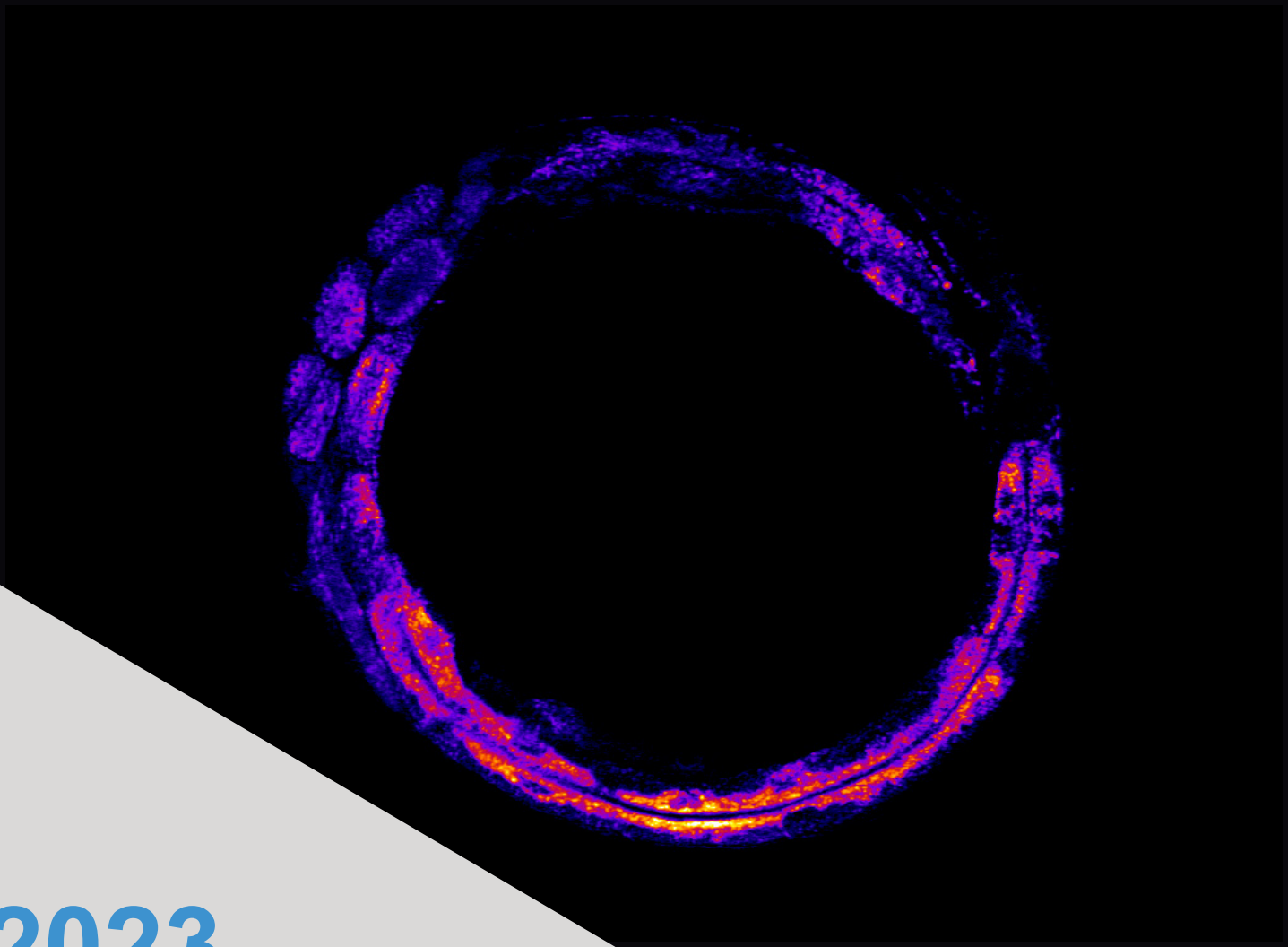

2023 KERN LIPID CONFERENCE

“Lipids in Aging, Lifespan and Aging-Associated Diseases”

ORGANIZERS:
Zoltan Arany, MD, PhD
Ebru Erbay, MD, PhD
Morgan Levine, PhD

August 14-16, 2023
Manor Vail Lodge

KLC

@KernLipid

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FThree Foundation

Cover Image Caption: "Worm Lipid" - Meng Wang, PhD, Howard Hughes Medical Institute-Janelia Research Campus - USA

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Fred Kern, Jr., M.D. (1918-1997)

Fred Kern, Jr. was graduated from the University of Alabama in 1939, and from Columbia University, College of Physicians & Surgeons, where he received his medical degree in 1943. After serving in the Medical Corps of the U. S. Army, he became a fellow at Cornell Medical College.

In 1952, Fred and his wife Bernie moved to Colorado, where Fred became Professor of Medicine and Chief of Gastroenterology at the University of Colorado Denver. Dr. Kern helped train generations of academic gastroenterologists who went on to teach at medical schools and research institutes in the United States, Canada, Australia, and Chile. A distinguished researcher himself, 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, thirty-one chapters in clinical textbooks, and more than two hundred 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 first organized in 1977 by Fred Kern, Jr. and Rolla Hill. After a few meetings, Dr. Kern restructured the conference with the assistance of Drs. Scott Grundy and Roger Davis. Fred's wife, Bernie, played a significant role in the development of the Aspen Lipid Conference as its first coordinator. The meetings became a yearly event in 1987 at the Given Institute of Pathobiology in Aspen. In 2011, the conference was moved to Vail, Colorado. After Dr. Kern's death in 1997, the Board of Directors voted to rename the conference in his honor, and it is now known as the Kern Lipid Conference.

Fred Kern, Jr. will always be remembered as a warm, intellectually challenging, and wise person whose dedication to bridging significant scientific achievements and clinical research served as the predominant basis for the development of this conference.

Franz Simon, M.D. (1936 – 2012)

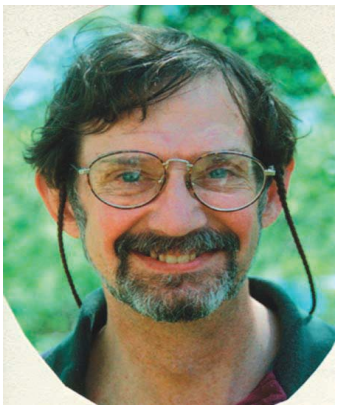
Franz Simon's essential passion was the world of scientific inquiry. He approached research with good humor and sportsmanship. His involvement with the Kern Lipid Conference stemmed from his primary commitment to young investigators, his belief in collaborative science, and his fascination with membrane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

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

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

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

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



David L. Williams, Ph.D.
(1946-2004)

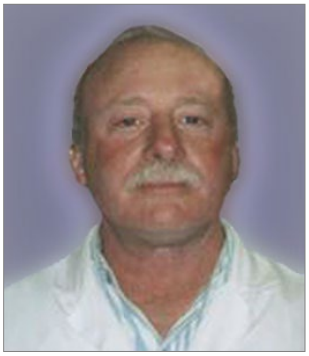
Born and raised in Pennsylvania, David Williams attended the University of California, Berkeley, and was graduated with a Bachelor of Arts degree in Zoology in 1967. He pursued further studies at Jack Gorski's laboratory at the University of Illinois and obtained his PhD with nine publications to his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

Previous Conference Titles and Kern Lecturers

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"

2023 Kern Lipid Conference

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

Monday, August 14, 2023 – Wednesday, August 16, 2023

Manor Vail Lodge, Vail, Colorado

Organizers:

Zoltan Arany, MD, PhD, University of Pennsylvania

Ebru Erbay, MD, PhD, Altos Labs

Morgan Levine, PhD, Altos Labs

Monday, August 14, 2023	
7-10am	**Breakfast** *Mt Powell* - Guest breakfast served daily from 7am-10am
Conference Check-In	
7:15-8:15am	**Conference Check-In** *Check-in is in the **boardroom**, across from the Piney Mountain Meeting Room.*
Opening Kern Lecturer Location: Piney Mountain Meeting Room	
8:15am	**Welcome Remarks & Opening Kern Lecturer Introduction** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University – USA
8:25am	**Opening Kern Lecture: "Lipid homeostasis and aging"** Anne Brunet, PhD, Stanford University - USA
Session 1: Droplets, Lipophagy and Aging Session Chair: Morgan Levine, PhD Session Co-chairs: Katharina Papsdorf, PhD, Stanford University & Debajyoti Das, PhD, University of California Los Angeles **Location: Piney Mountain Meeting Room**	
9:15am	**"Extracellular mitochondria in inter-organ signaling"** Clair Crewe, PhD, Washington University School of Medicine - USA
9:55am	**"Selective autophagy regulates fate of lipid droplets"** Susmita Kaushik, PhD, Albert Einstein College of Medicine - USA
10:35am	**Morning Break**
10:55am	*Cytek Biosciences-sponsored talk:* **"Cell-to-cell transfer of mitochondria in adipose tissues in obesity and aging"** Jonathan R. Brestoff, MD, PhD, Washington University School of Medicine – USA
11:15am	**"The Phase of Fat: The Biology of Cellular Lipid Storage"** Tobias Walther, PhD, Sloan Kettering Institute - USA
11:55am	*Nanolive-sponsored talk:* **"Label-free visualization and quantification of lipid droplet dynamics with Nanolive imaging"** Mathieu Frechin, PhD, Nanolive - Switzerland
12:10pm	**Lunch**

	Mount Powell
1:10-3:35pm	**Afternoon Break**
Session 2: Membrane Lipids in Aging Session Chair: Moshe Levi, MD Session Co-chairs: Christy Gliniak, PhD, University of Texas Southwestern Medical Center & Roxan Stephenson, PhD, National Institutes of Health **Location: Piney Mountain Meeting Room**	
3:35pm	**"Chemical Biology and Lipidomics Characterization of Functional Lipids"** Alan Saghatelian, PhD, Salk Institute - USA
4:15pm	**"Role of aging in shaping cell structure and function"** Dorota Skowronska-Krawczyk, PhD, University of California-Irvine - USA
4:55pm	**"Apolipoproteins in Aging and Neurodegeneration"** Zachary Levine, PhD, Altos Labs - USA
5:35pm	**"Obesity driven NAFLD-NASH in liver regeneration and aging"** Carlos Fernandez-Hernando, PhD, Yale University - USA
6:15-8:00pm	**Poster Session and Reception *cosponsored by LUCA Science Inc.& Lipotype Inc.*** *Notch and Mt Powell*
Tuesday, August 15, 2023	
7-10am	**Breakfast** *Mt Powell*
Session 3: Lipidomics, Genomics, Epigenomics in Aging Session Chair: Zoltan Arany, MD, PhD Session Co-chairs: Alessandra Ferrari, PhD, UCLA & Aleepta Guha Ray, PhD, University of Chicago **Location: Piney Mountain Meeting Room**	
8am	**"The interplay between circadian clocks and metabolism"** Gad Asher, MD, PhD, Weizmann Institute of Science - Israel
8:40am	**"Interpreting trajectories in feature space to extract biological time: Exploring lipid clocks of ageing"** Jan Gruber, DPhil, Yale-NUS - Singapore
9:20am	**"DNA methylation Biomarkers of Aging"** Morgan Levine, PhD, Altos Labs - USA
10am	**Morning Break**
10:30am	**"Role of Ribosome Heterogeneity in Regulating Aging"** Eric Greer, PhD, Washington University in St. Louis - USA
11:10am	**"Connecting the lipid universe to aging through big data and machine learning"** Max Unfried, PhD Candidate, National University of Singapore - Singapore
11:50am	*Columbus Instruments-sponsored talk:* **"Clambake: decoding metabolic cage data to derive components of energy expenditure"** Jonathan R. Brestoff, MD, PhD, Washington University School of Medicine – USA
12pm	**Introduction and Presentation of the Roger Davis Award Lecture *sponsored by Lipotype Inc.*** Robert H. Eckel, MD, University of Colorado Anschutz Medical Campus – USA
12:05pm	**Roger Davis Award Lecture *sponsored by Lipotype Inc.:* "Aberrant Lipid Metabolism Pinpoints Rational Parkinson's Disease Therapeutic Targets and Strategies"** Saranna Fanning, PhD, Harvard Medical School & Brigham & Women's Hospital - USA

12:30pm	**Lunch** *Mount Powell*
1:30pm	**Afternoon Break**
Wednesday, August 16, 2023	
7-10am	**Breakfast** *Mt Powell*
Session 4: Lipid Metabolism and Lipid Signaling in Aging Session Chairs: Ebru Erbay, MD, PhD & Robert H. Eckel, MD Session Co-chairs: Rachel Hohe, PhD Candidate, Cleveland Clinic/Case Western Reserve University & Angelina Holcom, PhD, University of Southern California/Buck Institute for Research on Aging & John Moley, BA, Washington University School of Medicine in St. Louis **Location: Piney Mountain Meeting Room**	
8:30am	**Presentation of the Franz Simon Poster Award *sponsored by Cayman Chemical* – Recipient To be Announced** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University – USA
8:40am	**"Lysosomal Lipid Signaling in Longevity Regulation"** Meng Wang, PhD, Howard Hughes Medical Institute-Janelia Research Campus - USA
9:20am	**"The role of endoplasmic reticulum architecture in metabolic homeostasis and disease"** Ana Paula Arruda, PhD, University of California-Berkeley - USA
10:00am	**"Turning the Oxygen and Vitamin Dials"** Isha Jain, PhD, University of California-San Francisco - USA
10:40am	**Morning Break**
11:00am	**"Correcting Endolysosomal Dysfunction and Autophagy in Alzheimer's disease - The Role of ApoE"** Joachim Herz, MD, UTSW - USA
11:40am	**Introduction and Presentation of the David L. Williams Lecture & Award *sponsored by AMSBIO*** Roger Newton, PhD, Espervita Therapeutics - USA
11:45am	**David L. Williams Lecture & Award *sponsored by AMSBIO:* "Visualizing lipid metabolic activities in brain during aging processes"** Lingyan Shi, PhD, University of California-San Diego – USA
12:15pm	**Lunch** *Mount Powell*
1:25pm	**"Oligodendrocyte lipid dysregulation in Alzheimer's disease"** Leyla Akay, PhD Candidate, MIT - USA
1:45pm	*GemPharmatech-sponsored talk:* **"Building Real-World Models and Enhanced Preclinical Service Capabilities"** Zhiying Li, PhD, GemPharmatech LLC - USA
2:10pm	**"Modulating metabolic pathways – impact on disease states"** Zhidan Wu, PhD, Pfizer - USA
Closing Kern Lecturer Location: Piney Mountain Meeting Room	
2:50pm	**Closing Remarks & Closing Kern Lecturer Introduction** Moshe Levi, MD, President, Kern Lipid Conference, Georgetown University – USA

3:00pm	**Closing Kern Lecture: "Imaging Interacting Organelles to Understand Metabolic Homeostasis"** Jennifer Lippincott-Schwartz, PhD, Howard Hughes Medical Institute-Janelia Research Campus - USA
3:50pm	**Afternoon Break**
Final Night Dinner & Dancing	
6-8pm	**Cocktail Reception & Dinner** - *Golden Peak Gardens* *(Cocktails and Dinner will be outside, weather permitting. Colorado evenings tend to be cool after sunset, please bring a jacket/sweater)*
8-10pm	**Music & Dancing –** *Ridge & River*

2023 Kern Lecturers

Anne Brunet, PhD is the Michele and Timothy Barakett Professor of Genetics at Stanford University School of Medicine and the Co-director of the Paul F. Glenn Laboratories for the Biology of Aging at Stanford University. Dr. Brunet obtained her B.Sc. from the Ecole Normale Supérieure in Paris and her Ph.D. from the University of Nice, France. She did her postdoctoral training with Dr. Michael Greenberg at Harvard Medical School. Dr. Brunet is interested in the molecular mechanisms of aging and longevity. Dr. Brunet's laboratory has developed an original line of investigation to understand aging based on the integration of model organisms with diverse lifespans – worms, fish, and mice. Using the worm *Caenorhabditis elegans*, the Brunet lab has identified pathways involved in delaying aging in response to external stimuli such as availability of nutrients and availability of the opposite sex. She made the exciting discoveries that lifespan extension can be regulated by chromatin modifiers and inherited in a transgenerational epigenetic manner. Her lab also uses mouse models to address complex questions about mammalian aging, notably mechanisms regulating neural stem cell aging. Importantly, the Brunet lab has pioneered the naturally short-lived African killifish as a new model to identify principles underlying aging and 'suspended animation'. Dr. Brunet has published over 100 peer-reviewed papers and reviews. She has received several awards, including the Pfizer/AFAR Innovation in Aging Research Award and the Vincent Cristofalo "Rising Star" Award in Aging Research. She received a Pioneer Award and a Transformative Award from the NIH Director's fund, which supports scientists who propose pioneering and transforming approaches to major challenges in biomedical research. In 2022, together with Dr. Andrew Dillin, she received the Lurie Prize in Biomedical Sciences.

