BIG ACADEMIC ALLIANCE

FEB 11 2022

4th Big Ten Academic Alliance Lipids Symposium

I Hotel & Conference Center

1900 South 1st Street
Champaign, IL 61820

FOREWORD

The inaugural Big Ten Academic Alliance Lipids Symposium was hosted by the Rutgers Center for Lipid Research on November 10, 2016. The symposium brought together a group of renowned speakers from Big Ten schools who shared their knowledge, results, and insights into how lipids relate to metabolic diseases. The theme of sharing research was further exemplified through a poster session and informal discussions. Collaborations, and most importantly, friendships resulted from the inaugural symposium with plans for future meetings. Subsequent symposia were held at Purdue University in 2018 and the University of Minnesota in 2019. We are delighted that the tradition continues with the University of Illinois hosting the meeting in 2022.

George M. Carman, Ph.D. | Board of Governors Professor & Distinguished Professor | Department of Food Science
Director, Rutgers Center for Lipid Research, New Jersey Institute for Food, Nutrition, & Health
Rutgers University | 61 Dudley Road, Rm 12 | New Brunswick, NJ 08901 | 848-932-0267

BTAAL SYMPOSIUM ORGANIZERS

Dr. Kimberly K. Buhman

Interim Associate Dean for Research at Purdue University College of Health and Human Sciences and Professor of Nutrition Science at Purdue University

2018

Dr. Douglas Mashek

Professor, Dept. Biochemistry, Molecular Biology and Biophysics, Dept. of Medicine/Div. of Diabetes, Endocrinology, and Metabolism, University of Minnesota

2019

Dr. Sayeepriyadarshini Anakk

Associate Professor, Molecular & Integrative Physiology, Division of Nutritional Sciences, Personalized Nutrition Initiative, CCIL, University of Illinois at Urbana Champaign

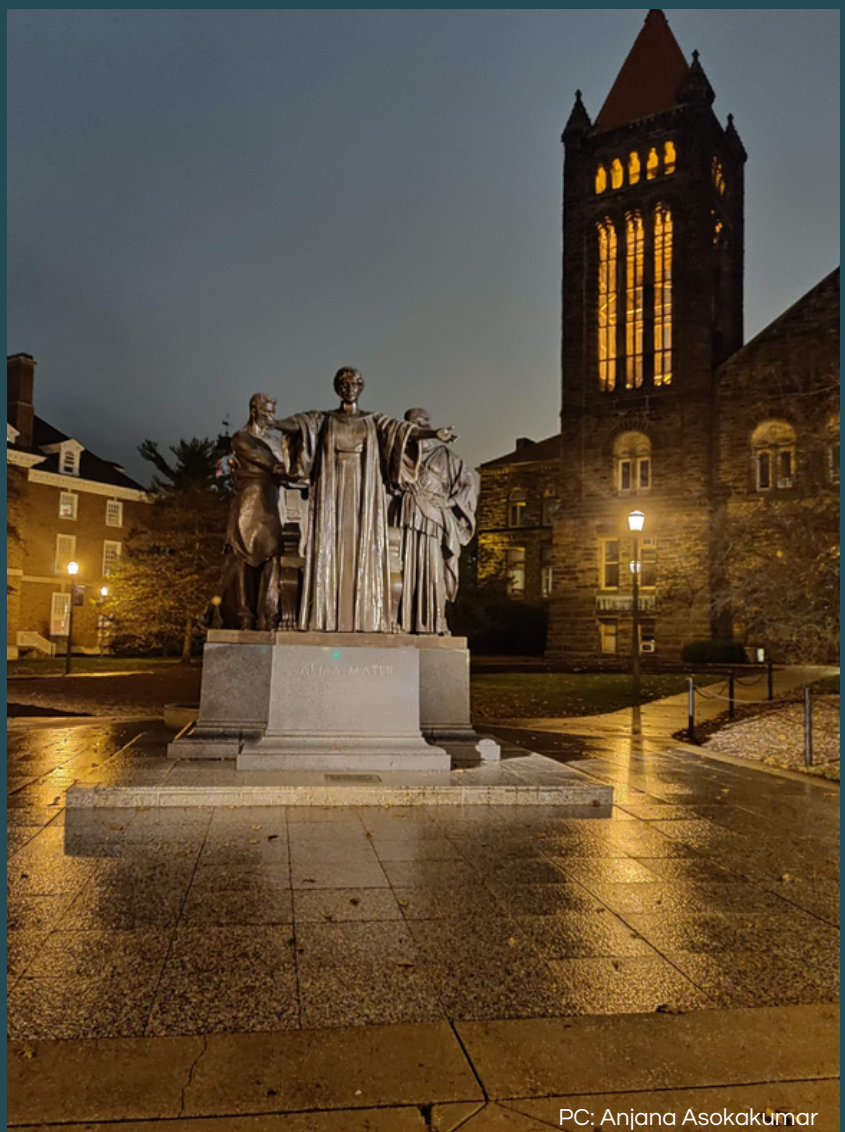
2022

Dr. Brandon S. Davies

Associate Professor of Biochemistry and Molecular Biology, Fraternal Order of Eagles Diabetes Research Center, University of Iowa Health Care

Incoming

Table of CONTENTS



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Symposium SCHEDULE

7:30-8:10 **CHECK-IN AND POSTER SETUP**

8:15-8:25 **INTRODUCTION AND WELCOME**

Dr. Susan Martinis, Vice Chancellor for Research & Innovation, University of Illinois, Urbana Champaign
Dr. Sayee Anakk, University of Illinois, Urbana Champaign

