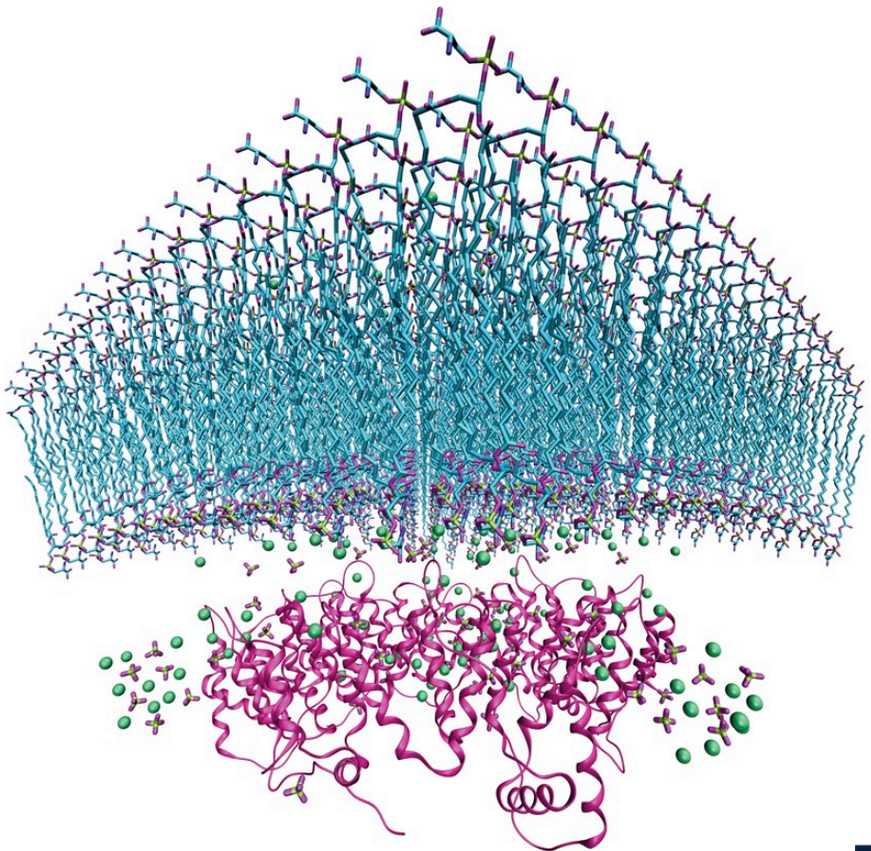
March 2-5, 2010

Dana Point, California

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.

DEUEL CONFERENCE ON LIPIDS



DEUEL Conference on Lipids

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2010 DEUEL Conference on Lipids

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 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 video-taping 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.

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Exciting Research News

Forum Discussions

Lipid Events Calendar

www.asbmb.org/lipidcorner

The Havel Lecture

The Havel Lecture was named after Dr. Richard J. Havel because he has done more than anyone else to keep the Deuel Conference going

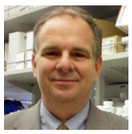
Richard J. Havel is known by many as "Mr. Lipoprotein, USA." He, more than any other investigator unraveled the complex metabolism of the plasma lipoproteins beginning with his pioneering work in the Anfinsen lab at the National Heart Institute in Bethesda, Maryland, where he was one of the first Clinical Associates from 1953-1956. His manuscript on the ultracentrifulgal separation of lipoproteins is one of the most frequently cited papers, rivaling Lowry's paper on protein measurement.

Richard Havel has published over 300 manuscripts. Their quality is attested to by his election to the National Academy of Sciences in 1983; the Institute of Medicine in 1989; 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.

Richard J. Havel Lecturers

2010 David J. Mangelsdorf, UT Southwest

"Nuclear receptor control of lipid metabolism"



2009 Stephen G. Young, UCLA School of Medicine, Los Angeles, CA

"Adventures in Lipid Metabolism"

2008 Helen H. Hobbs, University of Texas Southwestern Medical Cnter, Dallas, TX

"Going to Extremes to Identify Genetic Variations Contributing to Cardiovascular Risk"

2007 Ronald Evans, The Salk Institute for Biological Sciences, La Jolla, CA

"PPARdelta and the Marathon Mouse: Running Around Physiology"

2006 David Russell , University of Texas Southwestern Medical Center, Dallas, TX

"The Enzymes of Cholesterol Breakdown"

2005 Johann Deisenhofer, HHMI/UTSW Medical Center, Dallas, TX

"Structure of the LDL receptor"

2004 Jeffrey M. Friedman, Rockefeller University, New York, NY

"The Function of Leptin in Nutrition, Weight and Physiology"

2003 Bruce Spiegelman, Harvard Medical School, Boston, MA

"Transcriptional Control of Energy and Glucose Metabolism"

2002 Co-Lecturers Michael S. Brown & Joseph L. Goldstein, University of Texas Southwestern Medical Center, Dallas, TX

"SREBPs: Master Regulators of Lipid Metabolism" 2002 - Joseph L. Goldstein, UT Southwestern

Schedule of Events

	Tuesday, March 2	Wednesday, March 3	Thursday, March 4	Friday, March 5
7 AM		Breakfast 7-8:30 Dana Ballroom IV	Breakfast 7-8:30 Dana Ballroom IV	Breakfast 7-8:30 Dana Ballroom IV
8 AM				
		Session I 8:30-10:15 Dana Ballroom I – III	Session 2 8:30-10:15 Dana Ballroom I - III	Session 4 8:30-9:40 Dana Ballroom I - III
9 AM				Coffee Break Ballroom Foyer
10 AM		Coffee Break 10:00 Ballroom Foyer	Coffee Break 10:00 Ballroom Foyer	Session 4, Continued 10:30-12 Dana Ballroom I - III
11 AM		Session I, Continued 10:30-11:50 Dana Ballroom I - III	Session 2, Continued 10:30-12:30 Dana Ballroom I - III	
12 PM		Free Time	Free Time	
1 PM				
2 PM				
3 PM	Registration 3-6:30 Ballroom Foyer			
4 PM				
5 PM		DEUEL Board Meeting 5-6 Capistrano Room		
6 PM	Welcome Reception and Dinner 6:30-10 Del Mar Lawn	Dinner 6:00- 7:30 Dana Ballroom IV	Dinner 6:00-7:30 Dana Ballroom IV	
7 PM		HAVEL LECTURE 7:30-9:30 Dana Ballroom I - III	Session 3 7:30-9:30 Dana Ballroom I – III	
8 PM				
9 PM				
10 PM				

Meeting Program

2010 Deuel Conference on Lipids, March 2-5, 2010
Laguna Cliffs Marriott Resort, Dana Point, CA

SCHEDULE

Tuesday March 2

Tuesday March 2, 3 PM to 10 PM

3:00 Registration

6:30 Welcome Reception

Wednesday, March 3

Wednesday, March 3, 8:30 AM to 12:00 PM

Session Leader: Kathryn Moore

Session 1 **Macrophage Signaling in Lipid Metabolism and Disease**

8:30-9:05 "The path to macrophage foam cell formation"
Kathryn J. Moore, *New York University, New York*

9:05-9:40 "Tissue macrophages in inflammation-induced insulin resistance and dyslipidemia"
Jerrold Olefsky, *University of California, San Diego*

9:40-10:00 "Atherosclerosis and apoptosis in Abcg1-/-ApoE-/- mice"
Elizabeth Tarling, *University of California, Los Angeles*

10:15-10:30 Coffee Break

10:30-10:55 "Mechanisms of Atherosclerotic Lesion Regression"
Edward Fisher, *New York University, New York*

10:55-11:30 "Fatty acids and Acyl-CoAs, Macrophages, and Atherosclerosis"
Karin E. Bornfeldt, *University of Washington, Seattle*

11:30-11:50 "Characterization of oxidized lipids in cholesterol-fed zebrafish"
Yuri Miller, *University of California, San Diego*

Wednesday, March 3, 7:30 to 9:30 PM

Session Leader: Peter Tontonoz

The Havel Lecture

"Nuclear receptor control of lipid metabolism"
David J. Mangelsdorf, *University of Texas Southwestern Medical Center, Dallas*
Wine reception and Trainees' Poster Session

Thursday, March 4

Thursday, March 4, 8:30AM to 12:30 PM

Session Leader: Jay Horton

Session 2 **Mechanisms of Metabolic Control**

8:30-9:05 "Fat regulation in C. elegans"
Kaveh Ashrafi, *University of California, San Francisco*

9:05-9:40 "Lipins: Multifunctional lipid phosphatases"
Karen Reue, *University of California, Los Angeles*

9:40-10:00 "Cavin-2 is a cell surface cholesterol sensor linking caveolae to the cytoskeleton"
Michael Breen, *Boston University, Boston*

10:15-10:30 Coffee Break

10:30-10:55 "Oxysterol regulation of cholesterol homeostasis"
Daniel Ory, *Washington University, St. Louis*