Dr. Jennifer Lippincott-Schwartz is a Senior Group Leader at the Howard Hughes Medical Institute's Janelia Research Campus. She has pioneered the use of green fluorescent protein technology for quantitative analysis and modelling of intracellular protein traffic and organelle dynamics in live cells and embryos. Her innovative techniques to label, image, quantify and model specific live cell protein populations and track their fate have provided vital tools used throughout the research community. Her own findings using these techniques have reshaped thinking about the biogenesis, function, targeting, and maintenance of various subcellular organelles and macromolecular complexes and their crosstalk with regulators of the cell cycle, metabolism, aging, and cell fate determination. She is an elected member of the National Academy of Sciences, the National Academy of Medicine, the American Society of Arts and Sciences and the European Molecular Biology Organization. She is also a Fellow of The Biophysical Society, The Royal Microscopical Society and The American Society of Cell Biology. Her awards include the E.B. Wilson Medal of the American Society of Cell Biology, the Newcomb Cleveland Prize of the American Association for the Advancement of Science, the Van Deenen Medal, the Keith Porter Award of the American Society of Cell Biology, the Feodor Lynen Medal, and the Feulgen Prize of the Society of Histochemistry. She co-authored of the textbook "Cell Biology" with Tom Pollard and Bill Earnshaw and was President of the American Society of Cell Biology. Dr. Lippincott-Schwartz attended Swarthmore College, received her MS from Stanford University, and obtained her PhD in Biochemistry from Johns Hopkins University in 1986.

2023 Awards

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

Previous Award Recipients

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
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

First Name	Last Name	Company	Award
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

Last Name	First Name	Company	Award
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**

2023 Abstracts and Posters

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44	Das, Debajyoti	Identifying the selective lipophagy receptor for lipid droplet turnover in liver	University of California Los Angeles	A-3
45	Ferrari, Alessandra	Aster proteins facilitate dietary cholesterol uptake by mediating non vesicular transport in enterocytes	UCLA	A-4
46	Gliniak, Christy	Adipose tissue derived FGF21 improves healthspan and lifespan of obese male mice and is potentiated by the ablation of adiponectin	University of Texas Southwestern Medical Center	A-5
47	Guha Ray, Aleepta	Immune Cell Dynamics During Weight Cycling in Obese Mice	University of Chicago	A-6
48	Hermosilla Aguayo, Viviana	Malfunctioning of the ESCRT machinery leads to abnormal lipid synthesis and storage in embryonic development	University of California San Francisco	A-7
49	Hohe, Rachel	Macrophage Cholesterol Homeostasis and Inflammation Shaped by ASTER-C	Cleveland Clinic, Case Western Reserve University	A-8
50	Holcom, Angelina	Simultaneous neuronal expression of human amyloid-β and Tau genes drives global phenotypic and metabolomic changes in C. elegans	University of Southern California/Buck Institute for Research on Aging	A-9

51	Mahen, Kala	Activation of host receptor Taar5 plays a role in hypothalamic control of cold induced thermogenesis, eating behaviors, and circadian regulation	Cleveland Clinic	A-10
52	Massey, William	The 17:0 product of Bacterial Cyclopropane Fatty Acid Synthase Modulates Inflammatory Responses via IL-15 and IL-27p28/IL-30	Cleveland Clinic - Lerner Research Institute	A-11
53	Moley, John	Crosstalk Between the Microbiome and Rubicon Regulates Energy Homeostasis to Determine Susceptibility to Obesity with Age	Washington University School of Medicine in St. louis	A-12
54-55	Monroe, Blake	Electrophilic Lipid Peroxidation Products Effect Carbonyl Stress, Mitochondrial Dysfunction, and Cellular Senescence: Implications for Adipose Senescence in Aging and Obesity	University of Minnesota Twin Cities	A-13
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57-58	Murray, Christopher	Exploring the functional landscape of lipid metabolism in non-small cell lung cancer	Salk Institute for Biological Studies	A-15
59	Ojo, Oluwatomilayo	The uniqueness of different epicardial adipose depots and their contributions to cardiovascular diseases.	The University of Chicago	A-16
60	Pacheco Sanchez, Gabriela	Race-associated differences in the relationship between lipids and inflammatory markers in Type 2 Diabetes	University of California, Irvine	A-17
61	Pandey, Gautam	Liver regulatory variants provide insight into the molecular basis of aging-related lipid disorders	University of North Carolina at Chapel Hill	A-18
62	Papsdorf, Katharina	Lipid droplets and peroxisomes are co-regulated to drive lifespan extension in response to mono-unsaturated fatty acids	Stanford University	A-19

63	Price, Tara	Quantitative Trait Loci (QTL) analysis in a genetically diverse mouse model identifies Asah2 as a novel driver of lipoprotein subclasses	University of Wisconsin-Madison	A-20
64	Stephenson, Roxan	Understanding the relationship between lipid dysregulation and Alzheimer's disease risk	National Institutes of Health	A-21
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66-67	Tom, Emily	Essential role of ELOVL2 in maintenance of lipid homeostasis and RPE phagocytosis in retina	University of California, Irvine	A-23
68	Townsend, Logan	Adrenergic activity drives anxiety-like behavior through adipose tissue lipolysis dependent induction of GDF15	McMaster University	A-24
69	Turner, Jacqueline	Lysophosphatidic acid is a lipid-regulated immune checkpoint	University of Colorado Anschutz School of Medicine	A-25
70	Von Bank, Helaina	Regulation of extracellular acylcarnitine uptake and function by the carnitine transporter OCTN2	University of Wisconsin-Madison	A-26
71	Wartchow, Krista	Dysregulated Lipid Metabolism and ACSL6 Expression in Alzheimer's Disease: Insights from Spatial Lipidomic and Transcriptomic Analysis in a Mouse Model	Weill Cornell Medicine	A-27
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74	Guo, Zhen	Intact lysosomal lipolysis is required to suppress muscle catabolism	Washington University School of Medicine in St. Louis	P-1
75-76	Helsley, Robert	Deletion of Carnitine Palmitoyltransferase 1a from the Liver Reduces Hepatic Polyunsaturated Fatty Acids and Drives Microvesicular Steatosis in Female Mice	University of Kentucky	P-2
77	Mottillo, Emilio	Real-Time imaging of long-chain acyl-CoAs reveals a metabolic synapse in brown adipocytes and allosteric regulation of AMPK in white adipocytes	Henry Ford Hospital	P-3
78	Shi, Lingyan	Visualizing lipid metabolic activities in brain during aging processes	University of California-San Diego	NA
79	Sprenger, Kayla	Elucidating the role of TREM2/ApoE interactions in microglial activation and Alzheimer's disease with molecular simulations	University of Colorado Boulder	NA
80	Tsuji, Tadataka	Lipokines secreted from brown fat of long-lived mice regulate hepatic pathologies and metabolic abnormalities in obesity	Joslin Diabetes Center, Harvard Medical School	P-4
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81	Berry, Daniel	Age-dependent Pdgfr signaling drives adipocyte progenitor dysfunction to alter the beige adipogenic niche in male mice	Cornell University	P-5
82	Burstein, Ezra	An enteroendocrine-microbial axis in the large intestine controls host metabolism	University of Texas Southwestern Medical Center	NA
83	Keller, Amy	Perivascular adipose tissue remodeling modulates vascular mitochondrial metabolism	University of Colorado Anschutz Medical Campus/RMR	NA

			VA Medical Center	
84	Levi, Moshe & Jones, Bryce	Farnesoid X receptor agonism prevents neutrophil extracellular traps via reduced sphingosine-1-phosphate in chronic kidney disease	Georgetown University	NA
85	Malhi, Harmeet	Deletion of Sphingosine 1-Phosphate Receptor 1 in Myeloid Cells Attenuates Murine Metabolic Dysfunction-Associated Steatohepatitis	Mayo Clinic	P-6
86-87	Martinez-Lopez, Nuria	Paradoxical activation of mTORC2 during fasting regulates mitochondrial fission and fat metabolism.	University of California, Los Angeles	P-7
88	McIntire, Laura Beth	Endogenous nanoparticle dysregulation in Alzheimer's disease	Weill Cornell Medicine	NA
89	Mitsche, Matthew	Mboat7 Deletion Results in Dysfunction Mitochondria	University of Texas Southwestern Medical Center	P-8
90	Pepkowitz, Samuel	25-Hydroxy Vitamin D Insufficiency is Associated with Increased Serum Vitamin D Binding Protein	Cedars-Sinai Health System	NA
91	Unfried, Maximilian	Connecting the Lipid Universe to Aging and Disease through Big Data and Deep Learning	National University of Singapore	NA
Industry				
92	Fréchin, Mathieu & Johnson, Justine & Thyberg, Noah	Label-free visualization and quantification of lipid droplet dynamics with Nanolive imaging	Nanolive	NA
93	Johnson, Justine & Thyberg, Noah & Fréchin, Mathieu	Label-free visualization and quantification of lipid droplets to monitor drug effects on cellular phenotype	Nanolive	P-9
94	Labbé, Katherine	Specific activation of the integrated stress response	Calico Life Sciences	P-10

		uncovers novel regulation of central carbon metabolism and lipid droplet biogenesis		
95	Li, Zhiying & Moore, Kelsey	Characterization of B6-Chr1YP1: a Chromosome 1 Substitution Mouse Line as a Novel Model for Metabolic Syndrome by Phenotypic Screening	GemPharmatech LLC	P-11
96	Moss, Frank	Structural Roles for Polyunsaturated Lipids in Organelle Membranes	Altos Labs	P-12
97	Peloquin, Matt	High fat diet feeding leads to an increase in lipid species associated with metabolic dysfunction in dogs	Cellular Longevity Inc., dba Loyal	P-13

B cell subsets promote inflammation and metabolic dysfunction in aged visceral white adipose tissue during endotoxemia and sepsis.

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Sepsis is a life-threatening, systemic response to infection and is 13-times more likely to occur in individuals over 65, leading to hospitalization, increased mortality, and chronic repercussions. Immunosenescence, the simultaneous increase in low grade chronic inflammation and the decline of the immune response during aging, contributes to this increased susceptibility in older individuals. Visceral white adipose tissue (vWAT), a reservoir for aged immune cells, exhibits enhanced cellular recruitment and activation during metabolic diseases and aging. Immune cells restrict stimulated lipolysis in vWAT that is required for a productive inflammatory response in young mice; however, how these pathways interact during aging is unknown. Here we investigated the contribution of adipose B cell subsets to metabolic dysfunction and inflammation during endotoxemia and sepsis in old vWAT. vWAT from old mice exhibited exacerbated inflammation, including increased *Il6* and *Il1β*, and reduced CD69 expression in vWAT-resident B cells during endotoxemia and sepsis. Bacterial challenges also induced activation of the adipocyte lipase pathway, which peaked at four hours post-challenge in young mice but was completely ablated in vWAT from old mice. Life-long deficiency of B1 and B2 B cell subsets improved the homeostatic balance of immune cells within vWAT microenvironment, resulting in improved responses to endotoxemia, including increased pHSL and reduced *Tnfa* in vWAT in 20-month-old mice. In contrast, acute B2 B cell depletion was not sufficient to increase LPS-induced lipolysis or reduce inflammatory cytokines in vWAT from old mice, suggesting a role for B1 cells. B1 B cells from young and old vWAT, but not secondary lymphoid organs, were differentially activated by LPS or septic challenge indicating age-associated dysfunction that is localized to vWAT. Our results demonstrate that acute endotoxemia and sepsis result in immune and metabolic activation within the vWAT, both of which are dysfunctional during aging. These data reveal B cell subsets that may differentially impair adipocyte lipolysis and exacerbate the inflammatory response in vWAT following pathogenic challenge.

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Title: Investigating the association between lipid profiles and Alzheimer's disease outcomes: an analysis of the ADNI study

Introduction: Amyloid plaque accumulation in the brain is a hallmark of Alzheimer's disease. This pathological process may be driven by lipid dysregulation, however, the exact relationship between content of plasma derived endogenous nanoparticles had not yet been determined. The Apolipoprotein Eε4 (ApoE4) variant is the strongest risk factor for AD after age and ApoE4 carriers have severely dysregulated lipid profile. We interrogated lipidomic and endogenous nanoparticle platform from Alzheimer's Disease Neuroimaging Initiative (ADNI) for the association with the amyloid load, measured by the composite standardized uptake value ratio (SUVR) in amyloid Positron Emission Tomography (PET), Hippocampal volume (Free Surfer MRI) and Cognition progression.

Methods: The study included 901 participants, and collected data on endogenous lipids from ADNI nanoparticles, hippocampal volume, amyloid using the PET tracers florbetaben (FBB) and florbetapyr (FBP). A single serum and plasma sample was analyzed using an MRI-based method to measure blood biomarkers, lipid profiles, clinical information, and neuroimaging. We performed linear regression models, adjusting for covariates, using the *R maplet package*. In addition, we applied multiple comparison correction (FDR) to adjust for statistical significance for multiple measurements.

Results: Our study found that multiple lipids are associated with cortical amyloid burden SUVR in the temporal lobe, parietal and cingulate region in individuals not carrying the ApoE4 allele including low density lipoprotein-cholesteryl ester (LDL-CE). Hippocampal volume was associated with altered lipidomic profile in both carriers and non-carriers of the ApoE4 allele highlighting changes sphingomyelin (SM) and phosphatidylethanolamine species. We found a significant association of several lysophosphatidylcholine (LPC) species with cognition including Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) and Mini Mental State Exam (MMSE) with altered ADNI lipidomic profile in both carriers and non-carriers. In ApoE4 carriers we identified multiple lipids associated with dementia diagnosis including multiple LPC and SM species.

Conclusion: Our results provide valuable information about the relationship between endogenous nanoparticles and amyloid burden, hippocampal volume, and cognitive outcomes among ApoE4 allele carriers and non-carriers. Using the *R maplet package* for statistical analysis, the lipidomic approach yielded comprehensive analysis of lipidomic biomarkers in serum and plasma. It is highly likely that further research on endogenous nanoparticles will reveal novel molecular mechanisms and potential for clinical development.

Identifying the selective lipophagy receptor for lipid droplet turnover in liver

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Background: Lipophagy is a cellular mechanism for degradation of lipid droplets (LD) via autophagy. It is well-established that defects in lipophagy/autophagy lead to hepatic lipotoxicity across the broad pathophysiological spectrum of fatty liver disease. Indeed, dampened autophagy and steatosis during obesity underscore the importance of this pathway in liver pathobiology. Despite extensive research, little is known about the mechanisms of selective recognition, sequestration and degradation of LD by autophagosomes, such that lipophagy can be selectively targeted without affecting other forms of autophagy.

Methods: Animal models: Studies were performed in 2-10-month-old male and female 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/two-way ANOVAs and appropriate post-hoc testing.

Results: We report fasting-induced enrichment of selective phosphosites in liver that regulate hepatic lipid metabolism. From amongst these phosphoproteins, we identified a novel receptor for lipophagy that governs LD degradation in liver during fasting and lipid stress. We show that Casein kinase 2 (CSNK2)(EC 2.7.11.1)-mediated phosphorylation regulates the function of this novel protein towards LD sequestration. We have identified lipid binding and LC3 (light chain 3) interacting regions on this phosphoprotein, which allow binding to LD and autophagosomes, respectively, and inactivating these regions cause lipid accumulation. These findings have informed the generation of a highly sensitive and specific lipophagy reporter that will provide an efficient readout for lipophagy flux in cellulo and in vivo.

Conclusion: We have identified a previously unknown selective receptor that targets LDs for lysosomal degradation. Phosphorylation of this target is of crucial importance for the selective recognition and degradation of LDs in lysosomes. This discovery and the novel reporter will help develop novel compounds to selectively activate lipophagy to prevent human NAFLD and NASH.