SESSION ONE CHAIR: DR.GEORGE M. CARMAN

8:30-9:00
Harini Sampath, Ph.D.
Assistant Professor, Rutgers University,
Regulation of metabolic health by delta-9 desaturases

9:00-9:30
Timothy O'Connell, Ph.D.
Associate Professor, University of Minnesota
Free fatty acid receptor 4 attenuates heart failure preserved ejection fraction secondary to metabolic syndrome

9:30-10:00
Kristin Stanford, Ph.D.
Associate Professor, The Ohio State University
Signaling lipids in metabolic and cardiovascular disease

10:00-10:30 **COFFEE BREAK/POSTER BROWSING**

Symposium SCHEDULE

SESSION TWO CHAIR: DR. KIMBERLY K. BUHMAN

10:30-11:00
Bhagirath Chaurasia, Ph.D.
Assistant Professor, University of Iowa
Ceramide induced lipotoxicity in metabolic diseases

11:00-11:30
Emad Tajkhorshid, Pharm. D, Ph.D.
Professor, University of Illinois, Urbana Champaign
Microscopic View of Lipid Modulation of Protein Function

11:30-12:00
Cecilia Leal, Ph.D.
Associate Professor,University of Illinois at Urbana-Champaign
Biophysical and genetic cues regulating the structural remodeling of adipose tissue upon caloric excess

12:00-2:00 **LUNCH/POSTERS**

SESSION THREE CHAIR: DR. BRANDON S. DAVIES

2:00-2:30
Rebecca Hasson, Ph.D.
Associate Professor, University of Michigan
A biopsychosocial framework for assessing type 2 diabetes risk in youth

2:30-3:00
Judith Simcox, Ph.D.
Assistant Professor, University of Wisconsin-Madison
Discovering the regulation and remodeling of the plasma lipidome
with cold exposure

3:00-3:30
Greg Henderson, Ph.D.
Assistant Professor, Purdue University
Serum albumin and its role in the integration of lipid and glucose metabolism.

Meet THE SPEAKERS

Talk: Regulation of metabolic health by delta-9 desaturases

Dr. Harini Sampath

Assistant Professor of Nutritional Sciences and the Scientific Director of the Lipidomics Core at the New Jersey Institute for Food, Nutrition, and Health (IFNH), both at Rutgers University.

Dr. Sampath received her Ph.D from University of Wisconsin Madison followed by postdoctoral studies at Oregon Health Science University. Sampath laboratory utilizes nutritional, genetic, and biochemical approaches to study the regulation of cellular desaturases, including the multiple isoforms of the delta-9 desaturase, stearoyl-CoA desaturase (SCD). The monounsaturated lipid products of these enzymes play critical roles in lipid accumulation, cellular signaling, and maintenance of membrane fluidity with implications to numerous pathologies, including cardiometabolic diseases, intestinal inflammation, and cancers. The lab is focused on elucidating the cell-type specific regulation and roles of these enzymes, and their lipid substrates and products.

Talk: Free fatty acid receptor 4 attenuates heart failure preserved ejection fraction secondary to metabolic syndrome

Dr.Timothy O'Connell

Associate Professor, Department of Integrative Biology and Physiology at The University of Minnesota, School of Medicine

Dr. O'Connell graduated from The University of Illinois, Chicago with a BSc in engineering in 1990 and from The University of Michigan with a Ph.D. in Pharmacology in 1995. He then completed a post-doctoral fellowship in the laboratory of Dr. Paul C. Simpson at the University of California, San Francisco. In 2000, Dr. O'Connell was appointed the Lead Scientist for the Laboratory for the Development of Signaling Assays, one of eight laboratories comprising The Alliance for Cellular Signaling, headed by Dr. Alfred Gilman. In 2004, Dr. O'Connell joined the faculty in the Cardiovascular Health Research Center at Sanford Research/USD and in 2009 was promoted to Associate Director of Cardiovascular Research. In 2013, Dr. O'Connell joined Department of Integrative Biology and Physiology at The University of Minnesota and is currently an Associate Professor. The primary focus of his research is G-protein coupled receptors in heart failure.

Talk: Signaling lipids in metabolic and cardiovascular disease

Dr. Kristin I. Stanford

Associate Professor, Associate Professor, Department of Physiology and Cell Biology, Department of Internal Medicine, Endocrinology, Associate Director, Diabetes Metabolism Research Center, The Ohio State University

Dr. Stanford received her Ph.D. from the University of California-San Diego followed by post-doctoral studies at Harvard Medical School/Joslin Diabetes Center. Kristin's laboratory is focused on investigating the novel molecular mechanisms of exercise that improve metabolic and cardiovascular health. Exercise is a widely accepted modality to decrease blood glucose concentrations in patients with diabetes; even a single session of exercise can lower blood glucose concentrations by stimulating glucose uptake into the skeletal muscles. Exercise also has many additional health benefits, including lowering blood pressure, improving lipid levels and lowering the risk of heart disease. More recently, we have become interested in how exercise affects the lipidomic profile in humans and rodents, identifying signaling lipids that play a direct role to improve fatty acid oxidation and cardiac function. Given the profound clinical importance of the metabolic and cardiovascular effects of exercise, there is a great need to understand the underlying molecular mechanisms that mediate these metabolic improvements.

Talk: Ceramide induced lipotoxicity in metabolic diseases

Dr. Bhagirath Chaurasia

Assistant Professor of Internal Medicine and Molecular Medicine, University of Iowa.

