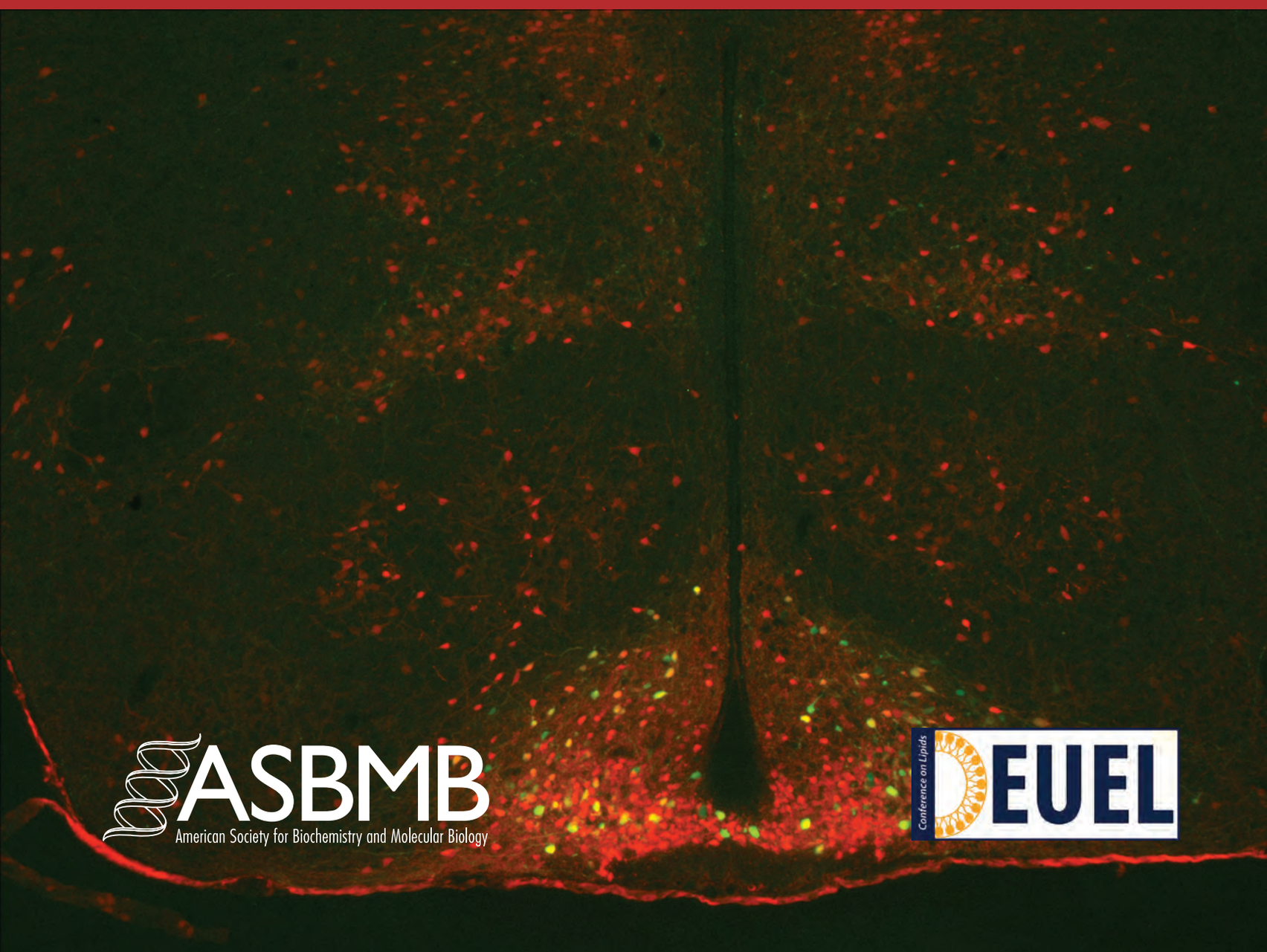
ASBMB-DEUEL CONFERENCE ON LIPIDS

March 6 – 9, 2018
Coronado, Calif.

More than any meeting in the lipid field, the Deuel Conference on Lipids provides a collegial and informal setting for close interactions between scientists from industry and academia.



ASBMB
American Society for Biochemistry and Molecular Biology

Conference on Lipids
DEUEL

2018 SPONSORS

ABIDE THERAPEUTICS

Cayman CHEMICAL

MERCK INVENTING FOR LIFE

Alnylam PHARMACEUTICALS

CSL Behring Biotherapies for Life™

NOVARTIS

AMGEN

Genentech

novo nordisk

ASBMB

IONIS PHARMACEUTICALS

Pfizer

AstraZeneca

Lilly

REGENERON science to medicine™

Avanti POLAR LIPIDS, INC.

JCI The Journal of Clinical Investigation

SANOFI

JLR Journal of Lipid Research

Table of Contents

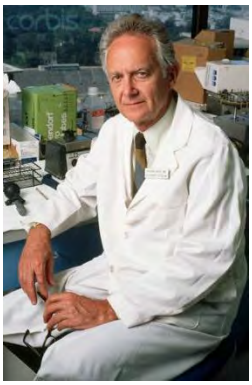
The ASBMB-Deuel Conference on Lipids, March 6 – 9, 2018

Hotel del Coronado, San Diego, Calif.

The Deuel Conference on Lipids was organized in 1955 by a small group of eminent West Coast investigators who were interested in lipid metabolism. Their goal was to establish a high-quality conference on lipids within the western part of the country, akin to forums provided by the Gordon Conferences on the east coast. Shortly after the Conference was organized, one of the founders, Dr. Harry Deuel, died—and the conference was named in his memory. The two-and-one-half day conference includes up to five scientific sessions, with an eminent lipid scientist chairing each session. Each session includes three to four original scientific presentations followed by in-depth discussions of the topic.

The relatively small size of the audience, a round-table format, and the absence of videotaping or recording, encourage informality and the free interchange of new hypotheses and scientific data. Lively discussions by conference participants are the highlight of the meeting.

About the Havel Award Lecture



The Havel Lecture was named after Richard J. Havel because he has done more than anyone else to keep the Conference vibrant. For many years, he organized the meeting, and each year he has energized the scientific discussions.

Richard J. Havel is known to many as "Mr. Lipoprotein, USA." Havel has unraveled the complex metabolism of plasma lipoproteins. As a Clinical Associate in the laboratory of Christian Anfinsen at the National Institute of Health (1953-1956) he published a manuscript on the complex metabolism of the plasma lipoproteins beginning with his pioneering work in the Anfinsen lab at the National Heart Institute in Bethesda, Maryland, where he was one of the first Clinical Associates from 1953–1956. This manuscript is one of the most frequently cited papers in the scientific literature, rivaling Lowry's paper on protein measurement.

Richard Havel has published over 300 manuscripts. The quality of his publications is reflected in his election to the National Academy of Sciences in 1983; the Institute of Medicine in 1989; and the American Academy of Arts and Sciences in 1992. He has received many other honors including the Bristol-Myers Squibb Award for Distinguished Achievement in Nutrition Research and the Distinguished Achievement Award from the AHA Council on Arteriosclerosis.

The first Havel Lecture was held on March 6, 2002, at the 2002 Deuel Conference on Lipids in Borrego Springs, California.

2018 Havel Award Lecturer

Michael Czech,
University of Massachusetts Medical School
"Crosstalk between fat metabolism and neuronal signalling"

PAST HAVEL AWARDEES

2017 
Peter Tontonoz, University of California, Los Angeles
"Transcriptional control of lipid metabolism in physiology and disease"

2016 
Sir Stephen O'Rahilly, University of Cambridge
"Obesity and insulin resistance; lessons from human genetics"

2015 
Thomas Sudhof, Stanford University
"Brown & Goldstein-inspired science off field: lipid membrane fusion at the synapse"

2014 
Rudolf Zechner, University of Graz
"Lipolysis - more than just the breakdown of fat"

2013 
Rick Lifton, Yale University
"From human genetics to validated therapeutic targets"

2012 
Gokhan Hotamisligil, Harvard University
"Inflammation, endoplasmic reticulum stress and lipids: emerging networks regulating metabolism"

2011 
Christopher K. Glass, University of California, San Diego
"Oxysterol regulation of macrophage gene expression"

2010 
David J. Mangelsdorf, University of Texas Southwestern Medical Center
"Nuclear receptor control of lipid metabolism"

2009 
Stephen G. Young, University of California, Los Angeles
"Adventures in lipid metabolism"

2008 
Helen H. Hobbs, University of Texas Southwestern Medical Center
"Going to extremes to identify genetic variations contributing to cardiovascular risk"

2007 
Ronald Evans, The Salk Institute
"PPARdelta and the marathon mouse: running around physiology"

2006 
David Russell, University of Texas Southwestern Medical Center
"The enzymes of cholesterol breakdown"

2005 
Johann Deisenhofer, University of Texas Southwestern Medical Center, HHMI
"Structure of the LDL receptor"

2004 
Jeffrey M. Friedman, Rockefeller University
"Oxysterol regulation of macrophage gene expression"

2003 
Bruce Spiegelman, Harvard Medical School
"Transcriptional control of energy and glucose metabolism"

2002 
Michael S. Brown and Joseph L. Goldstein, University of Texas Southwestern Medical Center
"SREBPs: Master regulators of lipid metabolism"

Schedule At-a-Glance

	Tuesday, 3/6	Wednesday, 3/7	Thursday, 3/8		Friday, 3/9
7AM		Breakfast 7:00-8:15	Breakfast 7:00-8:15	Board Meeting 7:00-8:15	Breakfast 7:00-8:15
8AM		Session 1 8:30-9:55	Session 3 8:30-9:55		Session 5 8:30-10:45
9AM					
10AM		Coffee Break 9:55	Coffee Break 9:55		
11AM		Session 1, Cont. 10:30 – 12:05	Session 3, Cont. 10:30 – 11:50		Closing 10:45
12PM		Free Time 12:05-4:30	Free Time 11:50-4:30		
1PM					
2PM					
3PM	Registration 3:00-5:00				
4PM		4:30-6:00 Poster Session 1	4:30-6:00 Poster Session 2		
5PM	Opening Reception and Dinner 5:00-7:30	6:00-7:15 Dinner	6:00-7:15 Dinner		
6PM					
7PM		7:15-9:15 Session 2	7:15-9:45 Session 4		
8PM	The Havel Lecture 7:40 – 8:30				
9PM					
10PM					

The ASBMB-Deuel Conference Program

Program Co-Chairs: Joel Elmquist (UT Southwestern Medical Center)
and David Mangelsdorf (UT Southwestern Medical Center)

Tuesday, March 6

3:00 – 5:00	Meeting Registration, Garden Patio
5:00 – 7:30	Opening Reception (Garden Patio) and Dinner (Ballroom, Victorian Building)
7:30 – 7:35	Welcome: Jay Horton, UT Southwestern Medical Center
7:35 – 7:40	The Havel Lecture Introduction David Mangelsdorf, UT Southwestern
7:40 – 8:30	The Havel Lecture **" Crosstalk between fat metabolism and neuronal signaling"** Michael Czech, University of Massachusetts Medical School

Wednesday, March 7

8:30 am– 12:05 pm
Session 1: Nutrients and complex behaviors, Ballroom, Victorian Building
Session Chair: **Joel Elmquist, University of Texas Southwestern Medical Center**

8:30 – 9:05	**"Hypothalamic melanocortin system and metabolism"** Tamas Horvath, Yale University
9:05 – 9:40	**"FGF21: From Thirsty to Thin"** Steven Kliewer, UT Southwestern
9:40 – 10:30	Coffee break
10:30 – 11:05	**"PCSK9 as a regulator of the cholesterol homeostasis"** Helen Hobbs, UT Southwestern
11:05 – 11:40	**"From Receptors to Behavior"** Charles Zuker, Columbia University
11:40 – 12:05	**"Macrophage-derived neurotrophic factor GDF15 mediates a novel neuro-immune interaction in adipose tissues"** Joshua Chang, Genentech Inc
12:05 – 4:30	Free time

4:30 – 6:00 Poster Session 1, Ballroom, Victorian Building

6:00 – 7:15 Dinner, Ballroom, Victorian Building

7:15 – 9:15 pm
Session 2: Neuroendocrine control of metabolism, Ballroom, Victorian Building
Session Chair: **Cynthia Hong, Pfizer**

7:15 – 7:50 **"GLP-1 action in the CNS and the regulation of metabolism "**
Darleen Sandoval, University of Michigan

7:50 – 8:25 **"Ghrelin and the metabolic responses to exercise training"**
Jeffrey Zigman, UT Southwestern

8:25 – 9:00 **"Proteostasis, neurons, and metabolism"**
Andrew Dillin, UC Berkeley

9:00 – 9:15 **"Cellular and Synaptic Reorganization after Exercise Training"**
Kevin Williams, UT Southwestern Medical Center

Thursday, March 8

8:30 – 11:50 am
Session 3: Inter-organ communication, Regent, Grande Hall
Session Chair: **Stephen Young, University of California, Los Angeles**

8:30 – 9:05 **"The neuropharmacology of FGF1 as an insulin sensitizer"**
Ronald Evans, The Salk Institute

9:05 – 9:40 **"CNS regulation of glycemia"**
Michael Schwartz, University of Washington

9:40 – 9:55 "**A strategy for discovery of endocrine interactions with application to whole-body metabolism"**
Marcus Seldin, University of California, Los Angeles

9:55 – 10:30 Coffee break

10:30 – 11:05 "**Leptin, glucocorticoids, and metabolic flux**"
Gerald Shulman, Yale University

11:05 – 10:20 **"A non-canonical-PPARγ/RXRα-binding sequence regulates leptin expression in response to changes in adipose tissue mass"**
Yinxin Zhang, The Rockefeller University

11:20 – 11:35 **"IDOL regulates systemic energy balance through control of CNS VLDLR expression"**
Stephen Lee, University of California, Los Angeles

11:35 – 11:50 **"Melanocortin-4 receptor expression in the ventromedial hypothalamus is dynamically regulated by estradiol and contributes to metabolic homeostasis specifically in females"**
William Kraus, University of California, San Francisco

11:50 – 4:30 Free time

4:30 –6:00 Poster Session 2, Ballroom, Victorian Building

6:00 – 7:15 Dinner, Ballroom, Victorian Building

7:15 – 9:45 pm
Session 4: CNS Pathways Regulating Peripheral Metabolism, Ballroom, Victorian Building
Session Chair: **Jay Horton, University of Texas Southwestern Medical Center**

7:15 – 7:20 Journal of Clinical Investigation Lectureship Award Introduction
Corinne Williams, Science Editor, JCI

7:20 – 7:55 Journal of Clinical Investigation Award Lecture
"Mitochondria function in the CNS"
Sabrina Diano, Yale University

7:55 – 8:00 Journal of Lipid Research Lectureship Award Introduction
Edward Dennis, Editor, JLR

8:00 – 8:35 Journal of Lipid Research Award Lecture
"CNS and metabolism"
Jens Brüning, MPI for Metabolism Research, Cologne, Germany

8:35 – 9:10 **"Adipose tissue and the nervous system"**
Ana Domingos, Instituto Gulbenkia de Ciencia, Portugal

9:10 – 9:45 **"Lipoproteins and Alzheimer's disease"**
Joachim Herz, UT Southwestern

8:30 – 10:45 am

Session 5: Therapeutic strategies, Regent, Grande Hall

Session Chair: **Christopher Glass, University of California, San Diego**

8:30 – 9:05	**"CNS pathways linking homeostatic and reward pathways"** Jeffrey Friedman, The Rockefeller University
9:05 – 9:20	**"Disruption of Steroid Receptor Coactivator-1 Signaling is Associated with Obesity"** Yong Xu, Baylor College of Medicine
9:20 – 9:35	Coffee break
9:35 – 10:10	**"Neuroendocrine polypharmacy"** Matthias Tschöp, Helmholtz Institute for Diabetes and Obesity, Germany
10:10 – 10:45	**"Melanocortin receptor regulation of energy balance"** Roger Cone, University of Michigan
10:45	Closing

Poster Presentations

= Abstract/Board Number

1	C2 domain–phosphorylated protein (CDP138) involved in hypothalamic protein trafficking and energy balance	**13**	3D structure of human plasma very low-density lipoprotein and intermediate-density lipoprotein by individual particle cryo-electron tomography
2	Liver X receptors protect dorsal root ganglion neurons from Western diet–induced endoplasmic reticulum stress: Potential role in obesity-induced neuropathy	**14**	Farnesoid X receptor activation by obeticholic acid reduces plasma low-density lipoprotein (LDL)-cholesterol in mice by up-regulating hepatic LDL receptor via a post-transcriptional mechanism
3	A TRPC5-TRPC1-CaV3 complex mediates leptin-induced excitability in hypothalamic neurons	**15**	FGF21, a liver hormone that inhibits alcohol intake in mice, increases in human circulation after acute alcohol ingestion and 3 days of binge drinking at Oktoberfest
4	Disruption of steroid receptor coactivator-1 signaling is associated with obesity	**16**	Dysregulated leptin gene expression leads to a leptin-responsive form of obesity
5	Stepwise processing analyses of the single-turnover PCSK9 protease reveal its substrate sequence specificity and link clinical genotype to lipid phenotype	**17**	Spontaneous non-alcoholic fatty-liver disease, non-alcoholic steatohepatitis, and hepatocellular carcinoma in mice with hepatocyte-specific disruption of Jak2 is reversed in mice with concomitant disruption of Jak2 in both liver and adipose tissue
6	Investigating key effectors of PCSK9 processing and low-density lipoprotein receptor degradation	**18**	The new role of lipin1 in myogenic progenitor differentiation to muscle and adipose tissues
7	A non-canonical PPARγ/RXRα-binding sequence regulates leptin expression in response to changes in adipose tissue mass	**19**	Somatic disruption of Ldlr with AAV-CRISPR as a novel method for atherosclerosis studies
8	A strategy for discovery of endocrine interactions with application to whole-body metabolism	**20**	Copper regulates energy metabolism in adipocytes through semicarbazide-sensitive amine oxidase
9	Engagement of an agouti-related protein–dorsal raphe neural circuit in exclusive control of energy expenditure but not appetite	**21**	The anti-obesity effects of FGF19 and FGF21 require β-Klotho in the central nervous system
10	Deciphering a novel neural circuit bridging the control of feeding and mood disorders	**22**	Structural basis of the lipid transfer mediated by phospholipid transfer protein
11	Brain serotonin neurons project to segregated downstream targets to control hunger-driven feeding and hedonic feeding	**23**	New volume-fluorescence imaging technique reveals the key role of local sympathetic arborizations in white adipose tissue metabolism
12	Deciphering a GABAergic neural circuit in dominant control of leptin-mediated feeding, body weight, and glucose homeostasis	**24**	A new paradigm in atherosclerotic calcification-closure of antioxidant paradox

25	Sustained diabetes remission induced by the action of fibroblast growth factor 1 (FGF1) in the hypothalamic arcuate nucleus	**37**	A novel long-acting FGF21 analogue significantly improves liver steatosis and inflammation and halts progression of fibrosis in preclinical models of NASH
26	The role of the KATP channel in the mesolimbic system of a high-fat diet–induced depression mouse model	**38**	Impact of AGPAT2 deficiency on the mRNA levels of enzymes involved in the glycerolipid synthesis in specific structures of the mouse brain
27	Fibroblast growth factor 21 is a protective pancreatic digestive enzyme secretagogue	**39**	Melanocortin regulation of histamine neuron activity
28	Eicosapentaenoic acid has a membrane orientation that correlates with potent antioxidant activity and reduced lipid disordering as compared with docosahexaenoic acid: X-ray diffraction analysis	**40**	Oleoylethanolamide treatment reduces neurobehavioral deficits and the brain pathology in a mouse model of Gulf War illness
29	Chemical composition and antioxidant and anticholine esterase potentials of essential oil of Monodora myristica (Africa nut) seeds	**41**	Brain-derived neurotrophic factor in the ventromedial hypothalamus: The intersection of exercise and anxiety?
30	Why do leptin levels fall with fasting?	**42**	Cannabinoid 1 receptor in steroidogenic factor 1 neurons regulates glucose homeostasis but not body weight
31	Identification of lipid biomarkers of inflammation and metabolic disturbances in Gulf War illness	**43**	APOE4-dependent deficits in brain lysophosphatidylcholine-docosahexaenoic acid and its transporter mfsd2a in Alzheimer's disease patients
32	The hormone fibroblast growth factor 21 (FGF21) stimulates drinking in response to ketogenic diet and alcohol	**44**	Molecular interactions of ANGPTL8 with ANGPTL3 and ANGPTL4: Consequences for activity of lipoprotein lipase
33	Human thermogenic adipose tissue development and metabolic disease	**45**	Phosphatidylcholine synthesis coordinates the metabolic response to dietary fat in the murine intestinal epithelium
34	c-Abl mediates tyrosine transcription factor EB phosphorylation and its cytoplasmic localization: Implications in the Niemann–Pick type C cholesterol lysosomal storage disease	**46**	12-Hydroxylated bile acids regulate food intake and gastric emptying through GPR119 in the intestine
35	Functional dissection of the central glucoregulatory circuits	**47**	Reactivation of myeloid cell TLR4 promotes LPS-induced acute inflammation and anorexia in mice
36	Macrophage-derived neurotrophic factor GDF15 mediates a novel neuro-immune interaction in adipose tissues	**48**	Role of de novo lipogenesis in white adipose tissue signaling to brown adipose tissue in regulating thermogenesis through neural circuitry

49	Identifying transcriptional targets of steroidogenic factor-1 in the ventromedial hypothalamus
50	Secreted micropeptides in the regulation of metabolic homeostasis
51	Functional analyses of DGAT enzymes in adipose tissue
52	Weight loss induced by FGF21 is associated with up-regulation of neurotensin and corticotropin-releasing hormone in dorsomedial hypothalamus and increased hepatic bile acid and glucose secretion in liver of DIO mice
53	Examining high-density lipoproteins in cerebral spinal fluid
54	Mechanisms coordinating de novo lipogenesis with triglyceride synthesis
55	IDOL regulates systemic energy balance through control of central nervous system very low-density lipoprotein receptor expression
56	Melanocortin-4 receptor expression in the ventromedial hypothalamus is dynamically regulated by estradiol and contributes to metabolic homeostasis specifically in females
57	Nitro-oleic acid distribution in lipoprotein triglycerides
58	Cellular and synaptic reorganization after exercise training

1

C2 domain–phosphorylated protein (CDP138) involved in hypothalamic protein trafficking and energy balance

Chaitanya Gavini[1], Emilie Verran[2], Joel Elmquist[3], Tiemin Liu[3], Virginie Mansuy-Aubert[1]

[1]Loyola University Chicago, Maywood, IL; [2]Augustana College, Rock Island, IL; [3]University of Texas Southwestern Medical School, Dallas, TX

Obesity is arguably the most crucial health concern, as 34% of the population in the United States is now obese. Melanocortin receptor 4 (MC4R) contributes to appetite control in hypothalamic neurons and is a promising target for anti-obesity treatments or drug development, but this is hindered by gaps in our understanding of its regulation. MC4R trafficking (to plasma membrane and/or endocytosis) has been shown to be key to regulation of energy balance and is altered in obesity and in the presence of lipids, but the cellular and molecular mechanisms of altered trafficking are largely unknown. Our studies identified a novel C2 domain–phosphorylated protein of 138 kDa (CDP138) that appears to contribute to the regulation of MC4R trafficking. We found that 1) the expression of CDP138 is altered by changes in diet, 2) baseline expression of CDP138 is lower in genetically obese and high fat–fed mice compared with controls, 3) CDP138 colocalizes and interacts with MC4R complex, and, 4) CDP138 knockout mice exhibit pronounced obesity due to an increase in food intake compared with control mice when fed a high-fat diet. Based on these findings, we hypothesize that CDP138 could be a trafficking protein involved in central regulation of energy balance by modulating hypothalamic receptors via nutritional status. These studies provide evidence for a novel pathway and targets to develop therapeutic drugs aimed at efficiently deceasing body weight in obese patients.