Aster proteins facilitate dietary cholesterol uptake by mediating non vesicular transport in enterocytes

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Intestinal cholesterol absorption is an important contributor to systemic cholesterol homeostasis. Niemann-Pick C1 Like 1 (NPC1L1), the target of the drug ezetimibe, assists in the initial step of dietary cholesterol uptake. However, how cholesterol moves downstream of NPC1L1 is unknown. Here we show that Aster-B and Aster-C are critical for non-vesicular cholesterol movement in enterocytes, bridging NPC1L1 at the plasma membrane (PM) and ACAT2 in the endoplasmic reticulum (ER). Enterocytes lacking Asters accumulate cholesterol at the PM and display evidence of ER cholesterol depletion, including decreased cholesterol ester stores and activation of the SREBP-2 transcriptional pathway. Aster-deficient mice have impaired cholesterol absorption, reduced chylomicron assembly and secretion, and are protected against diet-induced hypercholesterolemia. *In vivo* immunostaining and studies from enteroids proved that Aster proteins are recruited to the enterocyte plasma membrane in response to NPC1L1-dependent cholesterol accumulation. Finally, we show that the Aster pathway can be targeted with small molecule inhibitors to manipulate dietary cholesterol uptake. Our data support a model in which NPC1L1 enriches dietary cholesterol at the apical plasma membrane and Asters subsequently traffic this cholesterol to the endoplasmic reticulum. The findings identify the enterocyte Aster pathway as potential target for treatment of hypercholesterolemia.

Adipose tissue derived FGF21 improves healthspan and lifespan of obese male mice and is potentiated by the ablation of adiponectin

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Fibroblast growth factor-21 (FGF21) is a hormone secreted into circulation primarily by the liver that plays an important role in energy balance, glucose and lipid metabolism. Congenital hepatic overexpression of FGF21 in mice has been shown to increase lifespan, however the mice display dwarfism, making comparisons to normal sized control mice not ideal for the interpretation of aging studies.

Adipocytes also secrete FGF21, albeit at much lower levels than the liver, and are a key target for the anti-diabetic effects of FGF21. To determine whether FGF21 alters lifespan and healthspan, we characterized mice with doxycycline-inducible, adipocyte-specific overexpression of FGF21. This approach permits the study of FGF21 expression in adult mice. Adiponectin is critical for many of the actions of FGF21. To assess whether this premise applies to the aging process, we studied adipocyte-specific overexpression of FGF21 in the *presence or absence* of adiponectin by crossing them with adiponectin knockout (KO) mice. All studies were performed with mice fed a high-fat diet containing doxycycline beginning at 12 weeks of age.

Overexpression of FGF21 in adipocytes resulted in 1) increased systemic FGF21 at physiological levels, 2) prevention of weight gain and fat accumulation without a reduction of food intake, 3) improved glucose tolerance and insulin sensitivity, 4) increased energy expenditure, 5) increased circulating levels of adiponectin, 6) decreased circulating leptin and glucagon, and 7) no change in serum IGF compared to control mice. Surprisingly, the mice with overexpression of FGF21 on the adiponectin KO background displayed similar metabolic improvements.

Median survival increased in mice with adipose tissue FGF21 overexpression vs. control mice (2.24 vs. 1.76 years). Consistent the published literature, adiponectin KO mice displayed a lower median survival than control mice (1.58 vs. 1.76 years). We hypothesized that the lack of adiponectin may lower survival in mice that had overexpression of FGF21. Unexpectedly, the ablation of adiponectin concurrent with FGF21 overexpression resulted in *life extension* to 2.43 median years, compared to 2.24 years for mice with the FGF21 expression in the presence of adiponectin. Remarkably, higher circulating FGF21 increased lifespan to an exceptional degree in these mice fed a high-fat diet, with some mice living up to 3.30 years of age.

In summary, we show FGF21 overexpression in adipocytes directly or indirectly raises plasma FGF21 levels. In this setting, the mice exhibit the well-established anti-aging, anti-obesogenic, and anti-diabetic actions of FGF21. The question remains, how the ***loss*** of adiponectin potentiates the effects of FGF21 on lifespan. Adiponectin is an anti-inflammatory adipokine that alleviates metabolic dysfunction and protects against functional tissue decline during the aging process. Thus, our observation is in line with what is termed the "adiponectin paradox," in which the pathology of a handful of conditions are associated with high serum levels of adiponectin. This involves complex systems biology, and the FGF21-adiponectin axis warrants further study, particularly efforts to define the role of FGF21 secreted by adipose tissue. Overall, our data provides evidence that FGF21 has therapeutic potential for metabolic diseases that ultimately result in longevity, and adiponectin ultimately opposes some of these age-related beneficial effects of FGF21, leading to exceptional longevity for mice chronically exposed to a high fat diet.

Immune Cell Dynamics During Weight Cycling in Obese Mice

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Weight cycling, or yoyo dieting, is a widespread phenomenon that involves repeated cycles of weight loss and regain, often resulting in overall weight gain. Although weight loss is the most effective intervention for obesity-related diseases, we still lack a complete understanding of how weight loss promotes resolution and why weight cycling exacerbates inflammation. To shed light on these phenomena, we conducted a comprehensive investigation of immune cell dynamics across different stages of caloric restriction-induced weight loss and subsequent weight regain in obese mice. Using a combination of flow cytometry, immunohistochemistry, RT-PCR, and ELISA, we analyzed the relative abundance of immune populations in various fat depots (subcutaneous, visceral, and brown), bone marrow, and circulatory white blood cells to decipher the role of weight cycling in modulating the immune compartment across different sites. Our findings revealed minimal overlap in the immune compartment across tissues in response to both caloric restriction and weight regain. While caloric restriction led to a gradual decrease in many immune types in the circulation, their dynamics in different adipose depots were mixed. For instance, macrophages and NK cells initially increased with caloric restriction, followed by a gradual decrease upon weight stabilization, while T cells displayed the opposite pattern. These changes were largely reversed by weight regain. In conclusion, our detailed analyses provide valuable insights into how weight loss and regain influence inflammation and highlight the crosstalk between various adipose depots and central immune hubs.

Malfunctioning of the ESCRT machinery leads to abnormal lipid synthesis and storage in embryonic development

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Morphogenetic events are orchestrated by a multi-layered code of transcription factor-driven gene regulatory networks, epigenetic modifications, and signaling pathways. Signaling molecules, as well as their cell surface receptors, rely on the cell's endo-lysosomal pathway to prevent their accumulation on the cellular plasma membrane, which would have detrimental effects on development of the embryo. 1/3 of all human birth defects affect craniofacial morphogenesis, ranging from cosmetic defects to malformations that interfere with vital functions. By ENU-induced mutagenesis, we isolated a mouse line with craniofacial malformations characteristic of distinct human congenital syndromes. Mutant embryos harbor a constitutive hypomorphic mutation of *Vps25*, a gene that encodes a component of the ESCRT (Endosomal Sorting Complexes Required for Transport) machinery, a protein assembly required for endosomal trafficking and lysosomal degradation of activated membrane receptors. Homozygous mutant embryos (named $Vps25^{ENU/ENU}$) exhibit fully penetrant hypoplastic jaw, cleft palate, low-set ear pinna, edema, and polydactyly. Unlike mouse lines with constitutive loss of ESCRT-encoding genes, $Vps25^{ENU/ENU}$ embryos exhibit late embryonic lethality, providing the first evidence for critical roles of the ESCRT machinery in craniofacial morphogenesis. Mass Spectrometry analysis led us to detect upregulation of enzymes involved in *de novo* synthesis of long-chain ceramides and lipid droplet biogenesis in mutant *versus* wildtype craniofacial tissue. Ceramide, BODIPY, and PLIN-2 staining validated these results. Western blot and qPCR analyses showed that dysregulation of lipid metabolism occurs primarily in the embryonic surface epithelium. Importantly, tissue-specific inactivation of *Vps25* in the cephalic epithelium results in craniofacial defects that partially recapitulate those of *Vps25* constitutive hypomorphic mutant embryos. Additional lipidomic analyses will allow us to quantify specific lipid species in mutant *versus wild-type* craniofacial tissue. Our results support a new role of the ESCRT machinery in regulating metabolic processes during morphogenesis, opening new avenues for the design of new therapeutic approaches to early detect and treat craniofacial abnormalities.

Macrophage Cholesterol Homeostasis and Inflammation Shaped by ASTER-C

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In most mammalian cells the majority of cholesterol resides in the plasma membrane (PM), but regulation of cholesterol synthesis and metabolism primarily occurs at intracellular membranes such as the endoplasmic reticulum (ER), mitochondria, and nucleus. In order to maintain lipid homeostasis and balance cellular signaling, cholesterol trafficking from the PM to these membranes is a tightly regulated process. A recently identified family of ER-resident proteins called ASTERs (ASTER-A, -B, and -C) form membrane-membrane contact sites at cholesterol-rich lipid raft domains to facilitate nonvesicular influx of free cholesterol. ASTER-B was recently described as a liver X receptor (LXR)-stimulated cholesterol transporter that facilitates PM-to-ER sterol transfer, preceding formation of cholesterol ester (CE) storage in the adrenal gland. Our studies focus on the role of ASTER-C in macrophage cholesterol homeostasis and inflammation using complementary gain- and loss-of-function approaches in murine macrophages. Although not stimulated by LXR agonism itself, ASTER-C augments the magnitude of LXR agonist-stimulated reorganization of macrophage cholesterol homeostasis. ASTER-C knockout bone marrow-derived macrophages (BMDMs) have blunted LXR-stimulated expression of lipid metabolic genes such as ABCA1 and LPCAT3, whereas overexpression of ASTER-C in Raw 264.7 macrophages enhances LXR-stimulated expression of ABCA1. Furthermore, ASTER-C knockout BMDMs have blunted LXR-driven anti-inflammatory responses. We also observed functional consequences of ASTER-C deletion on macrophage cholesterol homeostasis. ASTER-C null macrophages have reduced cholesterol esterification rates. Additionally, macrophages lacking ASTER-C have blunted apoA1-stimulated cholesterol efflux, yet the ability of lipopolysaccharide (LPS) to suppress cellular cholesterol efflux is lost in ASTER-C null macrophages. Collectively, our studies have identified ASTER-C as a novel regulator of macrophage cholesterol homeostasis and inflammatory pathways. This work has broad spanning implications in diseases driven by abnormal cholesterol homeostasis and unresolved inflammation such as atherosclerosis, advanced liver disease, and diverse cancers.

Simultaneous neuronal expression of human amyloid-β and Tau genes drives global phenotypic and metabolomic changes in *C. elegans*

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Alzheimer's disease and Alzheimer's related diseases (ADRD) are a class of prevalent age-related neurodegenerative disorders characterized by the accumulation of amyloid-β (Aβ) plaques and Tau neurofibrillary tangles. The intricate interplay between Aβ and Tau proteins requires further investigation to better understand the precise mechanisms underlying disease pathology. The nematode *Caenorhabditis elegans* (*C. elegans*) serves as an invaluable model organism for studying aging and neurodegenerative diseases.

Here we performed an unbiased systems analysis of a *C. elegans* strain expressing both Aβ and Tau proteins within neurons. Intriguingly, even at an early stage of adulthood, we observed reproductive impairments and mitochondrial dysfunction consistent with substantial disruptions in levels of lipid and energy related metabolites. Notably, the simultaneous expression of these two neurotoxic proteins exhibited a synergistic effect, leading to accelerated aging in the model organism. Our comprehensive findings shed new light on the intricate relationship between normal aging processes and the etiology of ADRD. Specifically, we demonstrate the alterations to metabolic functions precede age-related neurotoxicity, offering critical insights into potential therapeutic strategies.

Activation of host receptor *Taar5* plays a role in hypothalamic control of cold induced thermogenesis, eating behaviors, and circadian regulation

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The hypothalamus is considered the center for homeostasis due to its control over circadian rhythms, eating behavior, and thermogenesis. Disruption of these outcomes are often associated with metabolic diseases such as obesity and cardiovascular disease. Cardiometabolic disease (CMD) affects nearly one third of the adult population globally and increases the propensity to develop coronary heart disease—the leading cause of death worldwide. Current therapies aimed at reducing the burden of CMD fall short in practice due to undesirable side effects. Our previous work has shown that inhibiting the production of the gut-derived metabolite trimethylamine (TMA) improves glucose tolerance and prevents weight gain in both healthy and obese mice. We had previously postulated that these results were related to TMA being converted to TMAO via FMO3, which has been implicated in many CMDs. However, our new preliminary data show that knocking out *Taar5*, a GPCR for TMA which has recently been discovered in the hypothalamus and other brain regions, improves cold-induced thermogenesis and decreases latency to scavenge for food. Additionally, there are circadian changes in metabolic tissues and the gut microbiota when *Taar5*$^{-/-}$ mice were compared to wildtype controls, further supporting evidence of hypothalamic perturbation. Interestingly, *Taar5*$^{-/-}$ mice show improvements in energy balance and thermogenesis when compared to wildtype controls, suggesting a metabolic role for *Taar5* in associated adipose tissues such and inguinal and brown fat. With this new data, we have hypothesized that TMA-*Taar5* signaling influences hemostatic regulation eating behavior, circadian rhythms, and thermogenesis in the hypothalamus. We propose that *Taar5* activation plays a restrictive role in hypothalamic activation of brown adipose tissue, thus improving thermogenesis when *Taar5* is not activated. The short-term impact of this project is the identification of a novel pathway that influences thermogenesis, circadian rhythms, and eating behaviors. The long-term impact of this project is the development of a potential therapeutic to target *Taar5* to change eating behaviors, circadian rhythms, and other metabolic measures in order to improve conventional CMD treatment outcomes.

The 17:0 product of Bacterial Cyclopropane Fatty Acid Synthase Modulates Inflammatory Responses via IL-15 and IL-27p28/IL-30

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The gut microbiome has been increasingly implicated in human health and disease. While many studies continue to focus on which microbes are present under different disease conditions and how their abundances change over the disease course or in response to therapeutic interventions, we instead focus on functional effects mediated by the microbiota via their capacity to produce unique metabolites such as cyclopropane fatty acids. To manipulate the *in vivo* levels of these lipids, we used two approaches: 1) monocolonization of germ-free mice with wild-type or cyclopropane fatty acid synthase (*cfa*) knockout *E. coli* and 2) infusion of exogenous cyclopropane fatty acid via subcutaneously implanted osmotic mini-pumps. Using these methods, we decreased and increased *in vivo* levels of the 17:0 cyclopropane fatty acid, *cis*-9,10-methylenehexadecanoic acid (CMHA), respectively, and found that upon systemic exposure to the pathogen-associated molecular pattern, lipopolysaccharide, Interleukin (IL)-15 and IL-27p28/IL-30 are modulated in a multiplex assay measuring 19 cytokines. Interestingly, systemic delivery of supplemental CMHA via the osmotic mini-pump resulted in altered secretion of many cytokines; however, loss of endogenous production by bacteria resulted in a more narrow scope of changes, including IL-15 and IL-27p28/IL-30. Together these results suggest that these two cytokines may be important locally in the gut where bacteria produce CMHA. Further suggesting the intestine as an important anatomical site for CMHA and this mechanism, correlation analyses using GTEx data show significant, positive association between the expression of the putative CMHA receptor, BAI1/ADGRB1, with IL-15, the IL-15 receptor alpha chain, and the IL-27 receptor alpha chain expression. Given these data, along with previous reports implicating IL-15 and IL-27 in inflammatory bowel diseases, our future and ongoing studies aim to determine whether signaling through BAI1/ADGRB1 is the predominant *in vivo* mechanism of the effects mediated by CMHA, identify dietary factors affecting microbial CMHA production, and understand how the *cfa*-CMHA-BAI1 axis is affected in surgically resected tissues from IBD and non-IBD patients.

Crosstalk Between the Microbiome and Rubicon Regulates Energy Homeostasis to Determine Susceptibility to Obesity with Age

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Emerging evidence implicates the role of fluctuations in microbially-derived metabolites throughout the lifespan as significant contributors to age-related metabolic disorders. In addition, defective mitophagy has been identified as a pivotal factor in the development of metabolic dysfunction with aging. However, the relationship between commensal bacteria and mitophagy is poorly understood. We demonstrate that Rubicon-deficient mice(*Rubcn*$^{-/-}$) acquire a distinct consortium of gastrointestinal bacteria that produce large amounts of cis-vaccenic acid (cVA), a monounsaturated fatty acid (C18:1n-1) released into host circulation, and become spontaneously obese as mice age while consuming a normal chow diet. cVA stimulates macrophages to produce interleukin (IL)-1β, a cytokine that induces mitophagy in adipocytes. Simultaneous deletion of *Rubcn* and IL-1 receptor 1 (*Il1r1*) rescues Rubicon-deficient mice from developing obesity. Furthermore, the metabolic dysfunction in mice lacking Rubicon was rescued by concurrently deleting the mitophagy protein Parkin. These findings indicate that microbially-derived fatty acids, such as CVA, activate an immunometabolic circuit in adipose tissue that drives obesity pathogenesis.