Dr. Chaurasia received his Ph.D. at University of Cologne, Germany with Prof. Brüning working on growth factor and inflammatory signaling in macrophages during obesity-associated insulin resistance. He did a brief stint at Evotec AG, an ambitious academic-industrial collaboration with Harvard, titled "CureBeta" to identify novel small molecules implicated in beta cell replication. He re-entered academia, as a postdoctoral fellow in the laboratory of Prof. Scott Summers investigating nutrient sensing mechanisms in the adipocyte, identifying a novel role for sphingolipids in thermogenesis. He demonstrated that removal of an essential enzyme for ceramide synthesis, Degs1 in mice prevented the development of obesity-induced insulin resistance and hepatic steatosis. These studies conclusively revealed that ceramides are important drivers of cardiometabolic disease. Dr. Chaurasia's research group focuses on understanding how ceramides impair nutrient sensing in adipose tissue and contribute to development of metabolic diseases.

Meet THE SPEAKERS

Talk: Seeing is Believing - Microscopic View of Lipid Modulation of Protein Function

Dr. Emad Tajkhorshid

Professor and Endowed Chair in the Biochemistry, and affiliate faculty in Chemistry, Bioengineering, Biophysics, Computational Science and Engineering, and the Carle-Illinois College of Medicine at UIUC.

Dr. Tajkhorshid received his Pharm. D. from Tehran University and a Ph.D. in molecular biophysics from Heidelberg, before moving to UIUC, where he did his postdoctoral studies in computational biophysics. He joined the faculty of Biochemistry in 2007 and was fast tracked to associate professor in 2010 and then to full professor in 2013. In 2015, he was named a University of Illinois Scholar and an Endowed Chair in Biochemistry.His laboratory pioneers computational techniques to investigate membrane proteins, in order to achieve the most detailed microscopic view of their function, e.g., mechanistic studies of membrane transport proteins, principles of energy transduction and coupling and lipid modulation in signaling proteins.

Talk: Biophysical and genetic cues regulating the structural remodeling of adipose tissue upon caloric excess

Dr. Cecilia Leal

Associate Professor and Racheff Faculty Scholar, Carle Illinois College of Medicine Affiliate, University of Illinois, Urbana-Champaign

Dr. Leal received a M.S. in Industrial Chemistry at the University of Coimbra, Portugal and a PhD in Physical Chemistry at the University of Lund, Sweden. She was a postdoctoral fellow at UC Santa Barbara before starting her appointment at UIUC in 2012. Cecilia received the 2021 & 2018 Dean's Award for Excellence in Research, the 2019 Provost Distinguished Promotion Award, and the 2016 NSF CAREER and NIH Director's New Innovator Awards. Our team is focused on this central question: how can we exploit the self-organization of biomolecular matter to generate new materials to advance therapy and technology?"

Meet THE SPEAKERS

Talk:A biopsychosocial framework for assessing type 2 diabetes risk in youth

Dr. Rebecca Hasson

.Associate Professor of Kinesiology and Public Health and Movement Science, Director, Childhood Disparities Research Laboratory, Director/Principal Investigator, InPACT, Active Schools & Communities Director, ESSI, at the University of Michigan

Dr. Hanson received her PhD from University of Massachusetts and was W.K. Kellogg Health Scholars Postdoctoral Fellow at the Center on Social Disparities in Health at the University of California-San Francisco. As Director of the Childhood Disparities Research Laboratory, she has rigorously examined the effects of built and social environments on pediatric physical activity and child health disparities. As Chair of the American College of Sports Medicine Strategic Health Initiative for Health Equity, she has also contributed to physical activity and health policy decisions. Her expertise in pediatric endocrinology, physical activity, implementation science, and health equity research have uniquely prepared her to examine the causes and consequences of childhood obesity disparities and develop behavioral interventions to mitigate these disparities.

Talk: Discovering the regulation and remodeling of the plasma lipidome with cold exposure

Dr. Judith Simcox

Assistant Professor in the department of biochemistry (adjunct Nutritional Sciences) at the University of Wisconsin Madison.

Dr. Simcox received her Ph.D. and continued her postdoctoral studies at the University of Utah. Her work as been featured on the cover of esteemed journals including Cell Metabolism and Nature Medicine. Judith has won numerous awards including the Paul Shurtleff Hatch and Heidi Hatch Ford Scholar award for outstanding diabetes research, the Leadership for Inclusive Excellence for her work to promote diversity in STEM, and the Harry and Evelyn Steenbock Career Advancement Award for promise as a new investigator. At the University of Wisconsin Madison, her team works to functionally characterize lipids, understand their role in disease etiology, and discovery genetic regulators of these lipids.

Meet THE SPEAKERS

Talk: Serum albumin and its role in the integration of lipid and glucose metabolism.

Dr. Gregory C. Henderson

Assistant Professor, Department of Nutrition Science, Purdue University

Dr. Henderson received a PhD in Integrative Biology from the University of California, Berkeley, followed by postdoctoral training in Endocrinology at the Mayo Clinic. He is now an assistant professor in the department of Nutrition Science at Purdue. His lab studies lipid metabolism in mouse models in relation to type 2 diabetes and insulin resistance. Specifically, the team focuses upon the relationship between plasma free fatty acid trafficking, hepatic lipid accumulation, and glucose metabolism. Metabolism and physiology is tested in live mice, followed by molecular biology and analytical chemistry based measurements on tissues. The work is aimed at discovering how altering the transfer of free fatty acids between tissues can alter metabolic health.

