utilizing a global Dhcr24 knock-in mouse model, we examine desmosterol regulation at 3.5 days and 3 months of age, revealing its impact on brain development and cell-type-specific functions.

We have found that genetic depletion of desmosterol in the brain at 3.5 days does not affect pups behavior, measured by ultrasonic vocalizations. However, adult mice with desmosterol depletion showed reduced locomotor activity, exploratory behavior and affected autonomic nervous system, measured by fewer feces. Moreover, scRNA-seq analysis revealed increased number of neurons in desmosterol depleted mice at 3.5 days, suggesting impaired pruning and neuronal reorganization.

Gene expression and pathway analysis indicated inflammasome inhibition and altered mitochondrial function in microglia, fewer reactive astrocytes, less astrocytes functionality and decreased expression of pruning genes in both microglia and astrocytes in desmosterol-depleted mice. These findings suggest that desmosterol depletion affect critical developmental processes like pruning and reactivity of astrocytes and microglia that may affect adult behavior.

In summary, our research highlights the essential role of desmosterol in brain maturation and neuronal pruning after birth. These results are of particular interest for understanding brain development and maturation associated with cholesterol metabolism, implicated the cell types, and their effect on neurodegenerative pathologies. Those findings may lead to new therapeutic approaches targeting desmosterol content in the brain to modulate neuronal pruning and brain plasticity.

Role of CD163 and extracellular vesicles in adipose tissue iron homeostasis

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Iron overload in metabolic organs has been linked to an increased risk of diabetes, and our group has shown that adipose tissue macrophages (ATMs) play an important role in protecting adipocytes from excessive iron accumulation in obesity. Iron homeostasis is regulated by a redundancy of transmembrane proteins that carefully manage cellular iron import and export. The scavenger receptor, CD163, is expressed exclusively on monocytes/macrophages and serves as an innate immune sensor for extracellular iron by clearing circulating hemoglobin/haptoglobin complexes. We show that CD163 null mice ($CD163^{-/-}$) present lower expression of iron regulatory genes (*Tfr1, Cisd1, Slc40a1*) in both ATMs and anti-inflammatory (M2-like) bone marrow-derived macrophages. As a consequence of lower extracellular iron clearance by $CD163^{-/-}$ ATMs, iron content was increased in inguinal adipocytes *in vivo*. Further, obese male $CD163^{-/-}$ mice exhibited pronounced glucose intolerance, insulin resistance, and higher circulating fatty acid content upon hyperinsulinemia; indicating an elevated release of fatty acids into the circulation is occurring in the fed state, which *may* be a consequence of greater iron in inguinal adipocytes. In addition to regulating tissue iron import, iron homeostasis can also be regulated by export via the transmembrane protein, ferroportin, which is the only known iron exporter. Isotope tracer studies from our lab have revealed a direct transfer of iron between adipocytes and macrophages. However, the direct uptake of iron from the extracellular space to macrophages is minimal, suggesting a direct connection for iron exchange between adipocytes and ATMs, which differs from the traditional pathway of iron export through ferroportin. To further test routes of iron transfer, we show that small extracellular vesicles (sEVs) may also function as a homeostatic mechanism to control parenchymal iron release. 3T3-L1 adipocytes treated with exogenous iron exhibited a pronounced increase in total sEVs release and ~40-fold higher iron content within the released sEVs. Therefore, we propose sEV iron export is a homeostatic mechanism aimed to release excess iron from adipocytes independent of ferroportin. Future studies will outline whether ATMs are responsible for adipocyte sEV iron clearance. Collectively, our findings demonstrate two distinct mechanisms designed to regulate adipocyte iron levels. One mechanism involves limiting excessive iron uptake through the scavenging of extracellular hemoglobin by CD163 on ATMs, and the other involves enhancing the export of iron from adipocytes through sEVs.

Defining the mechanism of microlipophagy in mammalian liver

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Background: Macrolipophagy is a well-defined genera-wide process for lysosomal lipid turnover. During macrolipophagy, cytoplasmic lipid droplets (LDs) are sequestered by LC3-positive autophagosomes, which then fuse with lysosomes to target LDs for lysosomal degradation. In contrast to macrolipophagy, microlipophagy remains poorly characterized and refers to the direct internalization of LDs by late endosomes. The functional significance of microautophagy in lipohomeostasis in mammalian cells remains underappreciated.
Methods: Animal models: Studies were performed in 3-8-month-old male C57BL/6 mice. Liver-specific *Atg7*^{KO} mice were generated by administration of AAV8-TBG-iCre and control and *Atg7*^{KO} livers were harvested after 8 weeks. DNA or siRNA transfection: Transfections in NIH3T3 cells and AML12 hepatocytes were performed using Lipofectamine3000. In vivo DNA and siRNA delivery was performed using in vivo-jetPEI® and Invivofectamine™ 3.0, respectively. Phosphoproteomics: Fed and 20-hour fasted liver homogenates, and control and 6-hour serum-starved AML12 hepatocytes were homogenized in 2% SDS + 5 mM DTT buffer, and proteins were digested in S-trap columns, and peptides analyzed by nLC-MS/MS. Confocal imaging: Hepatocytes in serum-free medium in presence or absence of oleic acid were subjected to multiplex colocalization using spinning disc super-resolution microscopy (Nikon CSU-W1). Statistical analyses were performed via unpaired Student's t-test or one or two-way ANOVAs followed by appropriate post-hoc testing.
Results: We report the marked enrichment of phosphorylated VPS4B, an important ATPase associated with the ESCRT (endosomal sorting complex required for transport), on LDs with fasting, and silencing VPS4B or expressing its phospho-mutant form blocked the colocalization of LDs with RAB7-positive compartment. This LD degradation occurred independently of core autophagic gene *Atg7,* suggesting a mechanism that is distinct from macrolipophagy. Spartin was recently shown to regulate macrolipophagy. Our data show that spartin does not enrich in *Atg7*^{KO} liver, but rather appears to interact with VPS4B. Furthermore, loss of spartin blocked the colocalization of LDs with RAB7 positive compartment but failed to prevent the sequestration of LDs by autophagosomes. We propose that VPS4B engages with spartin to regulate direct LD turnover by endosomal microautophagy, and that spartin does not play a significant role in macrolipophagy.
Conclusion: In this work, we have identified novel regulators of microlipophagy, and established its footprint in mammalian liver. Understanding these mechanisms will help develop new ways to treat chronic liver diseases, e.g., steatotic liver disease, where excessive LD accumulation is implicated.