2

Liver X receptors protect dorsal root ganglion neurons from Western diet–induced endoplasmic reticulum stress: Potential role in obesity-induced neuropathy

Raiza Bonomo[1], Chaitanya K. Gavini[1], Davis Thomas[1], David J. Mangelsdorf[2,3], Virginie A. Mansuy[1]

[1]Department of Cell and Molecular Physiology, Stritch School of Medicine, Loyola University Chicago, Maywood, IL; [2]Department of Pharmacology and [3]Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX

Painful diabetic neuropathy (DN) affecting small sensory neurons is one of the most common complications of obesity and type 2 diabetes. Whereas emerging clinical evidence demonstrates that DN is associated with dyslipidemia, the complex molecular and cellular neurobiology triggering the disease is unknown. Emerging evidence demonstrates the important contribution of complex pathways, including endoplasmic reticulum stress and inflammation. Recent OMICs data analyzing the peripheral nervous system (PNS; dorsal root ganglia (DRG) and associated nerves) of obese individuals have highlighted alterations in lipid nuclear receptors, which provide novel insight into the onset of DN. Liver X receptors (LXRs) α and β are nuclear transcription factors that respond to cholesterol or fatty-acid metabolites. Nuclear LXRs control gene programs in liver cells, adipocytes, and macrophages to regulate lipid metabolism, inflammation, and endoplasmic reticulum (ER) stress, although the specific physiological role of LXRs in neurons is difficult to interpret, given its broad tissue expression. Our tissue-specific deletion model unmasks an important role of LXR in small sensory neurons in type 2 DN pathogenesis. Our results show that LXR deletion in sensory neurons worsens the hypersensitivity induced by a Western diet (WD) associated with changes in neuronal gene program (ribo-tag model). In addition, treatment with the LXR agonist GW3965 improves the WD-induced mechanical allodynia *in vivo* and protects from palmitate-induced ER stress *in vitro*, further confirming a protective role for LXR in DN. Our data suggest that the lipid sensor LXRs in small sensory neurons respond to dietary lipid to maintain normal PNS function in the face of high-fat nutrition. We suspect chronic WD-induced LXR signaling alterations that will lead to ER stress, resulting in PNS dysfunction and type 2 diabetic neuropathy phenotype.

3

A TRPC5-TRPC1-CaV3 complex mediates leptin-induced excitability in hypothalamic neurons

Paula P. Perissinotti[1], Elizabeth Martínez-Hernández[1], Erika S. Piedras-Rentería[1]

[1]Physiology Department, Loyola University Chicago, Maywood, IL

Leptin-induced depolarization in POMC neurons is mediated via the Jak2-PI3 kinase-PLCγ pathway that ultimately activates TRPC channel activity, most likely a TRPC1-TRPC5 heteromer. This TRPC complex–induced depolarization is postulated to induce intracellular calcium release, subsequently triggering action potentials (APs) and increasing neuronal excitability; however, the downstream elements of this cascade are not well-defined yet. Here we used cultured neurons to establish the role of T-type Ca^{2+} channels in the leptin-signaling pathway in neuron excitability. Hypothalamic cultures were studied from 8 to 10 days *in vitro*. Immunocytochemistry analysis showed that POMC and NPY neurons were present in the culture, with POMC neurons being the majority of the cells analyzed (85% *versus* 15%, $n = 182$; $p < 0.05$, *z* test). Electrophysiological experiments confirmed that 86% of all neurons tested were leptin-activated, with their resting potential slightly depolarized, their rheobase decreased, and the number of APs increased upon application of 100 nM leptin. Interestingly, leptin application did not directly alter low voltage–activated currents, yet inhibition of T-type channels using 10 μM NNC 55-0396 completely abolished the effect of leptin, similarly to the effect seen with a 100 μM concentration of the TRPC channel blocker 2-APB. Basal excitability was also prevented by the T-type channel blocker, as seen with post-inhibitory rebound experiments and ramp protocols. Evidence shows that ion channels work in coordination as part of macromolecular complexes within cells; thus, we tested whether TRPC1/5 channels could be detected in complex with CaV3 channels. Immunoprecipitation experiments showed that both TRPC1 and C5 co-precipitate with either CaV3.1 or CaV3.2 (and vice versa). Moreover, given that the Na/Ca permeability through TRPC1/5 channels is ~0.95, to test whether this channel complex is physiologically relevant in the leptin cascade, we assessed the effect of leptin in the presence of intracellular calcium buffers with similar affinities but different binding rate constants. Indeed, the fast chelator BAPTA precluded the local effect of leptin, whereas EGTA (>100 times slower buffer) did not alter the leptin response, corroborating that calcium influx through TRPC1/5 and/or its contribution to membrane depolarization recruit adjacent T-type channels within the complex, increasing neuronal excitability.

4

Disruption of steroid receptor coactivator-1 signaling is associated with obesity

Yongjie Yang[1], Agatha Klaauw[2], Liangru Zhu[1], Tessa Cacciottolo[2], Bert O'Malley[1], Sadaf Farooqi[2], Yong Xu[1]

[1]Baylor College of Medicine, Houston, TX; [2]University of Cambridge, Cambridge, United Kingdom

Steroid receptor coactivator-1 (SRC-1) is a coactivator that modulates the activity of nuclear hormone receptors and transcription factors. Here, we showed that in the hypothalamus, SRC-1 interacts with phosphorylated STAT3 to potentiate the ability of leptin to stimulate transcription of the anorectic peptide pro-opiomelanocortin (Pomc). In mice, targeted deletion of SRC-1 in Pomc neurons attenuated their depolarization by leptin, decreased Pomc expression, and increased food intake, leading to diet-induced obesity. In humans, we identified 15 rare heterozygous variants in SRC-1 in 2,548 severely obese individuals. These variants impaired leptin-mediated Pomc reporter activity in cells, whereas four rare variants found in 1,117 non-obese controls did not. We generated a knockin mouse model of a human SRC-1 variant, which exhibited increased food intake and weight gain, providing additional evidence that disruption of SRC-1 contributes to human obesity. Targeting this molecular interaction to modulate leptin sensitivity may be useful in the treatment of obesity-related metabolic disease.

5

Stepwise processing analyses of the single-turnover PCSK9 protease reveal its substrate sequence specificity and link clinical genotype to lipid phenotype

John S. Chorba[1,2,3], Adri M. Galvan[2,3], Kevan M. Shokat[2,3]

[1]Division of Cardiology and Department of Medicine, Zuckerberg San Francisco General Hospital, San Francisco, CA; [2]Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA; [3]Howard Hughes Medical Institute, San Francisco, CA

Proprotein convertase subtilisin/kexin type 9 (PCSK9) down-regulates the low-density lipoprotein (LDL) receptor (LDL-R), elevating LDL cholesterol and accelerating atherosclerotic heart disease, making it a promising cardiovascular drug target. To achieve its maximal effect on the LDL-R, PCSK9 requires autoproteolysis. After cleavage, PCSK9 retains its prodomain in the active site as a self-inhibitor. Unlike other proprotein convertases, however, this retention is permanent, inhibiting any further protease activity for the remainder of its life cycle. Such inhibition has proven a major challenge to a complete biochemical characterization of PCSK9's proteolytic function, which could inform therapeutic approaches against its hypercholesterolemic effects. To address this challenge, we employed a cell-based, high-throughput method using a luciferase readout to evaluate the single-turnover PCSK9 proteolytic event. We combined this method with saturation mutagenesis libraries to interrogate the sequence specificities of both PCSK9 cleavage and proteolysis-independent secretion. Our results highlight several key differences in sequence identity between these two steps, complement known structural data, and suggest that PCSK9 self-proteolysis is the rate-limiting step of secretion. Additionally, we found that for missense single-nucleotide polymorphisms (SNPs) within PCSK9, alterations in both proteolysis and secretion are common. Last, we show that some SNPs allosterically modulate PCSK9's substrate sequence specificity. Our findings indicate that PCSK9 proteolysis acts as a commonly perturbed but critical switch in controlling lipid homeostasis and provide a new hope for the development of small-molecule PCSK9 inhibitors.

6

Investigating key effectors of PCSK9 processing and low-density lipoprotein receptor degradation

Adri M. Galvan[1,2], John S. Chorba[3], Kevan M. Shokat[1]

[1]Department of Molecular and Cellular Pharmacology and Howard Hughes Medical Institute, University of California, San Francisco, CA; [2]Pennsylvania State University College of Medicine, Hershey, PA; [3]Division of Cardiology and Department of Medicine, Zuckerberg San Francisco General and University of California, San Francisco, CA

Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds the LDL receptor (LDL-R) and induces lysosome-mediated degradation, increasing LDL cholesterol (LDL-C) and, consequently, cardiovascular risk. Thus, PCSK9 has emerged as a prime therapeutic target against heart disease. Self-proteolysis of PCSK9 produces a mature, yet catalytically inactive protein that is shuttled extracellularly to bind and chaperone LDL-R for degradation. We previously identified PCSK9 processing as two independent mechanisms: proteolysis and secretion. Whereas PCSK9 production involves two steps, little is known about modulators of PCSK9 and LDL-R binding. Studies have shown LDL-C to inhibit PCSK9-mediated degradation, and recently, heparan sulfate proteoglycans were found to be necessary chaperones for the LDL-R/PCSK9 interaction. Using a high-throughput luminescence assay, we investigated the relationship of these two effector proteins on PCSK9 processing, specifically determining the mechanism of inhibition of LDL-C. We also compared the effects of LDL-C variants, such as oxidized LDL-C and lipoprotein(a), on the hindrance of PCSK9-mediated degradation. With our gained insight into modulators of PCSK9 metabolism, we aim to expand prospective targets for small-molecule inhibitors of PCSK9.

7

A non-canonical PPARγ/RXRα-binding sequence regulates leptin expression in response to changes in adipose tissue mass

Yinxin Zhang[1,2], Robert Roeder[1], Jeffrey Friedman[1,2]

[1]Rockefeller University, New York, NY; [2]Howard Hughes Medical Institute, New York, NY

Leptin expression decreases after fat loss and is increased when obesity develops, and this quantitative regulation is essential for the homeostatic control of fat mass. We previously reported that a distant leptin enhancer (LE1), 16 kb upstream from the transcription start site (TSS), confers fat-specific expression in a BAC transgenic luciferase reporter mouse (BACTG). However, this and the other elements we identified do not appear to account for changes in leptin expression that accompany changes in adipose mass. In this report, we used ATAC-seq to identify a 17-bp non-canonical PPARγ/RXRα-binding site leptin-regulatory element 1 (LepRE1) and found that it is essential for the fat-regulated control of leptin expression. Whereas BACTG reporter mice with mutations in this sequence still show fat-specific reporter expression, luciferase is no longer decreased after food restriction and weight loss. Similarly, the increased expression of leptin reporter associated with obesity is also severely impaired. A functionally analogous LepRE1 site is also found in a second redundant DNA-regulatory element 13 kb downstream of the TSS. These data uncouple the mechanisms conferring qualitative and quantitative expression of the leptin gene and further suggest that a factor(s) that binds to LepRE1 quantitatively controls leptin expression and may be a component(s) of a lipid-sensing system in adipocytes.

8

A strategy for discovery of endocrine interactions with application to whole-body metabolism

Marcus M. Seldin[1], Simon Koplev[2], Prashant Rajbhandari[1], Laurent Vergnes[1], Peter Tontonoz[1], Karen Reue[1], Johan L. M. Björkegren[2], Aldons J. Lusis[1]

[1]UCLA, Los Angeles, CA; [2]Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY

Inter-tissue communication via secreted proteins has been established as a vital mechanism for proper physiologic homeostasis. Here, we report a bioinformatics framework that uses natural variation in transcript levels across tissues in a population to identify and functionally annotate endocrine circuits. This method, termed quantitative endocrine network interaction estimation (QENIE), can be applied to any collection of organs, tissues, or cell types sampled from a genetically diverse population and profiled using omics platforms. Many of the top-ranked candidates for each tissue–tissue axis uncovered by this method already have established mechanisms of endocrine communication, validating the approach. These include leptin, adiponectin, ghrelin, and many other key regulators of physiology. To prioritize discovery of putative endocrine factors, we considered relevant physiologic and clinical traits along with publicly available resources on tissue-specific gene expression. These efforts led to the identification of two new endocrine factors. The first is an adipose-derived protein, lipocalin-5, which enhances skeletal muscle mitochondrial activity, resulting in increased lean body mass and improved insulin sensitivity. The second involves a hepatic secreted protein (notum), which can promote adipose tissue thermogenesis, resulting in improved resistance to cold and increased energy expenditure *in vivo*. To demonstrate the general applicability of the approach, we identify and validate *in vivo* three additional secreted molecules involving communication between adipose and heart (SMOC1 and ITIH5) and within aorta (PPBP). Additionally, we provide evidence for the applicability of the method to human omics data. In conclusion, we have developed a population-based approach for identifying novel communication axes between tissues and cell types using correlation structure that is generally applicable to omics data sets.

9

Engagement of an agouti-related protein–dorsal raphe neural circuit in exclusive control of energy expenditure but not appetite

Yong Han[1], Guobin Xia[1], Dollada Srisai[2], Fantao Meng[3], Yanlin He[1], Sodikdjon Kodirov[2,4], Monica Farias[1], István Tóth[5], Amy Lee[2], Marcelo O. Dietri[6,7], Yong Xu[1], Qi Wu[1]

[1]Baylor College of Medicine, Houston, TX; [2]University of Iowa College of Medicine, Iowa City, IA; [3]University of Texas Southwestern Medical Center, Dallas, TX; [4]Neuroscience Institute, Morehouse School of Medicine, Atlanta, GA; [5]Szent Istvan University, Budapest, Hungary; [6]Yale University School of Medicine, New Haven, CT; [7]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Agouti-related protein (AgRP) neurons in the arcuate nucleus potently promote food intake and suppress energy expenditure. Whereas their role in promotion of food intake has been investigated, the neural circuit and associated neurotransmitter signaling underlying the AgRP neurons in regulation of energy expenditure are unclear. In this report, we show that acute ablation of a subpopulation of AgRP neurons projecting to the dorsal part of dorsal raphe nucleus (dDRN) results in normal food intake but potently augments energy expenditure, as indicated by increased intrascapular brown adipose tissue (iBAT) temperature, core body temperature, and oxygen consumption. Activation of AgRP projections to the dDRN by opto-/chemogenetics suppressed iBAT temperature without affecting food intake. Intriguingly, optogenetic activation of the AgRP-dDRN circuit abolished leptin-mediated increase of iBAT temperature. Furthermore, administration of AgRP to the dDRN caused significant inhibition of energy expenditure, but not feeding, in a dose-dependent manner. In contrast, microinjection of melanotan II (MTII), a MC4R agonist, into the dDRN increased energy expenditure. Calcium imaging, virus-mediated tracing, electron microscopy, and electrophysiological analysis indicated that AgRP directly modulates activity of serotonergic neurons in the dDRN by suppression of MC4R signaling. Genetic reactivation of MC4R in the dDRN increases thermogenesis and oxygen consumption without affecting food intake. Chemogenetic activation of 5-HT neurons in the dDRN causes significant increase in energy expenditure without changing food intake, which can abolish AgRP-mediated suppression of thermogenesis. Conversely, inhibition of these neurons leads to intact feeding yet decreased energy expenditure. Surprisingly, genetic inactivation of Tph2 in the dDRN influences energy expenditure but not feeding, which can abolish AgRP neuron-mediated energy expenditure. Last, we showed that the AgRP-DRN neural circuit mediates energy expenditure by stimulation of iBAT and promotion of beige intrascapular white adipose tissue. Together, these findings reveal a subpopulation of AgRP neurons that distinctly mediates energy expenditure by suppression of serotonergic signaling in the DRN via a MC4R-dependent mechanism.

10

Deciphering a novel neural circuit bridging the control of feeding and mood disorders

Guobin Xia[1], Yong Han[1], Fantao Meng[2], Yanlin He[1], Dollada Srisai[3], Monica Farias[1], Yong Xu[1], Qi Wu[1]

[1]Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX; [2]Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX; [3]Molecular Physiology and Biophysics, University of Iowa College of Medicine, Iowa City, IA

Obesity is co-morbid with major neurological diseases, such as depression, anxiety, and ADHD. So far, neural mechanisms underlying the functional linkage between body weight control and metal states are scarce. We identify a neural circuit in a cross-control of appetite and mood states. Genetic ablation of a subset of AgRP neurons projecting to the dBNST ($AgRP^{ARC\text{-}dBNST}$) or rapid inactivation of their GABA biosynthesis induces anxiety and depression-like behaviors, which can be fully reversed by chronic infusion of bretazenil, a $GABA_A$ receptor partial agonist, into the dBNST. Optogenetic stimulation of the $AgRP^{ARC\text{-}BNST}$ circuit significantly enhances the anxiety and depression level, whereas chemogenetic activation of the post-synaptic $MC4R^{dBNST}$ neurons leads to opposite responses. Notably, such manipulations impose no acute effect on feeding and body weight. Furthermore, phenotypes induced by ablation of the $AgRP^{dBNST}$ neurons are completely restored by chemogenetic silence of the $MC4R^{dBNST}$ neurons. *Htr3a*, encoding the 5-HT_3 receptor A subunits, displays robust differential expression profiles in the $MC4R^{dBNST}$ neurons. Suppression of the 5-HT_3R signaling in the dBNST or inactivation of the $5\text{-}HT^{DRN\text{-}dBNST}$ pathway abolishes the anxiety and depression-like behaviors in the $AgRP^{ARC\text{-}dBNST}$ ablation model. In contrast, mice with genetic deletion of 5-HT biosynthesis within the $5HT^{DRN\text{-}dBNST}$ neurons display anxiolytic and anti-depression responses. We further identify $GABA_A$ receptor α5 subunits (encoded by *Gabra5* gene) as the major inhibitory signaling within the $MC4R^{dBNST}$ neurons that counteracts the excitatory signals through the 5-HT_3R. Using the CRISPR/Cas9 and RNAi gene editing techniques, rapid and specific deletion of *Gabra5* within the $MC4R^{dBNST}$ neurons causes severe anxiety and depression, which is completely rescued as induced by genetic suppression of the $5HT_3$R receptor. Interestingly, mice with chronic high-fat diet (HFD) treatment display significant anxiety and depression. *In vivo* calcium optometry results show a bidirectional modulation of $MC4R^{dBNST}$ neurons in response to HFD and fasting. Importantly, HFD-induced mental dysregulation is fully reversible upon chemogenetic inhibition, suppression of $5HT_3$R signaling, or overexpression of $GABA_A$ receptor α5 of $MC4R^{dBNST}$ neurons. Together, we identify the $ARC^{AgRP::GABA}$-$dBNST^{MC4R::GABRA5::5HT3R}$-$DRN^{5\text{-}HT}$ circuit serving as a critical reciprocal linkage between feeding control and mental states, advocating a conceptual framework in discovery of dual therapeutics for obesity and mental diseases.