Poster 1

Increased Fatty Acid Synthesis and Catabolism Supports Metastatic Breast Cancer Cell Migration

Chaylen Andolino, Dorothy Teegarden, Kim Buhman
Department of Nutrition Science, Purdue University, West Lafayette, IN

Lipid accumulation is positively associated with breast cancer aggressiveness; however, mechanisms underlying the increase and role of stored lipid in breast cancer progression remain incompletely understood. We utilized non-metastatic MCF10A-ras and metastatic MCF10CA1a human breast cancer cells to determine differences in triacylglycerol (TAG) storage and catabolism for sustaining migration —a critical step in the metastatic cascade.MCF10CA1a cells have 90% more TAG than MCF10A-ras, although no significant difference in 14C-palmitate uptake. MCF10CA1a cells have greater palmitate synthesis from non-lipid substrate (acetate, glucose, and glutamine) compared to the MCF10A-ras cells, as well as higher protein levels of FA synthase (FASN). In accordance with these data, MCF10CA1a cells display greater flux of uniformly-labeled 13C-glucose and 13C-glutamine to the FA synthesis precursor, citrate, and lower intracellular citrate pool size compared to MCF10A-ras. Additionally, MCF10CA1a cells rely on FA oxidation (FAO) for cellular migration compared to MCF10A-ras cells (transwell migration assay, CPT1 inhibitor—etomoxir). Similarly, inhibitors of FA and TAG synthesis, as well as TAG catabolism, including inhibitors of FASN, diacylglycerol o-acyltransferases (1 and 2), and adipose triacylglycerol lipase, all reduced MCF10CA1a migration. Importantly, simultaneous inhibition of FAO (CPT1) and TAG lipolysis (ATGL) together provided no further reduction of cell migration compared to lipolysis inhibition alone. Our study indicates that metastatic MCF10CA1a cells accumulate TAG by increasing de novo lipogenesis, and that catabolism of these stores drives FAO-dependent migration.

Poster 2

Understanding the Lipid-Dependent function of SARS-CoV-2 E Protein

Emily David, Rob Stahelin
Purdue University College of Pharmacy

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for COVID-19, a disease which has resulted in the death of millions worldwide over the span of a year. COVID-19 ranges in severity of symptoms which are related to the inflammatory response. This inflammation can impact cardiac health and result in damage. Although the field has progressed significantly, there is still a critical gap in understanding virus-host lipid interactions that contribute to viral assembly and budding of this lipid-enveloped virus. There are four structural proteins encoded in the SARS-CoV-2 genome: membrane, envelope (E), nucleocapsid, and spike. These proteins give shape to the bilayer lipid coat that encapsulate the genomic core necessary for virus infection and replication. Although we know that these proteins are essential for viral reproduction and how they interact with each other, little is understood on how lipid species regulate their assembly. It is well established that inflammation is common during infection. One enzyme that participates in this process is ceramide kinase (CERK), which synthesizes the pro-inflammatory lipid, ceramide-1-phosphate (C1P). CERK is in fact a therapeutic target for a variety of inflammatory disorders. My primary goal is to define the relationship between CERK activity and SARS-CoV-2 assembly. We aim to understand the impact that CERK activity has on the localization and assembly of SARS-CoV-2 structural proteins. I am interested in how CERK regulates E protein localization and formation of virus-like particles and the process by which E-lipid interactions contributes to membrane curvature changes necessary for formation of new viral particles. Overall, I anticipate that this study will help define the relationships between a host enzyme and host membranes and the assembly of SARS-CoV-2.

Poster 3

Regulation of Endothelial Lipase by Angiopoietin-like 3

Kelli Sylvers-Davie, Ashley Segura-Roman, Alicia Salvi, Kylie Schache, Bharat Bhattarai, Rakshya Thapa, Lucy Langmack, and Brandon S. J. Davies
Department of Biochemistry, University of Iowa, Iowa City, IA 52242

High plasma triglyceride levels and low high-density lipoprotein (HDL) cholesterol levels are risk factors for atherosclerosis and cardiovascular disease. Both plasma triglyceride and HDL levels are regulated in part by the circulating inhibitor, angiopoietin-like 3 (ANGPTL3). ANGPTL3 acts on HDL by inhibiting the phospholipase, endothelial lipase (EL), which hydrolyzes the phospholipids of HDL thus decreasing plasma HDL levels. ANGPTL3 regulates plasma triglycerides by inhibiting lipoprotein lipase (LPL), the lipase primarily responsible for the clearance of triglycerides from the circulation. Our lab has previously found that ANGPTL3 requires angiopoietin-like 8 (ANGPTL8) to efficiently inhibit LPL but ANGPTL8 is unnecessary for EL inhibition. In this study, we have begun to characterize the mechanism of EL inhibition by ANGPTL3 and identify the structural features of ANGPTL proteins necessary for their inhibitory function. We found that inhibition of EL by ANGPTL3 is most likely catalytic as it is dose-, temperature-, and time-dependent. We also found that sub-stoichiometric levels of ANGPTL3 can inhibit multiple doses of active EL. We have identified specific residues of ANGPTL3 that are necessary for EL inhibition, but not LPL inhibition, suggesting that it may be possible to block the ability of ANGPTL3 to inhibit specific lipase targets. Finally, we found that a naturally occurring mutant ANGPTL8 (R59W) significantly alters inhibition of LPL but not EL.