10:55-11:30 "New insights into mechanisms for ER-associated degradation of HMG CoA reductase"
Russell Debose-Boyd, *University of Texas Southwestern, Dallas*

11:30-11:50 "Syndecan-1 mediated uptake of triglyceride-rich lipoproteins"
Erin Foley, *University of California, San Diego*

Thursday, March 4, 7:30 to 9:30 PM
Session Leader: Joseph Witztum

Session 3 **Systemic Approaches to Metabolic Disease**

7:30-8:05 "Metabolic mechanisms of tissue failure in type 2 diabetes"
Christopher Newgard, *Duke University*

8:05-8:40 "Hypothalamic regulation of energy balance"
Randy Seeley, *University of Cincinnati*

8:40-9:15 "Endothelial Control of Metabolism"
Jorge Plutzky, *Brigham and Women's Hospital, Boston*

9:15-9:35 "FGF15/19 and FGF21 govern fed and fasted responses in the liver"
Matthew Potthoff, *University of Texas Southwestern, Dallas*

Friday, March 5

Friday, March 5, 8:30 AM to 12:00 PM
Session Leader: Stephen G. Young

Session 4 **Human Metabolism and Therapeutic Opportunities**

8:30-9:05 **The JLR Lecture**
"Functional analysis of new genes regulating plasma lipoproteins"
Daniel J. Rader, *University of Pennsylvania, Philadelphia*

9:05-9:40 "New Connections Between Insulin Resistance, Diabetes and Cholesterol Metabolism"
C. Ronald Kahn, *Joslin Diabetes Center, Harvard Medical School*

9:40-10:00 Coffee Break

10:00-10:35 "Inflammation, adipocytes and modulation of HDL"
Muredach Reilly, **University of Pennsylvania, Philadelphia**

10:35-11:10 "Antisense Inhibition of ApoB:From Bench to Clinic"
Rosanne M. Crooke, *Isis Pharmaceuticals, Carlsbad*

11:10-11:45 "Therapeutic potential of FGF-21"
Murielle Veniant-Ellison, *Amgen, Thousand Oaks*

Poster Presentations

Feng Gao	Oakland Children's Hospital Research Institute, University of California, Davis, CA
Lale Ozcan	Department of Medicine, Columbia University, New York, NY
James Donkin	University of British Columbia, Vancouver, BC, Canada
Michael Breen	Boston University School of Medicine, Boston, MA
Longhou Fang	University of California at San Diego, La Jolla, CA
Michael Weinstein	University of California, Los Angeles, CA
Amanda Brown	Wake Forest University School of Medicine, Winston-Salem, NC
Matthew Potthoff	Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX
Jenny Kanter	University of Washington, Seattle, WA
Constance Voss	University of California, Los Angeles, CA
Claudio Villanueva	Howard Hughes Medical Institute, University of California, Los Angeles, CA
Elizabeth Tarling	University of California, Los Angeles, CA
Cynthia Hong	University of California, Los Angeles, CA
Katey Rayner	New York University School of Medicine, New York, NY
Philipp Wiesner	University of California, San Diego, CA
Janine van Gils	Netrin-1: A Multifunctional Guidance Cue That Promotes Atherosclerosis
Lynn Ulatowski	Case Western Reserve University, Cleveland, OH
Thomas Quad de Aguiar Vallim	Howard Hughes Medical Institute, University of California, Los Angeles, CA
Soo-Ho Choi	University of California, San Diego, CA
Erin Foley	University of California, San Diego, La Jolla, CA
Agata Bielska	Washington University School of Medicine, St. Louis, MO
Milka Koupenova-Zamor	Boston University School of Medicine, Boston, MA
Hatem Belguith	College of Applied Medical Sciences, Al-Jouf University, Saudi Arabia
Laura K. Cole	Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada

1
A Common Polymorphism in the Low Density Lipoprotein Receptor Gene Has Multiple Functional Effects on Modulation of Plasma Cholesterol Levels

Feng Gao, Marisa Medina, and Ronald Krauss
Oakland Children's Hospital Research Institute, University of California, Davis, CA

Abstract:

A common single nucleotide polymorphism (SNP) in LDLR exon 12 (rs 688), has been associated with increased plasma total and LDL-cholesterol. Although rs688 is known to promote exon 12 alternative splicing, it is not clear whether this effect is sufficient to explain the elevation in LDL-cholesterol. In a population of 1518 individuals we found that those homozygous for the rs688 T allele (n=243) had significantly higher levels of both LDL-cholesterol (4.4%) and triglyceride (8.7%) compared with heterozygous or homozygous carriers of the C allele ($p<0.02$). In vitro studies of immortalized lymphocytes from a subset of 173 individuals confirmed that homozygoticity for the T allele was associated with increased exon 12 alternative splicing (~6%, $p<0.05$) as well as modestly decreased levels of total LDLR mRNA (~4%, $p<0.05$). Increased levels of alternatively spliced LDL mRNA following cycloheximide treatment imply that this transcript undergoes nonsense-mediated decay, Finally, measurement of immunologically detectable cell surface LDL receptors by FACS analysis revealed a marked reduction in homozygotes for the T allele (~90%, $p<0.001$). The results suggest functional effects of rs 688 beyond those attributable to alternative splicing that result in increased plasma lipid levels.

2

New Link Between CaMKII, a Calcium-sensing Enzyme Activated by Endoplasmic Reticulum Stress, and Hepatic Gluconeogenesis

Lale Ozcan, Gang Li, and Ira Tabas

Department of Medicine, Columbia University, New York, NY

Abstract:

We have recently shown that endoplasmic reticulum (ER) stress-induced macrophage apoptosis, a critical process in the progression of advanced atherosclerotic lesions, involves the calcium-responsive kinase calcium/calmodulin-dependent protein kinase II (CaMKII). Moreover, recent work has revealed the presence of a remarkable amplification pathway in which CaMKII activation sustains the activation of two critical ER stress signaling branches involving IRE1a and PERK. These findings prompted us to turn our attention to another cell type that expresses CaMKII and in which ER stress may be linked to atherosclerosis, namely, the hepatocyte. In particular, in the setting of obesity, ER stress pathways are activated in hepatocytes and help promote insulin resistance. We first showed that CaMKII is activated in the liver of leptin-deficient (ob/ob) mice, a model of obesity, insulin resistance, and hepatic ER stress, but not in the liver of wild-type lean mice. Treatment of ob/ob mice with a specific CaMKII inhibitor decreased hepatic CaMKII activity, lowered fasting blood glucose, and decreased the expression of the gluconeogenic genes, G6Pase and PEPCK. In cultured hepatocytes, the increase in the expression of G6Pase and PEPCK induced by forskolin, a glucagon mimetic and cAMP activator, was blocked by CaMKII inhibition. We are currently exploring a possible mechanistic link between CaMKII activation and nuclear (transcriptionally active) forkhead box O1 (FoxO1), which induces the expression of G6Pase and PEPCK. These data suggest that ER stress-induced activation of CaMKII in liver during obesity contributes to increased hepatic glucose production and fasting hyperglycemia. This concept, together with our findings related to advanced lesional macrophage apoptosis, raise the possibility that therapeutic targeting of CaMKII may have particular benefit in plaque progression in insulin-resistant subjects.

3

ABCA1 Mediates the Beneficial Effects of the Liver X Receptor Agonist GW3965 on Amyloid Load and Object Memory in the APP/PS1 Model of Alzheimer Disease

James Donkin1, Sophie Stukas1, Veronica Hirsch-Reinshagen1, Dhananjay Namjoshi1, Anna Wilkinson1, Sharon May1, Jeniffer Chan1, Jianjia Fan1, Jon Collins2, and Cheryl Wellington1

1. University of British Columbia, Vancouver, BC, Canada
2. GlaxoSmith Kline, Research Triangle Park, NC

Abstract:

The cholesterol transporter ABCA1 moves lipids onto apolipoproteins including apolipoprotein E (apoE), which is the major cholesterol carrier in brain and a risk factor for Alzheimer disease (AD). In AD mice, ABCA1 deficiency exacerbates amyloidogenesis, whereas selective overexpression of ABCA1 ameliorates amyloid load, suggesting that ABCA1 plays a major role in Aß metabolism. Agonists of liver X receptors (LXR), including GW3965, induce ABCA1 expression, reduce Aß, and improve cognition in AD mice. However, the role of ABCA1 in the response to LXR agonists is unknown. Here, we evaluated behavioral and neuropathogical outcomes in GW3965-treated APP/PS1 mice with and without ABCA1. Treatment of APP/PS1 mice with GW3965 increased ABCA1, improved object memory, and improved Aß clearance without altering APP processing. ABCA1-deficient APP/PS1 mice failed to respond to GW3965 for each measure, demonstrating that ABCA1 is required for many of the beneficial effects of LXR agonists in AD mice.