Electrophilic Lipid Peroxidation Products Effect Carbonyl Stress, Mitochondrial Dysfunction, and Cellular Senescence: Implications for Adipose Senescence in Aging and Obesity

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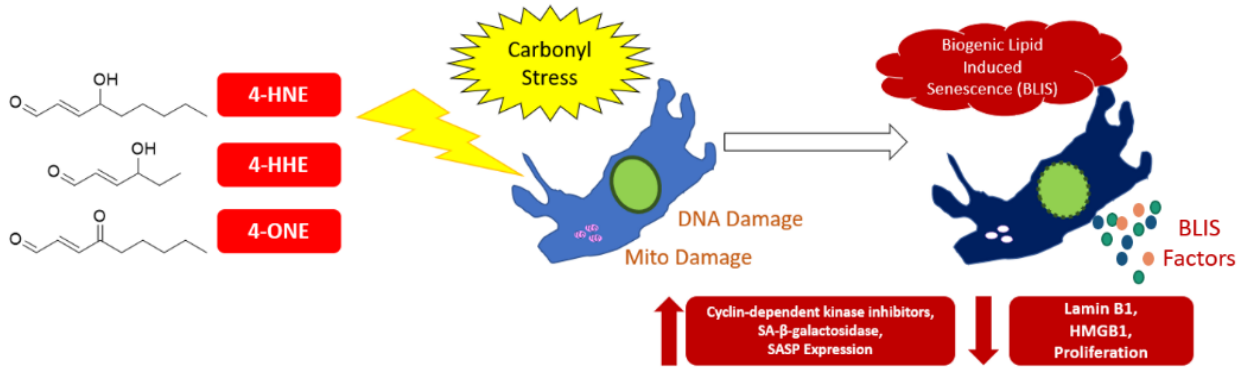
Accumulation of senescent cells in adipose tissue, particularly visceral depots, is increasingly becoming more appreciated as a causal factor in age- and obesity-associated metabolic dysfunction. Concomitant creation of an inflammatory milieu is thought to facilitate the development of systemic insulin resistance. As lipid peroxidation and pertinent drivers are shown to be associated with lifespan and age-related pathologies, we posit that resulting electrophilic lipid byproducts can incite or potentiate senescence in adipose. Produced abundantly in adipocytes by peroxidation of mitochondrial phospholipids, lipid aldehydes such as 4-hydroxynonenal (HNE) and 4-oxo-2-nonenal (ONE) covalently modify nucleophilic DNA and protein species and herein we hypothesize that carbonyl stress exerts genotoxicity, oxidative stress, and mitochondrial dysfunction to induce the senescence program in adipose progenitor cells. Present studies represent the first efforts to characterize cellular senescence brought on by lipid aldehydes.

Data from preliminary experiments using TNF-α treated 3T3-L1 adipocytes indicates cytokines induce 4-HNE synthesis and efflux into the extracellular milieu. IMR90 fibroblasts and murine adipose stem cells continuously exposed to lipid aldehydes for seven days exhibit initiation of the senescence program, characterized by induction of SA-β-gal activity and enhanced expression of CDKN1A ($p21^{Cip1}$), among other senescence markers. We've termed this type of senescence Biogenic Lipid Induced Senescence, BLIS. Associated with BLIS is the upregulation of an NFκB-independent subset of the putative human SASP. Transcriptomics reveal transcription factor activation accompanying BLIS programming, including p53, CEBPβ, PPARδ, and PPARγ. Furthermore, we demonstrated that permeabilization of mitochondrial membranes by BAK/BAX channels mediate the BLIS phenotype. The overall mechanism of lipid aldehyde associated senescence is multifaceted and likely to involve both DNA and mitochondrial protein modification, as we observed hallmarks of both genotoxicity and aberrant mitochondrial function concomitant with development of BLIS markers and alkylation of mitochondrial proteins. Indeed, 4-HNE exposure effects γH2AX foci and downstream p53/p21 signaling, as well as reduced mitochondrial spare capacity and increased ADP:ATP ratios. We also observed depletion of nuclear deacetylase SIRT1 with chronic lipid aldehyde exposure, offering an intriguing mechanistic link between enzymatic modification/loss-of-function and BLIS. L-carnosine, a carbonyl scavenger, ameliorated the development of the senescent phenotype in cultured cells and blunted expression of $p21^{Cip1}$ in visceral fat of diet-induced obese C57/Bl6J mice. Taken together, our results suggest that reactive lipid aldehydes can induce cellular senescence in human fibroblasts and adipose stem cells and that adipose senescence may be linked to lipid-mediated senescence induction in visceral fat tissue.

Graphical Abstract



[**All-*trans* retinoic acid induces lipolysis via autophagy in mouse adipocytes**]

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All-*trans* retinoic acid (atRA), the active form of vitamin A, stimulates the browning of white adipocytes and lipolysis through hormone-sensitive lipase (HSL). Some studies have proposed a new lipolysis pathway, lipophagy, which degrades a lipid droplet via autophagy in adipose tissue and the liver. However, the details concerning the regulation of lipolysis in adipocytes by atRA-mediated autophagy remain unclear. In this study, we investigated the effect of atRA on autophagy in the epididymal fat of mice and the molecular mechanisms of autophagy in differentiated 3T3-L1 cells. Western blotting revealed that atRA significantly reduced the protein levels of p62, a cargo receptor for autophagic degradation, and increased the lipidated LC3B (LC3B-II), an autophagic marker, protein expression in epididymal fat. Next, we confirmed that atRA activates autophagy flux in differentiated 3T3-L1 cells using the GFP-LC3-RFP-LC3ΔG probe. Furthermore, to clarify the effect of atRA on lipophagy, we evaluated NEFA concentrations in the media of differentiated 3T3-L1 cells treated with the knockdown of ATG5, an essential protein in autophagic induction. ATG5-knockdown partly suppressed the atRA-induced increase in NEFA concentrations in differentiated 3T3-L1 cells. We also examined the induction mechanisms of autophagy by atRA in 3T3-L1 adipocytes using western blotting. atRA did not increase the levels of phosphorylated-ULK1 and -Beclin1, the most popular proteins involved in autophagy induction. These results suggest that atRA may induce lipophagy through mechanisms other than phosphorylated-ULK1 and -Beclin1, resulting in partial lipolysis of adipocytes.

Exploring the functional landscape of lipid metabolism in non-small cell lung cancer

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Lung cancer is the leading cause of cancer-related deaths worldwide. The most common form of lung cancer, non-small cell lung cancer (NSCLC) spans multiple histological subtypes and genetic subsets that exhibit distinct clinical behaviors and responses to therapies. Identifying lineage- and genotype-driven phenotypic variations and understanding the underlying molecular mechanisms is of paramount interest, as it may uncover novel therapeutic vulnerabilities. Lipid metabolism plays a key role in tumorigenesis, as it fuels membrane biogenesis, influences membrane dynamics, supports energy storage, and generates signaling molecules. While de novo synthesis of fatty acids is critical for lung tumor growth, lipid metabolism encompasses a complex array of interdependent processes, many of which remain to be functionally defined in NSCLC. To examine the extent of heterogeneity in lipid metabolic state across lung tumors and its potential to vary with genotype and/or histological subtype, we performed lipidomic profiling on a collection of fresh-frozen human NSCLC samples. We identified lipid species that vary significantly in abundance in the presence of recurrent genetic driver alterations, including mutations in *KRAS*, *TP53*, and *STK11* (*LKB1*). A series of ceramide species were less abundant in *LKB1* mutant tumors as compared to wild-type, indicating that LKB1 activity may govern ceramide synthesis and/or turnover. In the context of histological subtype-specific variations, we observed significantly increased abundance of sphingolipids containing C26 acyl chains in squamous lung tumors as compared to lung adenocarcinomas. Consistently, the ceramide synthase CERS3, which mediates the synthesis of (dihydro)ceramides containing C26 and longer fatty acids, is more highly expressed in squamous lung tumors relative to adenocarcinomas and adjacent normal lung tissue. *CERS3* mRNA abundance highly correlates with that of *TP63* in human squamous lung tumors, and p63 binds within the first intron of *CERS3*, suggesting that sphingolipid composition could be shaped by p63-dependent regulation of *CERS3* expression. In parallel with lipidomic profiling of human NSCLC, we are conducting a CRISPR/Cas9 screen in genetically engineered mouse models of oncogenic KRAS-driven lung adenocarcinoma to interrogate the function of various lipid metabolic enzymes in supporting lung tumor initiation and/or maintenance, thereby potentially uncovering novel lipid metabolic dependencies. Specifically, we are perturbing lipid metabolic enzymes in both p53-deficient and Lkb1-deficient settings to determine whether tumor suppressor deficiencies influence lipid metabolic dependencies. These studies will establish a

foundation for understanding lipid metabolic heterogeneity as it relates to genotype and histological subtype in NSCLC as well as reveal potential therapeutic targets among lipid metabolic processes.

The uniqueness of different epicardial adipose depots and their contributions to cardiovascular diseases.

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Introduction: Visceral adiposity is a major driver for the development of cardiovascular disease. One visceral adipose tissue depot that uniquely regulates the heart is the epicardial adipose tissue, which covert up to 80% of the heart and arteries. Epicardial adipose tissue is increased in obese individuals and is associated with more severe cardiovascular disease. However, epicardial adipose tissue composition and functions in different cardiovascular pathologies is poorly understood. Even more so, it is unknown whether different epicardial adipose tissue locations differ and uniquely influence heart disease. Therefore, we are investigating the cellular and molecular composition of epicardial adipose tissue in an obese state and its influence on atherosclerosis and aortic stenosis.

Methodology: epicardial adipose tissue biopsies are obtained from patients undergoing heart surgery. Two distinct epicardial adipose tissue areas sampled: 1) near the apex of heart and 2) the area covering the atria, as well as subcutaneous adipose and peripheral blood. From these 4 tissues, nuclei are being isolated and will be used for single-nuclear RNA-sequencing. We will use Seurat for unbiased clustering and differential gene expression analysis, and CellphoneDB to investigate cell-cell communication. Molecular data will be integrated with clinical parameters (blood counts, lipid profiles, glycemia and chest computerized tomography) to identify cardiovascular diseases pathways that are modulated by obesity in one or both EAT depots.

Result: we are currently collecting patient samples optimizing our methodology. By the time of the conference, we will have data from several coronary artery disease patients and control subjects. Our result will identify types of cells present in different epicardial adipose tissue subtypes, their uniqueness to subcutaneous adipose tissue and blood cells; and their contribution to obesity and cardiovascular diseases.

Conclusion: This study will contribute to our understanding on the role of epicardial adipose tissue in obesity and different cardiovascular disease. Our findings may provide insights for developing interventions to manage these conditions.

Race-associated differences in the relationship between lipids and inflammatory markers in Type 2 Diabetes

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Research on social determinants of health indicate that African Americans (AA) have greater stress exposure throughout their lifespan. Stress is known to manifest in multiple processes like an inflammatory status and systemic dysregulation and/or overabundance of lipids (as seen in obesity). These processes can overlap and contribute to the appearance of health disparities. Type 2 Diabetes (T2D) is an inflammatory age-related health disparity that has a well-documented association with lipid dysregulation and race. In fact, research suggests an association between compromised lipid metabolism and chronic inflammation in this disease, which predominantly impacts AA. The integrative role of underlying biological factors, like lipids and inflammatory markers, in AA is poorly understood. To elucidate this role, we integrated biological information from clinical parameters, untargeted and targeted lipidomics datasets generated using Mass Spectrometry, and cytokines profiles generated using Luminex platform (53-cytokines). We used clinical information and plasma samples from a diverse cohort of 40 individuals from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, comparing groups equally matched by race, sex, age, BMI, and socioeconomic status. Our findings suggest that lipids and race are the main drivers of variability in this well-matched diverse cohort. Results from untargeted lipidomics show strikingly clear race and T2D dependent differences in plasma lipid profiles. Targeted lipidomics assessment suggested that ceramides, a bioactive lipid which accumulation is associated with metabolic diseases, was differentially increased in AA with T2D, compared to white people with T2D. Results from our comprehensive cytokine evaluation show that the reported T2D-associated Th17-inflammatory profile (IL-17A, IL-17F, IL-21 and IL-22) is likely exacerbated in AA with T2D. A signature composed of IL-27 (Th-17 cell differentiation inhibition) and Eotaxin (controlled inflammation) was increase in our white group, irrespective of T2D status; and IL-33 (tissue damaged release linked to physical stress or trauma) was increased in our AA with T2D group. Finally, our integrative analysis shows that both lipids and cytokines correlated distinctively with T2D-associated blood lipids measurements in AA and whites populations. Our study approach displays the potential of integrative analysis to elucidate features contributing to T2D in AA. Future directions will aim at testing the potential causative role of lipids in the development of inflammation *in vitro*. We anticipate this work to be the starting point for mechanistic studies addressing racial differences in modulation of inflammatory responses by lipids, for a better understanding of the immunometabolic contributors to T2D.

Liver regulatory variants provide insight into the molecular basis of aging-related lipid disorders

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Lipid-related metabolic disorders including non-alcoholic fatty liver disease (NAFLD) and dyslipidemia are a major health burden in aging populations and are partially regulated by genetic factors. Genome-wide association studies (GWAS) have identified hundreds of risk signals for lipid levels and related traits which are risk factors for NAFLD and dyslipidemia, although most target genes and mechanisms remain unknown. To understand the genetic regulation of NAFLD, dyslipidemia and other metabolic traits, we previously identified GWAS variants that may alter liver regulatory element activity and gene expression. Specifically, we identified GWAS signals that colocalized with liver chromatin accessibility quantitative trait loci (caQTL) and with liver expression quantitative trait loci (eQTL). In the current study, we tested a subset of these caQTL variants and their target genes at NAFLD and dyslipidemia GWAS signals. We evaluated the regulatory effects of variants by transcriptional reporter assays, and validated the target genes at these loci using CRISPR interference (CRISPRi). We observed significant allelic differences in transcriptional activity in HepG2 cells for variants at four GWAS signals for plasma levels of liver enzymes, LDL-cholesterol and triglycerides: rs13395911 near *EFHD1,* rs11644920 near *LITAF*, rs34003091 near *ZNF329,* and rs9556404 near *GPR180,* and we observed allelic differences in transcription factor binding at rs13395911. To validate target genes for the two non-promoter variants rs13395911 and rs11644920, we knocked down their surrounding enhancer elements in HepG2 cells expressing dCas9-KRAB construct and assessed the effects on expression of the predicted target and nearby genes. Specifically, we introduced ≥6 gRNAs for each element into cells via lentiviruses and measured gene expression 72 hours after transduction. Compared to cells infected with non-targeted control gRNAs, cells infected with gRNAs targeting enhancers surrounding rs13395911 and rs11644920 showed significantly (P<.05) lower expression levels of *EFHD1* (23.7% decrease) and *LITAF* (24.7% decrease). For both genes, the variant directions of effect on expression matched the caQTL and eQTL associations. Near *LITAF*, enhancer knockdown also reduced expression of adjacent genes in the same topological domain, *SNN* and *TXDC11*. Further studies will investigate the effects of enhancer knockdown on cellular processes. In summary, we used a scalable framework to demonstrate the functional regulatory effects of specific GWAS variants and identify their target genes, which will aid identification of the mechanisms underlying aging-related lipid disorders.

Lipid droplets and peroxisomes are co-regulated to drive lifespan extension in response to mono-unsaturated fatty acids

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Dietary mono-unsaturated fatty acids (MUFAs) are linked to human longevity and extend lifespan in several species. But the mechanisms by which MUFAs extend lifespan remain unclear. We show that an organelle network involving lipid droplets and peroxisomes is critical for MUFA-induced longevity in *Caenorhabditis elegans*. We find that MUFAs upregulate the number of lipid droplets – organelles involved in fat storage and hydrolysis – in fat storage tissues and that increased lipid droplet number is necessary for MUFA-induced longevity. Interestingly, the number of lipid droplets in young individuals within a population of worms predicts their remaining lifespan. Lipidomics datasets reveal that MUFAs also modify the ratio of membrane lipids and ether lipids—a signature associated with decreased lipid oxidation. In agreement with this, MUFAs decrease lipid oxidation in middle-aged individuals. Intriguingly, MUFAs upregulate not only lipid droplet number but also peroxisome number – organelles involved in oxidation and lipid metabolism. By performing a targeted screen, we identify genes involved in the joint increase of lipid droplets and peroxisomes and genes that uncouple these two organelles. This screen reveals that induction of both organelles is optimal for longevity. Our study uncovers an organelle network involved in lipid homeostasis and lifespan regulation, opening new avenues for interventions to delay aging.