Poster 4

Myotonic Dystrophy Type 1 Adversely Alters the Adult Hepatocellular Transcriptome

Zac Dewald1, Auinash Kalsotra1,2,3
1Department of Biochemistry, University of Illinois at Urbana-Champaign, Urbana, IL, USA, 2Cancer Center@Illinois, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, 3Carl R. Woese Institute for Genomic Biology, University of Illinois at Urbana-Champaign, Urbana, IL, USA

Myotonic Dystrophy type 1 (DM1) is multi-systemic muscular dystrophy, affecting 1 in 3000 people. DM1 is caused by a (CTG)n repeat expansion in the 3' UTR of the ubiquitously expressed gene DMPK. The (CUG)n containing RNAs resulting from the transcription of this diseased DMPK gene aggregate in the nucleus, forming foci which sequester various RNA binding proteins (RBPs). The most pivotal RBPs sequestered are the muscleblind-like (MBNL) family proteins, a group of splicing factors that play significant roles in the juvenile-to-adult development of many tissues. Their sequestration in DM1 severely inhibits this maturation process in many tissues. Recent studies show that DM1 patients have increased susceptibility toward glucose intolerance, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome. These findings suggest a predisposition for liver damage and dysfunction in DM1 patients; however, this possibility has gone uninvestigated.
To understand the effects of DM1 in the liver, we generated a hepatocyte-specific DM1 mouse model in which we can induce the expression of CUG containing RNA, specifically in the liver. Through these mice, we have shown how the expression of the toxic RNA in hepatocytes sequesters Mbnl proteins, causing a reduction in mature hepatocellular activity. We have characterized the transcriptomic changes driven by DM1 in the liver and have shown these lead to changes in liver morphology, inflammation, and necrosis, and increased lipid accumulation. We have demonstrated that DM1 sensitizes the liver to poor diet, increasing the likelihood of NAFLD development when patients consume high fat, high sugar diets. Finally, we have demonstrated that key proteins relevant to human NAFLD, such as Acaca, have altered structure and behavior in the DM1 disrupted liver.

Poster 5

Finasteride Treatment Is Associated with a Reduction in Plasma Cholesterol in Humans and a Delay in Atherosclerosis Progression in Mice

Patrick McQueen1*, Grace Rygiel2# Jaume Amengual 1, 2**, Ivan Pinos1*
1Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, Urbana, IL, (*jamespm3@illinois.edu),(ivanp2@illinois.edu), 2Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, Urbana, IL (**jaume6@illinois.edu), (rygiel2@illinois.edu)

Plasma cholesterol and sex hormones are strong risk factors associated with atherosclerosis, the leading cause of death worldwide. The objective of this study was to determine the role of finasteride, a drug that inhibits the activation of testosterone to dihydrotestosterone, on plasma lipid profile and atherogenesis. For our clinical study, we applied regression models to examine associations between circulating lipid profile and finasteride using the National Health and Nutrition Examination Survey database. After controlling for covariates, we observed a significant reduction in total cholesterol levels in subjects taking finasteride.

In our preclinical model, we tested the effect of finasteride in atheroprone low-density lipoprotein receptor-deficient (Ldlr-/-) mice fed increasing doses of finasteride for 12 weeks. Finasteride reduced circulating cholesterol levels and resulted in a reduction in lesion size, necrotic core area, and immune cell content. Global transcriptome analysis of liver showed an up-regulation of bile acid biosynthesis and oxidative phosphorylation, accompanied by a reduction in inflammatory markers. Our results show that finasteride is associated with a reduction in plasma cholesterol in both human and mice and highlight the potential role of this drug in the reduction of atherosclerosis.

Poster 6

Probing the Ability of White Adipose Tissue Sensory Nerves to Transmit Local Lipid Signals to the Brain

Gargi B. Mishra, Cory P. Johnson, Jake Willows, Magdalena Blaszkiewicz, Kristy L. Townsend
Department of Neurological Surgery, College of Medicine, The Ohio State University, Columbus, OH

White adipose tissue (WAT) is densely innervated by both sensory and sympathetic nerves, enabling bi-directional neural communication with the brain. When stimulated, sensory nerves send afferent action potentials to the brain, including the energy balance center in the hypothalamus, and they release neuropeptides to the tissue, such as calcitonin gene related peptide (CGRP). However, it is not yet known exactly which signals stimulate WAT sensory nerve activation. We have imaged the extent of sensory innervation of subcutaneous (sc)WAT for the first time, and demonstrated sensory nerves marked by advillin, Nav1.8, the cation channel TRPV1, and CGRP. We hypothesized that adipose tissue sensory nerves communicate fuel status to the brain following TRPV1 agonism by tissue lipids. To test this, we are utilizing the TRPV1 agonist 13-HODE in innovative intravital calcium imaging studies in WAT, and pilot data have demonstrated an increased calcium transient in WAT nerves following 13-HODE administration. In complementary time-course studies, we utilized the same intra-adipose 13-HODE delivery across 10min to 2 hours to assess acute sensory nerve activation. At 30 minutes post-injection, we observed a trend for increased lipolytic gene expression in scWAT (which fits with the known lipolytic role of CGRP), significant increases in cFOS (an immediate early gene that indicates neuronal activation) and CGRP expression in the DRG where sensory nerve cell bodies are localized, and increased appetite neuropeptide (proopiomelanocortin, or POMC) expression in the hypothalamus. Together, these data indicate that lipids in WAT are likely capable of communicating with the brain via afferent sensory nerves.

Poster 7

Role of Lecithin-Retinol Acyltransferase in Triglyceride Secretion.

Donald Molina Chaves, Jaume Amengual
Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign

Lecithin-retinol acyltransferase (LRAT) is involved in the esterification of retinol in the liver and other tissues. Studies suggest that the disruption of the LRAT gene leads to the formation of retinoic acid. Wild-type mice are resistant to vitamin A deficiency since retinyl esters are present in the liver for up to 75 weeks. However, in LRAT-/- mice fed a vitamin A-deficient diet, retinol is not detectable in most tissues after 6 weeks. We previously showed that retinoic acid exposure in mice and cell culture reduces hepatic lipid secretion. We hypothesize that LRAT-/- mice fed a high vitamin A diet have lower triglyceride secretion than mice fed a vitamin A-deficient diet. The objective of this study was to determine whether high levels of vitamin A consumption in LRAT-/- mice result in lower triglyceride secretion than in vitamin A deficiency. To this end, we fed LRAT-/- mice whether high vitamin A or vitamin A deficient diet for 8 weeks, and triglyceride secretion was measured every 2 weeks. Compared to vitamin A deficient LRAT-/- mice, we observed a significant reduction in triglyceride secretion in high vitamin A fed LRAT-/- mice by week 2. Overall, our findings provide insights into the role of LRAT and vitamin A in the secretion of triglyceride in mice.