4

Cavin-2 Is a Cell Surface Cholesterol Sensor Linking Caveolae to the Cortical Cytoskeleton

Michael Breen, Tovah Meshulam, Libin Liu, and Paul Pilch
Boston University School of Medicine, Boston, MA

Abstract:

Caveolae are small cell surface invaginations that are thought to be involved in numerous important physiological processes. It was formerly believed that expression of Caveolin-1 was sufficient to produce caveolae, but recent work has demonstrated an obligatory role for Cavin-1 in caveolae formation. Cavin-1 is a member of a group of caveolae-associated cytosolic adaptor proteins (Cavin-1-4) that affect caveolae morphology and dynamics. Cavin-1-null mice have no morphologically identifiable caveolae, are insulin-resistant, hypertriglyceridemic, and lipodystrophic, and recently published data identify Cavin-1 as a locus for human lipodystrophy. Caveolae are highly enriched in cholesterol, and cholesterol depletion causes caveolae to "flatten out." Thus, cholesterol depletion from 3T3-L1 adipocytes was achieved using methyl-ß-cyclodextrin, resulting in a rapid and extensive proteosomal degradation of Cavin-2 concurrent with movement of Cavin-1 from the plasma membrane to the cytosol. Similar effects were observed upon statin treatment. Moreover, cholesterol depletion results in a dramatic derangement in the cortical cytoskeleton, resulting in the formation of a detergent-resistant complex of cytoskeletal elements and a loss of cortical actin and tubulin staining as shown by immunofluorescence. Cortical cytoskeletal elements are intimately involved with caveolae, and it is most likely this interaction that is being affected by cholesterol depletion. This is supported by the fact that differentiated adipocytes from caveolin-1-null mouse embryonic fibroblasts fail to display cortical actin and tubulin staining, and cholesterol depletion in these cells has no effect on cytoskeletal elements. Taken together, these data demonstrate that Cavin-2 acts as a cholesterol sensor, which is required for Cavin-1 localization to the plasma membrane, and that cholesterol is required for formation of a cortical caveolar cytoskeleton in adipocytes.

5

Characterization of Oxidized Lipids in Cholesterol-fed Zebrafish

Longhou Fang1, Richard Harkewicz2, Karsten Hartvigsen1, Peter Shaw1, Tiffany Sayaphupha1, Joseph Witztum1, Sotirios Tsimikas1, and Yury Miller1

Departments of 1. Medicine and 2. Pharmacology, Chemistry, and Biochemistry, University of California at San Diego, La Jolla, CA

Abstract:

It is generally accepted that oxidation of low density lipoprotein (LDL) occurs in vivo and that oxidized LDL is an important factor in the development of atherosclerosis. We and others have previously identified oxidized cholesteryl esters (OxCE) and oxidized phospholipids (OxPL) as biologically active lipid components of OxLDL, present in atherosclerotic lesions. We have also characterized monoclonal antibodies EO6 and IK17, which recognize OxPL and MDA epitopes in OxLDL, respectively. We have recently established a hypercholesterolemic zebrafish model of early processes of atherosclerosis. Because optically transparent zebrafish larvae, fed a high cholesterol diet (HCD), can be used to monitor processes of vascular inflammation in live animals, in this study, we characterized oxidized lipid milieu in HCD-fed zebrafish. We found a strong EO6 signal in the plasma of adult zebrafish fed a HCD. In HCD-fed larvae, i.v. injected Alexa Fluor 488-labeled IK17 co-localized with lipid deposits accumulated in the vascular wall. We found in HCD-fed zebrafish larvae OxCE LC-MS signatures identical to those in oxidized human LDL and in murine atherosclerotic lesions. In addition, high levels of OxPL such as POVPC and various lysoPC molecules were detected in HCD-fed zebrafish larvae. Homogenates of HCD-fed zebrafish larvae induced membrane ruffling and cell spreading as well as ERK1/2 phosphorylation in murine macrophages. Moreover, homogenates of HCD-fed larvae bound to macrophages, and this binding was diminished by competition with mmLDL, or Cu-OxLDL, but not with native LDL. These data suggest that HCD-fed zebrafish are characterized by the presence of biologically active, oxidized lipid moieties, identical to those found in mammalian atherosclerotic lesions. Collectively, our new results support applications of zebrafish as a novel animal model suitable for studying the role of lipoprotein oxidation in early atherogenesis.

6

Chylomicronemia Elicits Atherosclerosis in Mice

Michael Weinstein1, Liya Yin1, Yiping Tu1, Xuping Wang1, Xiaohui Wu1, Lawrence Castellani1, Rosemary Walzem2, Aldons Lusis1, Loren Fong1, Anne Beigneux1, and Stephen Young1

1. University of California, Los Angeles, CA
2. Texas A&M University, College Station, TX2

Abstract:

The risk of atherosclerosis in the setting of chylomicronemia has been a topic of debate. In this study, we examined susceptibility to atherosclerosis in Gpihbp1-deficient mice (Gpihbp1–/–), which manifest severe chylomicronemia as a result of defective lipolysis. We found that Gpihbp1–/– mice on a chow diet have plasma triglyceride and cholesterol levels of 2812 ± 209 and 319 ± 27 mg/dl, respectively. Even though nearly all of the lipids were contained in large lipoproteins (50–135 nm), the mice developed progressive aortic atherosclerosis. In other experiments, we found that both Gpihbp1-deficient "apo-B48–only" mice and Gpihbp1-deficient "apo-B100–only" mice manifest severe chylomicronemia. Thus, GPIHBP1 is required for the processing of both apo-B48– and apo-B100–containing lipoproteins. We conclude that chylomicronemia causes atherosclerosis in mice. Also, we found that GPIHBP1 is required for the lipolytic processing of both apo-B48– and apo-B100–containing lipoproteins.

7

Cholesterol Intake Modulates Plasma Triglyceride Levels in GPIH-BP1-deficient Mice

Michael M. Weinstein1,2, Anne P. Beigneux1, Loren G. Fong1, and Stephen G. Young1,2

Departments of 1. Medicine and 2. Human Genetics, University of California, Los Angeles

Abstract:

GPIHBP1 is expressed in capillary endothelial cells of heart, adipose tissue, and skeletal muscle. In those tissues, GPIHBP1 binds lipoprotein lipase (LPL) and is essential for the LPL-mediated processing of triglyceride-rich lipoproteins. Gpihbp1–/– mice exhibit severe chylomicronemia, with plasma triglyceride levels ranging between 2000 and 5000 mg/dl, even on a low fat chow diet. When the mice were placed on a high fat, high cholesterol "Western" diet, plasma triglyceride levels initially increased to >20,000 mg/dl, but after 1–2 weeks the plasma triglycerides fell to 5000–10,000 mg/dl. Interestingly, an inhibitor of cholesterol absorption, ezetimibe, markedly attenuated this fall in plasma triglycerides. Thus, ezetimibe-treated Gpihbp1–/– mice had significantly higher plasma triglyceride levels.

We hypothesized that cholesterol somehow modulates the triglyceride metabolism in Gpihbp1–/– mice. To explore this issue, we fed Gpihbp1–/– mice a high fat diet containing either high (1.3%) or low (0.05%) amounts of cholesterol. Mice fed the high cholesterol diet had mean plasma triglyceride levels of 7000 mg/dl, whereas mice on the low cholesterol diet had triglyceride levels of 23,000 mg/dl.

We hypothesized that the high cholesterol diet led to a liver X receptor (LXR)-mediated increase in the expression of LPL in the liver, explaining the lower plasma triglyceride levels. Indeed, we showed that the hepatic expression of Lpl and three other LXR-responsive genes (Abca1, Abcg5, and Abcg8) was increased in response to the high cholesterol diet and reduced in response to ezetimibe.

8

Dietary Omega-3 Fatty Acids Promote Alternative Activation of Macrophages

Amanda Brown, Xuewei Zhu, Soonkyu Chung, J. Mark Brown, Lawrence Rudel, Martha Alexander-Miller, and John Parks

Wake Forest University School of Medicine, Winston-Salem, NC

Abstract:

Dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs), primarily eicosapentaenoate (EPA) and docosahexaenoate (DHA), attenuate chronic diseases such as atherosclerosis. However, fatty fish, the richest dietary source of n-3 PUFAs, is consumed in low quantities in the United States. Therefore, we sought to determine whether a botanical oil, echium oil (EO) from Echium plantagineum, which is enriched in stearidonic acid (SDA; 18:4 n-3), will decrease inflammation in a murine model of atherosclerosis. Mice were fed a basal diet containing 10% calories as palm oil (PO) and 0.2% cholesterol, supplemented with an additional 10% of calories as PO, EO, or fish oil (FO). The EO and FO diets decreased macrophage responses to Toll-like receptor-4 (TLR4) stimulation compared with PO. We also explored the possibility that n-3 PUFAs promote macrophage phenotype shifting from a more inflammatory (M1) to a less inflammatory (M2) alternative phenotype. Splenocytes were isolated from mice fed the diets and examined using flow cytometry for expression of the M2 marker, mannose receptor (CD206), in the macrophage population. There was a significant increase in CD206 expression on splenic macrophages from FO-fed mice and a trend toward an increase in EO-fed mice relative to PO-fed mice. To determine whether n-3 PUFAs prime macrophages for M2 activation, resident peritoneal macrophages were stimulated with interleukin-4. We detected increases in M2 marker gene expression in macrophages from mice fed EO and FO diets. In addition, we searched for the presence of n-3 PUFA-mediated phenotypic shifting in a non-human primate model. We observed a significant increase in CD206 expression in livers from animals fed diets enriched in n-3 PUFAs compared with those fed a saturated fat diet. These data suggest that n-3 PUFAs polarize macrophages toward an M2 phenotype, which may be atheroprotective. Ongoing studies will determine whether n-3 PUFAs alter the phenotype of lesion macrophages in the context of atherosclerosis.