Quantitative Trait Loci (QTL) analysis in a genetically diverse mouse model identifies *Asah2* as a novel driver of lipoprotein subclasses

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Cardiovascular disease (CVD) is the primary cause of death world-wide. Plasma lipoproteins (LDL and HDL) play critical roles in CVD development and progression. The lipid and protein composition of lipoprotein particles and how they might influence particle functionality is not fully understood. Identifying genetic drivers of lipoprotein lipid composition can provide key insights into lipoprotein particle functionality and contributions to CVD development. In a genetic screen of 500 Diversity Outbred (DO) mice fed a high-fat, high-sucrose diet, plasma lipoproteins were surveyed by ion mobility methodology, enabling us to perform quantitative trait locus (QTL) analysis. We identified 19 QTL for lipoprotein subclasses. To refine the QTLs and link them to disease risk in humans, we identified human homologues at each locus that contain SNPs associated with lipid traits in human GWAS. Through integration of mouse QTL analyses with human GWAS, *Asah2* was identified as a strong candidate driver of large HDL particles (HDL-2b). Others have shown *Asah2,* a neutral ceramidase, to be critical for intestinal sphingolipid metabolism. Ceramides, the sphingolipid substrate for *Asah2*, are associated with increased risk of adverse cardiovascular events; however, no studies have linked this gene to lipoprotein metabolism. Wild-type (+/+), heterozygous (+/-), or homozygous (-/-) whole-body *Asah2* knockout mice were fed a high-fat diet for 16 weeks. Plasma lipoproteins from female and male mice of each genotype were sized by ion mobility. Female $Asah2^{-/-}$ mice showed an increase in total lipoprotein particles over $Asah2^{+/+}$ mice ($p<0.01$), including a significant increase in HDL particles ($p<0.01$). $Asah2^{+/-}$ females were intermediate in total lipoprotein particle concentrations but were not statistically different from either $Asah2^{+/+}$ or $Asah2^{-/-}$ females ($p>0.12$). Lipoprotein particle concentrations were unchanged between genotypes of male mice ($p>0.08$). Leveraging natural genetic variation within the DO mouse stock, we identified *Asah2* as a novel driver of plasma lipoprotein size. Additional candidate genes were identified at several other QTL and are being considered for experimental validation. Our approach provides insights into genetic regulation of lipoprotein size, composition, and functionality, as well as mechanisms by which lipoprotein subfractions may affect cardiovascular disease risk.

Understanding the relationship between lipid dysregulation and Alzheimer's disease risk

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The intercellular accumulation of lipids in glia was one of the earliest observations of Alzheimer's Disease (AD) pathology. It has been well-established that risk for late-onset AD is impacted by variants in *apolipoprotein E* (*APOE*), which codes for the brain's most abundant lipoprotein. Common variants in *APOE* (*APOE2, APOE3,* and *APOE4*) differ from each other at just two amino acid positions. While *APOE4* is a primary genetic risk factor for late-onset AD, the *APOE2* allele is associated with lowered incidence. *APOE3*, the most common variant in the general population, is neutral with respect to AD risk. Despite this genetic correlation, the mechanisms by which *APOE* alters AD risk are poorly understood. Given APOE's role in lipid transport and the central role of lipids in cellular homeostasis, we hypothesize that *APOE4* increases AD risk by transforming the cellular lipidome.

In the brain, microglia are the resident immune cells, are key regulators of lipid homeostasis, and are implicated in AD pathogenesis. Using human induced pluripotent stem cell-derived microglia, we observed that microglia accumulate lipids upon inflammatory activation. These excess lipids amass in lipid droplets (LDs). We explored how cellular lipid content relates to microglia gene expression and vital microglial functions of cytokine secretion and phagocytosis. To do this, we used chemical modulators to alter cellular lipid burden. We find that neutral lipid synthesis is necessary for the morphological changes in response to microglia activation. Additionally, upon the reduction of neutral lipid synthesis in activated microglia, the expression of disease associated microglia genes decreases, while the expression of genes linked to a homeostatic microglia signature increases. The transcriptional regulation and secretion of certain inflammatory cytokines are also influenced by neutral lipid synthesis. When neutral lipid synthesis is reduced, and microglia cannot store lipids in LDs, proper phagocytosis and amyloid-beta clearance are also impaired. We are now exploring whether LD catabolism is also essential for glial function and the consequences of modulating lipid content in *APOE4* microglia. This study will further our understanding of how *APOE* modulates AD risk, and the findings can be exploited to reveal novel targets for therapeutic benefit.

Revealing Lipid Particle Diversity During Aging in Live *Caenorhabditis elegans*

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Lipid metabolism is a critical modifier of organismal growth and aging. Metabolic pathways, including lipid regulation, are evolutionarily conserved between *Caenorhabditis elegans* (*C. elegans*) and other metazoans, including humans. One major challenge to studying lipids in alive, intact *C. elegans* is to distinguish lipid-rich particles that serve as energetic reservoirs of the parent from those that are destined for the progeny. Broadband coherent anti-Stokes Raman scattering (BCARS) microscopy has revealed that the composition and dynamics of lipid particles are heterogeneous both within and between different tissues of this organism. While BCARS microscopy produces high-resolution images with very high information content, it is not yet a widely available platform. Here we report a new approach combining the lipophilic vital dye Nile Red and two-photon fluorescence lifetime imaging microscopy (2p-FLIM) for the *in vivo* discrimination of lipid particle sub-types. While it is widely accepted that Nile Red staining yields unreliable results for detecting lipid structures in live *C. elegans* due to strong interference of autofluorescence and non-specific staining signals, our results show that simple FLIM phasor analysis can effectively separate those signals and is capable of differentiating the non-polar lipid-dominant (lipid-storage droplets), polar lipid-dominant (yolk lipoprotein) particles, and the intermediates that have been observed using BCARS microscopy. An advantage of this approach is that images can be acquired using common, commercially available 2p-FLIM systems within about 10% of the time required to generate a BCARS image. Our work provides a novel, broadly accessible approach for analyzing lipid-containing structures in a complex, live whole organism context.

Essential role of ELOVL2 in maintenance of lipid homeostasis and RPE phagocytosis in retina

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ELOVL2 (Elongation of Very Long Chain Fatty Acids-Like 2) encodes a transmembrane protein that plays critical roles in the biosynthesis of omega-3 docosahexaenoic acid (DHA) (22:6n-3) and very long-chain polyunsaturated fatty acids (VLC-PUFAs), which are highly enriched in photoreceptors and essential for maintaining healthy visual function. Age-related or mutation-dependent loss of ELOVL2 activity has a profound impact on eye structure and function by modulating the availability of VLC-PUFAs and DHA.

To understand the biological role of Elovl2 in the aging mouse retina, we generated *Elovl2*-mutant mice encoding a cysteine-to-tryptophan substitution (C234W) using CRISPR-Cas9 technology and performed lipidomics analysis and immunohistochemistry analysis. Lipidomics data show disturbed lipid composition and a decrease in LC-PUFAs and VLC-PUFAs in free fatty acid (FA) and total FA level in $Elovl2^{C234W}$ retina and eyecup. Lipid ontology analysis of the significantly changed lipids in $Elovl2^{C234W}$ eye showed an association with high lateral diffusion and low bilayer thickness in both tissues, but an opposite effect on the transition temperature in $Elovl2^{C234W}$ retina and RPE. These results were surprisingly similar to the lipid ontology analysis of aging retina and eyecup. Moreover, $Elovl2^{C234W}$ mice exhibited sub-retinal deposits with similar composition to drusen, a pathological hallmark of dry age-related macular degeneration. All these findings suggested that our animal model closely mimics aging and accelerates phenotypes of AMD.

To further investigate the functional role of ELOVL2 in RPE cells, we used small interfering RNAs (siRNAs) directed against *ELOVL2* in ARPE19 cells and performed transcriptomic and lipidomic analyses, which showed significant changes in the plasma membrane homeostasis. Furthermore, we studied the effect of loss of *ELOVL2* on RPE phagocytosis by challenging cells with FITC-labelled rod outer segments (FITC-ROS) for 2 hours, following a previously established protocol, and quantified the proportion of surface-bound and internalized ROS. Phagocytosis of photoreceptor outer segment (POS) in *ELOVL2* knockdown ARPE19 cells was reduced ~30% compared to control. Flatmounts of $Elovl2^{C234W}$ RPE also show decreased phagosome number and average phagosome size compared to 18-month-old WT RPE, suggesting a disruption in RPE phagocytosis *in vivo*.

Overall, we found that disturbing lipid homeostasis through inactivating ELOVL2 affects visual function and, on a cellular level, affects phagocytic function of RPE cells. This study not only provides insight into the molecular role of *ELOVL2* in the aging

retina but also opportunities to explore therapeutic treatments for pathologic states such as age-related macular degeneration (AMD) using lipid-based approaches.

Adrenergic activity drives anxiety-like behavior through adipose tissue lipolysis dependent induction of GDF15

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Aging is associated with metabolic and psychological changes. Psychological stress leads to the rapid release of epinephrine that orchestrates the fight-or-flight response. This classic stress response involves metabolic changes including the activation of lipolysis and behavioral responses including anxiety, however the mechanisms linking these distinct responses are not understood. To try and understand how stress-induced peripheral adrenergic activation might affect behaviour, we acutely injected mice with epinephrine, which produced anxiety-like behaviour, as expected. RNA sequencing of epididymal white adipose tissue identified growth differentiating factor 15 (GDF15) as the most upregulated secreted factor in response to epinephrine. GDF15 is the most upregulated protein with aging and its receptor, GFRAL, is expressed exclusively in the hindbrain suggesting it might be a link between peripheral metabolic responses and psychological adaptations. Epinephrine rapidly increased circulating GDF15 without affecting expression in liver or kidney tissues. Acute psychological stress, in the form of immobilization restraint, increased circulating and adipose tissue GDF15 via beta-adrenergic receptors. Lipolysis is a critical downstream response to adrenergic signalling in adipose tissue and adipocyte-specific deletion of ATGL prevented adrenergic-induced GDF15 secretion, but in vivo and in vitro evidence showed adipocytes to not be the source of GDF15. Rather, epinephrine increased GDF15 expression in the stromal vascular fraction. Using bone marrow-derived macrophages, we show that saturated, but not unsaturated, fatty acids increase GDF15 secretion specifically from M2 polarized anti-inflammatory macrophages through a PPAR gamma-mediated mechanism. Finally, pharmacological GDF15 rapidly produced anxiety-like behaviour in mice and GDF15's receptor, GFRAL, was necessary for anxiety-like behaviour and the secretion of corticosterone in response to acute restraint stress. Thus, GDF15 is a lipid sensitive sensor linking metabolic changes with psychological stress.

Turner, Jacqueline

Title: Lysophosphatidic acid is a lipid-regulated immune checkpoint

Abstract: T cells play a critical role in anti-tumor immunity, yet CD8 T cells often become dysfunctional and/or exhausted during tumor progression. CD8 T exhaustion is defined as persistent T cell receptor (TCR) signaling resulting in a progressive loss of effector function. There are defined developmental pathways for CD8 T cell exhaustion that describe distinct subsets, including progenitor and terminally exhausted CD8 T cells. Yet, the mechanisms that regulate exhaustive differentiation and CD8 T cell fate are not fully understood. We show lysophosphatidic acid (LPA) is a bioactive lipid that signals on CD8 T cells to promote tolerogenic states through metabolic reprogramming and exhaustive differentiation. We identify a novel function of LPA signaling via LPA receptor 5 (LPAR5) to regulate CD8 T cell respiration, proton leak, reactive oxygen species, and lipid peroxidation. We show LPAR5 signaling on CD8 T cells induces dysfunctional metabolism, accumulates oxidative damage, and results in impaired anti-tumor immunity. Through extensive signaling analysis and immunophenotyping, we show LPA signaling potentiates terminal CD8 T cell exhaustion and induces dysfunctional intracellular signaling in a mechanism distinctly different from TCR signaling. Importantly, we show LPA regulates metabolic fitness and antigen-specific killing which are both critical determinants of CD8 T cell responses during immunotherapy in cancer. Next, we translated these findings into human studies where we first show LPA levels predict response to immunotherapy in stage IV melanoma patients. Together, our findings reveal that LPA serves as a lipid-regulated immune checkpoint by modulating metabolic efficiency through LPAR5 signaling on CD8 T cells. This body of work offers key insights into the basic mechanisms governing adaptive anti-tumor immunity and translates these finding to identify LPAR5 as an actionable target for a CD8 T cell directed therapy. Importantly, the findings presented here identify lipid signaling as a novel target to potentially reinvigorate progenitor exhausted CD8 T cells and rescue endogenous anti-tumor immune responses.

Regulation of extracellular acylcarnitine uptake and function by the carnitine transporter OCTN2

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Acylcarnitines are increased in the blood plasma with age-related metabolic disease and with physiological stress. In metabolic disease, plasma acylcarnitines are considered components of lipotoxic stress that indicate overloaded capacity of fatty acid oxidation. As they build up, acylcarnitines can cause cellular dysfunction, and treatment of cultured cells with acylcarnitines induces apoptosis at levels lower than corresponding free fatty acids. In physiological stress such as cold exposure, plasma acylcarnitines serve as a mobile lipid pool readily available to support sudden shifts in energy demand and induce insulin resistance. Despite their functional relevance, little is known about how acylcarnitines are transported from the plasma into cells. Elucidating how the transport and metabolism of extracellular acylcarnitines is regulated is critical for understanding their normal physiological function as well as their role in disease.

To investigate how acylcarnitine transport is regulated, we used differentiated brown adipocytes as a model for uptake—during cold exposure, plasma acylcarnitines are taken up by brown adipose tissue (BAT), and this uptake is decreased in aged mice. We found that uptake of fluorescently labeled palmitoylcarnitine increased with treatment of a B_3-adrenergic receptor agonist (CL-316,243), which models the activation of BAT by the sympathetic nervous system in response to cold. We also observed that acylcarnitine uptake decreased in the presence of excess carnitine, suggesting these substrates may compete for transport. From these data, we hypothesized acylcarnitine uptake is regulated though a plasma membrane transporter that is stimulated by B_3-adrenergic signaling and has established affinity for carnitine. The canonical carnitine transporter OCTN2 emerged as a top candidate, as OCTN2 expression increases with CL-316,243 (CL) treatment. Using CRISPR-Cas9-mediated gene knockout, we found OCTN2 is required for CL-induced acylcarnitine uptake, suggesting that OCTN2 is necessary for uptake into BAT during cold exposure. We also found that OCTN2 was sufficient for acylcarnitine uptake and acylcarnitine-induced toxicity in Chinese hamster ovary cells. Currently, we are exploring how human variants in OCTN2 impact acylcarnitine uptake and toxicity as well as the mechanisms of acylcarnitine toxicity across different cell types. This work will expand our understanding of how acylcarnitines function in physiology as well as age-related metabolic diseases associated with altered acylcarnitine profiles, including type 2 diabetes, fatty liver disease and cardiovascular disease.