11

Brain serotonin neurons project to segregated downstream targets to control hunger-driven feeding and hedonic feeding

Xing Cai[1], Yanlin He[1], Pingwen Xu[1], Yongjie Yang[1], Chunmei Wang[1], Ilirjana Hyseni[1], Yong Xu[1]

[1]Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX

Feeding can be driven by hunger (a state of nutritional deficit) to ensure survival. Feeding can also be triggered by hedonic properties of certain foods (e.g. Western diets) in the absence of nutritional deficit. Dysregulations of hunger-driven feeding and hedonic feeding both contribute to development of obesity. Better understanding the neurobiological mechanisms for these two types of feeding behaviors is essential to develop rational strategies to combat obesity and related co-morbidities, including diabetes. Emerging evidence and our preliminary data demonstrated a critical role of brain serotonin (5-HT) actions in suppressing both hunger-driven feeding and hedonic feeding. The aim of this study is to test that brain 5-HT neurons project to segregated downstream targets to control hunger-driven feeding and hedonic feeding, respectively. We used the "intermittent high fat-diet (HFD)" paradigm to assess hedonic feeding and the classic "fast-induced refeeding" paradigm to assess hunger-driven feeding. We also combined trans-synaptic neurotracing, wheat germ agglutinin (WGA), with channelrhodopsin-2 (ChR2)–assisted circuit mapping (WGA-CRACM), channelrhodopsin-2–assisted light stimulation, conditioned place preference (CPP), and food intake measurement. We found that 5-HT neurons in the dorsal Raphe Nuclei (5-HT^{DRN} neurons) innervate and activate pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus (POMC^{ARH} neurons) via 5-HT 2C receptors (5-HT2CRs), and 5-HT^{DRN} neurons also innervate and inhibit agouti-related peptide-expressing neurons in the ARH (AgRP^{ARH} neurons) via 5-HT1B receptors. Further, 5-HT^{DRN} neurons innervated and activated dopamine neurons in the ventral tegmental area (DA^{VTA} neurons) largely via 5-HT2CR–mediated mechanisms. ChR2-mediated photostimulation of the 5-HT^{DRN}–ARH circuit suppressed hunger-driven feeding but had no effect on hedonic feeding. On the other hand, photostimulation of the 5-HT^{DRN}–VTA circuit suppressed hedonic feeding but did not affect hunger-driven feeding. In the CPP tests, the activation of the 5-HT^{DRN}–ARH circuit transmitted a positive valence signal, but this signal was competed by the availability of low palatable foods (chow), whereas the 5-HT^{DRN}–VTA circuit transmitted a positive valence signal that was competed by hedonic foods (HFD). In conclusion, our studies identified the segregated 5-HT–downstream neural circuits controlling hedonic *versus* hunger-driven feeding, which may facilitate the development of selective serotonin-based therapies for obesity and associated diabetes.

12

Deciphering a GABAergic neural circuit in dominant control of leptin-mediated feeding, body weight, and glucose homeostasis

Yong Han[1], Guobin Xia[1], Monica Farias[1], Qi Wu[1]

[1]Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX

The hormone leptin is known to play a major role in control of glucose metabolism and feeding behaviors by acting upon the LepR-signaling pathway that widely distributes in the central nervous system. Although several LepR-expressing neuronal groups were identified in distinct brain regions involving the control of various metabolic functions of leptin, a dominant neural circuit that mediates the physiological roles of leptin remains elusive, largely due to the inadequate phenotypes found in genetic mouse models as a result of developmental and neural compensations. In this report, a novel, non-sense suppression-based, inducible genetic system is implemented to delete LepR signaling from AgRP neurons in the arcuate nucleus of adult animals within 4 days. Mice with rapid deletion of LepR from AgRP neurons show a drastic increase of food intake, massive weight gain, and severe glucose intolerance, developing in a rate with perfect manifestation of global leptin deficiency. Furthermore, a neural circuit comprising LepR-expressing AgRP neurons and downstream GABAergic neurons in the dorsomedial hypothalamic nucleus (DMH) is mapped by genetic and functional tracing approaches. Optogenetic manipulation of the $AgRP^{LepR}$-DMH^{GABA} neural circuit or the post-synaptic DMH^{MC4R} neurons strongly altered food intake and glucose tolerance in a bidirectional controlled manner. Among all major $GABA_A$ subunits examined in the DMH, *Gabra3* (encoding $GABA_A$ α3 subunits) displayed the most robust differential expression profiles in response to the inactivation of $LepR^{AgRP}$ signaling. Using a CRISPR/Cas9 *in vivo* gene editing technique, loss of *Gabra3* in $MC4R^{DMH}$ neurons reduced food intake and enhanced glucose intolerance. Surprisingly, chronic infusion of bicuculline into the DMH fully reversed the obesity and glucose intolerance as a result of acute deletion of $LepR^{AgRP}$ signaling. Furthermore, genetic ablation of $GABA^{DMH}$ neurons blunted the actions of leptin upon the control of glucose metabolism and food intake. In conclusion, we unveil a novel $ARC^{AgRP::GABA::LepR}$-$DMH^{GABA::MC4R::GABRA3}$ neural circuit and associated $GABA_A$ receptor signaling system in fundamental control of leptin-associated obesity and diabetes.

13

3D structure of human plasma very low-density lipoprotein and intermediate-density lipoprotein by individual particle cryo-electron tomography

Gang Ren[1], Yadong Yu[1], Yu-Lin Kuang[2], Dongsheng Lei[1], Xiaobo Zhai[1], Meng Zhang[1], Ronald M. Krauss[2]

[1]Lawrence Berkeley National Laboratory, Berkeley, CA; [2]Children's Hospital Oakland Research Institute, Oakland, CA

Human lipoprotein assembled in the liver and secreted into the circulation supply energy to peripheral tissues. Very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) lipolysis yields atherogenic low-density lipoproteins (LDLs) and VLDL remnants that strongly correlate with cardiovascular disease. Although the composition of VLDL particles has been well characterized, their 3D structure is elusive because of their variations in size, heterogeneity in composition, structural flexibility, and mobility in solution. Here, we employed cryo-electron microscopy and individual-particle electron tomography to study the 3D structure of individual VLDL and IDL particles (without averaging) both below and above their lipid phase transition temperatures. 3D reconstructions of VLDL and IDL and VLDL/IDL bound to antibodies revealed an unexpected polyhedral shape, in contrast to the generally accepted model of a spherical emulsion-like particle. The smaller curvature of surface lipids compared with high-density lipoprotein (HDL) may also reduce surface hydrophobicity, resulting in lower binding affinity to the hydrophobic distal end of the N-terminal β-barrel domain of cholesteryl ester transfer protein compared with HDL. The directional binding of cholesteryl ester transfer protein (CETP) to HDL and VLDL/IDL may explain the function of CETP in transferring triglycerides and cholesteryl esters between these particles. This first visualization of the 3D structure of VLDL/IDL could improve our understanding of the role of VLDL/IDL in atherogenesis.

14

Farnesoid X receptor activation by obeticholic acid reduces plasma low-density lipoprotein (LDL)-cholesterol in mice by up-regulating hepatic LDL receptor via a post-transcriptional mechanism

Amar B. Singh[1], Bin Dong[1], Fredric B. Kraemer[1], Jingwen Liu[1]

[1]Veterans Affairs Palo Alto Health Care System, Palo Alto, CA

The farnesoid X receptor (FXR) is a bile acid–activated nuclear receptor regulating bile acid and cholesterol metabolism. In mouse models, FXR activation attenuates development of atherosclerosis and reduces plasma total cholesterol (TC) and HDL-C. Our previous studies in hyperlipidemic hamsters showed that activation of FXR by obeticholic acid (OCA), an FXR agonist, lowered serum TC, HDL-C, and LDL-C. These effects were associated with increased expressions of SR-BI and LDL receptor (LDLR) in OCA-treated liver tissue. Whereas FXR mediated transcriptional activation of SR-BI, the major receptor for HDL-C, is well documented, molecular mechanisms underlying effects of FXR on LDLR expression in liver tissue have not been clearly defined. Here, we demonstrate that FXR activation by OCA in mice lowers serum LDL-C levels by up-regulating hepatic LDLR expression via a post-transcriptional mechanism involving LDLR mRNA–stabilizing protein HuR. We showed that administration of OCA to normolipidemic mice did not affect expressions of SREBP target genes, including PCSK9 and HMG-CoA reductase, but increased LDLR and HuR mRNA and protein levels, leading to reductions of LDL-C in circulation. To directly examine OCA effects on LDLR mRNA stability under *in vivo* conditions, we utilized transgenic mice (Alb-Luc-UTR) that express a luciferase-LDLR 3′-UTR transgene in the liver. OCA treatment led to significant rises in hepatic bioluminescence signals and Luc-UTR mRNA and LDLR mRNA levels as well as reductions in serum TC and LDL-C levels compared with vehicle-treated Alb-Luc-UTR mice. These effects were accompanied by up-regulation of hepatic HuR mRNA and protein levels in OCA-treated mice, whereas other LDLR mRNA–binding proteins were not affected by OCA treatment. Further studies in human primary hepatocytes and HepG2 cells corroborated our observations in mouse liver and demonstrated OCA-induced coordinated up-regulation of LDLR and HuR. Finally, utilizing siRNA technology, we demonstrate that knockdown of HuR attenuates OCA-induced LDLR mRNA and protein expressions in HepG2 cells. Altogether, our study is the first to demonstrate that FXR activation increases LDLR expression in liver tissue by increasing LDLR mRNA–stabilizing protein HuR, which is one underlying mechanism for FXR-mediated LDL-C–lowering effects observed in mice and possibly in other animal models.

15

FGF21, a liver hormone that inhibits alcohol intake in mice, increases in human circulation after acute alcohol ingestion and 3 days of binge drinking at Oktoberfest

Susanna Søberg[1,2], Emilie S. Andersen[3,4], Niels B. Dalgaard[3,4], Ida Jarlhelt[1], Nina L. Hansen[3], Nina Hoffmann[3], Anne Chenchar[1], Michal Jensen[2], Camilla Scheele[1,2], Trisha Grevengoed[1], Sam Trammell[1], Filip K. Knop[1,3,4,5], Matthew P. Gillum[1,5]

[1]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, Copenhagen, Denmark; [2]Center of Inflammation and Metabolism and Center for Physical Activity Research, Rigshospital, Copenhagen, Denmark; [3]Center for Diabetes Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark; [4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [5]Contributed equally

Excessive alcohol consumption is a leading cause of global morbidity and mortality. However, knowledge of the biological factors that influence *ad libitum* alcohol intake may be incomplete. Two large studies recently linked variants at the KLB locus with levels of alcohol intake in humans. KLB encodes β-klotho, co-receptor for the liver-derived hormone fibroblast growth factor 21 (FGF21). In mice, FGF21 reduces alcohol intake, and human Fgf21 variants are enriched among heavy drinkers. Thus, the liver may limit alcohol consumption by secreting FGF21. However, whether full-length, active plasma FGF21 (FGF21(1–181)) levels in humans increase acutely or subchronically in response to alcohol ingestion is uncertain. We recruited 10 healthy, young male subjects to receive an oral water or alcohol bolus with concurrent blood sampling for FGF21(1–181) measurement in plasma. In addition, we measured circulating FGF21(1–181) levels, liver stiffness, triglyceride, and other metabolic parameters in three healthy Danish men before and after consuming an average of 22.6 beers/person-day (4.4 g/kg-day of ethanol) for 3 days during Oktoberfest 2017 in Munich, Germany. We further correlated fasting FGF21(1–181) levels in 49 healthy, non-alcoholic subjects of mixed sex with reports of alcohol-related behaviors, emotional responses, and problems. Finally, we characterized the effect of recombinant human FGF21(1–181) injection on voluntary alcohol intake in mice. We show that alcohol ingestion (25.3 g, or ~2.5 standard drinks) acutely increases plasma levels of FGF21(1–181) 3.4-fold in humans. We also find that binge drinking for 3 days at Oktoberfest is associated with a 2.1-fold increase in baseline FGF21-(1–181) levels, in contrast to minor deteriorations in metabolic and hepatic biomarkers. Nevertheless, basal FGF21(1–181) levels do not correlate with differences in self-reported alcohol-related behaviors, responses, or problems in a small cohort of non-alcoholic subjects. Finally, we show that once-daily injection of recombinant human FGF21(1–181) reduces *ad libitum* alcohol intake by 21% in mice. We conclude that FGF21(1–181) is markedly increased in circulation by both acute and subchronic alcohol intake in humans and reduces alcohol intake in mice. These observations are consistent with the recently proposed role for FGF21(1–181) as a negative-feedback regulator of alcohol intake in humans.

16

Dysregulated leptin gene expression leads to a leptin-responsive form of obesity

O. S. Dallner[1], Y. Lu[1], K. Birsoy[2], K. Marinis[3], E. Werner[1], G. Fayzikhodjaeva[1], M. Lazar[3], J. Friedman[1, 4, *]

[1]Laboratory of Molecular Genetics, [2]Laboratory of Metabolic Regulation and Genetics, and [4]Howard Hughes Medical Institute, The Rockefeller University, New York, NY; [3]Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Leptin is an adipocyte hormone that functions as an afferent signal in a negative feedback loop between the hypothalamus and adipose tissue to maintain homeostatic control of body weight (Haslam, D. W., and James, W. P. (2005) Lancet 366, 1197–1209). Leptin is expressed exclusively in adipocytes and is quantitatively regulated such that changes in fat mass correlate with changes in gene expression (Maffei, M. et al. (1995) Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the db locus. Proc. Natl. Acad. Sci. U.S.A. 92, 6957–6960). However, although substantial progress in understanding the neural mechanisms of leptin action has been made, the molecular mechanisms controlling leptin gene expression in vivo are poorly understood (Friedman, J. M. (2009) Am. J. Clin. Nutr. 89, 973S–979S). A fuller understanding of the mechanism controlling leptin expression is of clinical importance, since low leptin levels can lead to an increase of food intake and body weight. Here, we report that adipocyte-specific and quantitative leptin expression is controlled by redundant cis elements and trans factors interacting with the proximal promoter in concert with an lncRNA (lncOb). Animals lacking lncOb develop obesity with lowered plasma leptin levels, confirming its role to quantitatively regulate the leptin gene. Diet-induced obese (DIO) animals lacking the lncOb RNA lose significant amounts of weight after leptin treatment, in contrast to control DIO animals, who do not. These results show that defects in the regulation of leptin gene expression can lead to a hypoleptinemic leptin-responsive form of obesity and provides a framework for elucidating the pathogenic mechanism in the subset of obese patients with low endogenous leptin levels.

17

Spontaneous non-alcoholic fatty-liver disease, non-alcoholic steatohepatitis, and hepatocellular carcinoma in mice with hepatocyte-specific disruption of Jak2 is reversed in mice with concomitant disruption of Jak2 in both liver and adipose tissue

Kevin Corbit[1], Aras Mattis[1], Nevan Krogan[1], David Jimenez-Morales[1], Ethan J. Weiss[1]

[1]University of California, San Francisco, CA

Insulin sensitivity naturally declines with age and insulin resistance correlates with several age-associated diseases. The insulin/insulin-like growth factor (IGF) axis is the major aging regulatory node in metazoans. IGF production itself is mediated by growth hormone (GH), but how IGF/GH signaling promotes age-related pathologies is unknown. Previously, we showed that mice with hepatocyte-specific disruption of Jak2 (JAK2L) develop aggressive non-alcoholic fatty-liver disease (NAFLD). When crossed to mice with adipocyte-specific disruption of Jak2 (JAK2A), JAK2LA mice are nearly completely protected from developing NAFLD. Given that NAFLD is known to progress to non-alcoholic steatohepatitis (NASH), we examined mice after 2 years of aging. We found that JAK2L mice develop NASH that closely resembles human NASH. Strikingly, 64% of JAK2L mice develop hepatocellular carcinoma (HCC), on regular chow. Remarkably, NAFLD, NASH, and HCC development in JAK2L mice all depend on adipocyte Jak2, as concomitant disruption of hepatocyte and adipocyte Jak2 (JAK2LA) reduces the severity and onset of fatty liver, inflammation, fibrosis, and carcinogenesis. Aged JAK2L mice are also lipodystrophic and have impaired adipose tissue mTORC1 signaling during the fasting-to-fed transition, whereas loss of adipocyte Jak2 prevents lipodystrophy and age-associated insulin resistance. Our results demonstrate that adipocytes mediate the development of liver pathologies and insulin resistance and suggest a paradigm shift toward targeting the adipocyte for treatment of metabolic liver disease, NASH, and HCC.

18

The new role of lipin1 in myogenic progenitor differentiation to muscle and adipose tissues

Abdulrahman Jama[1], Dengtong Huang[1], Abdullah A. Alshudukhi[1], Karim Nadra[2], Roman Chrast[2], Hongmei Ren[1]

[1]Department of Biochemistry and Molecular Biology, Wright State University, Dayton, OH; [2]Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland

Our previous work in global lipin1-deficient (fld) mice demonstrated that lipin1 played a novel role in skeletal muscle (SM) regeneration. Brown adipose tissue (BAT) and skeletal muscle originate from common myogenic factor 5-expressing (Myf5) progenitors. However, little is known about what controls the progenitors commit to the brown adipogenic lineage. This study using cell type–specific Myf5-cre;Lipin1fl/fl conditional knockout (Lipin1Myf5cKO) mice showed that lipin1 was a major determinant of SM development and BAT conversion. Depletion of lipin1 in $Myf5^{+}$ progenitors in Lipin1Myf5cKO mice promotes brown adipose tissue conversion indicated by inhibition of skeletal muscle development and expanded brown adipose tissue formation in the dorsal cervical region compared with control littermates. Results from lipin1-deficient myoblasts suggested that lipin1 regulated myoblast differentiation through the protein kinase C (PKC)/histone deacetylase 5 (HDAC5)/myocyte-specific enhancer factor 2C (MEF2c):MyoD–mediated pathway. Lipin1 deficiency leads to the suppression of PKC isoform activities, as well as the inhibition of their downstream target, class II deacetylase HDAC5 nuclear export, and consequently, the inhibition of MEF2c and MyoD expression in the SM of Lipin1Myf5cKO mice. Inhibition of MyoD induced accumulation of Pax7 expression levels, which may lead to an increased propensity for satellite cell self-renewal rather than progression through myogenic differentiation. Our findings provide insights into the signaling circuitry that regulates skeletal muscle development and have important implications for developing therapies
aimed at treating muscular dystrophy.

19

Somatic disruption of Ldlr with AAV-CRISPR as a novel method for atherosclerosis studies

Kelsey E. Jarrett[1], Alexandria M. Doerfler[1], Ayrea Hurley[1], Rachel Hsu[1], Marco De Giorgi[1], Ang Li[2], Henry J. Pownall[3], Ciaran Lee[2], Gang Bao[2], William R. Lagor[1]

[1]Baylor College of Medicine, Houston TX; [2]Rice University, Houston TX; [3]Houston Methodist Research Institute, Houston TX

Current methods to study genetic contributions to atherosclerosis are time-consuming and expensive. The Ldlr and Apoe knockout (KO) models are currently the gold standard, but they require extensive backcrossing to homozygosity and congenic status on the C57Bl/6 background. More rapid and efficient methods are needed to investigate the ever-growing list of candidate genes identified through human genetics. The clustered regularly interspaced short palindromic repeats/Cas9 (CRISPR/Cas9) genome editing system is a powerful new tool for gene disruption. We hypothesized that atherosclerotic lesion could be generated in adult mice via liver-directed somatic disruption of Ldlr using an all-in-one AAV-CRISPR vector, thus bypassing the need to cross to Ldlr KO mice. An adeno-associated viral (AAV) vector based on serotype 8 was used to deliver *Staphylococcus aureus* Cas9 (SaCas9) and small guide RNA targeting the Ldlr gene (AAV-CRISPR). This vector was compared head-to-head with AAV-mediated overexpression of a human gain-of-function variant of PCSK9, a recent model that mimics Ldlr KO through promoting degradation of the Ldlr protein. Adult C57BL6/J mice received either 1) saline, 2) AAV-CRISPR, or 3) AAV-hPCSK9 *versus* 4) germ line Ldlr KO mice. Animals were placed on a Western diet for 20 weeks and followed for changes in plasma lipids, atherosclerotic lesion burden, and editing efficiency. Disruption of Ldlr with AAV-CRISPR vector was robust, resulting in severe hypercholesterolemia and atherosclerosis on a standard Western diet. AAV-hPCSK9 also produced atherosclerotic lesions, as expected from previous reports. Lesion burden was slightly lower with AAV-CRISPR and AAV-hPCSK9 relative to germ line Ldlr KO mice. Unexpected sexual dimorphism was also observed with AAV-CRISPR, with the greatest effects seen in male mice. In summary, our all-in-one AAV-CRISPR vector is a rapid and efficient alternative to the use of Ldlr KO mice to study atherosclerosis.