9

FGF15/19 and FGF21 Govern Fed and Fasted Responses in Liver Through Reciprocal Regulation of PGC-1a

Matthew Potthoff 1, 2, 3, Takeshi Inagaki4, Jamie Boney-Montoya4, Xunshan Ding4, Tianteng He2, Moosa Mohammadi5, H. Eric Xu6, Robert Gerard4, Brian Finck7, David Mangelsdorf 1, 3, Shawn Burgess1, 2, and Steven Kliewer1, 4

Departments of 1. Pharmacology and 4. Molecular Biology and 2. Advanced Imaging Center and 3. Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX;
5. Department of Pharmacology, New York University School of Medicine, New York, NY;
6. Laboratory of Structural Sciences, Van Andel Research Institute, Grand Rapids, MI;
7. Center for Human Nutrition, Department of Medicine, Washington University School of Medicine, St. Louis, MO

Abstract:

The liver plays an essential role in adapting to fluctuations in nutrient availability by promoting energy storage during nutritional surfeit and mobilizing energy during fasting and starvation. Here, we show that the endocrine fibroblast growth factors, FGF15/19 and FGF21, which are induced by feeding and fasting, respectively, have opposing effects on liver metabolism. Fibroblast growth factor 21 (FGF21), a hormone that is induced in liver by fasting, rapidly induces hepatic expression of peroxisome proliferator-activated receptor coactivator protein-1 (PGC-1), a key transcriptional regulator of energy homeostasis. Using gene expression analysis combined with metabolic tracer studies, we demonstrate that FGF21 is sufficient to cause corresponding increases in fatty acid oxidation, tricarboxylic acid cycle flux, and gluconeogenesis without increasing glycogenolysis, whereas mice lacking FGF21 fail to induce PGC-1 expression fully in response to a prolonged fast and have impaired gluconeogenesis and ketogenesis. In contrast, fibroblast growth factor 15/19 (FGF15/19), a hormone that is induced in the intestine by feeding, represses hepatic PGC-1 expression, fatty acid catabolism, and gluconeogenesis. These results reveal a novel paradigm whereby endocrine FGFs, FGF15/19 and FGF21, act as secondary metabolic regulators to reciprocally regulate hepatic lipid and carbohydrate metabolism in the fed and fasted states following insulin and glucagon, respectively.

10

Macrophage Acyl-CoA Synthetase 1 Is Required for Fueling of Inflammation and Diabetes-accelerated Atherosclerosis in Mice

Jenny Kanter1, Farah Kramer1, Shelley Barnhart1, Michelle Averill1, Anuradha Vivekanandan-Giri2, Lei Li3, Lev Becker1, Wei Yuan1, Alan Chait1, Subramaniam Pennathur2, Jay Heinecke1, Rosalind Coleman3, and Karin Bornfeldt1

1. University of Washington, Seattle, WA;
2. University of Michigan, Ann Arbor, MI;
3. University of North Carolina, Chapel Hill, NC

Abstract:

Diabetes increases the risk of atherosclerosis through unknown mechanisms. Evidence suggests that fatty acids, and/or their acyl-CoA derivatives, affect the inflammatory potential of macrophages, thereby promoting atherosclerosis. We therefore investigated whether expression of long chain acyl-CoA synthetase 1 (Acsl1) in macrophages plays a role in their inflammatory potential and diabetic vascular disease. Macrophages harvested from a mouse model of type 1 diabetes (LDLR–/–;RIP-LCMV) exhibited increased expression of the inflammatory mediators inducible nitric-oxide synthase, interleukin (IL)-1 , and cytochrome c oxidase-2 (66 28, 6.8 2.6, and 8.5 1.6-fold increase, respectively) compared with controls. In addition, Acsl1 was up-regulated ($p < 0.05$) in macrophages from diabetic mice and by lipopolysaccharide (LPS)/interferon (IFN)- stimulation in bone marrow-derived macrophages (BMDM), suggesting a link among diabetes, inflammation, and Acsl1. LysM-Cre-loxP-mediated deletion of Acsl1 reduced the inflammatory potential of BMDM, diminishing IL-6, IL-12, and tumor necrosis factor- secretion ($p < 0.05$). We next performed bone marrow transplants (BMT) into LDLR–/–;RIP-LCMV mice. Acsl1 deletion had no effect on neutrolipid mass in isolated macrophages. Diabetes caused a 3-fold increase in atherosclerosis in the brachiocephalic artery ($p < 0.05$). Strikingly, macrophage Acsl1 deficiency abolished diabetes-accelerated atherosclerosis (from 2367 618 to 384 116 m2; $p < 0.05$), with no effect in nondiabetic mice. There were no differences in plasma lipids, glucose, or inflammatory markers. Elevated glucose (25 mM) increased the inflammatory potential and Acsl1 mRNA in LPS/IFN- -stimulated BMDM compared with BMDM in normal glucose (5.5 mM). Thus, diabetes promotes a proinflammatory macrophage phenotype, concomitant with increased expression of Acsl1. Deletion of macrophage Acsl1 renders these cells less inflammatory and abolishes diabetes-accelerated atherosclerosis. Our findings suggest that glucose-enhanced Acsl1 expression in macrophages is required for diabetes-accelerated atherosclerosis.

11

GPIHBP1 Interactions with Lipoprotein Lipase

Constance Voss1, Peter Gin1, Jenny Chen1, Shelly Tat1, André Bensadoun2, Loren G. Fong1, Stephen G. Young1, and Anne P. Beigneux1

1. University of California, Los Angeles, CA
2. Cornell University, Ithaca, NY

Abstract:

GPIHBP1, a glycosylphosphatidylinositol (GPI)-anchored protein of endothelial cells, is critical for the lipolytic processing of triglyceride-rich lipoproteins by lipoprotein lipase (LPL). A deficiency of GPIHBP1 in mice results in plasma triglyceride levels >3000 mg/dl, even on a low fat diet. GPIHBP1 expression in cultured cells confers the ability to bind LPL. There are two principal structural motifs in GPIHBP1: an amino-terminal acidic domain containing numerous aspartates and glutamates, and a cysteine-rich Ly6 motif. Previously, we showed that mutations in the acidic domain interfere with LPL binding. More recently, we showed that mutations in the conserved cysteines of the Ly6 domain abolish LPL binding. It seems likely that the acidic domain within GPIHBP1 interacts with the positively charged heparin-binding domains within LPL. However, the LPL domain that interacts with the GPIHBP1 Ly6 domain has never been defined. During the past few months, we discovered that a single missense mutation in a highly conserved region of LPL abolishes LPL binding to GPIHBP1. Additional mutagenesis experiments should make it possible for us to define more precisely the region of LPL that interacts with GPIHBP1. In related experiments, we tested the ability of other members of the lipase family, hepatic lipase (HL) and endothelial lipase (EL), to bind to GPIHBP1. Neither HL nor EL binds to GPIHBP1, as judged by two independent assay systems. In the future, testing the capacity of chimeric LPL–HL molecules to bind to GPIHBP1 should be useful in defining the region of LPL that interacts with GPIHBP1.

12

Identification of a Transcriptional Regulator of Adipogenesis by High Throughput Screening

Claudio Villanueva1, Hironori Waki1, Ronni Nielson2, Enrique Saez3, Susanne Mandrup1, 2, Enrique Saez3 and Peter Tontonoz1

1. Howard Hughes Medical Institute, University of California, Los Angeles, CA
2. University of Southern Denmark, Odense M, Denmark; 3The Scripps Research Institute, La Jolla, CA

Abstract:

Adipocytes are specialized cells that store lipids during times of caloric excess, mobilize them as free fatty acids during energy deficiency, and secrete several endocrine factors to regulate systemic energy metabolism. Peroxisome proliferator-activated receptor (PPAR), a ligand-activated transcription factor, is the master regulator of adipogenesis. In an effort to identify additional regulators that drive adipogenesis, we carried out a high throughput screen using 10T1/2 cells expressing the aP2 enhancer/promoter linked to a luciferase reporter. We identified several genes whose function has been described previously in adipogenesis, including PPAR , C/EBP , C/EBP , MAPKK6, and COE1, validating our screening strategy. In addition, we identified several novel adipogenic factors, including TLE3, a nuclear protein whose function had not been previously linked to adipogenesis. TLE3 expression is induced during adipocyte differentiation and is responsive to PPAR agonist stimulation both in vitro and in vivo. TLE3 belongs to a family of transcriptional co-repressors that work in concert with transcription factors to regulate gene expression. We show that TLE3 promotes adipocyte differentiation cooperatively with PPAR by coactivating PPAR transcriptional activity. Conversely, TLE3 knockdown reduces adipogenesis and the expression of PPAR target genes such as aP2 and CD36. Remarkably, in addition to its enhancing effects on PPAR , TLE3 also acts as a co-repressor for TCF and as an inhibitor of the Wnt signaling pathway, a major inhibitory pathway of adipogenesis. Induction of Wnt-responsive genes such as Nkd2 and Wisp2 by wnt3a is attenuated by expression of TLE3. These findings suggest a dual role for TLE3 in adipogenesis as both a feedforward activator of PPAR -dependent transcription and a repressor of the Wnt signaling pathway.