Liver Single-cell RNA Transcriptome Evolution in Response to Diet-induced MASH/Fibrosis

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Background:
MASH involves perturbations of hepatocytes, non-parenchymal liver cells (NPCs) and their interactions that result from insulin resistance. Here, we used single-cell sequencing (scRNA-seq) of hepatocytes and NPCs to determine the time-dependent gene expression changes in gene expression induced by two distinct MASH diets.

Methods:
Mice (n=9) fed Chow, Western (40% fat, 29% sucrose, 0.14% cholesterol), or AMLN diets (40% fat, 20% fructose, 9% sucrose, 2% cholesterol) for 24, 34, or 45 weeks. Mice were subjected to a partial hepatectomy for histology followed by liver perfusion for scRNA-seq. Analysis of scRNA-seq utilized Seurat, RNA velocity, and Cellrank.

Results:
324,827 high-yield single-cell transcriptomes were analyzed. After 45 weeks, liver collagen increased 22-fold and 15-fold on AMLN and Western diets, respectively. Histology sections revealed more prominent liver fibrosis in mice fed AMLN. Genes associated with the actin cytoskeleton, myofibroblast differentiation, and fatty acid catabolism were significantly induced in stellate cells (HSCs), with greater changes on the AMLN diet. Embryonically-derived and circulating monocyte-derived Kupffer cells (KCs) were markedly increased on the AMLN diet. Both diets significantly induced the differentiation of circulating monocytes to KCs at 34 weeks.

At 34 weeks, AMLN diet promoted hepatocyte de-differentiation, apoptosis through TNF-α signaling, and induced extracellular matrix formation and cell migration. The Western diet induced genes involved in intrinsic DNA damage via alternative splicing defect pathways along with extrinsic apoptosis via MAPK, p75 NTR receptor-mediated signaling, and NF-kB signaling. Both diets similarly induced ferroptosis and pyroptosis, but there was no evidence of necroptosis. Liver progenitor cell (LPC) proliferation and differentiation of cholangiocytes into myofibroblasts were induced by both diets with greater changes induced by the AMLN diet.

Albumin and ApoB expression gradually decreased especially in midzonal hepatocytes closest to pericentral region on both diets with a nadir at 26-34 weeks but regained near-normal expression at 45 weeks.

Conclusions:
Our study provides the first time-dependent nonparenchymal and hepatocyte single-cell sequencing transcriptome response to two commonly used MASH diets. The AMLN diet induced HSC activation and proliferation to a greater extent than the Western diet. Both diets induced LPC differentiation into cholangiocytes then to myofibroblasts. Pericentral and midzonal hepatocytes closest to pericentral region appear to be differentiating hepatocytes replacing hepatocytes that have undergone cell death.

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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.

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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.

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Conference Safety Plan

1R13HL176131-01 (PI, Brestoff; MPI Abumrad)

The Kern Lipid Conference is committed to providing a safe and just environment that is free from harassment and discrimination for all attendees. We expect that all participants will foster inclusivity, respect, and equity for all attendees, irrespective of their rank or eminence in the field. The conference will not tolerate sexual, racial, or ethnic harassment or any other form of harassment. Some examples of harassing behaviors may be:

- Unwelcome comments or behavior, including but not limited to drawings, written statements, social media posts, or verbal statements, related to an individual's race, ethnicity, color, national origin, sex, disability, religion, age, gender, gender identity, disability, marital status, sexual orientation, veteran status, or other protected class
- Unwelcome sexual advances or requests for sexual favors;
- Unwelcome teasing, joking, or flirting based on actual or perceived gender identity, gender expression, or sexual identity/orientation
- Retaliation

Any participant who believes they have been discriminated against or harassed is encouraged to report the incident(s). The Kern Lipid Conference has established multiple lines of communication to receive and address complaints of harassment. Any person may confidentially report alleged violations to the conference organizers by submitting a comment on the Kern Lipid Conference website (www.kernconference.org) or by directly reporting the alleged violation to the conference organizers or leadership team via email or verbal communication to the Conference Co-Chairs (Drs. Brestoff at brestoff@wustl.edu, Nada Abumrad at nabumrad@wustl.edu, and/or Gregory Steinberg at gstein@mcmaster.ca) and/or to the Kern Lipid Conference staff (Dr. Moshe Levi, President, at ml1742@georgetown.edu, or Kaitlyn Murphy, Conference Coordinator, at Kaitlyn.Murphy@georgetown.edu). Reports may be made at any time, including during non-business hours.

All received complaints will be reviewed as soon as possible by the conference co-chairs and leadership team, with the goals of understanding the nature of the complaint and agree on next steps. If any of those individuals is a party to the complaint, they will not be allowed to participate in those processes. This team will respond promptly, including by offering supportive measures, informing parties about the available complaint and investigation processes, and taking reasonable care to prevent and promptly correct discrimination or harassment. Any complaint that alleges a crime, including allegations of sexual or physical assault, will be referred to the Snowmass Police Department. The Kern Lipid Conference is committed to conducting prompt and equitable investigations and will appropriately address complaints. Upon completion of an investigation, individuals found to have engaged in acts of harassment, discrimination, or retaliation will be promptly disciplined. If circumstances warrant, disciplinary actions may include discontinuing their participation in the current conference without refund, barring their participation in future meetings, and/or loss of eligibility to receive conference awards supported by NIH funds.