Poster 8

Probing the Protein-Protein and Lipid-Protein Interaction Interfaces of Ebola Virus Matrix Protein VP40 With Mutagenesis.

Balindile Bhekiwe Motsa1, Prem P. Chapagain2, Robert V. Stahelin1
1 Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN,
2Physics, Florida International University, Miami, FL,

Filoviruses are filamentous RNA viruses of a genus which causes severe hemorrhagic fevers, they include Ebola and Marburg viruses (EBOV and MARV, respectively). They are some of the most dangerous pathogens known with high fatality rates. There is a great need for the development of therapeutics that target filoviruses, so it is important to get a detailed understanding of their virus life cycle. Filoviruses encode for the matrix protein, VP40, which is one of the most conserved viral proteins in the EBOV genome. VP40 regulates assembly and budding of new virions from the inner leaflet of the host cell plasma membrane. The trafficking and assembly of the VP40 dimer to the plasma membrane requires a network of protein-protein and lipid-protein interactions (PPIs and LPIs). In this work we study the effects of EBOV VP40 mutations that occur at the PPIs and LPIs on VP40 plasma membrane binding dynamics. We observed that mutations at the membrane binding interface affect VP40 affinity and assembly. The G198R and G201R mutations enhance VP40 assembly and budding by increasing interactions of VP40 with anionic lipids in the plasma membrane inner leaflet. In contrast, the G198D mutation significantly diminished VP40 assembly and budding most likely due to unfavorable interactions of this mutation with anionic lipids. We also observed that mutations at the dimer interface affect the propensity of VP40 to oligomerize. For instance, the L117A mutation located at the dimerization interface abolished assembly at the plasma membrane as well as viral budding. Thus, inhibition of VP40 dimerization led to a trafficking defect of VP40 to the plasma membrane, the site of V40 assembly and budding. Understanding the effects of single amino-acid substitutions on viral budding and assembly will be useful for explaining changes in the infectivity and virulence of different EBOV strains and will be useful for long-term drug discovery aimed at VP40 assembly dynamics.

Poster 9

Increased Sensitivity and Depth of Coverage When Probing the Lipidome on the SCIEX 7500 System

Mackenzie Pearson and Paul Norris
SCIEX, USA

When probing the lipidome for biomarkers, signaling lipids, or differences in phenotypes the need for sensitivity partnered with high-throughput capabilities can often be two large bottlenecks. To gain more sensitivity, sample cleanup and lengthy sample preparation procedures are required and can impact your turnaround time to biological insights. Depth of coverage can also be sacrificed to gain more sensitivity due to decrease duty cycles with a smaller list of analytes. Lipid mediators and structural lipids (phospholipids and neutral lipids) are two independent assays on the SCIEX 7500 system that have impressive gains in sensitivity. The lipid mediator panel includes over 130 compounds for quantitation and has an average gain in sensitivity by 40x compared to the SCEIX 6500+ system when using SRM 1950 as a sample matrix. A simple methanol crash was utilized for the lipid mediator assay to provide minimal sample preparation. For structural lipids, over 20 different lipid classes are monitored consisting of a list of over 2100 different lipid species to be measures. Using SRM 1950, we obtained 20x more coverage of the structural lipids on the SCIEX 7500 system compared to the SCEIX 6500+ system.

Poster 10

Stapled Peptides to Probe for Biophysical Studies of the Ebolavirus VP40 Dimer Interface

Roopashi Saxena1, Robert V Stahelin1, Atul Bhardwaj2, Benjamin Rathman2, Olaf G Weist2, Juan Del Valle2

1Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, 2University of Notre Dame.

Ebola virus (EBOV) belongs to the family of filoviruses, which is an enveloped single stranded RNA virus that causes hemorrhagic fever in humans. FDA approved use of two monoclonal antibodies for treatment and a vaccine against Zaire Ebolavirus. With emerging strains of EBOV (at least six known) and limited therapeutics, it is important to study the mechanisms of viral replication and viral assembly and budding.

EBOV encodes for matrix protein VP40 which is sufficient to form filamentous virus-like particles from host cell membrane in the absence of other filovirus proteins, eluding towards the importance of this protein-protein and protein-lipid interactions for viral assembly and budding. VP40 predominantly exists as a dimer to interact with cell membrane and as octamer to bind viral RNA. Equilibrium exists between different VP40 oligomers for successful viral infection. VP40 dimerizes by helix-helix interactions occurring at the hydrophobic alpha-helical N-terminal domain. We aim to probe this dimerization interface using stapled peptides. Residues 106-120 constitute the dimerization domain and computational analysis has assessed the role of each residue for binding. Combining computational data and mutant studies, alpha-helical peptides mimicking the dimerization interface were designed and a library of compounds was synthesized. Stapled peptides were screened for binding to VP40 using thermal shift analysis (TYCHO) and microscale thermophoresis (MST). FB02, FB05, FB06, FB09 and FC01 peptides exhibited binding to VP40 in TYCHO and binding affinities were compared using MST. We aim to optimize these stapled peptides to elucidate VP40 oligomerization equilibrium inside the host cell during EBOV infection.