13

Impaired Development of Atherosclerosis in Abcg1–/–Apoe–/– Mice: Identification of Specific Oxysterols That Both Accumulate in Abcg1–/–Apoe–/– Macrophages and Induce Apoptosis

Elizabeth Tarling1, Dragana Bojanic1, Rajendra Tangirala1, Xuping Wang1, Anita Lovgren-Sandblom2, Aldons Lusis1, Ingemar Bjorkhem2, and Peter Edwards1

1. University of California, Los Angeles, CA; 2Karolinska Institute, Stockholm, Sweden

Abstract:

ABCG1 is highly expressed in macrophages and endothelial cells, two cell types that play important roles in the development of atherosclerosis. We generated Abcg1–/–Apoe–/– DKO mice in order to understand the mechanism and cell types involved in changes in atherosclerosis following loss of ABCG1. DKO and Apoe–/– mice, and recipient Apoe–/– mice that had undergone transplantation with bone marrow from Apoe–/– or DKO mice were fed a western diet for 12-16 weeks prior to quantification of atherosclerotic lesions. These studies demonstrated that loss of ABCG1 from all tissues, or from only hematopoietic cells, was associated with significantly smaller lesions that contained increased numbers of TUNEL- and caspase-3-positive apoptotic Abcg1–/– macrophages. We also identified specific oxysterols that accumulate in the brains and macrophages of the Abcg1–/–Apoe–/– mice. These oxysterols promoted apoptosis and altered the expression of pro-apoptotic genes when added to macrophages in vitro. We conclude that loss of ABCG1 from all tissues or from only hematopoietic cells, results in smaller atherosclerotic lesions populated with increased numbers of apoptotic macrophages, by processes independent of ApoE. Specific oxysterols identified in tissues of Abcg1–/–Apoe–/– mice may be critical for these effects as they induce macrophage apoptosis and the expression of pro-apoptotic genes.

14

Liver X Receptor Regulates Cholesterol Uptake through Idol-dependent Ubiquitination of the Low Density Lipoprotein Receptor

Cynthia Hong, Noam Zelcer, Rima Boyadjian, and Peter Tontonoz

Howard Hughes Medical Institute and Department of Pathology and Laboratory Medicine,
University of California, Los Angeles, CA

Abstract:

Cellular cholesterol levels reflect a balance among uptake, efflux, and endogenous synthesis. Here, we show that the sterol-responsive nuclear receptor Liver X Receptor (LXR) acts to maintain homeostasis not only through promotion of cholesterol efflux, but also through suppression of low density lipoprotein (LDL) uptake. LXR inhibits the LDL receptor (LDLR) pathway through transcriptional induction of Idol (inducible degrader of the LDLR), an E3 ubiquitin ligase that triggers ubiquitination of the LDLR on its cytoplasmic domain, thereby targeting it for degradation. LXR ligand reduces, whereas LXR knockout increases, LDLR protein levels in vivo in a tissue-selective manner. Idol knockdown in hepatocytes increases LDLR protein levels and promotes LDL uptake. Conversely, adenovirus-mediated expression of Idol in mouse liver promotes LDLR degradation and elevates plasma LDL levels. The LXR-Idol-LDLR axis defines a complementary pathway to sterol response element-binding proteins for sterol regulation of cholesterol uptake.

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MicroRNA Control of Cholesterol Metabolism through Post-transcriptional Regulation of Genes Involved in Cholesterol Homeostasis

Katey Rayner1,*, Yajaira Suarez1,*, Alberto Davalos1, Saj Parathath1, Michael Fitzgerald2, Norimasa Tamehiro2, Edward Fisher1, Carlos Fernandez-Hernando1,#, and Kathryn Moore1,#

1. Leon H. Charney Division of Cardiology, Marc and Ruti Bell Vascular Biology and Disease Program, New York University School of Medicine, New York, NY
2. Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA*,# Equal contribution.

Abstract:

MicroRNAs (miRNAs) are a class of small RNAs capable of tightly regulating cellular processes by controlling gene expression at the post-transcriptional level. We postulated that microRNAs may provide a mechanism to fine tune cellular lipid metabolism regulatory pathways. To identify microRNAs that are potentially involved in the regulation of cellular cholesterol metabolism, we performed a genome-wide microRNA profile analysis of human macrophages in cholesterol-depleted and cholesterol-enriched states. We identified a subset of 21 microRNAs differentially modulated by cellular cholesterol levels, including a subset of miRs with predicted gene targets involved in cholesterol uptake, subcellular transport, and efflux. Using specific miR knockdown and overexpression, we identified miRs that regulate macrophage cholesterol metabolism programs. Under low sterol conditions, we show that miR-33 is up-regulated and inhibits the expression of the ATP-binding cassette (ABC) transporter, ABCA1, which mobilizes cholesterol from cells to apolipoprotein A1 (apoA1) in the formation of high density lipoproteins (HDL). The physiologic implications of this novel regulatory system were confirmed in vivo by demonstrating miR-33 regulation in a hyperlipidemic mouse model of atherosclerosis. Additionally, in vivo lentivirus-mediated overexpression of miR-33 in mice represses ABCA1 protein expression in the liver, reducing circulating HDL levels. Conversely, silencing of this miRNAs in vivo increases hepatic expression of this transporter and elevates plasma HDL cholesterol levels. In conclusion, our study identifies a novel mechanism by which cholesterol homeostasis is controlled in macrophages at the level of microRNA expression through targeting of genes involved in cholesterol metabolism pathways.

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Minimally Oxidized LDL and LPS Cooperatively Activate Macrophages via AP-1 and NF- B

Philipp Wiesner, Soo-Ho Choi, Felicidad Almazan, Christopher Benner, Wendy Huang, Susan Butler, Joseph L. Witztum, Christopher K. Glass, Yury I. Miller

University of California, San Diego, CA

Abstract:

Oxidized low density lipoprotein (LDL) is an important determinant of inflammation in atherosclerotic lesions. It has also been documented that certain chronic infectious diseases, such as periodontitis and chlamydial infection, exacerbate clinical manifestations of atherosclerosis. In addition, low level but persistent endotoxemia, so-called metabolic endotoxemia, is often found in diabetic and obese subjects and is induced in mice fed a high fat diet. In this study, we examined cooperative macrophage activation by low levels of bacterial lipopolysaccharide (LPS) and by minimally oxidized LDL (mmLDL) as a model for endotoxemia-complicated atherosclerosis. We found that both in vitro and in vivo, mmLDL and LPS (Kdo2-LipidA) cooperatively activated macrophages to express proinflammatory cytokines Cxcl2 (MIP-2), Ccl3 (MIP-1), and Ccl4 (MIP-1). From analyzing microarray data with a de novo motif discovery algorithm, we found that genes transcribed by promoters containing an AP-1 binding site were significantly up-regulated by co-stimulation with mmLDL and LPS. In a nuclear factor-DNA binding assay, the cooperative effect of mmLDL and LPS co-stimulation on c-Jun and c-Fos DNA binding, but not on p65 or p50 DNA binding, was dependent on mmLDL-induced activation of ERK1/2. In addition, mmLDL induced AP-1 derepression by removing the corepressor NCoR from the Cxcl2 and Ccl3 promoters. Unlike IKK -dependent NCoR derepression by LPS, mmLDL-induced NCoR release was dependent on JNK activity. Importantly, the mmLDL and LPS cooperative effect was evident at a threshold LPS concentration (1 ng/ml) at which LPS alone induced only a limited macrophage response. The cooperative engagement of AP-1 and NF- B by mmLDL and LPS may constitute a mechanism of enhanced inflammatory activation within atherosclerotic lesions leading to increased transcription of inflammatory cytokines.