Individuals who have questions, concerns, or complaints related to harassment are also encouraged to contact the conference organizer or the HHS Office of Civil Rights (OCR). For information about how to file a complaint with HHS OCR, please see OCR's webpage, Filing a Civil Rights Complaint https://www.hhs.gov/civil-rights/filing-a-complaint/index.html) Filing a complaint with the conference organizer is not required before filing a complaint of discrimination with HHS OCR, and seeking assistance from the conference organizer in no way prohibits filing complaints with HHS OCR. individuals can also notify the NIH about concerns of harassment, including sexual harassment, discrimination, and other forms of inappropriate conduct at NIH-supported conferences (see NIH's Find Help webpage https://grants.nih.gov/grants/policy/harassment/find-help.htm).

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Previous Conference Titles and Kern Lecturers

2023 "Lipids in Aging, Lifespan and Aging-associated Diseases"

Opening Kern Lecture: Anne Brunet, PhD,
Stanford University
"Lipid homeostasis and aging"

Closing Kern Lecture: Jennifer Lippincott-Schwartz, PhD
Howard Hughes Medical Institute-Janelia Research Campus
"Imaging Interacting Organelles to Understand Metabolic Homeostasis"

2022 "Therapeutic Aspects of Adipose Tissue Organ Crosstalk"

Kern Lecture: C. Ronald Kahn, MD
Joslin Diabetes
"microRNA Regulation Adipose Organ Crosstalk"

2019 "Signaling Lipids in Health and Disease"

Kern Lecture: Benjamin F. Cravatt III, PhD
Scripps Research Institute
"Lysophospholipid Signaling Pathways at the CNS- Immunology Interface"

2018 "Metabolic Regulation of Immunity, Cardiometabolic Diseases and Cancer: New Therapeutic Approaches"

Kern Lecture: David Sabatini, MD, PhD
MIT Biology and Whitehead Institute
"mTOR and lysosomes in growth control"

2017 "The Gut Microbiome, Bile Acids, and Regulatory Networks in Health and Disease: Emerging Therapeutic Approaches"

Kern Lecture: Gary D. Wu, MD
University of Pennsylvania
"Metabolic Cross Talk Between the Gut Microbiota and Its Host: Novel Therapeutic Opportunities"

2016 "Targets/Therapies for Diabetes, Atherosclerosis and NASH: A Dialogue between Academia and Industry on Innovation"

Kern Lecture: Roger J. Davis, Ph.D., F.R.S.
Howard Hughes Medical Institute**,** H. Arthur Smith Chair, UMASS Medical School, Worcester, MA
"Metabolic Stress Signaling"

2015 "**Emerging therapies for cardiovascular diseases: A dialogue between academic and pharmaceutical research"**

Kern Lecture: Antonio M. Gotto, Jr., MD, DPhil
Weill Cornell Medical College, New York, New York
"Residual Risk: Where Do We Go After Statins?"

2014 "**Evolving Concepts of HDL Function in Cardiometabolic Diseases and Beyond"**

Kern Lecture: Daniel J. Rader, MD,
University of Pennsylvania, Philadelphia, Pennsylvania
"Is it time to revise the HDL cholesterol hypothesis?"

2013 "Molecular Mechanisms and Pathophysiology of Lipid Storage"

Kern Lecture: Barbara Kahn, M.D.
Harvard Medical Center, Boston, Massachusetts
"Novel mechanisms by which adipose tissue regulates systemic insulin sensitivity and risk for diabetes"

2012 "Systems Biology, Lipidomics and Cardiometabolic Diseases"

Kern Lecturer: Leroy Hood, M.D, Ph.D.
Institute for Systems Biology, Seattle, WA
"Systems Medicine, Emerging Technologies, and Proactive P4 Medicine (Predictive, Preventive, Personalized, and Participatory)"

2011 "Emerging Discoveries of Lipid Effects on Organ Physiology and Pathobiology"

Kern Lecturer: David Mangelsdorf, Ph.D.
UT Southwestern Medical Center, Dallas, Texas
"Nuclear receptor/FGF signaling pathways and regulation of nutrient metabolism"

2010 "Lipids, Inflammation, and Stress Reactions in Atherosclerosis: Mechanisms, Imaging, and Therapy"

Kern Lecturer: Charles N. Serhan, Ph.D.
Brigham and Women's Hospital, Division of Medical Sciences Harvard University, Boston, MA
"A Novel Genesis of Pro-Resolving Lipid Mediators in Inflammation – Resolution"

2009 "Role of Nuclear Receptors and Coregulators in Insulin Resistance, Energy and Lipid Metabolism, Inflammation and Aging"

Kern Lecturer: Donald M. Small, M.D.
Boston University School of Medicine, Boston, MA
"The Happy Career of an M.D. in Biophysics. The Real Story, the People that Created the Research"

2008 "Frontiers in Regulation of Lipid Metabolism"

Kern Lecturer: Helen Hobbs, M.D.
UT Southwestern Medical Center, Dallas, Texas
"Rerouting Receptors to Reduce Heart Disease"

2007 "Diabetes, Obesity and Atherosclerosis"

Kern Lecturer: Jeff Gordon, M.D.
Washington University, St. Louis, Missouri
"Dining in with a few trillion friends: exploring the human gut microbiota and microbiome"

2006 "Developments in the Pathogenesis of Obesity & the Metabolic Syndrome"

Kern Lecturer: C. Ronald Kahn, M.D.
Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts
"Insulin Resistance in Liver: A Primary Force For Multiple Components of the Metabolic Syndrome"

2005 "HDL Metabolism and Nuclear Receptors: A New Frontier for the Treatment of Atherosclerosis"

Kern Lecturer: Ronald Evans, Ph.D.
Salk Institute, La Jolla, California
"PPARd and the Marathon Mouse: Runaway Physiology"

2004 "Atherosclerosis: An Inflammatory and a Metabolic Disease"

Kern Lecturer: Joseph L. Witztum, M.D.
University of California, San Diego, California
"Auto Antibody Responses in Atherosclerosis"

2003 "Molecular Regulation of Lipid Metabolism"

Kern Lecturer: Dr. Silvia Santamarina-Fojo, M.D., Ph.D.
National Heart, Lung & Blood Institute
National Institutes of Health, Bethesda, Maryland
"ABCA1, the Regulator of HDL Formation"