20

Copper regulates energy metabolism in adipocytes through semicarbazide-sensitive amine oxidase

Haojun Yang[1], Martina Ralle[2], Michael J. Wolfgang[1], Jason Burkhead[3], Chin-Nung Liu[1], Susana Rodriguez[1], Jack H. Kaplan[4], Guang Wong[1], Svetlana Lutsenko[1]

[1]Johns Hopkins University, Baltimore, MD; [2]Oregon Health and Science University, Portland, OR; [3]University of Alaska, Anchorage, AK; [4]University of Illinois, Chicago, IL

Differentiation of preadipocytes into mature fat cells is associated with a complex remodeling of transcriptional and metabolic programs. We show that copper homeostasis is an essential contributor to this remodeling. Upon differentiation, copper uptake increases to provide more copper to mitochondria and, especially, to the secretory pathway. This process is accommodated by up-regulation of the copper transporters Ctr1 and ATP7A. Increased copper flow to the secretory pathway is required to activate a simultaneously and markedly up-regulated semicarbazide-sensitive amine oxidase (SSAO). Copper deficiency or a limited transfer of copper to the secretory pathway causes inhibition of SSAO and an increase in the adipocyte volume and lipid content. Complete inactivation of SSAO results in adipocyte hypertrophy, increased fatty acid uptake and storage, down-regulation of pathways involved in glycolysis, and decreased sensitivity of glucose uptake to insulin. The addition of active recombinant SSAO during adipocyte differentiation prevents changes in the proteome and adipocyte enlargement. Altogether, the results demonstrate an essential role for copper in adipocyte maturation and function, identify a new physiological role for SSAO, and pave the way to better understanding of the role of a frequently observed copper misbalance in obesity.

21

The anti-obesity effects of FGF19 and FGF21 require β-Klotho in the central nervous system

Tian Lan[1,2], Steven Kliewer[1,2], David Mangelsdorf[1,3]

[1]Department of Pharmacology, [2]Department of Molecular Biology and [3]Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX

The pharmacologic effects of fibroblast growth factor 19 (FGF19) and FGF21 to increase metabolic rate and cause weight loss have been appreciated for many years. FGF19 and FGF21 belong to the family of endocrine FGFs that can enter the circulation and function as hormones. Signaling by FGF19 and FGF21 is mediated through a receptor complex composed of FGF receptors (FGFRs) and β-Klotho (KLB). The tissue distribution of KLB together with the FGF19- and FGF21-specific FGFR isoforms define the tissue-specific actions of FGF19 and FGF21. For example, the physiologic role of FGF19 as a postprandial intestinal hormone to repress hepatic bile acid synthesis is mediated by FGFR4/KLB, an FGF19-specific receptor expressed in the liver. Among the FGFR/KLB combinations, FGFR1c/KLB is activated by both FGF19 and FGF21. Previous gene expression profiling from our laboratory showed that FGFR1c/KLB is expressed in the adipose tissue and central nervous system (CNS), the two organs that are critical in the control of metabolic rate and body weight. We hypothesized that the pharmacologic actions of FGF19 and FGF21 are mediated through similar pathways involving effects on both the adipose tissue and CNS. To test this hypothesis, adipose tissue- and CNS-selective KLB knockout mice were generated and treated with FGF19 and FGF21. Our results suggest that FGF19 and FGF21 both act centrally to induce body weight loss. In contrast, although not required for weight loss effects, adipose tissue expression of KLB is crucial for mediating the acute insulin-sensitizing effects of the two hormones.

22

Structural basis of the lipid transfer mediated by phospholipid transfer protein

Jennifer Li[1], Meng Zhang[2], Xiaobo Zhai[2], John J. Albers[3], Simona Vuletic[3], Gang Ren[2]

[1]Department of Biomedical Science, Mercer University School of Medicine, Savannah, GA; [2]Molecular Foundry, Lawrence Berkeley National Laboratory, Berkeley, CA; [3]Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA

Human phospholipid transfer protein (PLTP) mediates the transfer of phospholipids among atheroprotective high-density lipoproteins (HDL) and atherogenic low-density lipoproteins (LDL) by an unknown mechanism. Delineating PLTP-mediated lipid transfer mechanism would be the first step toward understanding the underlying mechanisms, which is crucial for the treatment strategies of lipoprotein abnormalities and cardiovascular diseases. However, the structure and functionality of PLTP are not clearly understood yet. In this paper, using electron microscopy, optimized negative-staining, and single-particle image processing, we show that PLTP features a banana-shaped structure (length ~129 Å, width ~36 Å) with its N terminus being the more globular- and straight-shaped end and the C terminus being the more curve-shaped end. We hypothesize that the more globular-shaped and straight-shaped end might be the N terminus of PLTP, and the more curved end might be the C terminus of PLTP. Adding PLTP to HDL complex results in formation of an HDL-PLTP binary complex with ~80 Å of rod-shaped PLTP protruding from quasi-spherical HDL, whereas ~50 Å of the curvier N-terminal end of PLTP penetrates the HDL structure. Furthermore, adding PLTP to the complex of both HDL and LDL leads to the formation of a ternary complex with one terminal domain of PLTP penetrating into HD and another terminal domain of PLTP penetrating into LDL. These observations provide direct structural features of PLTP and its association with either HDL alone or HDL and LDL complex, which provides the direct molecular basis underlying the PLTP-mediated lipid transfer mechanisms.

23

New volume-fluorescence imaging technique reveals the key role of local sympathetic arborizations in white adipose tissue metabolism

Haochen Jiang[1], Ying Cao[2], Huanhuan Wang[2], Xiaofan Ding[1], Wenwen Zeng[1]

[1]Tsinghua University, Beijing, China; [2]Peking University, Beijing, China

Efferent signals from the central nervous system have essential roles in controlling the metabolism of white adipose tissues (WAT), and malfunction of such neural regulation leads to obesity and other profound metabolic disorders. We have previously reported that local sympathetic fibers in WAT can form synapse-like structures on adipocytes, and destruction of these neural structures inhibited the leptin-stimulated lipolysis (Zeng *et al.* (2015) *Cell Rep.* 10, 1226-1238). Recently, we have established a new volume fluorescence-imaging technique for adipose tissues, enabling the visualization of the intra-adipose neural network at single-fiber resolution on the whole-tissue level. Aided by this powerful technique, we observed that sympathetic arborizations are prevalent in mouse inguinal WAT, at a density that had been drastically underestimated by the conventional methods of immunohistochemistry. In fact, sympathetic fibers are in close apposition to over 90% of adipocytes in inguinal WAT. Furthermore, we found that genetic deletion of the neurotrophin receptor TrkA ablates the intra-adipose sympathetic network and, as a result, blocks the cold-induced beiging process of inguinal WAT. These results have therefore added to the essential functions of sympathetic efferent signal in regulating the WAT metabolism (Jiang *et al.* (2017) *Cell Metab.* 26, 429-436.e4). Also, we have exploited the new volume fluorescence-imaging technique to examine the remodeling process (*i.e.* plasticity) of local sympathetic arborizations in WAT. Interestingly, we observed that intra-adipose sympathetic arborizations decrease significantly in the obese condition (*e.g.* in the ob/ob mutant mice or in the high-fat diet–fed mice. In contrast, the density of sympathetic arborizations in inguinal WAT increases within days upon cold exposure, which is reversible by the thermo-neutral recovery. Moreover, we demonstrated that this temperature-sensitive sympathetic plasticity is regulated by the nerve growth factor (NGF) and TrkA signal. Functional blockage of NGF or TrkA can effectively inhibit the cold-induced beiging process of inguinal WAT. These results have together implicated a new layer of regulation in the sympathetic efferent control of WAT metabolism (Cao *et al.*, submitted for publication). In summary, our research has revealed the key structural basis connecting neural efferent signals with individual adipocytes, which has important implications for better understanding of the WAT metabolism under physiological and disease conditions.

24

A new paradigm in atherosclerotic calcification-closure of antioxidant paradox

Sampath Parthasarathy[1], Aluganti N. Chandrakala[1], Aladdin Riad[1]

[1]University of Central Florida, Orlando, Florida

Atherosclerotic lesions are formed by deposition of lipids in the intima of arteries. Upon exposure to oxidative stresses, low-density lipoprotein (LDL) is converted to highly atherogenic oxidized LDL particles, contributing to disease development and progression. Advanced disease stages may result in calcification of lesions. This calcification process is important, as it has been shown to be associated with stable plaques that are less prone to rupture. Calcification is present in lipid-rich domains of lesions, and it is generally assumed that calcium is present as calcium phosphate; however, neither the composition of the mineralized calcium deposits nor its relationship to lipid peroxidation is known. We hypothesize that lipid peroxide–derived azelaic acid (AzA), a dicarboxylic acid formed from the oxidation of oxo-nonanoic acid, induces calcification in smooth muscle cells, thereby providing the link between calcification and overall plaque burden, and association of calcification with the lipophilic region of the lesion. The potential of lipid peroxide–derived lipophilic dicarboxylic acid (DCA) to promote calcification upon exposure to vascular smooth muscle cells was tested. 13-Hydroperoxylinoleic acid (HPODE) treatment resulted in the cellular conversion to 9-oxononanoic acid and AzA, as determined by mass spectrometry analysis. Delivery of AzA via lysophosphatidylcholine micelles induced calcification of human aortic smooth muscle cells. AzA was identified in the mineralized calcium deposits of human atherosclerotic plaques. These results demonstrate that DCAs may contribute to atherosclerotic calcification, thus accounting for the latter's relationship to plaque burden and association with lipids. This study also challenges the dogma that arterial calcification represents the deposition of calcium phosphate. In addition, the results also make a connection between the oxidation of LDL lipids with calcification. As the oxidation of pro-inflammatory aldehydes to benign carboxylic acids is inhibited by antioxidants, the present study could explain why vitamin E-tocopherol-like antioxidants failed in human clinical trials.

25

Sustained diabetes remission induced by the action of fibroblast growth factor 1 (FGF1) in the hypothalamic arcuate nucleus

Jenny M. Brown[1], Jarrad M. Scarlett[1,2], Miles E. Matsen[1], Hong T. Nguyen[1], Anna Secher[3], Rasmus Jorgensen[3], Gregory J. Morton[1], Michael W. Schwartz[1]

[1]Diabetes Institute, University of Washington, Seattle WA; [2]Department of Pediatric Gastroenterology and Hepatology, Seattle Children's Hospital, Seattle WA; [3]Global Research, Novo Nordisk A/S, Maaloev, Denmark

Accumulating evidence suggests that the brain plays a key role in glucose homeostasis and thus is a potential target for the treatment of type 2 diabetes (T2D). Our recent finding that a single intracerebroventricular (icv) injection of FGF1 (3.0 µg) elicits sustained diabetes remission in rodent models of T2D supports this growing consensus. The aim of the current work was to pinpoint the brain area responsible for this action of FGF1. Although fibroblast growth factor receptors are expressed throughout the brain, our study was guided by our preliminary findings that 1) FGF receptor 1 and the specific integrin receptor ($\alpha_v\beta_3$) required for sustained FGF1 signaling are both concentrated in the hypothalamic arcuate nucleus-median eminence (ARC-ME) and 2) neuronal activation and sustained induction of the MAP kinase/ERK pathway (required for FGF1-induced cell proliferation and DNA synthesis) occurs specifically in this brain area following icv FGF1 injection. We therefore hypothesized that in rodent models of T2D, an action in the ARC-ME (a brain area known to participate in glucose homeostasis) mediates the sustained diabetes remission elicited by icv FGF1 injection. To test this hypothesis, we investigated the effect of a single microinjection of a low dose of FGF1 into the ARC (0.3 µg bilaterally, for a total of 0.6 µg) of Zucker diabetic fatty rats, a model of T2D. We found that FGF1 action limited to the ARC area was sufficient to induce remission of hyperglycemia lasting >3 weeks, whereas intra-arcuate microinjection of saline vehicle was without effect ($p < 0.05$ *versus* vehicle). In contrast, icv injection of the same total FGF1 dose (0.6 µg) had no significant effect on glycemia, indicating that sustained diabetes remission induced by intra-ARC microinjection of FGF1 was not due to action at some other site following leakage into ventricular cerebrospinal fluid. Furthermore, microinjection into the ARC of the same low dose of FGF1 recapitulates the prolonged (5-h) ERK activation induced in this brain area by icv injection of a larger dose. These findings collectively support the hypothesis that FGF1 action on ARC-ME is sufficient to explain the sustained diabetes remission induced by icv administration of a larger dose.

26

The role of the K_{ATP} channel in the mesolimbic system of a high-fat diet–induced depression mouse model

Pei-Chun Chen[1,2,3], Yun-Wen Chen[2,3,4], Jie-Kuan Lin[1,3]

[1]Department of Physiology, [2]Institute of Basic Medical Sciences, [3]College of Medicine, and [4]Department of Pharmacology, National Cheng Kung University, Tainan, Taiwan

Obesity, one kind of metabolic disorder, is associated with many chronic diseases, and chronic positive energy balance causes the resistance of metabolic hormones, including leptin, which participate in the processing of medical depression. Clinically depressed patients have shown anhedonia, which also appears in patients with obesity, indicating a dysregulation in the mesolimbic dopamine system. Several studies indicate that potassium channels in the mesolimbic system regulate the firing rate of dopamine neurons. Thus, adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channels, which are inward-rectifier potassium channels and act as a metabolic sensor to mediate electrical activity, may link to metabolic disorder and depression. Hence, we hypothesize that neuronal K_{ATP} channels in the mesolimbic dopamine system play a key role in obesity-induced depression. We found that 8-week-old B6 mice fed with 12 weeks of high-fat diet showed depressive-like behaviors, using a forced swim test and sucrose preference test. Analysis of catecholamine in the nucleus accumbens of high-fat diet–fed mice has further supported the depressive phenotype. Interestingly, total protein levels of the K_{ATP} channel were elevated in the high-fat diet–fed mice using immunoblotting and immunostaining assays. Implantation of miniosmotic pumps containing either K_{ATP} channel blocker showed improved glucose tolerance, insulin tolerance, and depressive behavior as well as triglyceride levels.

27

Fibroblast growth factor 21 is a protective pancreatic digestive enzyme secretagogue

Genaro Hernandez[1], Katie C. Coate[2], Curtis A. Thorne[3], ShengYi Sun[1], Tao D. Le[1], Kevin Vale[1], Steven A. Kliewer[1], David J. Mangelsdorf[1]

[1]University of Texas Southwestern Medical Center, Dallas, TX; [2]Samford University, Birmingham, AL; [3]University of Arizona, Tucson, AZ

Fibroblast growth factor 21 (FGF21) is a hormone that regulates metabolism in response to stresses, such as starvation. FGF21 is abundantly expressed in the exocrine pancreas, where its physiologic function remains to be elucidated. Here, we show that FGF21 is induced in the exocrine pancreas by refeeding and regulates digestive enzyme levels in a paracrine/autocrine fashion. FGF21 lowers digestive enzyme levels by stimulating secretion directly on the acinar cell through its receptor complex, FGFR/β-Klotho, and downstream PLC-IP_3R signaling. However, unlike the post-prandial secretagogue CCK, FGF21 does not induce pancreatic protein synthesis. Furthermore, pharmacological administration of FGF21 reduces the severity of both cerulein-induced and endoscopic retrograde cholangiopancreatography–induced pancreatitis. Thus, pancreatic FGF21 is a digestive enzyme secretagogue that could be used pharmacologically against instances of pancreatitis.

28

Eicosapentaenoic acid has a membrane orientation that correlates with potent antioxidant activity and reduced lipid disordering as compared with docosahexaenoic acid: X-ray diffraction analysis

Richard P. Mason[1,2], Samuel C. Sherratt[2], Robert F. Jacob[2]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Elucida Research LLC, Beverly, MA

The ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have distinct effects on rates of lipid oxidation, signal transduction pathways, and lipid raft formation, including cholesterol domains. These fatty acids have physiologic activities in the central nervous and cardiovascular systems. The basis for differences in their cellular effects may be due to their specific orientations in the membrane and subsequent effects on surrounding lipid structure and dynamics. Small-angle X-ray diffraction approaches were used to measure the effects of EPA and DHA on membrane structure composed of cholesterol at physiologic levels for vascular cells. Membrane vesicles composed of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) and cholesterol (C) (0.3 C:POPC mole ratio) were prepared and treated with vehicle, EPA, or DHA at a 1:10 mole ratio to POPC. The membrane structure was correlated with lipid fluidity, as determined by the apparent rotational correlation time (ARCT) measured for diphenylhexatriene. Electron density profiles generated from the diffraction data showed that EPA increased membrane hydrocarbon core electron density over a broad area, up to ±20 Å from the membrane center, indicating an extended orientation for EPA that would be stabilized by van der Waals interactions with surrounding phospholipid acyl chains. By contrast, DHA increased electron density in the phospholipid headgroup region starting at ±12 Å from the membrane center due to strong surface interactions. At the same time, incorporation of DHA into the membrane produced a reduction in electron density in the membrane hydrocarbon core centered ±7–9 Å from the membrane center. The membrane-disordering effects of DHA were consistent with experimental data providing measurements of decreased ARCT and promotion of cholesterol domains as compared with EPA or vehicle treatments. These differences in membrane structure and lipid dynamics are also consistent with experimental data demonstrating increased antioxidant activity for EPA compared with DHA and other related fatty acids in small dense lipoprotein particles. The effects of EPA on lipid structure and dynamics may explain the observed experimental differences between EPA and DHA under both normal and disease-like conditions of oxidative stress.

29

Chemical composition and antioxidant and anticholine esterase potentials of essential oil of *Monodora myristica* (Africa nut) seeds

Lateef A. Sulaimon[1], Rahmat A. Adisa[3], Efere M. Obuotor[2], Bello A. Ibrahim[1], Modinat O. Lawal[1]

[1]Crescent University Abeokuta, Ogun State, Nigeria; [2]Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria; [3]University of Lagos, Lagos State, Nigeria

Essential oils have been recognized as some of the most promising compounds in the development of novel products, particularly in the pharmaceutical, agricultural, food, and perfumery industries. The current research aimed at characterization of the chemical composition and antioxidant and anticholine esterase activities of the essential oil from *Monodora myristica* (Africa nut). Essential oil extraction was carried out by use of a steam distillation method in a modified Clevenger-type apparatus to obtain volatile oil. The chemical composition of the essential oil from seeds of *M. myristica* was determined using gas chromatography coupled with mass spectrometry (GC-MS), and its potentials as antioxidant and anticholine esterase were evaluated. The oil yield was 0.6% (w/w) in *M. myristica*. The GC-MS analyses identified a total of 58 compounds, corresponding to 100% of the total oil in *M.|myristica*. The essential oil was rich in monoterpenes and sesquiterpenes and their analogues, namely oxygenated monoterpenes and sesquiterpenes. The oil additionally contained diterpenes and non-terpenoid aliphatic and aromatic hydrocarbons. A significant antioxidant (IC_{50} value of 2,2-diphenyl-1-picrylhydrazyl = 4.63 ± 0.35 mg/ml) and anticholine esterase activity (IC_{50} = 1.21 ± 0.02 mg/ml) was obtained for the essential oil of *M. myristica*. The study established the chemical composition and antioxidant and anticholine esterase activity of the essential oil of the plant seeds. The moderate antioxidant and anticholine esterase potential of the essential oil from M. myristica is an indication of possible application in related *in vivo* studies for future therapeutic applications. The major compounds, monoterpenes and sesquiterpenes, could be used as a biomarker for the chemotaxonomical characterization of the species.

30

Why do leptin levels fall with fasting?

Alexandre Caron[1], Heather M. Dungan Lemko[2], Carlos M. Castorena[1], Teppei Fujikawa[3], Syann Lee[1], Caleb C. Lord[1], Newaz Ahmed[1], Charlotte E. Lee[1], William L. Holland[4], Chen Liu[1], Joel K. Elmquist[1]

[1]Division of Hypothalamic Research, University of Texas Southwestern Medical Center, Dallas, TX; [2]Howard Community College, Baltimore, MD; [3]Department of Cellular and Integrative Physiology, University of Texas Health Science Center, San Antonio, TX; [4]Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX

Leptin is critical for energy balance, glucose homeostasis, and for metabolic and neuroendocrine adaptations to starvation. A prevalent model predicts that leptin's actions are mediated through pro-opiomelanocortin (POMC) neurons that express leptin receptors (LEPRs). However, this model relies on studies using prenatal genetic manipulations, which may be subject to developmental compensation. Here, we tested the direct contribution of POMC neurons expressing LEPRs in regulating leptin secretion during fasting. We utilized a spatiotemporally controlled Lepr expression mouse model to delete LEPRs specifically in POMC neurons in adult mice. We report a dissociation between leptin's effects on glucose homeostasis *versus* energy balance in POMC neurons. We show that these neurons are dispensable for regulating food intake but are required for coordinating hepatic glucose production and for fasting-induced falls in leptin levels, independent of altered fat mass. We also identify a role for the $G_{i/o}$ protein-coupled receptors in regulating leptin production. Collectively, our findings highlight a previously unrecognized role of POMC neurons in regulating leptin levels.