Poster 11

Assessing the Interactions Between Lipoprotein Lipase and Cell-Surface Receptors.

Shwetha K. Shetty1, Gabriel Ewert1, Hannah Johnson1, and Brandon S.J. Davies1
1Department of Biochemistry, Fraternal Order of Eagles Diabetes Research Center, University of Iowa, 169 Newton Rd., PBDB 3326, Iowa City, IA 52242

LPL is the primary enzyme responsible for the hydrolysis of circulating triglycerides from triglyceride-rich lipoproteins (e.g. VLDL and chylomicrons), liberating fatty acids for tissue uptake. In addition to hydrolysis of triglycerides, LPL is also involved in whole lipoprotein clearance by non-catalytically bridging lipoproteins to cell surface receptors. In vivo and in cell culture, LPL can be cleaved by proprotein convertases, separating the N-terminal domain, which contains the catalytic domain, from the C-terminal domain, which is responsible for binding lipoproteins and cell-surface receptors. The purpose of our study is to investigate the ability of the C-terminal domain of LPL to bind its cell surface receptors, including GPIHBP1, VLDLR, LDLR, LRP1, and/or HSPGs, and to mediate bridging of lipoproteins. We also aim to identify LPL mutations that disrupt binding of LPL to VLDLR, LDLR, LRP1, and/or HSPGs, but retain catalytic function and the ability to bind GPIHBP1. Such mutations could be used in vivo to test the consequences of disrupting LPL bridging without disrupting LPL-mediated lipolysis. Using a split-luciferase NanoBiT assay to measure the interactions between LPL and cell surface receptors, we found that the cleaved C-terminal domain of LPL could bind both GPIHBP1-expressing and VLDLR expressing endothelial cells. We also began characterizing the ability of various LPL mutants to bind GPIHBP1, VLDLR, and LDLR.

Poster 12

Intestinal SEC16B Is Required for Dietary Lipid Absorption in Mice

Ruicheng Shi1, Wei Lu1, Ye Tian1, Bo Wang1,2,3,*
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Genome-wide association studies (GWAS) have identified genetic variants in SEC16 homolog B (SEC16B) locus to be associated with obesity and body mass index (BMI) in various populations. SEC16B encodes a scaffold protein located at endoplasmic reticulum (ER) exit sites that is implicated to participate in the trafficking of COPII vesicles in mammalian cells. However, the function of SEC16B in vivo, especially in lipid metabolism, has not been investigated. Here we demonstrated that intestinal SEC16B is required for dietary lipid absorption in mice. We showed that Sec16b intestinal knockout (IKO) mice, especially female mice, were protected from HFD-induced obesity. Loss of SEC16B in intestine dramatically reduced postprandial serum triglyceride output upon intragastric lipid load or during overnight fasting and high-fat diet (HFD) refeeding. Further studies showed that intestinal SEC16B deficiency impaired apoB lipidation and chylomicron secretion. These results revealed that SEC16B plays important roles in dietary lipid absorption, which may shed light on the association between variants in SEC16B and obesity in human.

The role of RBP4 in Vitamin A secretion in macrophages

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Introduction: Retinol Binding Protein 4 (RBP4) is the major transport protein of vitamin A in the blood. Macrophages also express RBP4, but whether these cells secrete RBP4 to the media remains unclear.
Hypothesis: We hypothesized that macrophages release vitamin A through the RBP4. We examined whether macrophages release RBP4 to the media, and whether the polarization status of these cells impacts RBP4 secretion in vitro.
Methods: We utilized peritoneal macrophages isolated from wild-type and RBP4 knockout mice. The cells were maintained in DMEM supplemented with 10% fetal bovine serum (FBS) at 37 °C until reaching 90-100% confluence. Two hours after plating the cells, we washed the media and replaced it with DMEM with 0.2% bovine serum albumin (BSA) or fresh growth media containing FBS. We polarized naive macrophages (M0) using interleukin 4 for 24 hours. After incubation, we collected the media and cells to measure intracellular and secreted RBP4 levels.
Results and Conclusion: Macrophage polarization increased RBP4 expression in macrophages. Our immunoprecipitation of analyses of RBP4 showed that RBP4 is secreted to the media, but our data suggest that this process is not dependent on the polarization status of the macrophages.

β-Carotene Mitigates Liver Inflammation During Atherosclerosis Regression

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Introduction: Atherosclerosis progression is characterized by the recruitment of macrophages in the arterial wall and other tissues such as the liver. The preliminary data from previous work done in the lab show that β-carotene, the precursor of vitamin A, delays atherosclerosis progression and accelerates atherosclerosis regression.
Objective: To determine whether β-carotene supplementation reduces macrophage content in the liver during atherosclerosis regression.
Methods: To accomplish this, we utilized a murine reversible model of atherosclerosis fed a vitamin A-deficient Western diet (WD-VAD) for 16 weeks. After this period, we harvested baseline mice, while the rest were subjected to atherosclerosis regression for three weeks. These mice were fed either WD-VAD or WD containing β-carotene. Livers were harvested for RNA sequencing and immunofluorescence analyses for different macrophage markers, including F4/80, CD68, CD45, and CD11b.
Results: RNA sequencing indicates that atherosclerosis regression reduces liver inflammation, and that this effect is enhanced by β-carotene. Furthermore, this reduction in inflammation is associated with a reduction in macrophage content. We confirmed these results by quantifying macrophage content in liver sections. Baseline mice showed a 2-fold and 3-fold increased number of macrophages in comparison to regression control and β-carotene, respectively.
Conclusion: We demonstrate that atherosclerosis regression reduces liver inflammation, and that these effects are enhanced by the supplementation of β–carotene.
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Cellular plasticity balances the metabolic and proliferation dynamics of a regenerating liver