2002 "Fatty Acid Transport and Metabolism: Impact on Insulin Action/Secretion and Body Weight Regulation"

Kern Lecturer: Gerald Shulman, M.D., Ph.D.
Yale University School of Medicine, New Haven, Connecticut
"Mechanisms of Fatty Acid Induced Insulin Resistance"

Previous Award Recipients

2023 Conference

David L. Williams Lecture and Scholarship Award – Winner

Lingyan Shi, PhD, University of California-San Diego – USA

David L. Williams Lecture and Scholarship Award – Runner Up

Emilio Mottillo, PhD, Henry Ford Hospital - USA

Roger Davis Investigator Award for Transitional Faculty – Winner

Saranna Fanning, PhD, Harvard Medical School & Brigham & Women's Hospital - USA

Roger Davis Investigator Award for Transitional Faculty – Runner Ups (in alphabetical order)

Zhen Guo, PhD, Washington University School of Medicine - USA
Robert Helsley, PhD, University of Kentucky - USA
Kayla Sprenger, PhD, University of Colorado Boulder - USA
Tadataka Tsuji, DDS, PhD, Joslin Diabetes Center, Harvard Medical School - USA

Franz Simon Poster Award sponsored by Cayman Chemical – Winner

Christy Gliniak, PhD, University of Texas Southwestern Medical Center - USA

2022 Conference

First Name	Last Name	Company	Poster Number
David L. Williams Lecture and Scholarship Award – Winner			
Ali	Javaheri	Washington University School of Medicine	N/A
Roger Davis Investigator Award for Transitional Faculty - Winner			
Ada	Weinstock	University of Chicago	A-1
Roger Davis Investigator Award for Transitional Faculty – Runner Ups			
Dorota	Kaminska	UCLA	A-2
Farnaz	Shamsi	New York University	A-3
Yang	Wang	UT Southwestern Medical Center	A-4
Xiangyu	Zhang	Washington University School of Medicine	A-5
Early Career Investigator Travel Stipend Awards			
Yonathan	Aberra	University of Virginia	E-1
Uche	Anozie	Vanderbilt University Medical Center	E-2
Cassandra	Atzrodt	Vanderbilt University	E-3
*Marc	Bornstein	University of Pennsylvania	E-4
Sivaprakasam	Chinnarasu	Vanderbilt University Medical Center	E-5
Katelyn	Dial	Georgetown University	E-6
Helena	Fisk	University of Southampton	E-7
Christy	Gliniak	UT Southwestern Medical Center	E-8
Zhen	Guo	Washington University in St. Louis	E-9
Donghua	Hu	Washington University in St. Louis	E-10
Krista	Hu	Columbia University	E-11
Se-Jin	Jeong	Washington University in St. Louis, School of Medicine	E-12
Franziska	Krautter	New York University Langone Health	E-13
Huyen	Le	Rutgers University	E-14
Andrew	Libby	University of Colorado Anschutz Medical Campus	E-15
Dongliang	Lu	Washington University in St. Louis, School of Medicine	E-16
Amanda	MacCannell	University of Leeds	E-17
William	Massey	Cleveland Clinic - Lerner Research Institute	E-18
Brian	Park	Tufts University	E-19

*Franz Simon Poster Award Winner

Kelsey	Pinckard	Vanderbilt University Medical Center	E-20
Jordan	Reed	University of Virginia	E-21
William	Trim	Brigham and Women's Hospital, Harvard Medical School	E-22
Alexa	Wade	Johns Hopkins University	E-23
Qianyi	Yang	University of Virginia	E-24
Yu-Sheng	Yeh	Washington University in St. Louis	E-25
Weinan	Zhou	University of Illinois at Urbana-Champaign	E-26
Poster Only			
Sharmila	Adapa	Vanderbilt University/Georgetown University	P-1 (Joint poster)
Shania	Davidson	Howard University/Georgetown University	
Yolander	Valentine	Virginia Commonwealth University	P-2
Industry			
Dushyant	Kshatriya	Research Diets Inc.	Z-1
Beixi	Wang	Bruker Mass Spectrometry	Z-2
Russell	Waugh	Bruker Mass Spectrometry	Z-3

2019 Conference

First Name	Last Name	Company	Award
Ruthellen	Anderson	University of South Dakota Sanford SOM	ECI
Andrea	Anderson	Virginia Commonwealth University	ECI
Warren	Anderson	University of Virginia	ECI
Noemi	Arias Rueda	Saint Louis University	ECI
Kelsy	Broadaway	UNC Chapel Hill	ECI
Ainara	Cabodevilla	New York University Langone Health,	ECI
Haili	Cheng	UT Southwestern Medical Center	ECI
John	Dean	Washington University School of Medicine in St. Louis	ECI
Luke	Engelking	UT Southwestern Medical Center	DLW ECI
Liyan	Fan	Case Western Reserve University	ECI
Fei	Fang	UT Southwestern Medical Center	Poster only
Brandon	Farmer	University of Kentucky	Poster only
Kevin	Francis	Sanford Research	Poster only
Christy	Gliniak	UT Southwestern Medical Center	ECI
Paul	Huang	Washington University School of Medicine	RD ECI
Asahiq	Hussain	University of Alberta	ECI
Brittany	Johnson	UT Southwestern Medical Center	ECI
Sander	Kersten	Wageningen University	Poster only
Boa	Kim	University of Pennsylvania	ECI
Debby	Koonen	University Medical Center Groningen	DLW ECI
Pierce	Lewien	University of Colorado Denver Anschutz Medical Campus	ECI
Andrew	Libby	Georgetown University Medical Center	ECI
Pingsheng	Liu	Institute of Biophysics, Chinese Academy of Sciences	Poster only