Dysregulated Lipid Metabolism and ACSL6 Expression in Alzheimer's Disease: Insights from Spatial Lipidomic and Transcriptomic Analysis in a Mouse Model

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Introduction: Alzheimer's Disease (AD) has been associated with genetic variations in lipid metabolic pathways, including Apolipoprotein E (ApoEε4). Aberrant incorporation of docosahexaenoic acid (DHA) has been observed in the entorhinal cortex of individuals carrying the ApoEε4 variant. Dysregulation of lipid homeostasis and the acyl chain remodeling pathway, as well as depletion of specific lipid acyl species, are implicated in AD pathogenesis. Additionally, lipidomic studies have highlighted changes in lipids during aging and in AD, including a reduction in polyunsaturated fatty acids (PUFAs), such as DHA, which play crucial roles in neuronal function. The dysregulation of acyl chain remodeling, including the Lands Cycle, has also been associated with AD. In this study, the aim was to generate a pipeline for brain spatial lipidomic and coordinate spatial transcriptomic analysis, focusing on cell type identification, in a mouse model of AD. The pipeline encompasses tissue processing, H&E staining, RNAscope, imaging mass spectrometry and spatial transcriptomics. **Methods:** Serial brain slices from a mouse model of AD were analyzed for gene expression using RNAscope and Visium Spatial Gene Expression. RNAscope quantification was performed on images captured at 40x magnification in the CA3 hippocampus region, and the number of NeuN, GFAP and Iba-1 positive puncta was quantified using the HALO software. **Results:** We observed higher ACSL6 expression in the AD model compared to wild-type animals, with colocalization primarily with NeuN expression in neurons, but not with GFAP or IBA-1 in astrocytes or microglia respectively. Spatial transcriptomics revealed differences in the expression of several genes involved in lipid metabolism. Imaging mass spectrometry detected differences in regional lipid content consistent with deficits in acyl chain remodeling in the AD mouse model. **Conclusion:** Dysregulation of lipid metabolism, including alterations in expression of enzymes involved in fatty acid metabolism like ACSL6, have been implicated in AD pathogenesis. We used imaging mass spectrometry and spatial transcriptomics to determine drivers in lipid dyshomeostasis. By integrating these techniques, we identified the Lands cycle acyl chain remodeling deficits in lipid metabolism, and corresponding gene expression using spatial transcriptomic profile. Further research is required to confirm and better understand these potential changes and their implications for disease etiology and progression.

Selective remodeling of the translatome underlies ketogenesis

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Fasting is associated with a range of health benefits, including brain function, improving metabolism and increasing longevity. How fasting signals elicit changes in gene expression at the level of the proteome to establish metabolic programs that underlie lipid catabolism and production of ketone bodies, an essential alternative fuel of energy, remain unknown. Here we show that paradoxically, while global translation is downregulated during fasting, hepatocytes selectively remodel the translatome to sustain lipid metabolism and ketogenesis. We discovered that the phosphorylation of the major cap binding protein, eukaryotic translation initiation factor (P-eIF4E) is induced during fasting. By employing a genetic and a genome-wide unbiased polysome sequencing, we show that P-eIF4E is responsible for controlling the translation of the entire ketogenesis pathway, including the master regulator of lipid metabolism in the liver, peroxisome proliferator-activated receptor alpha (PPARα). Importantly, eIF4E phosphorylation regulates those mRNAs through a specific translation regulon within their 5' untranslated regions. Genetically inhibition of eIF4E phosphorylation interrupts ketogenesis and lipid metabolism upon fasting. In addition, our findings reveal a new signaling property of fatty acids (FAs), which are elevated during fasting. Specifically, we uncovered that FAs enhances AMPK kinase activity which phosphorylates the mitogen-activated protein kinase-interacting kinase (MNK) that mediates phosphorylation and activation of eIF4E. Failure of selective translation activation through inhibition of MNK1 or AMPK impairs ketogenesis revealing a new lipid-mediated kinase signaling pathway that links ketogenesis to translation control. We further show that genetically inhibiting eIF4E phosphorylation also impairs ketogenesis in response to a ketogenic diet, and overexpression of PPARα rescues it. Thus, our findings unveil a novel fatty acid induced signaling pathway that activates selective translation, which underlies the rapid cellular response to fasting and ketogenesis.

Aberrant Lipid Metabolism Pinpoints Rational Parkinson's Disease Therapeutic Targets and Strategies

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In some fields, lipids droplets (LDs) have traditionally been viewed as simple storage organelles. It is clear LDs are not only multifaceted functional entities dynamically balancing intermediates and products between complex signaling pathways, but are vital reporters of health and disease, particularly in aging. Deeming LDs to be disease informants aids in pinpointing therapeutic targets. Our work on LDs indicated two candidate therapeutic targets for Parkinson's disease (PD) and synucleinopathies, one of which is now in clinical trials. LDs also revealed a unique therapeutic strategy based on LD homeostasis to be promising for disease treatment. These mechanistic insights yielded a new approach to membrane remodeling as a therapeutic strategy. The key question driving our research is: Can the distinct properties of disease-impacted LDs and membrane lipid remodeling pinpoint new disease-relevant therapeutic targets for patients with aging diseases?

Background: The PD-associated protein α-synuclein (αS) has physiologic and pathogenic interactions with membrane phospholipids and fatty acids (FAs), and alters lipid homeostasis. αS promotes LDs. LD content changes are associated with toxicity, neurodegeneration, and membrane trafficking defects. We identified a novel FA-related target, stearoyl-CoA desaturase (SCD), inhibition of which reverses numerous PD-relevant phenotypes. Here, we present our advancements pursuing distinct LD properties and membrane biology identifying new candidate targets and unique therapeutic strategy.

We systematically investigated another major source of cellular FAs, neutral lipid lipase (LIPE), as a candidate target. This approach is functionally distinct from, but as important as SCD. Increased wt/familial αS mutants increases monounsaturated fatty acid (MUFA) and lipidome dysregulation. Patients can have accumulated brain LDs at diagnosis, hence, a concern for generation of MUFAs through *degradation*. Using combined FA and lipidomic profiling with disease protein analyses we correlated cellular lipidome status with disease phenotype rescue.

Results (will include presenting unpublished data): We found balancing membrane unsaturated:saturated FAs (e.g. LIPE reduction) decreased PD-associated phenotypes. This stands in mechanistic agreement with our SCD work, augmenting the relevance of targeting FA metabolism. Mechanistically, we identified LIPE as regulating phospholipid-incorporated FAs. This is important given phospholipid membrane composition determines αS:membrane interactions and disease phenotypes. We propose a treatment strategy incorporating partial inhibition of both synthesis and degradation (co-regulating SCD and LIPE), ultimately balancing LD homeostasis. We show this additively reduces PD phenotypes. LDs are key indicators of health and disease and aided in generating a co-treatment strategy for patients, the ultimate use of LD biology to generate therapeutics in the neurodegenerative diseases field.

Intact lysosomal lipolysis is required to suppress muscle catabolism

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The physiological response to temporary nutrient restriction is fundamental across species. Although caloric restriction extends lifespan in many species, not only it is difficult to maintain in humans, but it may cause muscle loss and frailty, therefore negatively impacting healthspan during aging. Intermittent fasting strategies have been proposed as alternative to chronic caloric restriction, but debate exists as to whether intermittent fasting strategies might prevent or exacerbate muscle loss, and what the mechanisms might be. While studying the role of fasting/refeeding cycles (alternate day fasting) in cachexia, we discovered that healthy mice activate mammalian target of rapamycin (mTOR), inhibit transcription factor EB (TFEB), and downregulate the TFEB target growth differentiation factor-15 (GDF-15), leading to preservation of muscle mass. Genetic ablation of lysosomal acid lipase (LAL), the key enzyme in lipophagy, in cardiomyocytes revealed a critical role for lipophagy in the response to refeeding. In cardiomyocyte-specific LAL knockouts, we observed reduced mTOR activity and cardiac dysfunction specifically during refeeding. Compared to controls, cardiomyocyte-specific LAL knockouts exhibited enhanced LV mass loss, decreased cardiomyocyte cell size, and increased fibrosis when challenged with doxorubicin, a cardiotoxic chemotherapy that causes cachexia and cardiac atrophy. These changes were again associated with reduced mTOR activity and increased TFEB nuclear translocation, demonstrating that intact lysosomal lipolysis is necessary to suppress muscle catabolism both in response to fasting/refeeding and in a cachectic state. These studies reveal a previously unrecognized fundamental, cell-autonomous role for lysosomal lipolysis in the preservation of muscle mass.

Deletion of Carnitine Palmitoyltransferase 1a from the Liver Reduces Hepatic Polyunsaturated Fatty Acids and Drives Microvesicular Steatosis in Female Mice

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Background: Loss-of-function mutations in carnitine palmitoyltransferase 1a (CPT1a) associate with reductions in circulating polyunsaturated fatty acids (PUFAs). Loss of hepatic PUFAs contributes to the progression from nonalcoholic fatty liver disease (NAFLD) to more severe nonalcoholic steatohepatitis (NASH). Therefore, the goal of this study was to determine the impact of liver-specific CPT1a deletion (LKO) on PUFA metabolism and NAFLD.

Methods: Eight-week old male and female LKO (*Cpt1a*$^{\Delta Alb}$) and littermate controls (*Cpt1a*$^{F/F}$) were placed on a low-fat or high-fat diet (HFD; 60% kcal fat) for 15 weeks. Glucose and insulin tolerance tests were completed after 10 and 12 weeks on the diet, respectively. Mice were necropsied after a 16 hour fast to induce hepatic fatty acid oxidation, and tissues and serum were collected and utilized for shotgun lipidomics, matrix-assisted laser desorption ionization for mass spectrometry imaging (MALDI-MSI), bulk RNA sequencing, histology, transmission electron microscopy, and protein expression by immunoblotting.

Results: Male and female LKO mice did not exhibit a difference in total body weight or adiposity. Male LKO mice displayed improved insulin sensitivity, had lower circulating alanine aminotransferase (ALT) levels, but did not exhibit changes in hepatic triglycerides or cholesterol levels as compared to male control mice. Female LKO mice, however, displayed significant increases in serum ALT levels which associated with greater deposition of hepatic triglycerides and cholesterol, as compared to female control mice. Histologically, female LKO mice displayed diffuse, panlobular microvesicular steatosis, while male LKO mice exhibited slight periportal steatosis. Shotgun lipidomics revealed female LKO mice exhibited reductions in EPA and DHA-containing phospholipids. Utilizing MALDI-MSI, we observed spatial heterogeneity of 38:6 and 40:6 PE species in

control mice, which was absent with *Cpt1a* deficiency. Bulk RNA-sequencing analysis revealed that male LKO mice increased PPARα-target genes involved in mitochondrial (*Cpt2*, *Acadm*) and peroxisomal oxidation (*Acaa1b*, *Acox1*), while female LKO mice increased genes more involved in lipid droplet formation (*Plin2*, *Plin5*, *Cidec*) and inflammation (*Tnfa*, *Cd63*, *Mmp12*). Consistent with gene expression, protein levels of PLIN2, PLIN5, and G0S2 were significantly elevated in female LKO mice, which associated with impaired protein kinase a (PKA)-mediated triglyceride hydrolysis in these mice.

Conclusions: Liver specific deletion of CPT1a promotes sexually dimorphic NAFLD in female mice without influencing body weight or adiposity. Mechanistically, female LKO deplete their hepatic PUFAs and increase expression of genes involved in lipid droplet metabolism and inflammation, which collectively contribute to the more severe NAFLD observed in these mice.

Real-Time imaging of long-chain acyl-CoAs reveals a metabolic synapse in brown adipocytes and allosteric regulation of AMPK in white adipocytes

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Fatty acids are activated through ATP-dependent long chain acyl-CoA synthetases that conjugate fatty acids with coenzyme A (CoA) to generate acyl-CoAs. These acyl-CoAs are substrates to numerous enzymatic reactions that generate a multitude of important lipids. In addition, acyl-CoAs have been demonstrated to be allosteric regulators of enzymes and kinases. The generation and use of intracellular long-chain acyl-CoAs (LC-acyl-CoAs) is thought to be under tight spatial and temporal controls, yet the ability to image LC-acyl-CoAs in live cells is lacking, thus limiting our further understanding of these important lipids. We have developed a FRET sensor for LC-acyl-CoAs based on the allosterically regulated interaction between α/β hydrolase domain-containing 5 (ABHD5, also known as CGI-58) and Perilipin5. The genetically-encoded sensor rapidly detects intracellular LC-acyl-CoAs generated from exogenous and endogenous fatty acids, as well as exogenous synthetic ABHD5 ligands. Stimulation of lipolysis in brown adipocytes elevated intracellular LC-acyl-CoAs in a cyclic fashion, which was eliminated by inhibiting ATGL, the major triglyceride lipase and rate limiting enzyme for triacylglycerol hydrolysis. Interestingly, inhibition of LC-acyl-CoA transport into mitochondria elevated intracellular LC-acyl-CoAs and dampened their cycling. Together, these observations reveal an intimate feedback control between LC-acyl-CoA generation from lipolysis and utilization in mitochondria demonstrating a metabolic synapse between these two organelles. In white adipocytes, stimulation of lipolysis resulted in the rapid generation of LC-acyl-CoAs and the activation of AMPK. Inhibition of ATGL blocked the generation of LC-acyl-CoAs and AMPK activation. Moreover, the direct stimulation of lipolysis by pharmacological activation of ABHD5 independent of PKA stimulation, also activated AMPK. Finally, methods to raise intracellular LC-acyl-CoAs in adipocytes results in greater activation of AMPK. These results suggest that in response to lipolysis the generation of LC-acyl-CoAs function to allosterically activate AMPK. We anticipate that this sensor will be an important tool to dissect intracellular LC-acyl-CoA dynamics and signaling, as well to discover novel synthetic ABHD5 ligands.

Visualizing lipid metabolic activities in brain during aging processes

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Abstract

Numerous studies have demonstrated the association between brain lipid metabolism and biological aging, influenced by both dietary and genetic factors. However, the precise underlying mechanisms remain largely unknown. High-resolution imaging techniques offer a novel and powerful approach to comprehending the dynamics of lipid metabolism in its natural context. In our research, we employed deuterium water (D2O) probing in conjunction with stimulated Raman scattering (DO-SRS) microscopy to unveil how lipid metabolic activity in the brain of Drosophila melanogaster changes with age in a sex-dependent manner. Our findings revealed that the decrease in lipid turnover occurs earlier in female flies compared to males. Additionally, we observed that dietary restriction (DR) and the downregulation of the insulin/IGF-1 signaling (IIS) pathway, both known to extend lifespan, significantly enhanced brain lipid turnover in older flies. To further elucidate the mechanisms at play, we combined SRS imaging with deuterated bioorthogonal probes, specifically deuterated glucose and deuterated acetate. This combination allowed us to determine that, under DR treatment and downregulation of the IIS pathway, the brain's metabolic profile shifted towards utilizing acetate as the primary carbon source for lipid synthesis.

Short bio:

Prof. Lingyan Shi's research focuses on developing high resolution, high speed multimodal microscopy, and its applications for studying metabolic dynamics in aging and diseases. She discovered "Golden Window" for deep tissue imaging and developed metabolic imaging platform **DO-SRS**. Shi group transformed SRS into a super resolution multiplex microscopy with **A-PoD** and **PRM** algorithms. Dr. Shi holds 7 awarded patents. She won Blavatnik Regional Award for Young Scientist in 2018; Hellman Fellowship Award 2021; "Rising Star Award" by Nature Light Science & Applications in 2021; "Advancing Bioimaging Scialog Fellow" by RCSA and CZI; and Sloan Research Fellow Award in Chemistry 2023.

Elucidating the role of TREM2/ApoE interactions in microglial activation and Alzheimer's disease with molecular simulations

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Alzheimer's disease (AD) is a progressive and ultimately fatal neurodegenerative disease that impacts millions of Americans annually. Changes in brain morphology are the hallmark indicators of disease pathology, but the root cause of AD has yet to be identified. However, a small number of genetic variants have been linked to increased AD risk, including certain isoforms of apolipoprotein E (ApoE) and mutations in the microglial surface protein Triggering receptor expressed on myeloid cells 2 (TREM2). More specifically, ApoE4 and TREM2^{R47H} are the first and second greatest known genetic risks for late onset AD, respectively, and their direct interaction is thought to have synergistically detrimental impacts on AD pathology. Despite identification of these variants, the mechanisms by which TREM2 and ApoE interact on a molecular level and how these interactions are impacted by the presence of AD risk-associated mutations remain elusive. Herein, we describe the use of molecular docking and molecular dynamics simulations to investigate direct binding interactions between TREM2 and ApoE. These simulations illustrate the impact on ligand binding of several AD-associated mutations on TREM2's ligand binding patch (R47H, R62H, T96K) and isoforms of ApoE (ApoE2/3/4), in tandem with protective mutations of ApoE (R136S, V236E). Overall, this work provides novel insights into how potential antagonistic protein-protein interactions due to multiple mutations impact key ligand binding events at the microglial cell surface. More broadly, the observed changes in binding suggest possible alterations in downstream microglial signaling/activation, which could have important consequences for the onset and/or progression of AD.