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Netrin-1: A Multifunctional Guidance Cue That Promotes Atherosclerosis

Janine van Gils1, Merran Stewart2, Katey Rayner1, Luciana Fernandes3, Thomas McDonald4, Kevin O'Brien4, and Kathryn Moore1

1. NYU Langone Medical Center, New York, NY
2. Massachusetts General Hospital, Boston, MA
3. Federal University of Minas Gerais, Belo Horizonte, Brazil
4. University of Washington, Seattle, WA

Abstract:

The chronic inflammation underlying atherosclerosis is fueled by the persistence of lipid-laden macrophages in the artery wall. However, the mechanisms by which these immune cells become trapped are not well understood. We demonstrate that Netrin-1, a neuronal guidance molecule recently linked to the coordination of leukocyte migration, is expressed in human atheroma and negatively regulates macrophage migration. Incubation of macrophages with oxidized low density lipoprotein in vitro caused a 3-fold up-regulation of Netrin-1 protein. Furthermore, immunohistochemical analysis of human atherosclerotic lesions revealed abundant expression of Netrin-1 by macrophage foam cells. Migration assays showed that Netrin-1 differentially regulates cellular constituents of atheroma: Netrin-1 blocks macrophage migration via the receptor Unc5b, whereas it induces chemoattraction of coronary artery smooth muscle cells via a second Netrin-1 receptor, Neogenin. These data suggest that lesional expression of Netrin-1 from foam cells may promote atherosclerosis by retaining macrophages in the intima while simultaneously recruiting smooth muscle cells to this site. To test this, we reconstituted the bone marrow of Ldlr–/– mice with Netrin-1 (Ntn1)+/+ or Ntn1–/– fetal liver cells and measured atherosclerosis after 12 weeks of Western diet feeding. Chimeric Ntn1–/–Ldlr–/– mice show markedly reduced atherosclerosis in both the aortic sinus (Ntn1+/+ 0.31 mm2 versus Ntn1–/– 0.19 mm2, $p < 0.005$) and the aorta enface (Ntn1+/+ 1.40% versus Ntn1–/– 0.61%, $p < 0.05$), accompanied by decreased expression of the macrophage marker CD68. Together, these data identify novel immunomodulatory functions of Netrin-1 in the vessel wall that promote chronic inflammation and atherosclerosis.

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Roles of NPC1 and NPC2 Proteins in Vitamin E Transport

Lynn Ulatowski1, Robert Parker2, Steven U. Walkley3, Cristin Davidson3, Forbes Porter4, Nicole Yanjanin4, Thomas Kelley1, Deborah Corey1,Hirokuyi Arai5, and Danny Manor1

1. Case Western Reserve University, Cleveland, OH
2. Cornell University, Ithaca, NY;
3. Albert Einstein College of Medicine, Bronx, NY
4. NIH/NICHD, Bethesda, MD
5. University of Tokyo, Tokyo, Japan

Abstract:

Vitamin E is a collective term denoting a family of neutral plant lipids, of which RRR- -tocopherol (tocopherol) is preferentially retained in the body. Tocopherol's hydrophobic nature and ability to scavenge free radicals designate it the major lipid-soluble antioxidant in vertebrates. Neimann-Pick disease type C (NPC) is a lysosomal storage disorder that results from loss-of-function mutations in the NPC1 or NPC2 genes, which regulate sterol transport in the late-endocytic pathway. Mutations in either NPC1 or NPC2 genes result in massive accumulation of unesterfied cholesterol and other lipids, accompanied by neurodegeneration, hepatosplenomegaly, and premature death. We aimed to examine the roles of NPC proteins in tocopherol transport and to determine whether vitamin E levels are altered in NPC-null cells and mice, as well as in human NPC patients. Cultured immortalized human hepatocytes (IHH) in which NPC1 or NPC2 expression was "knocked-down" and human fibroblasts harboring a mutated NPC1 allele exhibited pronounced lysosomal accumulation of vitamin E. Tocopherol significantly accumulated in murine Npc1–/– and Npc2–/– livers, Npc2–/– cerebella, and Npc1–/– cerebral cortices. Plasma tocopherol levels in Npc1–/– and Npc2–/– mice, as well as in human NPC patients, were within the normal range. The binding affinity of tocopherol to the sterol-binding domain of NPC1 (NPC1-NTD) and to NPC2 was 2-3-fold lower than that of cholesterol. (The cholesterol binding assays were kindly performed by Rodney Infante, UT Southwestern, Dallas, TX). These observations indicate that functional NPC1 and NPC2 proteins are necessary for normal vitamin E transport.

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Role for Farnesoid X-activated Receptor in Hepatoprotection

Thomas Quad de Aguiar Vallim1,2, Florence Ying Lee1,2, Hansook K. Chong3, Timothy F. Osborne3, and Peter A. Edwards1,2,4

Departments of 1. Biological Chemistry and 2. Medicine, David Geffen School of Medicine and the 4. Molecular Biology Institute, University of California, Los Angeles, CA;
3. Department of Molecular Biology and Biochemistry, University of California, Irvine, CA

Abstract:

The nuclear receptor farnesoid X receptor (FXR, NR1H4) is known to regulate cholesterol, bile acid, lipoprotein, and glucose metabolism. We provide evidence to support a novel role for FXR in hepatoprotection. Pharmacological activation of FXR induces the expression of several genes involved in phase II and phase III xenobiotic metabolism. We used chromatin immunoprecipitation-based genome-wide response element analyses coupled with luciferase reporter assays to identify functional FXR response elements within promoters, introns, or intragenic regions of these genes. Consistent with the observed transcriptional changes, FXR gene dosage is correlated positively with the degree of protection in APAP-induced hepatotoxicity in vivo. Furthermore, we demonstrate that pretreatment of wild-type mice with an FXR-specific agonist provides significant protection from APAP-induced hepatotoxicity. Based on these findings, we propose that FXR plays a role in hepatic xenobiotic metabolism and when activated, provides hepatoprotection against toxins such as APAP.

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Spleen Tyrosine Kinase (Syk) Regulates TLR4-dependent Proinflammatory Effects of Minimally Oxidized Low Density Lipoprotein

Soo-Ho Choi

University of California, San Diego, CA

Abstract:

Atherosclerosis is a chronic inflammatory disease of the vascular wall. Low density lipoprotein (LDL), retained and modified (e.g. oxidized) in the intima of large arteries, induces many inflammatory responses in vascular cells and thereby promotes the development of atherosclerosis. In our previous studies, we have demonstrated that minimally oxidized LDL (mmLDL) induces expression of proinflammatory cytokines and actin polymerization in macrophages via Toll-like receptor 4 (TLR4)-dependent pathways. In our recent work, we demonstrated that mmLDL and its active components, cholesteryl ester hydroperoxides, induced robust membrane ruffling and cytoskeletal rearrangement in macrophages, leading to fluid-phase uptake (macropinocytosis) of lipoproteins and the foam cell formation. The signaling mechanism of these processes involved interaction of TLR4 with spleen tyrosine kinase (Syk), phosphorylation of both TLR4 and Syk, and ERK1/2-dependent activation of small GTPases Rac, Cdc42, and Rho. In addition, Syk was also required for mmLDL and lipopolysaccharide-induced proinflammatory signaling cascades, leading to activation of NF- B and AP-1 transcription programs and macrophage inflammatory protein-2 and interleukin-6 cytokine expression. To validate the functional role of Syk with primary macrophages, we have isolated peritoneal resident macrophages from Syk(fl/fl) mice and infected them with an adenovirus expressing Cre recombinase to generate macrophage-specific Syk knockdown. The mmLDL-induced phosphorylation of ERK1/2 and Akt as well as intracellular lipid accumulation were significantly inhibited in Syk knockdown primary macrophages. These results suggest that Syk is a key regulator of mmLDL-induced proinflammatory signaling in macrophages. Taken together, these data suggest that Syk recruitment to the receptor complexes, such as TLR4/MD-2, induced by modified lipoproteins, may play an important role in vascular inflammation and the development of atherosclerosis.

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Syndecan-1-mediated Uptake of Triglyceride-rich Lipoproteins

Erin Foley, Kristin Stanford, and Jeffrey Esko

University of California, San Diego, La Jolla, CA

Abstract:

Lipoproteins transport triglycerides and cholesterol through circulation. As they circulate, lipases act on the triglycerides, generating fatty acids for energy production and storage in different tissues. The remnant particles are then cleared in the liver via several endocytic receptors. Previous work has demonstrated that heparan sulfate proteoglycans act as receptors because diminished sulfation of heparan sulfate by inactivation of GlcNAc N-deacetylase/N-sulfotransferase-1 in hepatocytes (Ndst1f/fAlbCre+) results in accumulation of plasma triglyceride-rich lipoproteins (1). We have now identified syndecan-1 (Sdc1) as the primary heparan sulfate proteoglycan receptor mediating hepatic clearance (2). Sdc1–/– mice exhibited prolonged circulation of injected human very low density lipoprotein (VLDL) and intestinally derived chylomicrons, and adenovirus containing syndecan-1 corrected the clearance defect in vivo. Cross-breeding mutants defective in syndecan-1 and Ndst1 (Sdc1–/– Ndst1f/fAlbCre+) did not accentuate triglyceride accumulation beyond the level observed in each single mutant, indicating that syndecan-1 is the primary proteoglycan clearance receptor. Immunoelectron microscopy showed expression of syndecan-1 on the microvilli of hepatocyte basal membranes facing the space of Disse where lipoprotein uptake occurs. Syndecan-1 receptors are abundant on hepatocytes, exhibit saturable binding and inhibition by heparin, and facilitate degradation of labeled VLDL in vitro. Current studies are focused on expressing mutant forms of syndecan-1 in cultured primary hepatocytes and in Sdc1–/– mice to explore the relevant structural features of the molecule for binding and the mechanism of endocytosis.