Irfan	Lodhi	Washington University School of Medicine	DLW
Ailine Gisela	Lopez Manosalva	University of Groningen	ECI
Matthew	Mitsche	UT Southwestern Medical Center	RD ECI
Emilio	Mottillo	Henry Ford Hospital	RD
Michael	Nash	University of Colorado Denver Anschutz Medical Campus	ECI
Chase	Neumann	Cleveland Clinic Foundation	ECI
Vivek	Peche	Washington University in St Louis	ECI
David	Presby	University of Colorado Denver Anschutz Medical Campus	ECI
Li	Qiang	Columbia University	DLW ECI
Philip	Ruppert	Wageningen University	ECI
Isabel	Schlaepfer	University of Colorado Denver Anschutz Medical Campus	Poster only
Ivana	Semova	Boston Children's Hospital	ECI
Sze Kiat	Tan	University of Miami	ECI
Yuki	Tatenaka	Dojindo Molecular Technologies, Inc.	Poster only
Jacqueline	Turner	University of Colorado Denver Anschutz Medical Campus	ECI
Yang	Wang	UT Southwestern Medical Center	ECI
Katharine	Williams	Merck	Poster only

2018 Conference

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Warren	Anderson	University of Virginia	ECI
Noemi	Arias Rueda	Saint Louis University	ECI
Lara	Bou Khzam	New York University	ECI
Vincenza	Cifarelli	Washington University Medical School	RD
Ismail	Cimen	Cardiovascular Prevention, Klinikum der Universität München, Ludwig-Maximilians-University of Munich	ECI
David	Cistola	Texas Tech University Health Sciences Center El Paso	Poster Only
Hanna	Erickson	University of Illinois at Urbana-Champaign	ECI
Trent	Evans	Washington University in St. Louis	ECI
Sully	Fernandez	Univeristy of Penssylvania	ECI
Dalia	Gaddis	La Jolla Institute	Poster Only
Hector	Galvez	Salk Institute for Biological Studies	ECI
Itsaso	Garcia-Arcos	SUNY Downstate Medical Center	Poster Only
Jun	Guo	Shanghai Institute of Biochemistry and Cell Biology	ECI
Rebecca	Haeusler	Columbia University	DLW
Syed	Hamid	Cedars-Sinai Medical center	ECI
Shuaishuai	HU	Dublin Institute of technology	ECI
Shohei	Kohno	University of Colorado Denver	ECI
Sai Santosh Babu	Komakula	Rutgers, The State University of New Jersey	ECI
Alexandra	Kuhlmann	Yale University	ECI
Britta	Kumley	SUNY Downstate Medical Center	ECI
Andrew	Libby	University of Colorado Denver	ECI
Penn	McClatchey	Vanderbilt University	ECI
Michael	Nash	University of Colorado, Anschutz Medical Campus	ECI
Sunil	Nooti	University of Alabama at Birmingham	ECI
Cathy	O'Hare	Perspectum Diagnostics	Poster only
Babajide	Oluwadare	NYU Langone School of Medicine	ECI
Antwi-Boasiako	Oteng	Wageningen University	ECI
Lindsey	Padgett	La Jolla Institute for Allergy and Immunology	ECI

Vipulkumar	Patel	University of North Texas Health Science Center	ECI
Ariane	Pessentheiner	University of California, San Diego	ECI
Patrycja	Puchalska	University of Minnesota	ECI
Cyndya	Shibao	Vanderbilt University	Poster Only
Yuji	Shiozaki	University of Colorado-Denver	ECI
Taylor	Soderborg	University of Colorado Denver	ECI
Ian	Williams	Vanderbilt University	ECI
John	Winkler	University of British Columbia	ECI
Shihao	Xu	Yale University	ECI
Yanchao	Xu	UT Southwestern Medical Center	ECI
Risa	Yoshida	Tokushima University	ECI
Steven	Zhao	University of Pennsylvania	ECI

2017 Conference

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Anakk	Sayeepriyadarshini	University of Illinois Urbana-Champaign	DLW Runner Up
de Boer	Jan Freark	University Medical Center Groningen, University of Groningen	ECI
Devlin	Abigail Sloan	Harvard Medical School	RD Winner
Fu	Ting	Salk	ECI
Gliniak	Christy	Cleveland Clinic Lerner Research Institute	Poster Only
Gorkhali	Sachi	University of Colorado at Denver	ECI
Jacome Sosa	Miriam	Washington University in St. Louis	ECI
Kohno	Shohei	University of Colorado Denver	ECI
Koonen	Debby	University Medical Center Groningen	Poster Only
Kreznar	Julia	University of Wisconsin - Madison	ECI
Libby	Andrew	University of Colorado at Denver	ECI
Luo	Yuhuan	University of Colorado at Denver	ECI
Melchior	John	University of Cincinnati	ECI
Pathak	Preeti	NEOMED	ECI
Peterfy	Miklos	Western University	Poster Only
Qi	Bin	University of Colorado Boulder	Poster Only
Ranjit	Suman	University of California, Irvine	ECI
Schugar	Rebecca	Cleveland Clinic	Poster Only
Sedgeman	Leslie	Vanderbilt University	ECI
Semova	Ivana	Boston Children's Hospital	ECI
Shewale	Swapnil	University of Pennsylvania	ECI
Shiozaki	Yuji	University of Colorado at Denver	ECI
Soderborg	Taylor	University of Colorado Denver	ECI
Tarling	Elizabeth	University of California Los Angeles	DLW Winner
Thyagarajan	Baskaran	University of Wyoming	Poster Only
Traeger	Lindsay	University of Wisconsin Madison	ECI
Veldkamp	Kelsey	University of Wisconsin-Madison	ECI
Wang	Dong	University of Colorado at Denver	ECI
Varticovski	Lyuda	NIH	Poster Only