31

Identification of lipid biomarkers of inflammation and metabolic disturbances in Gulf War illness

James E. Evans[1,2], Utsav Joshi[1,2,3], Ross Joseph[1], Shara Oberlin[1], Heather Langlois[1], Andrew P. Keegan[1], Tanja Emmerich[1,2], Nancy Klimas[4,5], Kimblerly Sullivan[6], Fiona Crawford[1,2,3], Michael Mullan[1,2,3], Laila Abdullah[1,2,3]

[1]Roskamp Institute, Sarasota, FL; [2]James A. Haley Veterans' Hospital, Tampa, FL; [3]Open University, Milton Keynes, United Kingdom; [4]NOVA Southeastern University, Ft. Lauderdale, FL; [5]Miami Veterans Affairs Medical Center, Miami, FL; [6]Boston University School of Public Health, Boston, MA

Approximately 30% of the veterans of the 1991 Gulf War (GW) suffer from a disorder called Gulf War illness (GWI), characterized by symptoms that include fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and gastrointestinal problems. The etiology of GWI is believed to involve exposure to a variety of neurotoxicants, such as pesticides and anti-nerve agents. Many symptoms of GWI resemble those of subjects with chronic fatigue syndrome (CFS), despite the differences in etiological origins. The main objective of this study was to identify specific and sensitive lipid biomarkers for GWI in plasma that can help distinguish veterans with GWI from subjects with CFS. We performed LC-MS lipidomic analysis on plasma from affected and control GW veterans and civilian controls and subjects with CFS who were matched for general demographics. Lipidomics was performed on Folch lipid extracts by nano-scale, reverse-phase liquid chromatography with a 45-min solvent gradient and interfaced to a high-resolution, high-mass-accuracy LTQ-Orbitrap mass spectrometer, where both positive and negative ion full-scan spectra were acquired at 30,000 mass resolution. Peaks for individual lipid molecular species were identified and quantified relative to class-specific internal standards using TraceFinder software (Thermo Scientific). This platform is routinely used to identify and quantify plasma lipids from more than 18 lipid classes, including 300–400 individual molecular species. The findings from these studies supplement our previously reported studies on phospholipid profiles in GWI veterans. In the current study, we have identified several differences between control and GWI veterans and those with CFS for several major classes of lipids, which include triglycerides, cholesterol esters, monoglycerides, diglycerides, cholesterol, ceramides and hexosylceramides, and sphingomyelins. We conclude that lipidomics technology is a powerful tool for identifying novel blood-based biomarkers of complex and chronic multisymptom illnesses, which are difficult to diagnose and treat.

32

The hormone fibroblast growth factor 21 (FGF21) stimulates drinking in response to ketogenic diet and alcohol

Parkyong Song[1], Christoph Zechner[1,2,3], Genaro Hernandez[1], José Cánovas[4], Yang Xie[5], Varun Sondhi[1,2], Martin Wagner[6], Vanessa Stadlbauer[6], Angela Horvath[7,8], Bettina Leber[7,8], Ming Chang Hu[2,3], Orson W. Moe[2,3,9], David J. Mangelsdorf[1,10], Steven A. Kliewer[1,11]

[1]Department of Pharmacology, [2]Department of Internal Medicine, [3]Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, [5]Department of Clinical Sciences, [9]Department of Physiology, [11]Department of Molecular Biology, and [10]Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX; [4]Departments of Biochemistry and Molecular Biophysics and Neuroscience, Columbia University, New York, NY; [6]Department of Gastroenterology and Hepatology and [7]Department of Transplantation Surgery, Medical University of Graz, Graz, Austria; [8]Center for Biomarker Research in Medicine (CBmed), Graz, Austria

Alcohol and high-fat, low-carbohydrate ketogenic diets can cause osmotic stress and increased water consumption. Here, we show that the hormone FGF21 is required for this drinking response in mice. Circulating levels of FGF21 are increased by alcohol consumption in humans, and by both alcohol and ketogenic diets in mice. Concordantly, mice lacking FGF21 fail to increase water intake in response to either alcohol or a ketogenic diet. FGF21's dipsogenic effect is partially blunted by either selectively disrupting β-Klotho expression in $Sim1^{+}$ neurons, which are highly enriched in the PVN, or by systemic administration of β-blockers. Given that FGF21 is also known to suppress alcohol intake in favor of pure water, this work identifies FGF21 as a fundamental neurotropic hormone that governs water balance in response to dehydrating dietary stresses.

33

Human thermogenic adipose tissue development and metabolic disease

Silvia Corvera[1], So Yun Min[1], Raziel Rojas-Rodriguez[1], Tiffany DeSouza[1], Khanh-van Tran[1]

[1]University of Massachusetts Medical School, Worcester, MA

Adipose tissue plays a central role in whole-body energy homeostasis. It can store and release energy, communicate energy status to other tissues, and regulate core body temperature. These functions are carried out by specific subtypes of adipocytes localized preferentially in distinct anatomical depots. The developmental mechanisms that give rise to different adipocyte types in different anatomical localizations are unknown but are of great interest, as variation in these processes is associated with risk of obesity and metabolic diseases. We and others have previously found that adipocyte progenitor cells are tightly associated with the adipose tissue vasculature and proliferate *in vitro* under pro-angiogenic culture conditions in which the vasculature of adipose tissue expands. We used this approach to generate human adipocyte progenitors from three distinct anatomical sites: subcutaneous neck (NeckSQ), peri-carotid (Carotid), and subcutaneous abdominal tissue (AbdSQ). We differentiated adipocytes from these progenitors and assessed their responsiveness to thermogenic stimulation. We then used whole expressed genome arrays and hierarchical clustering analyses to find genes varying significantly as a function of anatomical localization, adipogenic differentiation, and thermogenic responsiveness. A small set of genes was identified that varied significantly with both localization and thermogenic responsiveness. Genes in this set were associated previously with modulation of cAMP signaling. To validate this finding, we measured the expression of these genes in adipose tissue from individuals with obesity and with type 2 diabetes and found significant decreases, correlating with their known suppressed thermogenic capacity. *In vitro*, knockdown resulted in decreased induction of thermogenic genes. Together, these results identify genetic signatures in pre-adipocytes and differentiated adipocytes associated with the human thermogenic phenotype and suggest a model whereby large differences in the function of human adipocytes between different depots can be potentially achieved through expression of a few key genes that modulate their responsiveness to external stimuli.

34

c-Abl mediates tyrosine transcription factor EB phosphorylation and its cytoplasmic localization: Implications in the Niemann–Pick type C cholesterol lysosomal storage disease

Pablo S. Contreras[1,2,3], Pablo J. Tapia[1,2,3], Ivana Peluso[4], Chiara Soldati[4], Macarena Las Heras[3], Andres D. Klein[4], Diego L. Medina[4], Andrea Ballabio[4], Silvana Zanlungo[3], Alejandra R. Alvarez[1,2]

[1]Laboratorio Señalización Celular, [2]CARE-Chile-UC, and [3]Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [4]Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli, Italy

The transcription factor EB (TFEB) is the master regulator of lysosomal biogenesis and function and the autophagy pathway. The activity and translocation to the nucleus of TFEB depends on its phosphorylation state. The inhibition of the pro-apoptotic tyrosine kinase c-Abl increases Lamp1 protein levels and autophagy flux. The aim of this work was to analyze whether c-Abl inhibition promotes TFEB nuclear translocation and, as a consequence, ameliorates cholesterol accumulation in the lysosomal storage disease Niemann-Pick type C (NPC). We modulated c-Abl using an siRNA and different c-Abl inhibitors and followed TFEB-GFP subcellular localization. Also, we evaluated the TFEB tyrosine phosphorylation status by immunoprecipitation and phospho-Tyr Western blotting in cells overexpressing c-Abl. In addition, we evaluated cholesterol accumulation by filipin staining in NPC1 human fibroblasts, NPC mice, and cells (NPC1 null fibroblasts and Hepa 1–6 and HT22 cells treated with the U18666A drug (U18)) treated with the c-Abl inhibitors. TFEB is phosphorylated by c-Abl in tyrosine. Also, c-Abl inhibition induces TFEB nuclear translocation. In addition, c-Abl inhibitors reduced cholesterol accumulation in NPC1 human fibroblasts and mice, but not in Hela TFEB-KO cells treated with U18, indicating a TFEB-dependent effect. Our data strongly suggest that TFEB tyrosine phosphorylation by c-Abl impacts TFEB nuclear translocation, suggesting a novel signaling pathway involving these two proteins. Probably, this signaling would modulate cholesterol homeostasis in NPC disease.

35

Functional dissection of the central glucoregulatory circuits

Shi-Bing Yang[1]

[1]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

The hypothalamus is the major commander to control somatic activities and innate behaviors, such as hunger, thirst, and body temperature. For example, the hypothalamus receives peripheral information, such as nutrients (glucose, fatty acids, and amino acids) and hormones (leptin, ghrelin, and insulin) and modulates the energy metabolism of a variety of peripheral tissues, such as the liver and skeletal muscle, via the autonomic nervous system, by controlling insulin sensitivity as well as the hepatic gluconeogenesis. Earlier studies have found that acute infusion of glibenclamide, a KATP channel blocker, into the third ventricle abolishes hormonally and nutritionally induced suppression of hepatic gluconeogenesis. In addition to that, our data indicated that central infusion of glibenclamide paradoxically impaired glucose tolerance in aged mice. Our genetic labeling has further revealed that the neurons in the dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), and arcuate nucleus are involved in the central regulation of peripheral glucose homeostasis. Last, our results also showed that the pharmacoactivation of neurons in the DMH induced the glucose intolerance in mice fed with a high-fat diet. Our study has demonstrated that the central nervous system may become a promising therapeutic for treating metabolic disorders.

36

Macrophage-derived neurotrophic factor GDF15 mediates a novel neuro-immune interaction in adipose tissues

Joshua C. Chang[1], Steffen Durinck[1], Nadia Martinez-Martin[1], Mark Z. Chen[1], Zora Modrusan[1], Andrew S. Peterson[1], Shannon J. Turley[1], Junichiro Sonoda[1]

[1]Genentech Inc., South San Francisco, CA

In response to environmental and nutrient stress, the compositions of stromal vascular fraction in adipose tissues change to accommodate new homeostatic requirements. Pro-inflammatory type 1 immune cells accumulate in obese visceral adipose tissues (VAT) and promote insulin resistance. In contrast, type 2 immune cells, in particular alternatively activated M2 macrophages, are predominant in the lean VAT and important for tissue homeostasis. The role of M2 macrophages in the cold-induced browning of subcutaneous adipose tissue (SCAT) and thermogenesis has also been proposed, but the notion remains controversial. Using flow-cytometric and tissue-imaging analyses, we observed that cold-induced sympathoactivation in obese VAT triggers a depot-specific tissue remodeling that involves extracellular matrix formation, angiogenesis, an M1-to-M2 shift in macrophage composition, an increase in sympathetic nerve fiber innervation, and emergence of UCP1-positive beige adipocytes (i.e. VAT browning). Unexpectedly, pharmacological depletion of M2 macrophages prevents VAT browning without affecting SCAT browning under cold challenge. Using RNAseq analysis of M2 macrophages isolated from VAT, we found that M2 macrophages increased the production of growth differentiation factor 15 (GDF15) in response to cold. GDF15 was recently identified as a factor that activates the receptor tyrosine kinase RET signaling via the coreceptor GDNF receptor-α–like (GFRAL), primarily found in the central nervous system. We found Gfral mRNA expression also in the periphery, in the tissue containing the sympathetic chain ganglia, consistent with the notion that GDF15 acts directly on peripheral nerve, acting as a neurotrophic factor. Administrations of recombinant GDF15 into obese and diabetic mice increased sympathetic fiber innervation and browning in the white adipose tissues while reducing body weight and ameliorating diabetes. These results propose a previously unrecognized neuro-immune circuit mediated by the cold-activated M2 macrophages and the neurotrophic factor GDF15.

37

A novel long-acting FGF21 analogue significantly improves liver steatosis and inflammation and halts progression of fibrosis in preclinical models of NASH

Emma Henriksson[1], Jenny Norlin[1], Elisabeth Galsgaard[1], Rikke K. Kirk[1], Günaj Rakipovski[1], Birgitte Andersen[1]

[1]Novo Nordisk A/S, Global Research, Denmark

Metabolic syndrome has been shown also to associate with non-alcoholic steatohepatitis (NASH), and there is an unmet medical need for treatment of this serious disease that can progress into cirrhosis and hepatocellular carcinoma. Fibroblast growth factor 21 (FGF21) is an important non-mitogenic regulator of energy and lipid metabolism. In this study, we aim to investigate a long-acting FGF21 analogue for its effect on hepatic steatosis, injury, inflammation, and fibrosis in two metabolic, diet-induced mouse models for NASH. In an intervention study, C57Bl6J mice were fed a high-fat, -fructose, and -cholesterol diet (FFC) for 34 weeks, followed by 8 weeks of subcutaneous treatment with a long-acting FGF21 analogue (0.2–0.05 mg/kg/day), aiming to induce a 10% weight reduction to compare the effect to a weight-matched control group. In a prevention study, the atherosclerotic prone LDLr knockout mice were fed a Western diet (high-fat, high-sucrose, and high-cholesterol) and treated subcutaneously for 17 weeks with the FGF21 analogue (0.1 and 0.3 mg/kg/day). Plasma and liver parameters were analyzed in both studies. In FFC-fed mice treated for 8 weeks, the FGF21 analogue significantly improved metabolic parameters, such as body weight reduction and a decrease in plasma cholesterol. Moreover, liver steatosis, liver inflammation, liver cholesterol, and liver injury as determined by alanine transaminase (ALT) were all significantly reduced. Vehicle-treated mice showed progression of fibrosis for the 8-week period, whereas progression was inhibited by the FGF21 analogue. Similar findings were seen in the 17-week prevention study (*i.e.* a significant reduction in liver steatosis, plasma ALT, and triglyceride as well as a dose-dependent prevention of fibrosis). Interestingly, FGF21 was able to significantly lower plasma cholesterol despite the lack of LDLr. A novel long-acting FGF21 analogue was proven efficient as NASH therapy in two separate preclinical studies, with significant impact on liver steatosis, liver inflammation, and progression of fibrosis. Addressing the underlying metabolic disease may be an attractive therapeutic option to battle NASH, and future clinical studies are warranted to investigate the potential of FGF21 as a novel therapeutic option for NASH patients.

38

Impact of AGPAT2 deficiency on the mRNA levels of enzymes involved in the glycerolipid synthesis in specific structures of the mouse brain

Lila Gonzalez-Hodar[1], Silvana Zanlungo[2], Anil Agarwal[3], Victor Cortes[1]

[1]Department of Nutrition and [2]Department of Gastroenterology, Diabetes and Metabolism, Pontificia Universidad Católica de Chile, Santiago, Chile; [3]Division of Nutrition and Metabolic Diseases, University of Texas Southwestern Medical Center, Dallas, TX

The gene expression and functional implications of the different enzymes involved in the glycerolipid synthesis in the central nervous system are poorly known. Germ line mutations in one of these enzymes, AGPAT2, cause congenital generalized lipodystrophy in humans and mice. It remains unknown whether AGPAT2 deficiency determines alterations in brain lipid homeostasis. The aims of this study were to determine 1) the mRNA levels of enzymes involved in glycerolipid synthesis in different structures of the normal mouse brain and 2) whether AGPAT2 deficiency results in changes in the expression level of these enzymes. Cerebral cortex, hypothalamus, hippocampus, and cerebellum were dissected from 9–14-week-old wild-type (WT) and Agpat2$^{-/-}$ mice. Total RNA was isolated, and mRNA abundance was measured by real-time PCR. In WT mice, GPAT1, AGPAT1, AGPAT2, AGPAT3, AGPAT4, LIPIN1, LIPIN2, DGAT1, DGAT2, and MGAT1 were present at the mRNA level in all brain structures. GPAT2, LIPIN3, and MGAT2 were not detected. GPAT1 was more abundant in the cerebellum and hypothalamus than in other structures. Of AGPAT enzymes, AGPAT1 was the most abundant in the cerebral cortex and hippocampus, whereas AGPAT4 was the most abundant in the hypothalamus and cerebellum. The mRNA abundance of all AGPAT isoforms as well as LIPIN1 and DGAT1 was higher in the cerebellum and hypothalamus than in other structures. The mRNA levels of LIPIN2 were higher in the hypothalamus, and the levels of DGAT2 were higher in the cerebral cortex and hypothalamus, in comparison with other structures. In the Agpat2$^{-/-}$ mice, mRNA levels of GPAT1, AGPAT1, AGPAT3, AGPAT4, LIPIN2, and MGAT1 were lower in all studied structures, in comparison with WT mice. LIPIN1 mRNA levels were decreased exclusively in the hypothalamus and cerebellum. We conclude that enzymes involved in glycerolipid synthesis are differentially expressed across structures of the mouse brain, and AGPAT2 deficiency changes the expression pattern of these enzymes. The functional impact of these changes on brain glycerolipid homeostasis and its implication in whole-body metabolic regulation in Agpat2$^{-/-}$ mice remain to be studied.

39

Melanocortin regulation of histamine neuron activity

Natalie J. Michael[1], Carlos M. Castorena[1], Alexandre Caron[1], Syann Lee[1], Jeffrey M. Zigman[1], Kevin W. Williams[1], Joel K. Elmquist[1]

[1]Division of Hypothalamic Research, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX

The histaminergic neurons of the tuberomammillary nucleus (TMN) in the posterior hypothalamus provide the sole source of histamine to the brain. Histaminergic TMN neurons are well-recognized for their role in regulating arousal and wakefulness. These neurons also contribute to multiple other physiological functions, including the regulation of energy homeostasis. The TMN has reciprocal connections with numerous hypothalamic nuclei involved in regulating energy homeostasis, including the arcuate nucleus. Evidence suggests that melanocortin 4 receptors (MC4R) are expressed within the TMN, and α-melanocyte–stimulating hormone immunoreactive fibers make synaptic contacts with histaminergic neurons. However, the ability of the melanocortin system to regulate histaminergic neuron activity has never been explored. We performed whole-cell patch-clamp electrophysiology on TMN neurons from mice expressing tdTomato driven by Cre-recombinase in histidine decarboxylase (HDC)-positive cells, the enzyme responsible for catalyzing the decarboxylation of L-histidine to histamine. Intact brain slices containing the TMN were treated with melanotan II (melanocortin receptor agonist, 100 nM), and electrophysiological responses were recorded. Our data suggest that subsets of TMN HDC-positive neurons respond to melanotan II. Results from these studies will provide crucial information regarding the way in which signals reflective of metabolic status and arousal are integrated within the hypothalamus.

40

Oleoylethanolamide treatment reduces neurobehavioral deficits and the brain pathology in a mouse model of Gulf War illness

Utsav Joshi[1,2,3], James Evans[1,2,3], Ross Joseph[1,3], Tanja Emmerich[1,3], Nicole Saltiel[1,3], Carlyn Lungmas[1,3], Sarah Oberlin[1], Heather Langlois[1,3], Joseph Ojo[1,2,3], Daniel Paris[1,2,3], Michael Mullan[1], Chao Jin[1], Nancy Klimas[4,5], Kimberly Sullivan[6], Fiona Crawford[1,2,3], Laila Abdullah[1,2,3]

[1]Roskamp Institute, Sarasota, FL; [2]Open University, Milton Keynes, United Kingdom; [3]James A. Haley Veterans' Hospital, Tampa, FL; [4]NOVA Southeastern University, Ft. Lauderdale, FL; [5]Miami Veterans Affairs Medical Center, Miami, FL; [6]Boston University School of Public Health, Boston, MA

Ethanolamides are natural ligands of the nuclear receptor PPAR-α and are widely known for their role in the control of appetite and pain. Anti-inflammatory properties of ethanolamides are downstream of PPAR-α activation, resulting in the inhibition of NF-κB. Considering the anti-inflammatory properties of ethanolamides, we used oleoylethanolamide (OEA) to treat neuroinflammation in a mouse model of chronic Gulf War illness (GWI), a multisymptom condition that affects nearly 30% of veterans from the 1990-1991 Gulf War (GW). The pathology of GWI is thought to involve chronic activation of microglia and astroglia in the brain, and clinical symptoms include fatigue, pain, and cognitive impairment. At present, there are no therapies that can help treat the underlying pathology of GWI. The goal of this study is to examine the therapeutic potential of OEA in targeting the central nervous system–based pathology of GWI in a well-established mouse model. Male 9-week-old C57BL6 mice were co-administered 0.7 mg/kg PB and 200 mg/kg PER in a single intraperitoneal injection in dimethyl sulfoxide (DMSO) daily for 10 days to generate the mouse model, with the control group receiving DMSO only. At 5 months post-exposure, OEA was administered at 10 mg/kg/day (based on a 5-g daily food intake) in mouse chow for up to 6 months. We examined learning at 1 month and spatial memory at 2 months after treatment with OEA. We also examined anxiety and fatigue at 5 and 6 months after treatment, respectively. Six months after OEA treatment, mice were euthanized for lipidomic, biochemical, and immunohistochemistry analyses. Our findings suggest that OEA treatment improves learning and memory and reduces fatigue behavior in this GWI mouse model. Activation of NF-κB induced by PB + PER in the brain of GWI mice was reduced by OEA treatment *in vivo*. We also observed accumulation of very long-chain fatty acid in the brains of GW agent–exposed mice. Oleoylethanolamide treatment reduced elevated astroglia and microglia activation in GW agent–exposed mice. Oleoylethanolamide was also able to reduce pro-inflammatory cytokine levels. Our studies indicate that OEA could be useful as a potential treatment for GWI, which needs further investigation.

41

Brain-derived neurotrophic factor in the ventromedial hypothalamus: The intersection of exercise and anxiety?