Lipokines secreted from brown fat of long-lived mice regulate hepatic pathologies and metabolic abnormalities in obesity

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Brown adipose tissue (BAT) plays a significant role in promoting metabolic benefits by consuming energy and secreting signaling molecules that facilitate inter-organ crosstalk. Ames dwarf homozygous (Dwarf) mice, known for their extended longevity, have enhanced BAT activity. Using targeted LC-MS/MS, we previously identified several elevated lipid species in the BAT of Dwarf mice (Dwarf-BAT) compared to the control heterozygous (Het) mice, and any of these lipid species are linked to healthy aging. To determine if Dwarf-BAT could directly convey metabolic benefits, we transplanted either Dwarf-BAT or Het-BAT into recipient Het mice fed with a high-fat diet. Mice receiving Dwarf-BAT transplants exhibited an improvement in glucose tolerance and insulin sensitivity. Importantly, transplantation of Dwarf-BAT significantly reduced high-fat-induced hepatic steatosis, accompanied by reduced triacylglycerol levels and decreased expression of genes involved in hepatic lipogenesis and inflammation. Lipidomic analyses revealed that 18-HETE (hydroxy-5Z,8Z,11Z,14Z-eicosatetraenoic acid) level was significantly elevated in the circulation of mice receiving Dwarf-BAT transplants. The level of 18-HETE was also significantly higher in BAT and circulation of the Dwarf mice compared to those in the Het mice, suggesting that Dwarf-BAT could secrete 18-HETE. In humans, circulating levels of 18-HETE were inversely correlated with body mass index, fasting plasma insulin level, hemoglobin A1c, and insulin resistance. Additionally, plasma 18-HETE levels were higher in healthy individuals than in those with nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) and were negatively correlated with NAS steatosis score in histology, and liver stiffness and steatosis quantified by ultrasound imaging. In diet-induced NASH and NAFLD mouse models, 18-HETE administration led to improved glucose tolerance and insulin intensity, reduced liver steatosis and fibrosis, and upregulation of fatty acid oxidation genes, such as *Pparα* and *Cpt2*. Consistent with *in vivo* findings, 18-HETE also decreased lipid accumulation in mouse hepatocytes. In *C. elegans*, 18-HETE extended the lifespan. Taken together, these findings suggest that Dwarf-BAT-derived 18-HETE can counteract diet-induced metabolic abnormalities and hepatic steatosis through the increase of hepatic fatty acid oxidation.

Age-dependent Pdgfrβ signaling drives adipocyte progenitor dysfunction to alter the beige adipogenic niche in male mice

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Abstract: Perivascular adipocyte progenitor cells (APCs) can generate cold temperature-induced thermogenic beige adipocytes within white adipose tissue (WAT), an effect that could counteract excess fat mass and metabolic pathologies. Yet, the ability to generate beige adipocytes declines with age, creating a key challenge for their therapeutic potential. Here we show that ageing beige APCs overexpress platelet derived growth factor receptor beta (*Pdgfrβ*) to prevent beige adipogenesis. We show that genetically deleting *Pdgfrβ*, in adult male mice, restores beige adipocyte generation whereas activating *Pdgfrβ* in juvenile mice blocks beige fat formation. Mechanistically, we find that Stat1 phosphorylation mediates Pdgfrβ beige APC signaling to suppress *IL-33* induction, which dampens immunological genes such as *IL-13* and *IL-5*. Moreover, pharmacologically targeting Pdgfrβ signaling restores beige adipocyte development by rejuvenating the immunological niche. Thus, targeting Pdgfrβ signaling could be a strategy to restore WAT immune cell function to stimulate beige fat in adult mammals.

An enteroendocrine-microbial axis in the large intestine controls host metabolism

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“Nutrient handling is an essential function of the gastrointestinal tract. Most nutrient absorption occurs in the small intestine and is coordinated by hormone-producing intestinal epithelial cells known as enteroendocrine cells (EECs). In contrast, the colon mostly reclaims water and electrolytes, and handles the influx of microbially-derived metabolites, including short chain fatty acids (SCFA). Hormonal responses of small intestinal EECs have been extensively studied but much less in known about the role of colonic EECs in metabolic regulation. To address this core question, we investigated a mouse model deficient in colonic EECs. We found that colonic EEC deficiency leads to hyperphagia and obesity. Surprisingly, colonic EEC deficiency results in altered microbiota composition and metabolism, which we found through antibiotic treatment and transfer to germ free recipients, to be both necessary and sufficient for the development of obesity. Moreover, studying stool and blood metabolomes, we found that differential glutamate production by intestinal microbiota corresponds to increase appetite due to EEC loss. Finally, we show that colonic glutamate administration can directly increase food intake and activate appetite centers in the central nervous system. These observations shed light on an unanticipated host-microbiota axis in the colon, part of a larger gut-brain axis, that regulates host metabolism and body weight.”

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Perivascular adipose tissue remodeling modulates vascular mitochondrial metabolism

Diabetes increases cardiovascular disease (CVD) risk. Diabetes-mediated vascular pathology proceeds differently in men and women. We reported that housing rats at thermoneutral (30°C, TN) conditions alters perivascular adipose tissue (PVAT) phenotype. We also observed related abnormalities in vasoreactivity and mitochondrial function with sex-differences. We hypothesized that TN-mediated PVAT phenotypic transformation alters brown adipose tissue (BAT) regulator PRDM16, fatty acid composition, fatty acid (FA) transporter FATP1, and mitochondrial lipid oxidation in a sex-dependent manner. Male and female Wistar rats were housed at room temperature (24°C, RT) or TN for 16 weeks. Endpoints included PVAT phenotypic characterization, RNA seq analysis, and PVAT mitochondrial respiration. PVAT phenotype was morphologically different between TN and RT rats, with rats housed at TN having 19.7% less BAT phenotype overall ($p<0.05$). UCP-1 expression was lower in animals housed at TN ($p=0.06$). PRDM16 was significantly dampened in all animals at TN ($p<0.05$), and notably decreased in males at TN (80.6%, $p<0.05$). Loss of BAT markers was associated with changes in FA regulation. Genomic expression of FATP1 was lower in all animals at TN, more prominently in females. Palmitoleic and arachidonic acids were significantly lower in TN females (48.5% and 15.5%, respectively, $p<0.05$) and males (63.0% and 40.1%, respectively, $p<0.05$). PVAT of all animals housed at TN showed mitochondrial respiration significantly diminished in lipid substrate experiments for state 3, 4, and uncoupled ($p<0.05$ for all), aligning with our previous reports in aorta. These data support a model wherein altered PVAT phenotype and FA composition impacts lipid transport and utilization. These changes are associated with differential impact on vascular impairment between females and males. These results provide insights into sex differences in PVAT contributions to vascular disease progression and vascular crosstalk.

Farnesoid X receptor agonism prevents neutrophil extracellular traps via reduced sphingosine-1-phosphate in chronic kidney disease

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Background: Activation of the farnesoid X receptor (FXR) reduces renal inflammation, but the underlying mechanisms remain elusive. Neutrophil extracellular traps (NETs) are webs of DNA formed when neutrophils undergo specialized programmed cell death (NETosis). Sphingosine-1-phosphate (S1P) is a signaling lipid that stimulates NETosis via its receptor on neutrophils. Here, we identify FXR as a negative regulator of kidney NETosis via repressing S1P signaling in male but not female mice.

Methods: We determined the effects of the FXR agonist obeticholic acid (OCA) in mouse models of adenosine phosphoribosyltransferase deficiency and Alport syndrome. We assessed renal NETosis by immunofluorescence in these models and in biopsies from patients with Alport syndrome (6 male, 9 female). We also inhibited de novo sphingosine production in Alport mice to show a causal relationship between S1P signaling and renal NETosis.

Results: Renal FXR activity is greatly reduced in both models, and OCA prevents kidney fibrosis, inflammation, and lipotoxicity. OCA reduces renal neutrophilic inflammation and NETosis in male adenine and Alport mice, but not in female adenine mice. Extensive NETosis was also identified in human Alport kidney biopsies. Kidney sphingosine kinase 1 (Sphk1) expression is increased in mice with kidney disease and reduced by OCA in male but not female mice. Also, Sphk1 expression correlates with NETosis in male but not female mice. Short-term inhibition of sphingosine synthesis reduces neutrophilic inflammation and NETosis.

Conclusion: FXR agonism represses kidney Sphk1 expression in male but not female mice. This inhibits renal S1P signaling, thereby reducing neutrophilic inflammation and NETosis in a sex-dependent manner.

Funding: NIH/NIDDK grant numbers F30DK129003, R01DK127830, R01DK116567

Deletion of Sphingosine 1-Phosphate Receptor 1 in Myeloid Cells Attenuates Murine Metabolic Dysfunction-Associated Steatohepatitis

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One of the key players in metabolic dysfunction-associated steatohepatitis (MASH) progression is immune cell-driven inflammation. These include macrophages, monocytes, NK cells, T cells, NKT cells, and B cells which differentially express the sphingosine 1-phosphate (S1P) family of receptors, $S1P_1$ – $S1P_5$. We have previously demonstrated that pharmacological S1P receptor modulation ameliorates MASH which is associated with attenuated hepatic macrophage accumulation and altered intrahepatic T cell populations. Due to the prominent role of monocyte-derived macrophages in the sterile inflammation of MASH, we hypothesized that deletion of S1P receptor 1 in myeloid cells may ameliorate MASH by reducing recruitment of proinflammatory monocyte-derived macrophages in to the liver. $S1PR_1$ floxed mice, were crossed with *Lyz2-Cre* mice to generate myeloid cell specific knockout mice, termed $S1pr1^{MKO}$. A murine MASH model was established by dietary feeding of C57BL/6 male mice with a diet high in fructose, saturated fat, and cholesterol (FFC) for 24 weeks. Liver injury and inflammation were determined by histological and gene expression analyses. Intrahepatic leukocyte populations were analyzed by flow cytometry, mass cytometry by time-of-flight (CyTOF), immunohistochemistry, and mRNA expression. Histological examination of livers from FFC-fed $S1pr1^{MKO}$ mice demonstrated a reduction in liver inflammatory infiltrates in FFC-fed $S1pr1^{MKO}$ compared to littermate $S1pr1^{loxp/loxp}$ controls. There was a corresponding reduction in alanine aminotransferase (ALT), a sensitive marker for liver injury. A significant decrease in monocyte-derived macrophage accumulation was noted in the livers of FFC-fed $S1pr1^{MKO}$ mice compared to $S1pr1^{loxp/loxp}$. Normalized gene expression analyses revealed a significant increase in *Timd4* (resident macrophage marker) and *Marco* (non-inflammatory macrophage marker) expression in FFC-fed $S1pr1^{MKO}$ mice, and significant decrease in *Ly6G* (proinflammatory neutrophil marker) in $S1pr1^{MKO}$ mice. Quantification of Picro-Sirius Red positive areas confirmed a significant decrease collagen deposition in FFC-fed $S1pr1^{MKO}$ mice. Gene ontology pathway analysis revealed a significant enrichment of the PPARγ and MAPK pathway in the $S1pr1^{MKO}$ mice. In conclusion, deletion of $S1P_1$ in myeloid cells results in substantial attenuation of liver injury, inflammation, monocyte-derived macrophage accumulation, and fibrosis in murine MASH.

Paradoxical activation of mTORC2 during fasting regulates mitochondrial fission and fat metabolism.

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Introduction: Aging associates with a decline in mitochondrial function which, in turn, predisposes to diverse age-related diseases. Mitochondria adapt to changes in nutrient availability and lack thereof through changes in dynamics and respiration. However, we do not completely understand the mechanisms driving these mitochondrial adaptations when nutrients are scarce. **Methods:** Animals: Studies were performed in 2-10-month-old male and female mice. Liver-specific *Rictor* knock-out (*Rictor*^{KO}) mice were generated by injecting *Rictor*$^{flox/flox}$ mice with AAV8-TBG-iCre for 8 weeks. DNA/siRNA transfections: In vitro transfections were performed using Lipofectamine3000. Liver-specific delivery of DNA was performed via In vivo-jetPEI®, and siRNA was delivered using Invivofectamine™ 3.0. Subcellular fractionation was performed as described by Wieckowski MR et al. Nat Protoc (2009). Phosphoproteomics: Liver homogenates and mitochondrial-associated membranes (MAM) or co-IP eluents were resuspended in 2% SDS/5 mM DTT buffer, digested in S-trap columns, and peptides were analyzed by nLC-MS/MS. Confocal imaging: Serum-starved cells exposed to MitoTracker™ Green FM (to stain for mitochondria) were tracked via laser scanning microscopy. Statistics: Unpaired Student's T-test, one-way or two-way ANOVA followed by appropriate multiple-comparisons tests. **Results:** We have found that fasting paradoxically reactivates the nutrient-sensitive mTORC2 pathway in liver. This mTORC2 reactivation supports fasting-induced increases in mitochondrial fission and respiration. Accordingly, inactivation of mTORC2 in liver by knocking-out its regulatory protein, RICTOR (*Rictor*^{KO}), impairs fasting-induced increases in fission and mitochondrial respiration. Consequently, fasted *Rictor*^{KO} livers exhibit marked accumulation of triglycerides due to failure to mobilize these lipids. Using quantitative phosphoproteomics, we identified a new role for mTORC2 in driving mitochondrial fission in liver by regulating the recruitment of a cascade of novel downstream targets at MAMs, which are contact sites for ER-mediated mitochondrial fission. Interestingly, we have also found that this fasting-induced mTORC2 reactivation and mitochondrial fission are each markedly suppressed with age. **Conclusions:** Nutrients activate mTOR signaling for anabolic functions; however,

fasting-induced reactivation of mTORC2 plays an unexpected role in mitochondrial division and respiration, a response that is suppressed with age. Since loss of RICTOR associates with decreases lifespan, stimulating mTORC2 to restore mitochondrial fission and respiration may be a novel strategy to extend healthspan and lifespan.

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Title: Endogenous nanoparticle dysregulation in Alzheimer's disease

Genetic and functional evidence are emerging supporting metabolic failure and lipid dysregulation in Alzheimer's disease (AD) and aging. Genome wide association studies (GWAS) have identified risk variants for AD involved in lipid metabolism and trafficking. Lipidomic data from human biospecimens and mouse models corroborate lipid dyshomeostasis and supply evidence for Lands cycle dysregulation in disease progression. We tested the hypothesis that lipids associated with acyl chain remodeling were selectively dysregulated in AD using publicly available data sets as well as in human biospecimens and mouse models of AD. We found acyl chain remodeling defects could be modeled in lipidomic data from Religious Order Study, Memory Aging Project (ROS-MAP) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). To determine the functional consequences of dysregulation of acyl chain remodeling, we used novel lipid binding assays, including functionalized carbon nanotubes, to identify specific lipid binding with amyloid β-peptide (Aβ). We found that lipids with polyunsaturated acyl chains altered aggregation state and secondary structure of Aβ. Further, NMR studies identified a specific binding site on Aβ for phosphatidylcholine harboring docosahexaenoic acid. Endogenous nanoparticles immune-isolated from human cerebral spinal fluid further corroborated specificity for lipid species involved in acyl chain remodeling in carriers of the apolipoprotein E4 allele, at high risk for developing AD. Our studies identified acyl chain remodeling deficits in system-wide studies of phospholipid dysregulation and disease progression. We showed preferential binding of phospholipids with polyunsaturated acyl chains to Aβ-peptide which resulted in functional consequences in Aβ structure, aggregation and endogenous nanoparticle formation. Altered acyl chain content across phospholipid classes across disease progression reflects functional changes and dysregulation of endogenous nanoparticles.