References

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22

Synthesis of the Enantiomer of Oxysterol Antagonist LY295427

Agata Bielska, Daniel Ory, and Douglas Covey

Washington University School of Medicine, St. Louis, MO

Abstract:

Tight regulation of cholesterol is crucial to proper cellular functioning because excess free cholesterol is toxic to cells and is associated with atherosclerosis and heart disease. Cellular cholesterol homeostasis is regulated by oxygenated cholesterol metabolites called oxysterols. Although the importance of oxysterols in the acute regulation of cholesterol homeostasis is known, the precise molecular mechanisms through which oxysterols exert their effects remain to be elucidated. It was recently discovered that the oxysterol 25-hydroxycholesterol (25-HC) has disordering effects in the membrane and that the enantiomer of 25-HC is as effective as natural 25-HC in regulating acute cholesterol homeostatic pathways. This result implies that 25-HC exerts cholesterol-regulatory control through nonenantioselective membrane effects. To test this hypothesis, we synthesized both the natural (nat) and enantiomeric (ent) forms of the known oxysterol antagonist LY295427. LY295427 was synthesized from 4-cholestenone in two steps according to a published procedure. Ent-LY295427 was synthesized in 28 steps, using ent-testosterone as an intermediate. Using these sterol probes, we will examine the ability of both enantiomers to antagonize specific 25-HC-regulated pathways. This approach takes advantage of the fact that enantiomers have identical physical properties (i.e. identical effects on the membrane), whereas their interactions with chiral molecules are quite different. Thus, pathways controlled by changes in membrane properties and organization will be equally activated by both nat and ent compounds, whereas pathways controlled by a specific interaction with an effector molecule will only be activated with nat compounds. The proposed studies will provide insight into the role of transcription-independent mechanisms in regulation of cholesterol homeostasis.

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A2b Adenosine Receptor as a New Regulator of Liver Lipid Synthesis and Atherosclerosis

Milka Koupenova-Zamor1, Dan Yang1, Hillary Johnston-Cox2, Katya Ravid1, 2, 3, 4

Departments of 1. Biochemistry and 2. Medicine and 3. Whitaker Cardiovascular Institute and 4. Evans Center for Interdisciplinary Biomedical Research , Boston University School of Medicine, Boston, MA

The A2b adenosine receptor (A2bAR) is highly expressed in bone marrow macrophages and in vascular smooth muscle cells. For that purpose, we cross-bred the A2bAR knockout created by our group with ApoE-null mice to create A2bAR,ApoE double knockout model (dKO). We have found that atherosclerosis was more pronounced when A2bAR was eliminated after Western diet or with age on regular chow diet. Bone marrow transplantation experiments indicated that the majority of the signals for lesion formation in the dKO mice do not originate from bone marrow cells. Our dKO model showed elevated levels of plasma cholesterol and triglycerides concentrated in the very low density lipoprotein particles. Liver lipids showed a similar pattern of elevated lipoproteins. Protein analysis by Western blotting determined that a possible reason for the elevated levels of lipoproteins is that the transcription factor SREBP-1 is involved in regulation of genes related to fatty acid synthesis and cholesterol such as ACC and AACS. Culture of primary hepatocytes isolated from ApoE mice after Western diet determined that inhibition of A2bAR by specific antagonists results in elevation of SREBP-1 levels compared to the reducing effect of this receptor by its specific agonist BAY. Furthermore, TLC experiments after 14C-labeled acetate in primary hepatocytes determined that cholesterol and triglycerides follow the same pattern of up-regulation as the liver itself. Thus, this study is the first to highlight the significance of the A2bAR in protecting against vascular lesion formation during atherosclerosis. We highlight a novel mechanism by which A2bAR regulates SREBP-1 levels and the consequent balance of plasma cholesterol and triglycerides.

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LIPABASE: A Data Base for Lipase (EC 3.1.1.3) Family Enzymes

Hatem Belguith1, Abdelmonaem Messaoudi2, Imen Ghram2, and Jeannette Ben Hamida2

1. College of Applied Medical Sciences, Al-Jouf University, Saudi Arabia
2. Unité de Protéomie Fonctionnelle et de Biopréservation Alimentaire, Institut Supérieur des Sciences de Tunis, Tunisia

Abstract:

Lipases are enzymes that play an important role in lipid metabolism and are produced by a variety of organisms. Compared with animal, bacterial, and fungal, little is known about plant lipases. Although lipases belong to many different protein families, they have the same architecture, the /ß-hydrolase fold, and a conserved active site signature, the GxSxG motif. Physicochemical profiles for 131 lipases enzyme are made, including amino acid composition (acidic, basic, hydrophobic, polar, absent, and common amino acids), atomic composition, molecular mass, theoretical pI, extinction coefficient, absorbance at 280 nm, instability index, aliphatic index, and grand average of hydropathicity (GRAVY). Statistical analysis of these lipases sequences shows that bacterial lipolytic enzymes are the most represented one (73%). Despite intense studies of plant lipase, few have been purified and cloned (6.1% of sequences are of plant origin), we clarify the percentage of these enzymes compared with bacterial, fungal (11.5%), and animal (9.2%). For 60%, the amino acid sequence length varies from 250 to 350; most have molecular masses ranging from 30 to 40 kDa. Bacterial, plant, and fungal lipases have a neutral or slightly acid pI (5-7), animals have a slightly alkaline pI (7-9). Calculated Pearson coefficients (r = 0.849) revealed a positive correlation between sequence length and number of serine residues, indicating that serine content is fairly constant. The distribution of basic and acidic residues among lipase sequences show that the majority of them display a basic pattern, 37% having from 20 to 30 basic residues.

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Impaired Phosphatidylcholine Biosynthesis Reduces Atherosclerosis and Prevents Cardiac Dysfunction in ApoE deficient mice

Laura K. Cole1, Vernon W. Dolinsky2, Jason R.B. Dyck2 and Dennis E. Vance1

1. Molecular and Cell Biology of Lipids and Department of Biochemistry, School of Molecular and Systems Medicine and the 2. Cardiovascular Research Centre, Faculty of Medicine and Dentistry, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada.

Abstract:

Phosphatidylcholine (PC) is the predominant phospholipid component of circulating lipoproteins. The majority of PC is formed by the choline pathway. However, approximately one third of hepatic PC can also be synthesized by phosphatidylethanolamine N-methyltransferase (PEMT). PEMT is required for normal secretion of very low density lipoproteins from the liver. We hypothesized that lack of PEMT would attenuate atherosclerosis and improve myocardial function. Investigate the contribution of PEMT to atherosclerotic lesion formation and cardiac function in mice that lack apolipoprotein E. Methods and Results: Mice deficient in apolipoprotein E (Pemt+/+/Apoe-/-) and mice lacking both PEMT and apoE (Pemt-/-/Apoe-/-) were fed a chow diet for one year. PEMT deficiency significantly reduced hepatic triacylglycerol (by 39%) and cholesteryl ester (by 37%), accompanied by an ~60% increase in AMP-activated protein kinase activity. In addition, the atherogenic lipoprotein profile of plasma of Apoe-/- mice was significantly improved by PEMT deficiency with lower levels of triacylglycerol (45%) and cholesterol (~25%) in the very low density lipoprotein and low-density/intermediate density lipoprotein fractions, respectively ($p<0.05$). Atherosclerotic lesion area was reduced by ~30 %, and aortic cholesteryl ester and cholesterol content were also reduced by ~40% by PEMT deficiency ($p<0.05$). By in vivo echocardiography we detected a ~50 % improvement in systolic function in the Pemt-/-/Apoe -/- compared to Pemt +/+/Apoe-/- mice ($p<0.05$).