Kimberly H. Cox[1], Carlos M. Castorena[1], Alexandre Caron[1], Charlotte Lee[1], Syann Lee[1], Joel K. Elmquist[1]

[1]Division of Hypothalamic Research, University of Texas Southwestern Medical Center, Dallas, TX

The ventromedial hypothalamus (VMH) is critical for responding to metabolic challenges, such as high-fat diet or exercise. Importantly, the VMH is the only site in the brain that has neurons expressing steroidogenic factor-1 (*Sf-1*), a transcription factor required for VMH development and energy homeostasis. Using a transgenic mouse model to postnatally ablate *Sf-1*–expressing neurons (and thus specifically target the VMH without altering its development), our laboratory has demonstrated that VMH *Sf-1* neurons are required for obese mice to fully benefit from exercise training. *Sf-1* neurons have also previously been implicated in the regulation of anxiety behavior in mice. However, the downstream effectors of *Sf-1* signaling that promote these responses are unknown. *Sf-1* and brain-derived neurotrophic factor (*Bdnf*) are co-expressed within the VMH, and their expression is altered by exercise training, suggesting that *Bdnf* signaling acts downstream of *Sf-1* within VMH neurons. *Bdnf* in other brain regions has also been implicated in mediating anxiety behaviors. Thus, the purpose of this study was to examine the effects of *Bdnf* within the VMH on both the response to exercise and regulation of anxiety. To address this question, we generated mice lacking *Bdnf* specifically from the VMH (SF1-cre-BDNF-flox). Adult (8–12-week) males and females and Cre-negative controls were divided into two test groups, half following a moderate exercise protocol and the other half remaining sedentary controls. Mice were given an endurance test to measure their baseline physical fitness, followed by daily treadmill training (15 m/min) for 1 h/day, 5 days/week for 2 weeks. Body weights and body compositions (via NMR) were taken weekly, and 2 h after the last training bout, brain, adipose, and muscle tissues were removed and rapidly frozen to extract RNA and measure gene expression via quantitative RT-PCR. An additional cohort of sedentary mice underwent behavioral phenotyping (open field, elevated plus maze, and light/dark transition) in the University of Texas Southwestern Behavioral Core. Our data suggest that loss of *Bdnf* in the VMH prevents a reduction in body fat in response to exercise training in male mice and, in female mice, increases anxiety behaviors.

42

Cannabinoid 1 receptor in steroidogenic factor 1 neurons regulates glucose homeostasis but not body weight

Carlos M. Castorena[1], Teppei Fujikawa[2], Alexandre Caron[1], Newaz I. Ahmed[1], Amanda G. Arnold[1], Jiwon Lee[1], Claudia R. Vianna[1], William L. Holland[3], Syann Lee[1], Chen Liu[1], Joel K. Elmquist[1]

[1]Internal Medicine, Division of Hypothalamic Research, [2]Department of Cellular and Integrative Physiology, and [3]Internal Medicine, Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX

Obesity and type 2 diabetes are associated with dysregulation of the endogenous cannabinoid system. Whereas cannabinoid 1 receptor (CB1R) inverse agonists reduce adiposity and improve glucose homeostasis, these drugs have deleterious psychiatric side effects. CB1R expression is widespread, and the specific sites mediating the beneficial and untoward effects of CB1R drugs remain unclear. Evidence suggests that the inverse agonists may act on key sites within the central nervous system to improve metabolism. Using our unique mouse models, we deleted or "re-expressed" CB1Rs within steroidogenic factor 1 (SF1) neurons of the ventromedial hypothalamus (VMH). Similar body weights were observed between mice lacking CB1R from SF1 neurons (CB1RSF1-KO) *versus* controls. As expected, CB1R-null mice had reduced body weights and were protected from high-fat diet–induced obesity. Selective re-expression of CB1R in SF1 neurons (CB1RSF1-RE) did not alter these reductions in body weight. CB1RSF1-KO had improved glucose tolerance compared with controls, whereas CB1RSF1-RE had impaired glucose tolerance despite having reduced body weight. Furthermore, treatment with CB1R inverse angonists improved glucose homeostasis in control and CB1RSF1-RE mice, but not in CB1RSF1-KO mice. Our results indicate that CB1Rs of the VMH are critical for regulating whole-body glucose homeostasis, independent of body weight.

43

APOE4-dependent deficits in brain lysophosphatidylcholine-docosahexaenoic acid and its transporter mfsd2a in Alzheimer's disease patients

Laila Abdullah[1], James E. Evans[1], Ben Shackleton[2], Charis Ringland[1], Utsav Joshi[1], Ross Joseph[1], Joseph Ojo[1], Michael Mullan[1], Fiona Crawford[1], Corbin Bachmeier[1]

[1]Roskamp Institute, Sarasota, FL; [2]Icahn School of Medicine at Mount Sinai, New York, NY

The contribution of apolipoprotein E (APOE) E4 to Alzheimer's disease (AD) pathology is characterized by the presence of severe cerebral amyloid angiopathy (CAA), increased blood–brain barrier breakdown, and reduced cerebral vascularization in E4 carriers. It has been proposed that the diminished capacity of the apoE4 protein to transport docosahexaenoic acid (DHA), an essential fatty acid that is required for the structural and functional maintenance and vascular integrity of the brain, also contributes to AD pathogenesis. Studies have shown that lysophosphatidylcholine (LPC) is a major carrier of DHA to the brain and is transported through major facilitator superfamily domain–containing 2A (mfsd2a) enriched at the brain endothelial cells. However, it remains to be determined whether there are any differences between healthy and AD brain for LPC-DHA and mfsd2a levels in relation to the E4 allele. We performed liquid chromatography/mass spectrometry–based lipid analysis of the cerebrovascular and parenchymal fractions from autopsied human brain tissue of pathologically confirmed AD cases and controls. We performed antibody-based examination of the mfsd2a protein in the cerebrovasculature from these subjects. These studies were also performed on brain homogenates from transgenic mice with human APOE and five AD mutations (EFAD). In the cerebrovascular and parenchymal fractions, LPC-DHA levels were lower in E4 carriers with AD compared with control E4 carriers. We observed an E4-dependent decrease in protein levels of mfsd2a in the brain cerebrovasculature. The mfsd2a expression was lower in E4 carriers compared with non-carriers. Stratification of LPC-DHA by CAA showed that its levels were reduced in E4-positive AD patients with severe CAA. In addition, brain levels of LPC-DHA and mfsd2a expression were lower in E4FAD mice compared with E3FAD mice. These findings demonstrate that brain LPC-DHA deficiencies in E4 carriers may be due to reduced mfsd2a expression and partly associated with severe CAA. Thus, targeting this transport mechanism may improve the bioavailability of DHA in the brains of E4 carriers who are at risk of developing AD.

44

Molecular interactions of ANGPTL8 with ANGPTL3 and ANGPTL4: Consequences for activity of lipoprotein lipase

Oleg Kovrov[1], Erika Larsson[1], Kristian Kølby Kristensen[2,3], Michael Ploug[2,3], Gunilla Olivecrona[1]

[1]Department of Medical Biosciences, Umea University, Umea, Sweden; [2]Finsen Laboratory, Rigshospitalet, Copenhagen, Denmark; [3]Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark

Lipoprotein lipase (LPL) is the key enzyme in energy metabolism that facilitates uptake of triglycerides from plasma lipoproteins for storage by white adipose tissue, for ATP production in active muscles, and for heat in brown adipose tissue. Such important processes need to be tightly regulated based on the overall requirements of the body. Angiopoietin-like (ANGPTL) proteins 3, 4, and 8 serve as metabolic switches for LPL activity; they inactivate LPL in tissues that do not require uptake of lipolysis products from triglycerides at a particular moment. ANGPTL3 and ANGPTL4 are independent regulators of LPL activity, whereas ANGPTL8, the most recently discovered family member, has been demonstrated to work together with ANGPTL3 for control of LPL activity. It was shown that both of these ANGPTL proteins need to originate from the same cell for ANGPTL8 to cause additional inhibition of LPL activity. In our *in vitro* studies, using bacterially expressed ANGPTL proteins, we have observed that ANGPTL8 interacts with both ANGPTL3 and ANGPTL4. This occurs only when the ANGPTL proteins are mixed under fully denaturing conditions and then allowed to refold together. Similar to previously published studies, ANGPTL8 was capable of inactivating LPL only when folded together with ANGPTL3. We observed that ANGPTL8 had effects on LPL activity even when present in much lower concentrations than those of ANGPTL3. In contrast, increased concentrations of ANGPTL8 refolded together with ANGPTL4 were found to cause rapid aggregation of the complex and loss of the ability of ANGPTL4 to inactivate LPL. Further studies indicated that all three members of the ANGPTL family act on LPL via the same mechanism, involving promotion of heat-induced monomerization of active dimeric LPL. This was prevented if LPL was bound to glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1, the endothelial LPL transport protein that is known to protect LPL from heat-induced inactivation. Overall, our data support the view that ANGPTL8 may function as an additional metabolic control switch, which directs triglycerides to tissues that need them the most by activating ANGPTL3 and possibly by inactivating ANGPTL4.

45

Phosphatidylcholine synthesis coordinates the metabolic response to dietary fat in the murine intestinal epithelium

John P. Kennelly[1,2], Jelske N. van der Veen[1,3], Randal C. Nelson[1], Kelly-Ann Leonard[2], Rick Havinga[4], Jean Buteau[2], Folkert Kuipers[4], René L. Jacobs[1,2,3]

[1]Group on the Molecular and Cell Biology of Lipids, [2]Department of Agricultural, Food, and Nutritional Science, and [3]Department of Biochemistry, University of Alberta, Edmonton, AB, Canada; [4]Departments of Pediatrics and Laboratory Medicine, University of Groningen, The Netherlands

Phosphatidylcholine (PC) is an abundant component of biological membranes and lipoprotein particles. The enzyme CTP:phosphocholine cytidylyltransferase-α (CTα) regulates *de novo* PC synthesis in the intestine. To determine the role of PC synthesis in small-intestinal physiology, we deleted CTα in the intestinal epithelium of mice. We generated intestine-specific CTα knockout mice (iCTα$^{-/-}$ mice) using inducible Cre-Lox recombination. Control and iCTα$^{-/-}$ mice were fed a carbohydrate-based chow or a high-fat diet. Plasma lipid and hormone concentrations were assessed after fasting and refeeding. Intestinal fatty acid absorption was quantified after oral gavage of [^{3}H]triolein and measurement of label in plasma over time as well as label distribution in sequential intestinal segments. Gene expression microarray analysis was conducted on intestinal epithelial cells. Bile composition was assessed after gallbladder cannulation. Loss of intestinal CTα reduced PC concentrations in the small intestine by ~30%. When fed a high-fat diet, iCTα$^{-/-}$ mice showed impaired fatty acid absorption, reduced chylomicron lipidation, and enhanced postprandial secretion of GLP-1 and PYY. Transcriptional programs regulating fatty-acid metabolism were repressed in iCTα$^{-/-}$ intestines, whereas those of inflammation were increased. Loss of intestinal CTα induced crypt hyperproliferation and goblet cell depletion. Biliary bile acid, cholesterol, and phospholipid secretion was stimulated in iCTα$^{-/-}$ mice, indicative of accelerated enterohepatic cycling. We conclude that intestinal PC synthesis regulates dietary fat absorption, enteroendocrine hormone secretion, enterohepatic circulation of bile acids, and the intestinal immune response in mice.

46

12-Hydroxylated bile acids regulate food intake and gastric emptying through GPR119 in the intestine

Sei Higuchi[1], Tiara R. Ahmad[1], Enrico Bertaggia[1], Kristian K. Jensen[2], Liangsu Wang[2], Rebecca A. Haeusler[1]

[1]Naomi Berrie Diabetes Center and Department of Pathology and Cell Biology, Columbia University, New York, NY; [2]Merck Research Laboratory, Kenilworth, NJ

One important risk factor of obesity is considered to be excessive food intake. Feeding behavior is governed partly by lipid mediators in the gastrointestinal tract. Particularly, intestinal lipid plays an important role in regulation of satiation through gastric emptying. Bile acids (BAs) are synthesized from cholesterol in the liver and modulate intestinal lipid metabolism. Previously, we reported that a certain subset of BAs, the 12-hydroxylated BAs (12-OH BAs), are positively correlated with body mass index in humans. Furthermore, our recent studies show that deficiency of the essential enzyme to produce 12-OH BAs, Cyp8b1, reduces body weight and impairs lipid absorption in mice. We also find that Cyp8b1 deficiency reduces *ab libitum* food intake. From this evidence, we hypothesized that Cyp8b1 deficiency reduces gastric emptying and food intake by modulating lipid metabolism in the intestine. We found that Cyp8b1 deficiency decreased both solid-phase and liquid-phase gastric emptying, and dietary lipid was both necessary and sufficient for this effect. Antagonization or knockout of the 2-monoacylglycerol receptor GPR119 normalized the slow gastric emptying and reduced food intake of Cyp8b1-deficient mice. These data suggest that 12-OH BAs regulate gastric emptying and food intake by modulating dietary lipid absorption and GPR119 activation in the intestine. Suppression of Cyp8b1 may be a novel target to reduce gastric emptying and increase satiation for obesity and diabetes treatment.

47

Reactivation of myeloid cell TLR4 promotes LPS-induced acute inflammation and anorexia in mice

Lin Jia[1], Shuwen Qian[2], Claudia Vianna[1], Newaz Ahmed[1], Charlotte Lee[1], Syann Lee[1], Laurent Gautron[1], Joel Elmquist[1,3]

[1]Division of Hypothalamic Research and [3]Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX; [2]Department of Biochemistry and Molecular Biology, Fudan University Shanghai Medical College, Shanghai, China

It has been demonstrated that the Toll-like receptor 4 (TLR4)-mediated signaling pathway plays a critical role in lipopolysaccharide (LPS)-induced acute infection and associated sickness behavior. Specifically, TLR4 is highly expressed in immune cells. Although accumulating studies have shown the requirement of TLR4-expressing myeloid cells in the production of inflammatory cytokines following LPS treatment, direct *in vivo* evidence of whether activation of myeloid cell TLR4 is sufficient to induce vigorous innate immune response and suppress food intake is still lacking. To answer this question, we generated a new mouse model that enabled us to specifically restore the endogenous TLR4 expression in myeloid cells on a TLR4-null background. We found that, in response to LPS treatment, mice with reactivated TLR4 expression in myeloid cells had dramatically elevated circulating Tnfα and IL-6 levels. In addition, restoration of myeloid cell TLR4 expression in mice promoted LPS-induced hypoglycemia, which was associated with elevated expression of macrophage Glut1. Furthermore, a low-dose LPS (100 ng/kg body weight) injection greatly suppressed food intake and reduced weight gain in myeloid cell TLR4-reactivated mice. In contrast, TLR4-null mice were resistant to the aforementioned LPS-induced alterations. These findings suggest that activation of myeloid cell TLR4 contributes to acute LPS-induced cytokine production, hypoglycemia, and inflammation-associated anorexia. Moreover, our unique mouse model will be a very useful tool to evaluate the sufficiency of the tissue-specific Tlr4 gene in disease development.

48

Role of *de novo* lipogenesis in white adipose tissue signaling to brown adipose tissue in regulating thermogenesis through neural circuitry

Adilson Guilherme[1], Felipe S. Henriques[1], David J. Pedersen[1], Alexander Bedard[1], Alexandra Lee[1], Elizabeth Henchey[1], Kamal Rahmouni[2], Irfan J. Lodhi[3], Clay F. Semenkovich[3,4], Michael P. Czech[1]

[1]Program in Molecular Medicine, University of Massachusetts Medical School Worcester, MA; [2]Department of Pharmacology, University of Iowa Carver College of Medicine, Iowa City, IA; [3]Division of Endocrinology, Metabolism, and Lipid Research and [4]Department of Cell Biology and Physiology, Washington University School of Medicine, Washington University School of Medicine, St. Louis, MO

Subcutaneous adipose tissue (sWAT) plays an important role in energy homeostasis and is recognized as an important source of secreted factors that communicate with other organs. We recently reported that down-regulation of *de novo* fatty acid synthesis (DNL) via genetic deletion of adipocyte fatty acid synthase (FASN) in mice housed at mild-cold conditions (*i.e.* 22°C) expands sympathetic neurons in sWAT associated with adipose browning (Guilherme *et al.* (2017) *Mol. Metab.* **6,** 781–796). Here we show that sWAT sensory neurons are activated by FASN KO and tested whether BAT thermogenesis is also regulated by DNL. We deleted FASN in all mature white and brown adipocytes (Ad-FASNKO) or only in brown adipocytes (UCP1-FASNKO) by generating mice in which the tamoxifen (Tx)-inducible adiponectin-ER-Cre or the UCP1-ER-Cre drivers were used to delete adipocyte FASN, respectively. As expected, deletion of FASN in mature Ad-FASNKO mice induced strong sWAT "browning" with high UCP-1 expression and improved glucose tolerance. Interestingly, when brown adipocytes in Ad-FASNKO mice were first "whitened" by housing mice at thermo-neutrality (30°C), Tx administration also induced "browning" of these whitened brown adipocytes. However, this effect was not cell-autonomous because Tx failed to have this effect in tissue culture. Tx also failed to have this effect in the UCP1-FASNKO mice. Thus, FASN KO in white adipocytes appears to cause adipocyte browning in WAT as well as BAT through a non-cell autonomous mechanism. We obtained evidence that neuronal signaling from WAT to WAT and WAT to BAT may be the underlying mechanism for these effects by finding increased tyrosine hydroxylase and neuropeptide Y content in WAT and BAT in Ad-FASNKO but not UCP1-FASNKO mice. Consistent with that possibility, Ad-FASNKO mice but not UCP1-FASNKO mice showed activated cAMP/PKA signaling in WAT and BAT, reflecting release of catecholamines from sympathetic neurons. Further experiments identified neurotrophic factors produced by adipocytes deleted for FASN that can enhance neuronal outgrowth. Thus, the DNL pathway in white adipocytes may control thermogenic programming in WAT as well as systemic glucose metabolism through regulation of neuronal signaling to the CNS that then enhances sympathetic outputs into both WAT and BAT depots.

49

Identifying transcriptional targets of steroidogenic factor-1 in the ventromedial hypothalamus

Steven Wyler[1], Kimberly Cox[1], Caleb Lord[1], Charlotte Lee[1], Rong Wan[1], Angie Bookout[1], Syann Lee[1], Chen Liu[1], Joel Elmquist[1]

[1]Division of Hypothalamic Research, University of Texas Southwestern Medical Center, Dallas, TX

The increasing prevalence of obesity and adult-onset diabetes represents a major health crisis in the United States. These disorders result from a complex interaction of multiple genetic, environmental, and behavioral factors. Within the hypothalamus resides multiple nuclei required for the regulation of metabolic homeostasis. One nucleus termed the ventromedial hypothalamus (VMH) facilitates glucose homeostasis and metabolic adaptation to challenges such as high-fat diet and exercise. A majority of these neurons express the orphan nuclear receptor, steroidogenic factor (SF-1), which is required for both the development and metabolic function of this nucleus. Identification of genes regulated by SF-1 will facilitate our understanding of the function of VMH neurons. To identify direct transcriptional targets of SF-1, we generated a new mouse line where we tagged the endogenous SF-1 protein with a 2×Ty1 tag. PCR confirmed the correct insertion of the Ty1 epitope, and immunohistochemistry against Ty1 revealed restricted expression to the VMH in the adult brain. Importantly, using chromatin immunoprecipitation (ChIP), we found enrichment for SF-1 binding at promoters of putative direct targets, Cnr1 and Bdnf. Additionally, the Ty1-SF-1 mice have normal serum-luteinizing hormone, follicle-stimulating hormone, and corticosterone levels, which are all disrupted in SF-1 null mice. Collectively, these data suggest that the Ty1 tag does not drastically interfere with SF-1 binding to target DNA or affect its interaction with other proteins, and it will be suitable for future genome-wide ChIP-binding assays. Finally, to screen potential metabolic targets of SF-1, we developed a strategy to test orthologs of SF-1–enriched genes in *Drosophila*. UAS-RNAi lines were crossed to nsyb-Gal4 to generate neuroendocrine-specific knockdown of target genes. As an initial assessment of metabolic disruption, flies were subjected to a starvation assay. Through this screen, we identified several VMH-enriched genes with altered resistance to starvation. Combined use of *Drosophila* and mouse models will help uncover novel genes involved in the metabolic function of the VMH.

50

Secreted micropeptides in the regulation of metabolic homeostasis

Angie L. Bookout[1,2], Zhaoning Wang[2], Eric N. Olson[2], Joel K. Elmquist[1]

[1]Department of Internal Medicine, Division of Hypothalamic Research, and the [2]Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX

Cardiometabolic disease continues to be a major health burden worldwide. Our goal is to uncover new pathways to understand how a novel class of proteins called micropeptides may work in the hypothalamus to regulate whole-body metabolism. Our prediction that one such micropeptide, which we call B03, is a novel neuropeptide and contributes to metabolic homeostasis could reveal unique opportunities to modulate these pathways *in vivo* and offers possibilities for a new generation of therapeutics for cardiometabolic disease. Mice with genetic deletion of B03 have elevated plasma lipids and reduced respiratory exchange rates, leading to our hypothesis that B03 has a role in metabolic homeostasis by communicating nutritional status between neurons. This project will determine whether the micropeptide B03 is required to maintain whole-body energy balance through actions within the brain. First we will further characterize the metabolic outcomes of genetic deletion of B03 in the whole animal. We will subject B03 knockout animals to metabolic stress paradigms, including diet-induced obesity as well as severe hypoglycemia. These animals will then undergo a series of assessments using state-of-the-art techniques, including metabolic cages to measure energy expenditure, neuroendocrine assays, and gene expression measurements in liver and adipose. We will next determine the exact cellular identity of neurons expressing B03 using histochemical techniques. Finally, we will delete or re-express B03 only in neurons using a combination of cre- and flp-recombinase tools and assess the animals as stated above to determine the requirement of the brain in mediating the effects of B03 on metabolic homeostasis. Taken together, these studies will test the hypothesis that B03 is a novel neuropeptide that contributes to metabolic homeostasis by acting within the brain in response to nutritional challenge.