Mboat7 Deletion Results in Dysfunction Mitochondria

Preethi Chandrasekaran, Chai-Wan Kim, and Matthew Mitsche

University of Texas Southwestern Medical Center, Center for Human Nutrition

Variants in or adjacent to MBOAT7 have been association with increased risk of numerous diseases, including fatty liver, cirrhosis, autism, and renal clear cell carcinoma. Mboat7 is a 20:4 and phosphatidylinositol (PI) specific acyltransferase. Previous we (and others) shows that deletion of hepatic *MBOAT7* (LSKO) caused steatosis, increasing *SREBP1c* activation resulting increase *de novo* lipogenesis, and increased rate of PI biosynthesis. Here we demonstrate that LSKO of Mboat7 also results in mitochondrial disfunction. Mitochondria in LSKO mice lack internal organized cristae structure and have a 50% reduction in oxygen consumption rate. There is an 80% reduction in hepatic cardiolipins and a shift in the cardiolipin precursor, phosphatidylglycerols (PG), from the mitochondria to the ER, with no net change in total hepatic PG. These phenotypes persisted with hepatic deletion of both *SCAP* and *MBOAT7.* No change was observed in the mRNA of cardiolipin biosynthesis or remodeling enzymes and no change was observed in the rate of lyso-cardiolipin acyltransferase rate. To further investigate this phenotype, we generated mice with tissue specific deletions of *mboat7* in either the heart (HSKO) or adipose tissue (ASKO). HSKO of *Mboat7* caused a nearly doubling of heart weight, a significant reduction in fractional shortening and ejection fraction, and a 3-fold increase in systolic volume with no change in diastolic volume. Mitochondrial phenotype was similar to LSKO mice, where they lacked organized cristae and had a significant reduction in oxygen consumption. Cardiolipins were decreased and mitochondrial PG was reduced, while no change in total cardiac PG was detected. No change in SREBP mRNA targets was detected. Mitochondria derived from brown adipose tissue of ASKO mice also had similar characteristics to the HSKO and LSKO mice, where they lacked cristae, had a significant reduction in oxygen consumption, decreased cardiolipins, and decreased mitochondrial PGs. Thus in three independent tissue specific knockouts of Mboat7 we see dysfunctional and misshapen mitochondria likely caused by a deprivation of cardiolipin, similar to Bartlett syndrome. We hypothesize that this is caused by over-production of PI, which deprives cardiolipin and PG of their common precursor CDP-DAG

ABSTRACT: 25-Hydroxy Vitamin D Insufficiency is Associated with Increased Serum Vitamin D Binding Protein

AUTHOR: Pepkowitz, Samuel

BACKGROUND: The serum concentration of Vitamin D Binding Protein (VDBP) has been reported not to be affected by the concomitant serum concentration of 25-hydroxy cholecalciferol (25VD). Prior publications have noted that VDBP concentration is unaffected or only slightly increased by the administration of 25VD to raise the serum 25VD concentration beyond the normal reference range. No previously published studies have measured VDBP levels in otherwise normal individuals who were insufficient or deficient in 25VD.

METHODS: Serum samples obtained from healthy blood donors were stored frozen at -60 degrees C. Batch assay for VDBP was performed using a research-only ELISA kit (ALPCO Catalogue # 30-2314) according to the manufacturer's directions. 25VD, albumin, and alpha fetoprotein assays were performed on our routine hospital-based laboratory analyzers.

RESULTS: For 25VD less than 34 ng/mL the VDBP concentration demonstrated a significant concave inverse relationship. While many 25VD insufficient/deficient subjects had no VDBP increase from the observed 25VD-sufficient reference range, approximately 20% had markedly increased results.

CONCLUSIONS: The product of the gc-gene while commonly designated Vitamin D Binding Protein, is perhaps more clinically important for its interactions with both the innate and adaptive immune systems and fatty acid transport than its transport of Vitamin D metabolites. Our findings that insufficient 'vitamin D' can be associated with increased VDBP suggests that increased VDBP may be responsible for many of the clinical associations attributed to low 25VD. The megalin-assisted transport of VDBP-bound palmitic acid within the Central Nervous System may play a role in Alzheimer's Disease and other neurodegenerative conditions.

Title:
Connecting the Lipid Universe to Aging and Disease through Big Data and Deep Learning

Authors:
Maximilian Unfried, Michael Ben Ezra, Bo Burla, Federico Torta, Markus R. Wenk, Morten Scheibye-Knudsen, Brian K. Kennedy

Abstract:
Lipids represent a diverse group of biomolecules that play crucial roles in signaling, structural integrity, and energy storage. They are pivotal in understanding diseases and the aging process. Yet neither do we know what most lipids do, nor how many lipids are in our body, or even exist in the universe.

By leveraging the capabilities of Deep Neural Networks and Big Data, we merge Computational Chemistry with Natural Language Processing to establish a connection between the Lipid Universe and aging as well as disease.
Through our research, we have unveiled the vast uncharted territory of the Lipid Universe, estimating the presence of 2-4 million unclassified lipids. Furthermore, employing Deep Learning techniques enables us to generate, optimize and categorize novel lipids effectively. Additionally, by mapping PubMed data to these unclassified lipids we can infer biological function and pathways. Lastly, we can identify lipids with potential geroprotective properties, lead compounds for specific disease indications, or even substitutes for Yamanaka Factors in chemical reprogramming.

Speaker Biography:

Name: Max Unfried
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Affiliation: National University of Singapore
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Biography:

Max is a business minded scientist, pursuing a PhD in the Kennedy Lab at the National University of Singapore. His research combines methodologies from AI, Complexity Science, and Lipidomics to investigate aging biology. In the past he held various leadership positions in financial and life science startups.
Currently, he is part of the core team of VitaDAO, a collective that funds and promotes longevity research, and scientific advisor to Longevity startups and Venture Funds.

Label-free visualization and quantification of lipid droplet dynamics with Nanolive imaging

Nell Saunders[1], Hope Amos[2], Justine Johnson[2], Noah Thyberg[2], Hugo Moreno[2], Lorenzo Archetti[2], Alexandre Jeanne[2], Sebastien Equis[2], Agathe Marguier[2], Timothy Wai[3], Olivier Schwartz[3], **Mathieu Fréchin**[2]

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Lipid droplets play a critical role in cellular metabolism, signaling and disease. Imaging them unaltered is a challenge that, if met, could greatly advance our understanding of cellular processes and lead to better human health. Our holotomographic microscopy platform combined with our machine vision solution enables the imaging and quantification of lipid droplets within live cells without dyes or fluorescence, at high resolution in a time- and cost-effective way. We then exploit our capacity to quantify lipid droplets as well as other cellular compartments to study SARS-CoV-2 infection cycle. We report the label-free detection of mitochondria, lipid droplets, nuclei, and nucleoli from early infection to death. We show that SARS-CoV-2 induces drastic changes in lipid droplets localization, and lipid droplet dry mass. The label-free quantification of cellular organelles during SARS-CoV-2 infection is essential to understand the global impact of coronaviruses on cell function. Altogether this presentation shows the potential of AI-enhanced holotomographic microscopy for the study of cellular biology.

Label-free visualization and quantification of lipid droplets to monitor drug effects on cellular phenotype

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Nanolive imaging platforms automatically measure and analyze cellular responses, label-free to increase confidence in lead candidates at an in vitro preclinical stage. The quantitative and qualitative data produced give a deeper understanding of the therapeutic mode of action, for more biologically relevant conclusions that can help to de-risk the following in vivo stages of drug development.

In this experimental dataset, 6 drugs were screened simultaneously on 3T3 pre-adipocytes in a 96-well plate. 4 concentrations of each drug were tested in triplicate within the same plate. Images of every well were captured every 60 minutes. Cytotoxicity metrics including the type of cell death (apoptosis or necrosis), and death rate were measured over time using Nanolive's label-free LIVE Cell Death Assay. Lipid droplet response was quantified using the label-free Smart Lipid Droplet Assay; this included the change in dry mass per lipid droplet, and the change in lipid droplet count per cell over time.

Using these two approaches to analyze the same dataset, we were able to determine, in one experiment, which treatment conditions had a cytotoxic effect, and which influenced lipid metabolism and storage. A label-free approach both improved the in vitro relevancy of data by avoiding confounding factors such as fluorescence that could influence cellular phenotype, and enabled retroactive analysis of multiple processes using Nanolive's AI-powered digital analyses.

Specific activation of the integrated stress response uncovers novel regulation of central carbon metabolism and lipid droplet biogenesis

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The integrated stress response (ISR) is a central signaling pathway induced by a variety of insults, but how its outputs contribute to downstream physiological effects across diverse cellular contexts remains unclear. Using a synthetic tool, we specifically and tunably activated the ISR and performed multi-omics profiling to define the core modules elicited by this response in the absence of co-activation of parallel pathways commonly induced by pleiotropic stressors. We found that the ISR can elicit time- and dose-dependent gene expression changes that cluster into four modules with ATF4 driving only a small but fast and sensitive module that includes many amino acid metabolic enzymes. We showed that ATF4 was required to reroute carbon utilization towards amino acid synthesis derived both from glucose and reductive carboxylation of glutamine and away from the tricarboxylic acid cycle and fatty acid biogenesis revealing a new role for ATF4 in modulating cellular energetics. We also discovered an ATF4-independent reorganization of cellular lipids that promotes triglycerides synthesis and accumulation of lipid droplets that was essential for cell survival. Together, we demonstrate that a minimal ISR-inducing system is sufficient to trigger formation of two distinct cellular structures, stress granules and lipid droplets, and a previously unappreciated metabolic state.

Characterization of B6-Chr1YP1: a Chromosome 1 Substitution Mouse Line as a Novel Model for Metabolic Syndrome by Phenotypic Screening

Li, Zhiying & Moore, Kelsey
GemPharmatech LLC

Metabolic syndrome (MetS) is a cluster of clinical manifestations including: (1) obesity, abdominal adiposity or insulin resistance, (2) impaired glucose metabolism, (3) hypertension, and (4) atherogenic dyslipidemia. Genetic factors are of great significance in MetS, which contributes to individual and inter-familial differences. The inbred genetic background of existing mouse models limits the in-depth research towards MetS, due to the highly conserved genetic background of each strain. Here, we report the generation of wild mouse-derived Chr1 substitution strains to enrich the genetic background of existing inbred strains and circumvent this limitation. Through phenotype screening, we identified that B6-Chr1YP1 mice (Strain Number: D000750, abbreviated as CSS750) displayed spontaneous MetS phenotypes, including accelerated increase in body weight and fat content after sexual maturation, and the presence of early hepatic steatosis, glucose intolerance and insulin resistance which are absent among B6 mice.

To investigate the mechanism of MetS in B6-Chr1YP1, transcriptome analysis of liver tissue was compared between B6-Chr1YP1 mice fed with chow diet and B6 fed with 60% fat diet (also known as DIO). A total of 72 genes were shared between these two groups, the GO enrichment analysis of which showed that the main biological processes were related to lipid metabolisms, including “long-chain fatty acid metabolic process” and “short-chain fatty acid transmembrane transporter activity”. Notably, of 150 genes that were only differentially expressed in B6-Chr1YP1 mice, 46% belonged to chromosome 1, indicating that the substituted chromosome 1 exerted remarkable effects on the spontaneous MetS of B6-Chr1YP1.

To evaluate the clinical relevance of B6-Chr1YP1, mice were treated with MGL-3196 and Tirzepatide. Both showed obvious pharmaceautical effect on correcting the MetS phenotype of B6-Chr1YP1 mice. In particular, MGL-3196 exhibited stronger lipid lowering effect among B6-Chr1YP1 mice (average reduction was 3.71 mmol/L for cholesterol and 1.56 mmol/L for LDL-C) than that among B6 (2.89 mmol/L for cholesterol and 0.82 mmol/L for LDL-C).

Taken together, B6-Chr1YP1 mice, a wild mouse-derived Chr1 substitution strain exhibits spontaneous MetS phenotypes and responds effectively to high fat diet and clinically proven pharmaceutical reagents. This is a new model for MetS research and preclinical evaluation of novel therapies in metabolic disorders.

Structural Roles for Polyunsaturated Lipids in Organelle Membranes

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The remodeling of biological membranes is an essential process that maintains their necessary shapes, sizes, compositions, and connectivity. Despite the importance of membrane remodeling, many aspects of membrane fusion and fission remain poorly understood, including how proteins assemble on membranes and convert chemical energy into mechanical forces needed to deform membranes. We utilize a combination of chemical synthesis, biophysics, cryo-electron microscopy (cryo-EM), and molecular dynamics (MD) simulations to investigate how one class of fission proteins (ESCRT-III) remodels membranes and alters the physical properties of lipid bilayers to lower the energy barrier for membrane fission. To study the nanoscale structure of highly constricted bilayers, we have generated cryo-EM reconstructions of ESCRT-III-bound membranes with brominated analogs of lipids, which strongly scatter electrons, to reveal lipid leaflet asymmetry induced by high curvature and molecular details of lipid packing. Due to curvature stress from membrane constriction, lipids with negative spontaneous curvature are enriched in the inner leaflet, and lipids with positive spontaneous curvature are enriched in the outer leaflet. Additionally, the ESCRT-III proteins highly distort the structure of the bilayer by substantial thinning of the concave leaflet and displacing lipid headgroups at protein-membrane contact sites. Next, we generated an array of mutants to systematically vary the charge, size, hydrophobicity, and aromaticity of the residues proximal to the bilayer to investigate how the chemical environment created by the proteins around the lipid bilayer generates and stabilizes curvature. Finally, we investigated the role of lipid structure in remodeling by systematically varying lipid composition and observing the change in the energy needed to remodel vesicles into nanotubes. Together, these data provide insight into how ESCRT-III proteins can alter membrane structure to overcome the energetic barrier to curvature generation and ultimately fission.

High fat diet feeding leads to an increase in lipid species associated with metabolic dysfunction in dogs

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The consumption of a high fat diet (HFD) results in increased adiposity, free fatty acid (FFA) levels and insulin resistance leading to poor metabolic outcomes. While preclinical studies investigating HFD-induced metabolic dysfunction are well-described in rodents, HFD feeding in dogs may represent a more translationally relevant model that mimics pathophysiological changes occurring in humans with metabolic dysfunction. We therefore investigated the impact of chronic HFD feeding on fasting metabolic markers, lipidomic profiles and insulin sensitivity in two studies in dogs.

Study 1

Twenty-one male dogs (mixed beagle and mongrels) aged 3-7 years old were sampled at baseline while on a normal diet (ND) and again 10-12 weeks after ND (n=10) or HFD-feeding (n=11) for fasting parameters, lipidomic profiling and insulin sensitivity assessed by intravenous glucose tolerance test (IVGTT). HFD was achieved by augmenting the maintenance diet with pork lard to achieve a 74% final fat content diet.

Study 2

Twenty-four male dogs (beagles) aged 3-7 years old were sampled after 9 weeks while on a ND (n=12) or HFD (n=12) and again 17 weeks after ND or HFD-feeding for fasting parameters and lipidomic profiling. Additionally, insulin sensitivity was assessed by oral glucose tolerance test (OGTT) at 5 weeks of ND or HFD feeding and again after 15 weeks after ND or HFD feeding.

In both studies, feeding a HFD produced an increase in body weight compared to ND-fed dogs ($p>0.001$). HFD-feeding also led to increases in fasting insulin and leptin, while impairing insulin sensitivity measured by IVGTT(SI)($p<0.05$) in Study 1 and OGTT (insulin AUC)($p>0.05$) in Study 2.

Lipidomic profiling revealed that HFD-feeding resulted in significant increases in lipid species associated with metabolic dysfunction compared to dogs fed a normal diet when measured via gas chromatography-mass spectrometry (GC-MS) ($p>0.05$). In both studies FFA was also quantified via a clinically used non-esterified fatty acids (NEFA) assay. Neither study demonstrated any change in NEFA levels at all time points measured. Moreover, there was minimal agreement between the GC-MS FFA quantification and the clinically used NEFA quantification.

These data confirm that HFD-feeding in beagle and mongrel dogs recapitulates metabolic dysfunction seen in other preclinical species, as well as aspects of metabolic dysfunction in human populations. Additionally, clinically used NEFA assays may be insufficient to detect biologically relevant changes in FFA levels in response to metabolic stressors such as HFD.

Vail Summer Activity Ideas

· Free Time through the European-style Vail Village (over 100 shops, pubs and restaurants, which are accessible by walking out our door)
· Walking, hiking and mountain biking on Vail Mountain.
· Take Gondola One (Vail Village) or Gondola 19 (Lionshead) up to the top of Vail Mountain.
· Located at the top of the Eagle Bahn Gondola, Adventure Ridge at Vail has fun activities for all ages at over 10,000 ft, perfect for Colorado family vacations! Enjoy activities like climbing, disc golf, and tubing, or just take in the views while eating BBQ on Talon's Deck.
· Bike Rentals – Venture Sports, offers bike rentals, guided and unguided tours of Vail Pass, shuttles will drop cyclists on a paved bike path (no cars) at the top of Vail Pass, and they enjoy a 3,000 ft. vertical coast downhill back into the Vail Village. Guided tours include gourmet snacks, bottled water and a first-aid /CPR certified guide.
· Jeep Tours through Nova Guides, Lakota Guides or Timberline Tours
· Golf or schedule a scramble at your choice of over half a dozen golf courses in a 30-minute radius, including the award-winning Red Sky Golf Club
· Go to the Spa (Manor Vail Spa offering 10% off treatments for Kern Lipid attendees)
· Bowling at Bol – A tres chic bowling alley in Vail Village
· Enjoy Manor Vail's two pools and 4 hot tubs, heated year-round. We just completed a 7.5-million-dollar renovation on the mountain side pool, hot tubs and restaurant
· Enoy a stroll through Betty Ford Alpine Gardens, a two-minute walk from Manor Vail Lodge

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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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