2016 Conference

Last Name	First Name	Company	Award
Allen	Ryan	Vanderbilt University Medical Center ***2016 Franz Simon Poster Winner**	ECI
Bruce	Kimberley	University of Colorado Denver	ECI
Chang	Hye Rim	New York University Medical Center	ECI
Choi	Joseph	Johns Hopkins University School of Medicine	Poster Only
Cistola	David	University of North Texas Health Science Center at Fort Worth	Poster Only
Deodhar	Sneha	University of North Texas Health Science Center at Fort Worth	Poster Only
Gaddis	Dalia	La Jolla Institute ***2016 Franz Simon Poster Winner**	ECI
Gonzalez-Baro	Maria	Universidad Nacional de La Plata	Poster Only
Gonzalez-Hurtado	Elsie	Johns Hopkins University School of Medicine	Poster Only
Guo	Yi	Mayo Clinic	Poster Only
Imi	Yukiko	University of Tokushima	Poster Only
Kaput	Kate	National Jewish Hospital/ESJH/SCL health	ECI
Lee	Jieun	Johns Hopkins University School of Medicine	ECI
Lei	Xia	Johns Hopkins University School of Medicine	ECI
Libby	Andrew	University of Colorado Denver	ECI
Little	Hannah	Johns Hopkins University School of Medicine	ECI
Liu	Xueqing	Intercept Pharmaceuticals, Inc.	Poster Only
Lodhi	Irfan	Washington University School of Medicine	RD
Lord	Caleb	UT Southwestern Medical Center	ECI
Michell	Danielle	Vanderbilt University Medical Center	ECI
Mishra	Ina	University of North Texas Health Science Center, Fort Worth	ECI
Palmisano	Brian	Vanderbilt University Medical Center	ECI
Patel	Vipulkumar	University of North Texas Health Science Center, Fort Worth	ECI

Peterfy	Miklos	Cedars-Sinai Medical Center	Poster Only
Pietka	Terri	Washington University School of Medicine	Poster Only
Ranjit	Suman	University of California, Irvine	ECI
Rasheed	Adil	University of Toronto	ECI
Rong	Shunxing	UT Southwestern Medical Center	ECI
Roteta	Leslie	Vanderbilt University	Poster Only
Santoro	Ylenia	University of California Irvine	ECI
Shiozaki	Yuji	University of Colorado Denver	ECI
Singh	Rajesh	Weill Cornell Medical College	ECI
Soderborg	Taylor	University of Colorado Denver	ECI
Spears	Larry	Washington University School of Medicine, St. Louis	ECI
Tan	Stefanie	Johns Hopkins University School of Medicine	ECI
Vallim	Thomas	UCLA	DLW
Villanueva	Claudio	University of Utah School of Medicine	Poster Only
Wang	Dong	University of Colorado Denver	ECI
Weinstock	Ada	New York University School of Medicine	ECI
Zhu	Lin	Vanderbilt University Medical Center	ECI

2015 Conference

Last Name	First Name	Company	Award
Abdullah	Laila	Roskamp Institute	ECI
Allen	Ryan	Vanderbilt University	ECI
Besenboeck	Carolin	Medical University of Graz	ECI
Bruce	Kimberley	University of Colorado	ECI
Chi	Xun	University of Iowa	ECI
Çimen	Ismail	Bilkent University	ECI
Das	Madhurima	Boston University School of Medicine	ECI
Day	Emily	McMaster University	ECI
Ehrhardt	Nicole	Cedars-Sinai Medical Center	Poster Only
Garcia-Arcos	Itsaso	Mount Sinai	ECI
Hsieh	Joanne	Columbia University	ECI
Hwang	Seonghwan	University of Texas Southwestern Medical Center	ECI
Liu	Minjing	Boston University School of Medicine	Poster Only
Jo	Uoungah	UT Southwestern medical center	ECI
Juliano	Rebecca	Amarin Pharma, Inc.	Poster Only
Jun	DongJae	UT Southwestern medical center	ECI
Kikuchi	Takuya	University of Tsukuba	ECI
Krysa	Jacqueline	University of Alberta	ECI
Luo	Yuhan	University of Colorado	ECI
Melchior	John	University of Cincinnati	ECI
Michell	Danielle	Vanderbilt University	ECI
Mitrofanova	Alla	University of Miami	ECI
Otis	Jessica	Carnegie Institution	Poster Only
Palmisano	Brian	Vanderbilt University *2015 Franz Simon Poster Winner	ECI
Pasha	Hamza	University of Colorado Anschutz Medical Campus	ECI
Razani	Babak	Washington University School of Medicine	DLW
Robinson	Michelle	UNT Health Science Center	Poster Only
Scerbo	Diego	Columbia University	ECI

Shewale	Swapnil	Wake Forest School of Medicine	ECI
Soderborg	Taylor	University of Colorado Denver	ECI
Steinacher	Daniel	Medical University of Vienna	ECI
Sungelo	Mitchell	University of Colorado Anschutz Medical Campus	ECI
Thierer	James	Carnegie Institution for Science	ECI
Vickers	Kasey	Vanderbilt Univ. School of Medicine	ECI
Westerterp	Marit	Columbia University	RD
Yu	Tian	University of Colorado Denver	ECI
Zhou	Liye	SUNY downstate medical center	ECI

2014 Poster Presentations	
Allen, Ryan	Vanderbilt University
Besenböck, Carolin	Medical University of Graz
Borja, Mark	Children's Hospital Oakland Research Institute
Chuang, Chia-Chi	Wake Forest School of Medicine
Cuffe, Helen	Wake Forest School of Medicine
Dummer, Patrick	NIH/NIDDK
Garcia-Arcos, Itsaso	Columbia University
Hong, Cynthia**	UCLA
Jay, Anthony	Boston University Medical Campus
Libby, Andrew	University of Colorado Denver
Liu, Jing	Columbia University
Masuda, Masashi	University of Colorado Denver
Mei, Xiaohu	Boston University Medical Campus
Melchior, John	University of Cincinnati
Pajvani, Utpal*	Columbia University
Palmisano, Brian	Vanderbilt *2014 Franz Simon Poster Winner
Pedigo, Christopher	University of Miami Miller School of Medicine
Pitts, Reynaria	University of Colorado Denver
Pijut, Sonya#	University of Kentucky
Pollard, Ricquita	Wake Forest School of Medicine
Robinson, Michelle	University of North Texas Health Science Center
Schlaepfer, Isabel	University of Colorado Denver
Seldin, Marcus	University of California Los Angeles
Serkova, Natalie	University of Colorado Denver
Shewale, Swapnil	Wake Forest School of Medicine
Sungelo, Mitchell	University of Colorado Denver
Vickers, Kasey*	Vanderbilt University School of Medicine
Warrier, Manya	Cleveland Clinic Lerner Research Institute
Weckerle, Allison	Wake Forest School of Medicine
Westerterp, Marit	Columbia University