51

Functional analyses of DGAT enzymes in adipose tissue

Chandramohan Chitraju[1,2], Grisell Diaz-Ramirez[2], Jane J. Lee[1], Niklas Mejhert[1], Joel T. Haas[2], Carrie A. Grueter[2], Jason E. Imbriglio[3], Shirly Pinto[3], Suneil K. Koliwad[2], Robert V. Farese, Jr.[1,4,5], Tobias C. Walther[1,4,5,6]

[1]Department of Genetics and Complex Diseases, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA; [4]Broad Institute of Harvard and MIT, Cambridge, MA; [6]Howard Hughes Medical Institute, Boston, MA; [2]Gladstone Institute of Cardiovascular Disease, San Francisco, CA; [3]Merck & Co., Inc., Kenilworth, NJ; [5]Contributed equally

Triglyceride (TG) storage in adipose tissue provides the major reservoir for metabolic energy in mammals. TG synthesis in adipose tissue is catalyzed by acyl-CoA:diacylglycerol acyltransferase (DGAT) enzymes, DGAT1 or DGAT2. Both DGAT enzymes catalyze the same reaction, utilizing diacylglycerol and fatty acyl-CoAs as substrates, but are evolutionarily unrelated. The functional roles of the two enzymes in adipose tissue have remained unclear. To address this, we generated mice that lack either or both enzymes in adipocytes. We find that DGAT1 is up-regulated during lipolysis in adipose tissue, where it mediates fatty acid re-esterification and protects adipocytes from lipid-induced endoplasmic reticulum stress. In contrast, DGAT2 is up-regulated with feeding. Although global knockout of DGAT2 is perinatal lethal, mice lacking DGAT2 in adipocytes are surprisingly healthy, with nearly normal levels of adipose fat. The adipocyte-specific deletions show that DGAT1 and DGAT2 have partial redundancy in adipocyte TG storage, although DGAT1 contributes more to diet-induced obesity. However, deletion of both DGAT enzymes in adipose tissue results in mice with lipodystrophy with complete loss of white adipose tissue and intrascapular brown adipose tissue. Our studies reveal that DGAT1 and DGAT2 account for all TG synthesis in adipose tissue and that the two enzymes can partially compensate for each other but have specific functional roles.

52

Weight loss induced by FGF21 is associated with up-regulation of neurotensin and corticotropin-releasing hormone in dorsomedial hypothalamus and increased hepatic bile acid and glucose secretion in liver of DIO mice

Marina Kjaergaard[1,2], Helle Keinicke[1], Gao Sun[1], Linu M. John[1], Anna Secher[1], Birgitte S. Wulff[1], Birgitte Andersen[1], Kirsten Raun[1]

[1]Global Research, Novo Nordisk A/S, Maaloev, Denmark; [2]Clinical Medicine, Copenhagen University Hospital, University of Copenhagen, Denmark

Fibroblast growth factor 21 (FGF21) has multiple metabolic effects and targets several organs, such as brain, liver, adipose tissue, etc. The main effects induced by FGF21 in rodents are weight loss induced by increased energy expenditure (EE) and improved lipid and glucose metabolism. To understand the regulatory mechanisms behind FGF21-induced weight loss, the hypothalamic gene expression profile was characterized in arcuate nucleus and dorsomedial hypothalamus (DMH) of the brain and in the liver. Diet-induced obese C57BL/6J male mice were treated with FGF21 (0.6 mg/kg/day, twice per day) and by diet intervention, by switching from high-fat diet to chow for 18 days. As expected, FGF21 lowered body weight independent of food intake and therefore likely caused by increased EE. Within DMH, FGF21 up-regulated neurotensin (NT) and corticotropin-releasing hormone (CRH) mRNA compared with vehicle and CR. The increase in CRH may be driven by the increase in NT (Rowe *et al.* (1995), Mazzocchi *et al.* (1997), and Crooke *et al.* (2009)), consequently inducing increase in EE. Within the liver, the gene expression profile suggests that FGF21 increased hepatic uptake of fatty acids and lipoproteins from blood, channeled TGs toward production of cholesterol and bile acid for secretion, reduced lipogenesis, and increased hepatic glucose output. The weight loss and improved lipid and glucose metabolism may also be induced by a reduction in inflammatory and oxidative stress response observed in both brain and liver. Interestingly, the hepatic expression of short-form leptin receptor (Ob-Ra) was highly induced, and the mechanism of this up-regulation is not presently known. In summary, the weight loss induced by FGF21 was probably caused by increased EE. The increased mRNA levels of NT and CRH in the DMH and the hepatic bile acid and glucose secretion from the liver could potentially play a role in increasing energy expenditure.

53

Examining high-density lipoproteins in cerebral spinal fluid

Tamar Gubeladze[1], James Feng[1], Kate T. Creasy[1], Lisa Conboy[1], Megan Richie[1], John P. Kane[1]

[1]University of California, San Francisco, CA

Cholesterol is vital to normal brain development and proper physiological function, learning, and memory. Dysregulation in cholesterol metabolism can lead to diseases of the central nervous system (CNS), including Alzheimer's disease. Cholesterol in the CNS is primarily transported by high-density lipoproteins (HDL) that characteristically contain apolipoproteins A1 and E. We have previously shown that there are over 20 unique species of HDL in human plasma, many of which have distinct biological functions in addition to cholesterol transport. We recently reported that HDL carries a number of cytokines and is possibly directly involved in mediating inflammatory responses. Differential HDL-cytokine profiles correlate with cardiovascular disease risks, and therefore we aim to examine whether CNS-HDL profiles have similar relationships. We collected surplus cerebral spinal fluid (CSF) samples from patients at the University of California San Francisco Lumbar Puncture Clinic. After samples were utilized for diagnostic and clinical purposes, surplus CSF samples without red blood cell contamination were transferred for use in this study. CSF samples representing conditions ranging from benign (headache, tinnitus), to inflammatory, neoplastic, and other organic CNS disorders (Parkinson's, dementia) were examined. Samples were separated by two-dimensional gel electrophoresis and analyzed for expression of apolipoproteins A1 and E. We isolated HDL from the samples and quantified the expression of 65 cytokines in the HDL fraction and whole CSF to determine inflammatory signaling relationships that become altered in neurological disorders. Finally, we measured the amount of preβ-HDL, a known biomarker of cardiovascular disease, in the CSF samples to test whether there is a common underlying mechanism of impaired HDL metabolism in neurological and cardiovascular diseases. Our project characterizes the HDL speciation of CSF in different neurological conditions, illustrating differences in HDL metabolism in CNS disorders. Our future studies will aim to clarify the properties of HDL that are dysregulated in more severe neurological conditions to elucidate disease mechanisms and points of early detection and interventions for these conditions.

54

Mechanisms coordinating *de novo* lipogenesis with triglyceride synthesis

Aditi Jatkar[1,2,3], Niklas Mejhert[1,2,3], Chandramohan Chitraju[1,2], Tobias C. Walther[1,2,4,5], Robert V. Farese, Jr.[1,2,4]

[1]Department of Genetics and Complex Diseases, Harvard T.H. Chan School of Public Health, Boston, MA; [2]Department of Cell Biology, Harvard Medical School, Boston, MA; [3]Broad Institute of Harvard and MIT, Cambridge, MA; [4]Howard Hughes Medical Institute, Boston, MA; [3]Contributed equally

Fatty acids (FAs) are used by cells for energy and as building blocks for other lipids and membranes. When in excess, FAs are stored as triglycerides (TGs) in lipid droplets. How the production of FAs by *de novo* lipogenesis (DNL) is coordinated with storage depots is largely unknown. The master regulator of DNL is SREBP-1c, a transcription factor that up-regulates the expression of more than 30 lipid synthesis genes. We now show that cellular TG storage capacity is coordinated with SREBP-1c activation. Our previous studies in mice showed that overexpression of the TG synthesis enzyme DGAT2 (acyl-CoA:diacylglycerol acyltransferase 2) increases expression of SREBP-1c and its target genes, and we now show that genetic loss of DGAT2 decreases this response. In cells, pharmacological inhibition of DGAT2 retains both SREBP-1 and SREBP-2 in the endoplasmic reticulum, thus preventing their activation. Other COPII cargo proteins, such as cystic fibrosis transmembrane receptor and ATF-6, trafficked normally through the secretory pathway, indicating that the processing block was specific for SREBPs. Our studies indicate that the block in SREBP trafficking is probably caused by a specific but yet unidentified mechanism involving SCAP or Insig-1, the interacting partners of SREBP. Lipidomics experiments show that DGAT2 inhibition results in the accumulation of several sphingolipid species, suggesting that these may be proximal mediators of the regulatory step. In summary, we have uncovered a new connection between TG synthesis and DNL and hypothesize the existence of a feedback mechanism that coordinates FA storage with FA synthesis.

55

IDOL regulates systemic energy balance through control of central nervous system very low-density lipoprotein receptor expression

Stephen D. Lee[1], Christina Priest[1], Jie Gao[1], Jason Kim[1], Prashant Rajbhandari[1], Peter Tontonoz[1], Cynthia Hong[1]

[1]UCLA, Los Angeles, CA

Liver X receptors limit the cellular uptake of lipids through transcription of the E3 ubiquitin ligase "inducible degrader of the LDL receptor" (IDOL), which targets lipoprotein receptors for lysosomal degradation. We previously demonstrated that the LXR-IDOL pathway exerts species-specific effects on levels of lipoproteins through control of low-density lipoprotein receptor (LDLR) protein levels. However, the broader contributions of IDOL to systemic metabolism are unknown. Here we show that loss of IDOL in mice is protective against the development of diet-induced obesity and metabolic dysfunction. Unexpectedly, analysis of a series of tissue-specific knockout mice reveals that IDOL affects energy balance, not through its actions in metabolic tissues, but though its actions in the central nervous system (CNS). Furthermore, we identify very low-density lipoprotein receptor (VLDLR) rather than LDLR as the key mediator of IDOL effects on systemic metabolism. These studies identify a role for the CNS IDOL-VLDLR pathway in energy balance and susceptibility to diet-induced obesity.

56

Melanocortin-4 receptor expression in the ventromedial hypothalamus is dynamically regulated by estradiol and contributes to metabolic homeostasis specifically in females

William C. Krause[1], Holly A. Ingraham[1]

[1]Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA

Estrogen receptor α (ESR1)-expressing neurons in the ventrolateral region of the ventromedial hypothalamus (VMHvl) promote energy expenditure and maintain metabolic homeostasis in females. However, the connection between ESR1 activity in the VMHvl and the neural circuits that regulate metabolism is not well defined. As part of an effort to identify ESR1 effectors in the hypothalamus, we found that the melanocortin-4 receptor (*Mc4r*) is transcriptionally up-regulated by endogenous (protesrus) or exogenous increase in circulating estradiol. *Mc4r* mRNA induction localizes to the VMHvl. Similarly, two independent reporters confirm enrichment of this metabolic sensor in the ESR1-expressing neurons in the female VMHvl. Given that MC4R signaling promotes energy expenditure, we hypothesized that its regulation by ESR1 provides an interface between the VMHvl and broader circuitry regulating energy homeostasis. To confirm a physiological role for the VMHvlMC4R neurons, we took advantage of a re-activatable *Mc4r* allele (loxTB *Mc4r*) in which a transcription-blocking sequence prevents gene expression. As expected, by 8 weeks of age, both male and female loxTB *Mc4r* mice are significantly heavier than control littermates. *Sf1-Cre* removes the inhibitory loxTB element and restores VMHvl *Mc4r* mRNA expression. Remarkably, body weights of female loxTB *Mc4r*;*Sf1-Cre* mice are significantly decreased compared with loxTB *Mc4r* littermates. In contrast, consistent with ESR1-mediated regulation of *Mc4r* expression, there is no body weight change in male loxTB *Mc4r*;*Sf1-Cre* mice. Preliminary metabolic analysis indicates that energy expenditure and physical activity levels are increased in the loxTB *Mc4r*;*Sf1-cre* females compared with loxTB *Mc4r* mice. Ongoing efforts in the laboratory are under way to characterize changes in VMHvl neuron physiology in response to melanocortinergic input and the sensitization of this response by ESR1-mediated regulation of *Mc4r*. Collectively, our data indicate that the VMHvl neurons integrate steroid hormone and central metabolic signals to set appropriate energy expenditure levels. In addition, the intersection of ESR1 and MC4R signaling may contribute to the stronger obesity phenotype associated with loss/mutation of MC4R in female rodents and humans.

57

Nitro-oleic acid distribution in lipoprotein triglycerides

Marco Fazzari[1,2], Sonia R. Salvatore[2], Dario A. Vitturi[2], Steven R. Woodcock[2], Bruce A. Freeman[2], Francisco J. Schopfer[2]

[1]Fondazione Ri.MED, Palermo, Italy; [2]Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA

Nitro-fatty acids (NO_2-FA) are endogenous electrophilic signaling mediators that act by forming reversible Michael adducts with glutathione and cysteine residues in target proteins. In this regard, NO_2-FA modulate cellular homeostasis and protective responses through Nrf-2 and heat shock factor activation and down-regulate inflammatory responses by inhibition of NF-κB and soluble epoxide hydrolase. Despite the recent advances in NO_2-FA pharmacology and highly promising preclinical and clinical data, our understanding of NO_2-FA absorption, distribution, and storage is greatly diminished by technical challenges. These are characterized by the complexity displayed of NO_2-FA reversible thiol reactivity, the NO_2-FA incorporation into a wide variety of complex lipids, and their instability under enzymatic and non-enzymatic hydrolysis conditions. Herein, we investigated the mechanism and kinetics of absorption, metabolism, and distribution of the prototypical 10-nitro-oleic acid (NO_2-OA) using a model of rat lymph fistula and dog oral gavage. We established esterification as a main yet unexplored mechanism of NO_2-FA distribution through HPLC–high-resolution MS/MS analysis of triacylglycerides. NO_2-OA and its main inactive metabolite nitro-stearic acid (NO_2-SA) were found esterified in rat lymph fluid and dog plasma after oral supplementation. Moreover, quantitative HPLC–MS/MS analysis of free and esterified fractions confirmed a preferential time-dependent NO_2-OA and NO_2-SA incorporation into lymphatic chylomicrons. In this regard, esterified NO_2-FA levels in lymph were ~22–50-fold higher than the free levels, whereas no difference was found in rat portal plasma. Of note, NO_2-OA was mainly found esterified in dog plasma after single oral dosing, whereas NO_2-SA metabolite levels were higher in the non-esterified fraction. Furthermore, after 14 days of oral dosing, a 5-fold decrease in net NO_2-OA esterification was found compared with day 1. Finally, the new positional (10-nitro-octadec-8-enoic acid) and geometrical (*Z*-10-nitro-octadec-9-enoic acid) isomers of NO_2-OA were detected and described. In summary, we demonstrated that the main distribution mechanism of NO_2-OA involves esterification, which inhibits electrophilic interactions with blood components and further protects the delivery of these electrophilic signaling molecules to target tissues by bypassing hepatic first-pass metabolism.

58

Cellular and synaptic reorganization after exercise training

Zhenyan He[1], Lihn Liu[1], Sadia Afrin[1], Kevin W. Williams[1]

[1]Division of Hypothalamic Research, University of Texas Southwestern Medical Center, Dallas, TX

Hypothalamic pro-opiomelanocortin (POMC) and neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons are critical nodes of a circuit within the brain that sense key metabolic cues as well as regulate feeding behavior, energy expenditure, and glucose metabolism. Importantly, intrinsic cellular properties of these neurons are highly sensitive to metabolic state. This includes a rapid reorganization of synaptic inputs and electrophysiological properties to facilitate adaptations to altered energy balance. Although the cellular properties of these neurons have been investigated in the context of obesity, much less is known about the effects of exercise training. We performed whole-cell patch-clamp electrophysiology on identified POMC and NPY/AgRP neurons after exercise. Exercise resulted in a depolarization and increase in firing rate of arcuate POMC neurons. The increased excitability of POMC neurons was concomitant with increased excitatory input to these neurons. In agreement with recent work suggesting that leptin plays an important role in the synaptic (re)organization of POMC neurons, we found that POMC neurons that express leptin receptors appeared more sensitive to exercise-induced changes in biophysical properties. Opposite to the cellular effects observed in POMC neurons, NPY neurons were inhibited following exercise. Together, these data support a rapid reorganization of synaptic inputs and biophysical properties in response to exercise, which may facilitate adaptations to altered energy balance and glucose metabolism.

Author Index

Name	Abstract/Poster Board Assignment
Elmquist, J. K.	39
Elmquist, J. K.	42
Elmquist, J. K.	41
Elmquist, J. K.	30
Elmquist, J.	1
Elmquist, J. K.	50
Elmquist, J.	49
Elmquist, J.	47
Emmerich, T.	31
Emmerich, T.	40
Evans, J.	40
Evans, J. E.	43
Evans, J. E.	31
Farese Jr., R. V.	54
Farese, Jr, R. V.	51
Farias, M.	9
Farias, M.	10
Farias, M.	12
Farooqi, S.	4
Fazzari, M.	57
Feng, J.	53
Freeman, B. A.	57
Friedman, J.	7
Fujikawa, T.	30
Fujikawa, T.	42
Galsgaard, E.	37
Galvan, A. M.	5
Galvan, A. M.	6
Gao, J.	55
Gautron, L.	47
Gavini, C.	1
Gavini, C. K.	2
Gillum, M. P.	15
Gonzalez-Hodar, L.	38
Grevengoed, T.	15
Grueter, C. A.	51
Gubeladze, T.	53
Guilherme, A.	48
Haas, J. T.	51
Haeusler, R. A.	46
Han, Y.	9
Han, Y.	12
Han, Y.	10
Hansen, N. L.	15
Havinga, R.	45
He, Y.	10
He, Y.	9
He, Y.	11
He, Z.	58
Henchey, E.	48
Henriksson, E.	37
Henriques, F. S.	48
Hernandez, G.	27
Hernandez, G.	32
Higuchi, S.	46
Hoffmann, N.	15
Holland, W. L.	30
Holland, W. L.	42
Hong, C.	55
Horvath, A.	32
Hsu, R.	19
Hu, M.	32
Huang, D.	18
Hurley, A.	19
Hyseni, I.	11
Ibrahim, B. A.	29
Imbriglio, J. E.	51
Ingraham, H. A.	56
Jacob, R. F.	28
Jacobs, R. L.	45
Jama, A.	18
Jarlhelt, I.	15
Jarrett, K. E.	19
Jatkar, A.	54
Jensen, K. K.	46
Jensen, M.	15
Jia, L.	47
Jiang, H.	23
Jimenez-Morales, D.	17
Jin, C.	40
John, L. M.	52
Jorgensen, R.	25

Name	Abstract/Poster Board Assignment	Name	Abstract/Poster Board Assignment
Joseph, R.	31	Leber, B.	32
Joseph, R.	40	Lee, A.	48
Joseph, R.	43	Lee, A.	9
Joshi, U.	43	Lee, C. E.	30
Joshi, U.	40	Lee, C.	41
Joshi, U.	31	Lee, C.	49
Kane, J. P.	53	Lee, C.	47
Kaplan, J. H.	20	Lee, C.	19
Keegan, A. P.	31	Lee, J. J.	51
Keinicke, H.	52	Lee, J.	42
Kennelly, J. P.	45	Lee, S. D.	55
Kim, J.	55	Lee, S.	47
Kirk, R. K.	37	Lee, S.	49
Kjaergaard, M.	52	Lee, S.	42
Klaauw, A.	4	Lee, S.	41
Klein, A. D.	34	Lee, S.	39
Kliewer, S. A.	32	Lee, S.	30
Kliewer, S. A.	27	Lei, D.	13
Kliewer, S.	21	Leonard, K.	45
Klimas, N.	31	Li, A.	19
Klimas, N.	40	Li, J.	22
Knop, F. K.	15	Lin, J.	26
Kodirov, S.	9	Liu, C.	30
Koliwad, S. K.	51	Liu, C.	42
Koplev, S.	8	Liu, C.	49
Kovrov, O.	44	Liu, C.	20
Kraemer, F. B.	14	Liu, J.	14
Krause, W. C.	56	Liu, L.	58
Krauss, R. M.	13	Liu, T.	1
Kristensen, K.	44	Lodhi, I. J.	48
Krogan, N.	17	Lord, C.	49
Kuang, Y.	13	Lord, C. C.	30
Kuipers, F.	45	Lungmas, C.	40
Lagor, W. R.	19	Lusis, A. J.	8
Lan, T.	21	Lutsenko, S.	20
Langlois, H.	40	Mangelsdorf, D.	21
Langlois, H.	31	Mangelsdorf, D. J.	2
Larsson, E.	44	Mangelsdorf, D. J.	27
Las Heras, M.	34	Mangelsdorf, D. J.	32
Lawal, M. O.	29	Mansuy, V. A.	2
Le, T. D.	27	Mansuy-Aubert, V.	1