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The adult liver has an exceptional ability to regenerate, but how it maintains its specialized functions during regeneration is unclear. We used partial hepatectomy (PHx) in tandem with single-cell transcriptomics to track cellular transitions and heterogeneities of ~22,000 liver cells through the initiation, progression, and termination phases of mouse liver regeneration. Our results uncovered that, following PHx, a subset of hepatocytes transiently reactivates an early-postnatal-like gene expression program to proliferate, while a distinct population of metabolically hyperactive cells appears to compensate for any temporary deficits in liver function. We found that hepatocyte proliferation after PHx initiates in the midlobular region while periportal and pericentral areas retain their metabolically active state to preserve essential liver functions. We further demonstrated that regenerating hepatocytes redeploy key developmental regulons, which are guided by extensive ligand-receptor-mediated signaling events between hepatocytes and nonparenchymal cells. Additionally, we evaluate regenerative programs under pathological contexts such as alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH), as well as from aged mice. We demonstrate that such abnormalities hinder proper hepatic regeneration and display unique trends in serum levels of NEFA, cholesterol, phospholipids, and triglycerides during regeneration.

Optimizing The Use Of Liver Specific Adeno-Associated Viruses To Investigate Cholesterol Metabolism In Mice

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Introduction: The low density lipoprotein receptor (LDLR) is a membrane receptor expressed in many tissues. In the liver, the LDLR mediates the uptake and recycling of LDL to regulate plasma cholesterol levels. LDLR-deficient mice (Ldlr-/- mice) are the model commonly used in cardiovascular research. When Ldlr-/- mice are fed Western diet (rich in fat and cholesterol), these mice develop atherosclerotic lesions similar to those found in human arteries.
Aim of the study: To manipulate the expression of LDLR by using liver-specific adeno-associated viruses (L-AAVs). One one side, we utilized a L-AAV to over-express LDLR (L-AAV-LDLR), and a second L-AAV to reduce LDLR expression. This second vector will over-express the proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein implicated in LDLR degradation (L-AAV-PCSK9). A third vector over-expressing green fluorescent protein was used as control (L-AAV-GFP).
Methods: Either wild-type (WT) or Ldlr-/- mice were fed a Western diet for six weeks. We monitored cholesterol levels in plasma on a weekly basis.
Results and Conclusions: On one side, L-AAV-LDLR injection into Ldlr-/- mice favored a drastic decrease in plasma cholesterol and an up-regulation in LDLR mRNA and protein expression in the liver. L-AAV-PCSK9-injected WT mice experienced a progressive increase in plasma cholesterol, unlike those mice injected with L-AAV-GFP. Overall, our results show that L-AAVs are functional and can serve as a tool to promote atherosclerosis progression in WT mice and atherosclerosis regression in Ldlr-/- mice.

Poster 17

Hepatic Phospholipid Remodeling by Lysophosphatidylcholine Acyltransferase 3 Modulates Insulin Sensitivity and Systemic Metabolism

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The liver plays a central role in regulating glucose and lipid metabolism. Aberrant insulin action in the liver is a major driver of insulin resistance, but the underlying mechanisms are not fully understood. Here we show that hepatic membrane phospholipid composition controlled by Lysophosphatidylcholine acyltransferase 3 (Lpcat3) regulates insulin signaling and systemic glucose and lipid metabolism. Hyperinsulinemia induced by high-fat diet (HFD) feeding augments hepatic Lpcat3 expression and membrane unsaturation. Loss of Lpcat3 in the liver improves insulin resistance and blunts lipogenesis in both HFD-fed and genetic ob/ob mouse models. Mechanistically, Lpcat3 deficiency directly facilitates insulin receptor endocytosis and signal transduction, and indirectly enhances Fibroblast growth factor 21 (FGF21) secretion, energy expenditure, and glucose uptake in adipose tissue. Ablation of Lpcat3 by antisense oligonucleotides improves obesity and insulin resistance in HFD-fed and ob/ob mice. These findings provide insights into the pathogenesis of selective insulin resistance that could inform future therapy.

Poster 18

Chronic Cholestasis Results in Defective Adipose Tissue Storage and Function

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Patients with liver diseases display elevated systemic bile acids (BAs). Cholestasis is associated with fat loss, however, the direct consequence of chronically increased BAs on adipose tissue remains unclear. We showed BA uptake into adipocytes and found that elevated BAs reduce lipid accumulation and cause mitochondrial dysfunction in vitro. Intriguingly, using a genetic mouse model for juvenile onset cholestasis (Farnesoid X receptor (Fxr); Small heterodimer (Shp) double knockout (DKO)) and a chronic 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-induced cholestasis mouse model, we found that the cholestatic DKO and DDC-fed mice accumulate higher BA levels within adipose tissue, loss fat mass, exhibit lower body temperature, and recapitulate the mitochondrial dysfunction. Thermoneutral housing (30°C) abolished the reductions in lipogenic gene transcript levels and brown fat mass noted in both chow- and high fat diet-fed DKO compared to WT mice, indicating a deficit in brown fat function during cholestasis. Mechanistically, we found decreased expression of uncoupling protein 1 (Ucp1) in high BA-treated brown adipocytes and brown adipose tissue from both DKO and DDC-fed mice, and pharmacological activation of UCP1 in the presence of BAs can alleviate the mitochondrial dysfunction in vitro. Overall, these findings demonstrate that chronic BA excess has detrimental impact on the adipose tissue mitochondria, which is a potential mechanism underlying fat loss and hypothermia observed in cholestatic liver diseases.

NOTES

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