***Winner – David L. Williams Lectureship and Award – tied**

Winner – **Roger Davis Investigator Award for Transitional Faculty

#Poster Presentation Only – Not selected for ECI Award

2013 Award Winners *Winner – David L. Williams Lectureship and Award **Winner - Roger Davis Investigator Award for Transitional Faculty	
Allen, Ryan	Saint Louis University
Andres, Allen	San Diego State University
Baldan, Angel*	**Saint Louis University**
Chen, Elaine	Baylor College of Medicine
Civelek, Mete	University of California Los Angeles
Cuffe, Helen	Wake Forest University
Depner, Christopher	Oregon State University
Ding, Shiying	Boston University School of Medicine
Faulkner, Rebecca	UT Southwestern Medical Center
Funai, Katsuhiko	Washington University
Goedeke, Leigh	NYU School of Medicine
Guo, Yi	Mayo Clinic
Kim, Hyeonwoo	UT Southwestern Medical Center
Kim, YounKyung	Rutgers University
King, Martina	University of Colorado Anschutz Medical Campus
Koliwad, Suneil	University of California San Francisco
Langhi, Cedric	Saint Louis University
Lee, Han	Mayo Graduate School
Lian, Jihong	University of Alberta
Liu, Mingxia	Wake Forest University
Marquart, Tyler	Saint Louis University
Masuda, Masashi	University of Colorado Anschutz Medical Campus
Meyers, Nathan	Boston University
Morris, Lindsey	UT Southwestern Medical Center
Ota, Asuka	Stanford University
Pellinen, Jacob	University of Colorado Anschutz Medical Campus
Rai, Priyanka	Tata Institute of Fundamental Research
Ramirez, Cristina	New York University
Razani, Babak**	**Washington University School of Medicine**
Robblee, Megan	University of California, San Francisco
Stafford, John	Vanderbilt University School of Medicine
Thomas, Gwyn	Wake Forest University
Tsai, Luke TH	Baylor College of Medicine
Wang, Yan	UT Southwestern Medical Center
Wang, Xiaoxin	University of Colorado Anschutz Medical Campus
Wei, Hao	University of Washington

2012 Award Winners *Winner – David L. Williams Lectureship and Award **Winner - Roger Davis Investigator Award for Transitional Faculty	
†Bennett, Brian	University of North Carolina, Chapel Hill
Bi, Xin	Wake Forest University School of Medicine
***Brown, J. Mark**	**Wake Forest University School of Medicine**
Chen, Jenny	University of California, Los Angeles
Chong, Brandi	University of Colorado Denver
Civelek, Mete	University of California, Los Angeles
Cox-York, Kimberly	Colorado State University
Csaki, Lauren	University of California, Los Angeles
Ehrhardt, Nicole	Cedars Sinai Medical Center
Erbilgin, Ayça	University of California, Los Angeles
Gao, Feng	Children's Hospital Oakland Research Institute
Giral, Hector	University of Colorado Denver
Hahm, Bumsuk	University of Missouri, Columbia
Hasin, Yehudit	University of California, Los Angeles
Huang, Yiqi	University of Virginia
Martin, Lisa	University of California, Los Angeles
Masuda, Masashi	University of Colorado Denver
Maury, Eleonore	Northwestern University
Mei, Xiaohu	Boston University School of Medicine
Mitsche, Matt	UT Southwestern Medical Center
Parks, Brian	University of California, Los Angeles
Psychogios, Nikolaos	Massachusetts General Hospital
Qiu, Liru	University of Colorado Denver
Rau, Christoph	University of California, Los Angeles
†Razani, Babak	Washington University School of Medicine
****Schlegel, Amnon**	**University of Utah School of Medicine**
Smathers, Rebecca	University of Colorado Denver
‡Staffford, John	Vanderbilt University School of Medicine
Suhalim, Jeffrey	University of California, Irvine
Trent, Chad	Columbia University
†Wang, Hong	University of Colorado Denver
Wang, Jessica	University of California, Los Angeles
Wang, Xiaoxin	University of Colorado Denver
Yu, Tian	University of Colorado Denver
Yu, Chi-Yi	Children's Hospital Oakland Research Institute

2011 Award Winners *Winner – David L. Williams Lectureship and Award **Winner - Roger Davis Investigator Award for Transitional Faculty	
Andres, Allen	San Diego State University
Bedoya, Candy	Cedars-Sinai Medical Center
Bennett, Brian	University of California, Los Angeles
****Biddinger, Sudha**	**Children's Hospital of Boston**
Chong, Brandi	University of Colorado Anschutz Medical Campus
Crawford, Peter	Washington University
Huang, Yongcheng	UT Southwestern Medical Center and HHMI
Jun, Dong-Jae	UT Southwestern Medical Center
Lian, Jihong	University of Alberta
Makowski, Liza	University of North Carolina
Marshall, Stephanie	Wake Forest School of Medicine
Masuda, Masashi	University of Colorado Anschutz Medical Campus
McDaniel, Allison	Wake Forest University School of Medicine
Melchior, John	Wake Forest University School of Medicine
Meyers, Nathan	Boston University
Mitsche, Matthew	Boston University
Miyazaki, Makoto	University of Colorado Anschutz Medical Campus
***Moschetta, Antonio**	**Consorzio Mario Negri Sud, Chieti, Italy**
Park, Tae-Sik	Gachon University
Rehrer, Charles	University of Colorado Anschutz Medical Campus
Schlaepfer, Isabel	University of Colorado Anschutz Medical Campus
Schlegel, Amnon	University of Utah
Stafford, John	Vanderbilt University
Wahlig, Jessica	University of Colorado Anschutz Medical Campus
Wang, Chen-Yu	University of Wisconsin Madison
Wang, Hong	University of Colorado Anschutz Medical Campus
Wang, Yan	UT Southwestern Medical Center and HHMI