Name	Abstract/Poster Board Assignment
Martínez-Hernández, E.	3
Martinez-Martin, N.	36
Mason, R. P.	28
Matsen, M. E.	25
Mattis, A.	17
Medina, D. L.	34
Mejhert, N.	51
Mejhert, N.	54
Meng, F.	9
Meng, F.	10
Michael, N. J.	39
Min, S.	33
Modrusan, Z.	36
Moe, O. W.	32
Morton, G. J.	25
Mullan, M.	31
Mullan, M.	40
Mullan, M.	43
Nadra, K.	18
Nelson, R. C.	45
Nguyen, H. T.	25
Norlin, J.	37
O'Malley, B.	4
Oberlin, S.	40
Oberlin, S.	31
Obuotor, E. M.	29
Ojo, J.	40
Ojo, J.	43
Olivecrona, G.	44
Olson, E. N.	50
Paris, D.	40
Parthasarathy, S.	24
Pedersen, D. J.	48
Peluso, I.	34
Perissinotti, P. P.	3
Peterson, A.	36
Piedras-Rentería, E. S.	3
Pinto, S.	51
Ploug, M.	44
Pownall, H. J.	19
Priest, C.	55
Qian, S.	47
Rahmouni, K.	48
Rajbhandari, P.	55
Rajbhandari, P.	8
Rakipovski, G.	37
Ralle, M.	20
Raun, K.	52
Ren, G.	22
Ren, G.	13
Ren, H.	18
Reue, K.	8
Riad, A.	24
Richie, M.	53
Ringland, C.	43
Rodriguez, S.	20
Roeder, R.	7
Rojas-Rodriguez, R.	33
Saltiel, N.	40
Salvatore, S. R.	57
Scarlett, J. M.	25
Scheele, C.	15
Schopfer, F. J.	57
Schwartz, M. W.	25
Secher, A.	25
Secher, A.	52
Seldin, M. M.	8
Semenkovich, C. F.	48
Shackleton, B.	43
Sherratt, S. C.	28
Shokat, K. M.	5
Shokat, K. M.	6
Singh, A. B.	14
Søberg, S.	15
Soldati, C.	34
Sondhi, V.	32
Song, P.	32
Sonoda, J.	36
Srisai, D.	9
Srisai, D.	10
Stadlbauer, V.	32
Sulaimon, L. A.	29

Name	Abstract/Poster Board Assignment
Sullivan, K.	40
Sullivan, K.	31
Sun, G.	52
Sun, S.	27
Tapia, P. J.	34
Thomas, D.	2
Thorne, C. A.	27
Tontonoz, P.	8
Tontonoz, P.	55
Tóth, I.	9
Trammell, S.	15
Tran, K.	33
Turley, S.	36
Vale, K.	27
Van der Veen, J. N.	45
Vergnes, L.	8
Verran, E.	1
Vianna, C. R.	42
Vianna, C.	47
Vitturi, D. A.	57
Vuletic, S.	22
Wagner, M.	32
Walther, T. C.	54
Walther, T. C.	51
Wan, R.	49
Wang, C.	11
Wang, H.	23
Wang, L.	46
Wang, Z.	50
Weiss, E. J.	17
Williams, K. W.	39
Williams, K. W.	58
Wolfgang, M. J.	20
Wong, G.	20
Woodcock, S. R.	57
Wu, Q.	9
Wu, Q.	10
Wu, Q.	12
Wulff, B. S.	52
Wyler, S.	49
Xia, G.	12
Xia, G.	10
Xia, G.	9
Xie, Y.	32
Xu, P.	11
Xu, Y.	11
Xu, Y.	9
Xu, Y.	10
Xu, Y.	4
Yang, H.	20
Yang, S.	35
Yang, Y.	4
Yang, Y.	11
Yu, Y.	13
Zanlungo, S.	34
Zanlungo, S.	38
Zechner, C.	32
Zeng, W.	23
Zhai, X.	22
Zhai, X.	13
Zhang, M.	13
Zhang, M.	22
Zhang, Y.	7
Zhu, L.	4
Zigman, J. M.	39

Deuel Board Members

CHAIR

JAY HORTON (2018)
Department of Internal Medicine, Molecular Genetics
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390

MEMBERS

ALAN ATTIE (2018)
Department of Biochemistry
University of Wisconsin-Madison
433 Babcock Drive
Madison, WI, 53706-1544
Tel: (608) 262-1372

DAN BLOOMFIELD (2018)
Merck & Co.
126 E. Lincoln Avenue
PO BOX 2000
Rahway, NJ, 07065-0900
Tel: (732) 594-0800

KARIN BORNFELDT (2018)
Department of Pathology,
Diabetes and Obesity
University of Washington
South Lake Union Campus
Box 358055
815 Mercer Street
Seattle, WA 98109
Tel:(206) 543-1681

ROSANNE CROOKE (2021)
Ionis Pharmaceuticals
Antisense Drug Discovery
2855 Gazelle Court
Carlsbad, CA 92010
Tel: (760) 603-2326

BRANDON DAVIES (2022)
Department of Biochemistry
University of Iowa
Iowa City, IA 52242
Tel: (319) 335-3225

JESPER GROMADA (2019)
Metabolism and Muscle Department
Regeneron Pharmaceuticals
777 Old Saw Mill River Road
Terrytown, NY 10591
Tel: (914) 847-7971

CYNTHIA HONG (2021)
Pfizer
CVMET
610 Main Street
Cambridge, MA 02139
(617) 674-6586

HOLLY INGRAHAM (2022)
UCSF
Cellular and Molecular Pharmacology
1550 4th Street
Rock Hall 284F
San Francisco, CA 94598
Tel: (415) 517-3401

SEKAR KATHIRESAN (2018)
Massachusetts General Hospital
Center for Human Genetic Research
185 Cambridge St
Boston, MA 02114
Tel: (617) 643-7995

FREDRIC KRAEMER (2018)
Division of Endocrinology, S005
Stanford University Medical Center
Stanford, CA 94305-5103
Tel: (650) 493 5000 x 63184

KATHRYN MOORE (2021)
New York University School of Medicine
Medicine (Division of Cardiology)
522 First Avenue, Smilow 705
New York, NY10016
Tel: (212) 263-9259

KERRY-ANNE RYE (2021)
University of New South Wales
School of Medical Sciences
Lipid Research Group
Level 4E, Wallace Wurth Building
Sydney, Australia 2052

JEAN SCHAFFER (2019)
Washington University St. Louis School of Medicine
Division of Biology and Biomedical Sciences
Campus Box 8226
660 S. Euclid Ave.
St. Louis, MO 63110-1093

ROSHNI SINGARAJA (2020)
Translational Laboratories in Genetic Medicine
National University of Singapore
Singapore

ALAN TALL (2020)
Department of Medicine
Columbia University
630 West 168th St.
New York, NY 10032
Tel: (212) 305-4899

ELIZABETH TARLING (2022)
Department of Medicine
Columbia University
630 West 168th St.
New York, NY 10032
Tel: (212) 305-4899

MURIELLE VENIANT (2019)
Department of Metabolic Disorders
Amgen, Inc.
One Amgen Center Drive
Mail stop29-1-A
Thousand Oaks, CA 91320
Tel: (805) 447-8009
Fax: (805) 499-0953

TOBIAS WALTHER (2022)
Harvard School of Public Health
665 Huntington Ave
Building 1, Rm 205
Boston, MA 02115
Tel: (617) 432-1273

JOSEPH WITZTUM (2020)
Univ California, San Diego
Biomedical Science Building-Room 1080
9500 Gilman Drive
La Jolla, CA 92093-0682
Tel: 858-534-4347

RUDOLF ZECHNER (2019)
Institute of Molecular Biosciences
Karl Franzens Universität Graz
Heinrichstraße 31
8010 Graz
Tel: +43 316 380 1900

PROGRAM COMMITTEE CHAIRS

JOEL ELMQUIST (2018)
UT Southwestern Medical Center
Division of Hypothalamic Research
Department of Internal Medicine
5323 Harry Hines Blvd.
Dallas, TX 75390-9051
Tel: (214) 648-2911

DAVID MANGELSDORF (2018)
UT Southwestern Medical Center
Pharmacology/HHMI
6001 Forest Park Road, ND9.124A
Dallas, TX 75390-9041
Tel: (214) 645-5957

TREASURER/FUNDING

CHRISTOPHER K. GLASS
University of California San Diego
Cellular & Molecular Medicine
9500 Gilman Drive, MC 0651
GPL Room 217
La Jolla CA 92093-0651

2018 ASBMB-Deuel Attendees

Laila Abdullah
The Roskamp Institute
sgoulet@roskampinstitute.org

Christopher Allan
UCLA
cmallan@mednet.ucla.edu

Kimberly Alonge
University of Washington
kalonge@uw.edu

Birgitte Andersen
Novo Nordisk
btta@novonordisk.com

Jean-Mathieu Berger
UT Southwestern
jean-mathieu.berger@utsouthwestern.edu

Raiza Bonomo
Loyola University Chicago
rbonomo@luc.edu

Angie Bookout
UT Southwestern
angie.bookout@utsouthwestern.edu

Jenny Brown
University of Washington
jennymb@uw.edu

Jens Bruening
Max Planck Institute for Metabolism Research
bruening@sf.mpg.de

Xing Cai
Baylor College of Medicine
xing.cai@bcm.edu

Alexandre Caron
UT Southwestern Medical Center
alexandre.caron@utsouthwestern.edu

Carlos Castorena
UT Southwestern
carlos.castorena@utsouthwestern.edu

Joshua Chang
Genentech
jchang0803@gmail.com

Pei-Chun Chen
National Cheng Kung University
pcchen@mail.ncku.edu.tw

Mohan Chitraju
Harvard University
chitraju@hsph.harvard.edu

John Chorba
University of California San Francisco
john.chorba@ucsf.edu

Roger Cone
Life Sciences Institute
rcone@umich.edu

Pablo Contreras
Pontificia Universidad Católica de Chile
prcontre@uc.cl

Victor Cortes
Pontificia Universidad Catolica de Chile
vcortesm@gmail.com

Silvia Corvera
Univ of Massachusetts Medical School
silvia.corvera@umassmed.edu

Kimberly Cox
University of Texas Southwestern Medical Center
kimberly.cox@utsouthwestern.edu

Kate Townsend Creasy
UCSF
kate.creasy@ucsf.edu

Rosanne Crooke
Ionis Pharmaceuticals
rcrooke@ionisph.com

Michael Czech
Univ of Massachusetts Medical Center
michael.czech@umassmed.edu

Olof Dallner
Rockefeller University
odallner@rockefeller.edu

Brandon Davies
University of Iowa
brandon-davies@uiowa.edu

Edward Dennis
University of California, San Diego
edennis@ucsd.edu

Sabrina Diano
Yale University
sabrina.diano@yale.edu

Andrew Dillin
UC Berkeley
dillin@berkeley.edu

Ana Domingos
Fundação Calouste Gulbenkian – IGC
dominan@igc.gulbenkian.pt

Bart Duell
Oregon Health and Science University
duellb@ohsu.edu

Joel Elmquist
UT Southwestern Medical Center
joel.elmquist@utsouthwestern.edu

James Evans
The Roskamp Institute
jevans@roskampinstitute.org

Ronald Evans
The Salk Institute for Biological Studies
evans@salk.edu

Marco Fazzari
University of Pittsburgh Medical Center
maf167@pitt.edu

James Feng
University of California, San Francisco
james.feng@ucsf.edu

Jeffrey Friedman
Rockefeller University
Jeffrey.Friedman@mail.rockefeller.edu

Adri Galvan
UCSF
adrigalvan66@gmail.com

Jie Gao
UCLA
JieGao@mednet.ucla.edu

Chaitanya Gavini
Loyola University Chicago
cgavini@luc.edu

Matthew Gillum
University of Copenhagen
gillum@sund.ku.dk

Christopher Glass
University of California - San Diego
ckg@ucsd.edu

Lila Gonzalez
Pontificia Universidad Catolica de Chile
ldgonzal@uc.cl

Barbara Gordon
ASBMB
bgordon@asbmb.org

Jesper Gromada
Regeneron Pharmaceuticals
jesper.gromada@regeneron.com

Tamar Gubeladze
UCSF
tamargubeladze@gmail.com

Adilson Guilherme
Univ of Massachusetts Medical School
adilson.guilherme@umassmed.edu

Yong Han
Baylor College of Medicine
yongh@bcm.edu

Cuiwen He
UCLA
cuiwenhe@chem.ucla.edu

Genaro Hernandez
UT Southwestern Medical Center
genaro.hernandez@utsouthwestern.edu

Joachim Herz
University of Texas-Southwestern Medical Ctr.
Joachim.Herz@UTSouthwestern.edu

Sei Higuchi
Columbia University
sh3440@cumc.columbia.edu

Helen Hobbs
UT Southwestern Medical Center
helen.hobbs@utsouthwestern.edu

Cynthia Hong
Pfizer
cynthia.hong@pfizer.com

Jay Horton
Univ of Texas Southwestern Medical Center
jay.horton@utsouthwestern.edu

Tamas Horvath
Yale University
tamas.horvath@yale.edu

Xuchen Hu
UCLA
xuchenhu@mednet.ucla.edu

Rodney Infante
UTSW Medical Center
rodney.infante@utsouthwestern.edu

Holly Ingraham
UCSF
Holly.ingraham@ucsf.edu

Puneeth Iyengar
UT Southwestern Medical Center
puneeth.iyengar@utsouthwestern.edu

Bharat Jaishy
UT Southwestern Medical Center, Dallas, TX
jaishybp@yahoo.com

Aditi Jatkar
Harvard University
ajatkar@g.harvard.edu

Lin Jia
UT Southwestern Medical Center
lin.jia@utsouthwestern.edu

Jeff Johnson
Cayman Chemical Company
jeff@caymanchem.com

Utsav Joshi
The Roskamp Institute
ujoshi@roskampinstitute.net

John Kane
U Calif-San Francisco Cardiovasc Res Inst
john.kane@ucsf.edu

John Kennelly
University of Alberta
jkennell@ualberta.ca

Steven Kliewer
Southwestern Medical Center
steven.kliewer@utsouthwestern.edu

Oleg Kovrov
Umea University
oleg.kovrov@umu.se

Fredric Kraemer
Stanford University School of Medicine
fbk@stanford.edu

William Krause
University of California, San Francisco
william.krause@ucsf.edu

William Lagor
Baylor College of Medicine
lagor@bcm.edu

Tian Lan
UT Southwestern
tian.lan@utsouthwestern.edu

William Lands
Fellow, AAAS
wemlands@att.net

Philip Larsen
Sanofi-Aventis Deutschland GmbH
PhilipJust.Larsen@sanofi.com

Joseph Layne
Novartis Institutes for Biomedical Research
joseph.layne38@gmail.com

Stephen Lee
University of California, Los Angeles
sdlee@mednet.ucla.edu

Luis Leon Mercado
UT Southwestern Medical Center
Luis.LeonMercado@UTSouthwestern.edu

Jennifer Li
Mercer University
LI_J@mercer.edu

Jingwen Liu
VA Palo Alto Health Care System (154P)
jingwen.liu@va.gov

Ken Loh
Rockefeller University
hloh@rockefeller.edu

Ichiro Manabe
Chiba University
manabe-tky@umin.ac.jp

David Mangelsdorf
UT Southwestern Medical Center
Davo.Mango@UTSouthwestern.edu

Virginie Mansuy Aubert
Loyola University Chicago
vmansuyaubert@luc.edu

Andre Marette
Laval University
andre.marette@criucpq.ulaval.ca

Preston Mason
Brigham and Women's Hospital, Harvard Medical School
rpmason@elucidaresearch.com

Aras Mattis
UCSF
aras.mattis@ucsf.edu

Natalie Michael
UT Southwestern
natalie.michael@utsouthwestern.edu

Eric Murphy
University of North Dakota
eric.murphy@med.und.edu

Katsuyuki Nakajima
Nakajima & Associates, Co., Ltd.
nakajimak05@ybb.ne.jp

Sridaran Natesan
Sanofi
Lisa.Smith@sanofi.com

Yumiko Oishi
Tokyo Medical and Dental University
yuooishi-circ@umin.ac.jp

Sampath Parthasarathy
University of Central Florida
spartha@ucf.edu

Erika Piedras-Renteria
Loyola University Chicago
epiedra@luc.edu

Christina Priest
UCLA
CPriest@mednet.ucla.edu

Kevin Qian
UCLA
kqian@mednet.ucla.edu

Oswald Quehenberger
University of California - San Diego
oquehenberger@ucsd.edu

Kirsten Raun
Novo Nordisk A/S
kira@novonordisk.com

Gang Ren
Lawrence Berkeley National Laboratory
gren@lbl.gov

Hongmei Ren
Wright State Univeristy
Hongmei.ren@wright.edu

Denis Richard
Quebec Heart and Lung Institute
denis.richard@criucpq.ulaval.ca

Kerry-Anne Rye
University of New South Wales
karye@ozemail.com.au

Darleen Sandoval
University of Michigan
darleens@umich.edu

Francisco Schopfer
University of Pittsburgh
fjs2@pitt.edu

Qi Wu
Baylor College of Medicine
qiw@bcm.edu

Steven Wyler
UT Southwestern
Steven.Wyler@utsouthwestern.edu

Guobin Xia
Baylor College of Medicine
gxia@bcm.edu

Yong Xu
Baylor College of Medicine
yongx@bcm.edu

Haojun Yang
Johns Hopkins
yanghaojun0113@gmail.com

Shi-Bing Yang
Institute of Biomedical Sciences, Academia Sinica
sbyang@ibms.sinica.edu.tw

Stephen Young
University of California Los Angeles
sgyoung@mednet.ucla.edu

Jessica Yue
University of Alberta
jessica.yue@ualberta.ca

Wenwen Zeng
Tsinghua University
wenwenzeng@tsinghua.edu.cn

Yinxin Zhang
Rockefeller University
zhangyinxin04@gmail.com

Jeffrey Zigman
UT Southwestern Medical Center
jeffrey.zigman@utsouthwestern.edu

Charles Zuker
Columbia University/HHMI
lr2653@cumc.columbia.edu

Notes

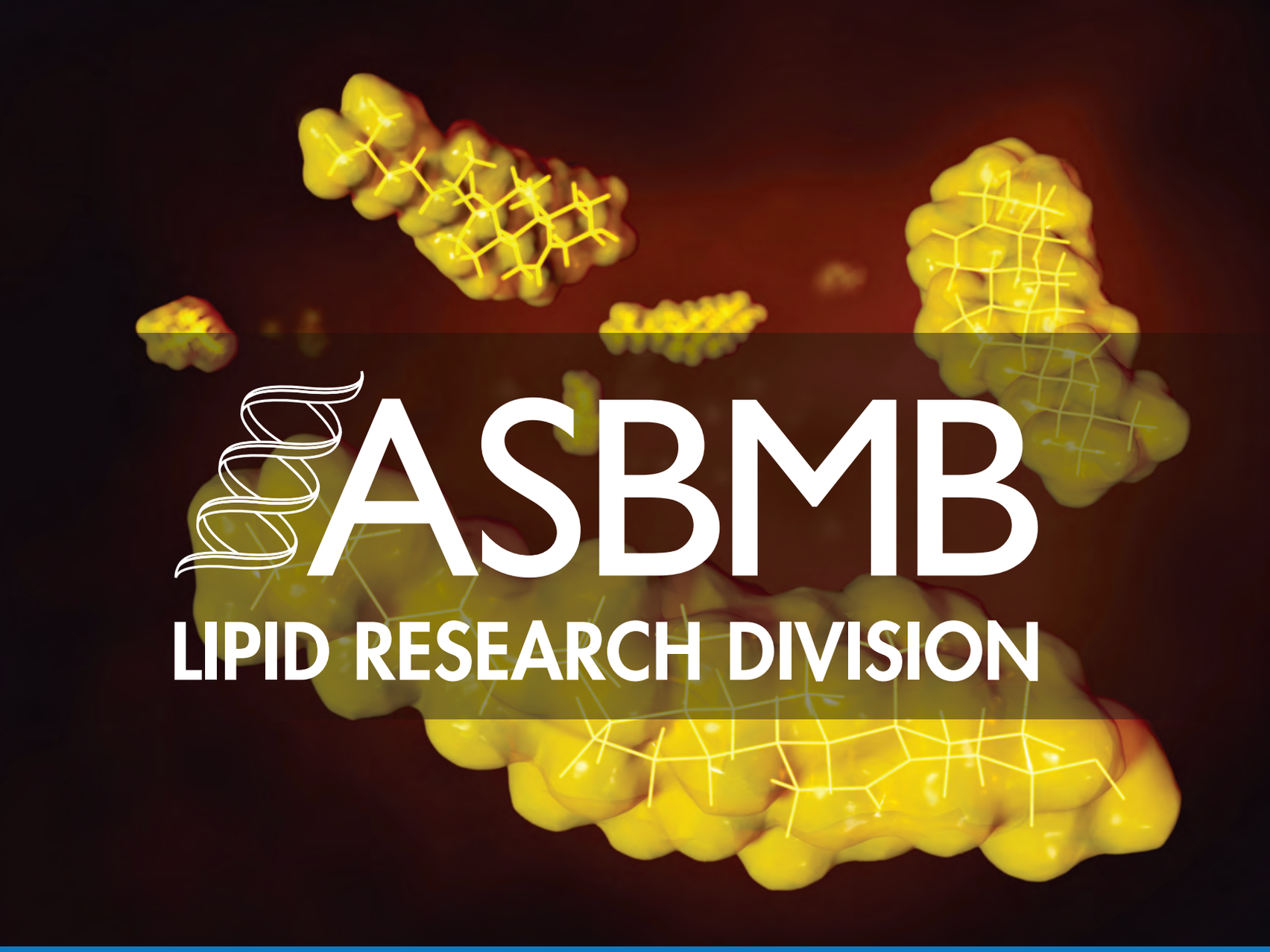
Notes

Notes

Notes

Notes

Notes



You're invited to join the Lipid Research Division of the ASBMB

The Lipid Research Division was born from a grassroots discussion of broad concerns shared by all lipid research scientists. These included issues such as increased national and international visibility for lipid research and increased funding for lipid research. We invite you to join this community, contribute to the ongoing discussions and help support the lipid community.

www.asbmb.org/lipidcorner

ASBMB-DEUEL 2019

March 5 – 8

Laguna Cliffs Marriott

Dana Point, Calif.

ASBMB
American Society for Biochemistry and Molecular Biology

Conference on Lipids
DEUEL