2010 Award Winners *Winner – David L. Williams Lectureship and Award **Winner - Roger Davis Investigator Award for Transitional Faculty	
Abi Mosleh, Lina	UT Southwestern Medical Center
Brown, J. Mark	Wake Forest University School of Medicine
Caldas, Yupanqui	University of Colorado, Denver
Cortes, Victor	UT Southwestern Medical Center
***Fernandez-Hernando, Carlos**	**New York University School of Medicine**
Jia, Lin	Wake Forest University School of Medicine
Lord, Caleb	Wake Forest University School of Medicine
Miyazaki, Makoto	University of Colorado, Denver
Mutungi, Gisella	UT Southwestern Medical Center
Nagareddy, Prabhakara	Columbia University
Rong, Shunxing	Wake Forest University School of Medicine
Sampey, Brante	University of North Carolina at Chapel Hill
Stafford, John	Vanderbilt University Medical Center
Umetani, Michi	UT Southwestern Medical Center
Wang, Hong	University of Colorado, Denver
Wang, Xiaoxin	University of Colorado, Denver
Wei, Xiaochao	Washington University, St. Louis
****Yvan-Charvet, Laurent**	**Columbia University**

2009 Award Winners *Winner – David L. Williams Lectureship and Award **Winner - Roger Davis Investigator Award for Transitional Faculty	
Altman, Robin	University of California, Davis
Badman, Michael	**Beth Israel Deaconess Medical Center**, Harvard
Bennett, Brian	University of California, Los Angeles
****Brown, J. Mark**	**Wake Forest University School of Medicine**
Choudhury, Mahua	University of Colorado Denver
Dwyer, Jenn	University of California, Los Angeles
Erbay, Ebru	Harvard School of Public Health
***Finck, Brian**	**Washington University School of Medicine**
Gao, Xuan	Boston University
Giles, Erin	University of Colorado Denver
Guan, Hong-Ping	UT Southwestern Medical Center
Haeusler, Rebecca	Columbia University
He, Shaoqing	UT Southwestern Medical Center
Hiyama, Yaeko	Columbia University
Jia, Lin	Wake Forest University School of Medicine
Jo, Youngah	UT Southwestern Medical Center
Liu, Jingjing	University of Kentucky
Liu, Yuhang	Boston University Dept of Physiology and Biophysics
Nguyen, Andrew	UT Southwestern Medical Center
Patel, Monika	University of Toronto
Potthoff, Matthew	UT Southwestern Medical Center
Schlaepfer, Isabel	University of Colorado Denver
Thomas, Tiffany	Columbia University
Wilhelm, Ashley	Wake Forest University Health Sciences

2008 Award Winners *Winner – David L. Williams Lectureship and Award		
Barish	Grant	The Salk Institute for Biological Studies
Brown	Jonathan	Wake Forest University
Chung	Soonkyu	Wake Forest University
Cortés	Víctor	UT Southwestern Medical Center
Das	Akash	Wake Forest University
Erbay	Ebru	Harvard University
Haller	Jorge	Boston University
Kang	Kihwa	Harvard School of Public Health
Karasinska	Joanna	University of Toronto
Koliwad	Suneil	University of California San Francisco
Lee	Joon	UT Southwestern Medical Center
Lee	Jung-Ting	University of Washington
Makowski	Liza	Duke University
***Muoio**	**Deborah**	**Duke University Medical Center**
Orozco	Luz	University of California, Los Angeles
Rodriguez-Agudo	Daniel	MCV/VA Medical Center
Ruggles	Kelly	Columbia Univeristy
Steig	Amy	University of Colorado Denver
Stob	Nicole	University of Colorado Denver
Wu	Sulin	University of California, Los Angeles

2007 Award Winners *Winner – David L. Williams Lectureship and Award		
Andres	Allen	San Diego State University
Badman	Michael	Beth Israel Deaconess Medical Center Boston
Bell	Thomas	Wake Forest University School of Medicine
Brown	Jonathan	Wake Forest University School of Medicine
Chung	Soonkyu	Wake Forest University School of Medicine
Davies	Brandon	University of California Los Angeles
Donkor	Jimmy	David Geffen School of Medicine at UCLA
Finck	Brian	Washington University School of Medicine
***Furuhashi**	**Masato**	**Harvard University Boston**
Graf	Gregory	University of Kentucky Lexington
Grefhorst	Aldo	UT Southwestern Medical Center
Hoofnagle	Andrew	University of Washington Seattle
Makowski	Liza	Duke University Durham
McNutt	Mark	UT Southwestern Medical Center
Mittendorfer	Bettina	Washington University School of Medicine
Moon	Young-Ah	UT Southwestern Medical Center
Mulya	Anny	Wake Forest University School of Medicine
Mungrue	Imran	University of California Los Angeles
Rodriguez-Agudo	Daniel	MCV/VA Medical Center Richmond
Romeo	Stefano	UT Southwestern Medical Center
Schauer	Irene	University of Colorado Health Sciences Center
Senokuchi	Takafumi	Columbia University New York
Shechtman	Caryn	Columbia University New York
Temel	Ryan	Wake Forest University School of Medicine
Wang	Hong	University of Colorado Health Sciences Center
Yu	Liqing	Wake Forest University School of Medicine
Zhu	Xuewei	Wake Forest University School of Medicine

2006 Award Winners *Winner – David L. Williams Lectureship and Award		
Flowers	Matthew	University of Wisconsin-Madison
González Baró	Maria	University of La Plata, Argentina
Kublaoui	Bassil	UT Southwestern Medical Center
Liang	Guosheng	UT Southwestern Medical Center
MacLean	Paul	University of Colorado Health Science Ctr
Petrovan	Ramona	The Scripps Research Inst
Qadri	Ishtiaq	University of Colorado Health Sciences Ctr
Seimon	Tracie	Columbia University
Stob	Nicole	University of Colorado at Boulder
Vergnes	Laurent	UCLA
Wolfgang	Michael	Johns Hopkins University
Yang	Jian	University of South Alabama
***Yu**	**Liqing**	**Wake Forest University**