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Columbia University
Department of Medicine and Cellular Biology
630 W. 168th Street, PH8-E-101B
New York, NY 10032-3702
Tel: (212) 305-9430
FAX: (212) 305-4834
Email:iat@columbia.edu

Members
Dennis E. Vance, Ph.D.(Chair, 2011)
University of Alberta
Molecular and Cellular Biology of Lipids Group
328 Heritage Medical Research Center
Edmonton, AB T6G 2S2 Canada
Tel: (780) 492-8286
FAX: (780) 492-3383
Email: dennis.vance@ualberta.ca

Peter Tontonoz, M.D., Ph.D.(Chair, 2012)
University of California, Los Angeles
Howard Hughes Medical Institute
675 Charles E. Young Drive, South
Los Angeles, CA 90095-1662
Tel: (310) 206-4546
FAX: (310) 267-0382
Email: ptontonoz@mednet.ucla.edu

Mason W. Freeman, M.D.
Novartis Institutes for Biomedical Research
100 Technology Square, Room 5151
Cambridge, MA 02139
Tel: (617) 871-7110
FAX: (617) 871-7050
Email: mason.freeman@novartis.com

Joachim Herz, M.D.
University of Texas Southwestern Medical Center
Dept. of Molecular Genet.
5323 Harry Hines Boulevard
Dallas, TX 75390-9046
Phone: (214) 648-5633
FAX: (214) 648-8804
Email: joachim.herz@utsouthwestern.edu

Murielle Véniant-Ellison, Ph.D.
Department of Metabolic Disorders
Amgen, Inc.
One Amgen Center Drive
Mail stop 29-1-A
Thousand Oaks, CA 91320
Tel: (805) 447-8009
FAX: (805) 499-0953
Email:mveniat@amgen.com

Cheryl Wellington
Department of Pathology & Laboratory Medicine
University of British Columbia
Child & Family Research Institute
CMMT, Rm I-3002, 950 West 28th Avenue
Vancouver, BC V5Z 4H4
Tel: (604) 875-2000(6825)
Fax: (604) 875-3819
Email: cheryl@cmmt.ubc.ca

Karin Bornfeldt (2014)
Department of Pathology
Room E-501, Health Sciences Bldg.
University of Washington
Box 357470
Seattle, WA 98195-7470
Tel:(206) 543-1681
Fax: (206) 543-3644
Email: bornf@u.washington.edu

Karen Reue (2014)
Department of Human Genetics
David Geffen School of Medicine at UCLA
695 Charles E. Young Drive South
Los Angeles, CA 90095
Tel.: 310-794-5631
Fax: 310-794-5446
Email: reuek@ucla.edu

Todd Kirchgessner (2014)
Bristol-Myers Squibb
Rm 21.1208F
311 Pennington-Rocky Hill Road
Pennington, NJ 08534
Tel: 609 818-3262
Fax: 609 818-7877
Email: todd.kirchgessner@bms.com

Treasurer/Funding
Stephen G. Young, M.D.
University of California, Los Angeles
Department of Medicine
Division of Cardiology
650 Charles E. Young Drive, South
47-123 CHS Building
Los Angeles, CA 90095
Phone: (310) 825-4934, FAX: (310) 206-0865
Email:sgyoung@mednet.ucla.edu

Local Arrangements
Barbara A. Gordon
American Society for Biochemistry and Molecular Biology
9650 Rockville Pike
Bethesda, MD 20814
Tel: (301) 634-7145
FAX: (301) 634-7108
Email: bgordon@asbmb.org
Program Committee Chairs

Peter Tontonoz, M.D., Ph.D. (Chair, 2010)
University of California, Los Angeles
Howard Hughes Medical Institute
675 Charles E. Young Drive, South
Los Angeles, CA 90095-1662
Tel: (310) 206-4546
FAX: (310) 267-0382
Email: ptontonoz@mednet.ucla.edu

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New York University Medical Center
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Department of Medicine
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1959 NE Pacific Street
Seattle, WA 98195
Tel: (206) 543-3158
FAX: (206) 685-3781
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Jay Horton, M.D. (Co-Chair, 2011)
University of Texas Southwestern Medical Center
Department of Molecular Genetics and Internal Medicine
5323 Harry Hines Boulevard
Dallas, TX 75390-9046
Tel: (214) 648-9677
FAX: (214) 648-8804
Email: jay.horton@utsouthwestern.edu

Program Chairs 2012

Karin Bornfeldt (2012)
Department of Pathology
Room E-501, Health Sciences Bldg.
University of Washington
Box 357470
Seattle, WA 98195-7470
Tel:(206) 543-1681
Fax: (206) 543-3644
Email: bornf@u.washington.edu

Ira A. Tabas, M.D., Ph.D. (2012)
Columbia University
Department of Medicine and Cellular Biology
630 W. 168th Street, PH8-E-101B
New York, NY 10032-3702
Tel: (212) 305-9430
FAX: (212) 305-4834
Email:iat1@columbia.edu

Conference Attendees

Peter Akerblad
AstraZeneca R&D
MoIndal, NO
Sweden
SE43183
Telephone: 46317763596
Email: peter.akerblad@astrazeneca.com

Alfred Alberts
Merck Research laboratories
156 Brewster Road
Wyckoff, NJ
USA
07481
Telephone: 2016708330
Email: aalberts@optonline.net

Kaveh Ashrafi
UCSF
N412C Genentech Hall, MC2240
600 16th St.
San Francisco, CA
USA
94158-2517
Telephone: 4155144102
Email: kaveh.ashrafi@ucsf.edu

Salman Azhar
VA Palo Alto Health Care System
GRECC-182B
3801 Miranda Avenue
Palo Alto, CA
USA
94304
Telephone: 6508583933
Email: salman.azhar@va.gov

Anne Beigneux
UCLA
A2-237 CHS Bldg
650 Charles E. Young Dr. South
Los Angeles , CA
USA
90095
Telephone: 3108259422
Email: abeigneux@mednet.ucla.edu

Hatem Belguith
Applied Medical Sciences
Skaka
Saudi Arabia
2014
Telephone: 96646257328
Email: belguith.hatem@gmail.com

Andre Bensadoun
Cornell
321Savage Hall
Ithaca, NY
USA
14853
Telephone: 6075929904
Email: ab55@cornell.ed

B. Ganesh Bhat
Genomics Institute of the Novartis Research Foundation
10675 John Jay Hopkins Dr
San Diego, CA
USA
92121
Telephone: 8583324698
Email: gbhat@gnf.org

Agata Bielska
Washington University School of Medicine
660 S. Euclid Avenue
Saint Louis, MO
USA
63104
Telephone: 3143621724
Email: bielskaa@wusm.wustl.edu

Daniel Blom
Merck
126 East Lincoln Avenue
RY80T-A100
Rahway, NJ
USA
07065
Telephone: 7325945002
Email: Daniel_blom@merck.com

Karin Bornfeldt
University of Washington
South Lake Union Campus, Box 358055
815 Mercer Street
Seattle, WA
USA
98109
Telephone: 2065431681
Email: bornf@u.washington.edu

Teresa Brandt
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA
USA
92008
Telephone: 760-603-2738
Email: tbrandt@isisph.com

Michael Breen
Boston University School of Medicine
72 East Concord Street
Boston, MA
USA
02118
Telephone: 6176384045
Email: mbreen@bu.edu

Amanda Brown
Wake Forest University Health Sciences
One Medical Center Blvd.
Winston-Salem, NC
USA
27157
Telephone: 3367163598
Email: amabrown@wfubmc.edu

Anna Calkin
UCLA
MRL6-629
675 Charles E Young Dr S
Los Angeles, CA
USA
90095
Telephone: 3102064622
Email: acalkin@mednet.ucla.edu

Guoqing Cao
Lilly Research Laboratories
359 Merrill Street
Indianapolis, IN
USA
46285
Telephone: 3174333535
Email: guoqing_cao@lilly.com

Alan Chait
University of Washington
Mailstop 356426, 1959 NE Pacific
Seattle, WA
USA
98195
Telephone: 2065433158
Email: achait@u.washington.edu

Michael Chang
Limerick BioPharma
601 Gateway Blvd
Suite 1050
South San Francisco, CA
USA
94080
Telephone: 6507420110
Email: hkirks@limerickbio.com

Arthur Charles
UCSF
44 Marie Street
Sausalito, CA
USA
94965
Telephone: 9493038208
Email: art.charles@ucsf.edu

Soo-Ho Choi
University of California, San Diego
9500 Gilman Dr.
La Jolla , CA
USA
92093
Telephone: 8585344407
Email: soc002@ucsd.edu

Laura Cole
University of Alberta
320 HMRC
Edmonton, AB
Canada
T6G 2R3
Telephone: 7804927310
Email: lcole@ualberta.ca

Rosanne M. Crooke
Executive Director of Cardiovascular Research
Antisense Drug Discovery
Isis Pharmaceuticals
1896 Rutherford Road
Carlsbad, CA
USA
92008
Telephone: 7606032326
Email: RCrooke@isisph.com

Brandon Davies
UCLA
A2-237 CHS
650 Charles E. Young Dr. South
Los Angeles , CA
USA
90095
Telephone: 3102674675
Email: bdavies@mednet.ucla.edu

Jean Davignon
Clinical Research Institute of Montreal
110 Pine Ave West
Montreal, QC
Canada
H2W 1R7
Telephone: 514987562
Email: davignj@ircm.qc.ca

Russell DeBose-Boydd
Howard Hughes Medical Institute/UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas , TX
USA
75390-9046
Telephone: 2146483467
Email: Russell.DeBose-Boyd@utsouthwestern.edu

James Donkin
University of British Columbia
950 West 28th Ave
Vancouver , BC
Canada
V5Z4H4
Telephone: 6048752345
Email: jdonkin@cmmt.ubc.ca

P. Barton Duell
Oregon Health & Science Univeristy
3181 SW Sam Jackson Park Road
L465
Portland , OR
USA
97239
Telephone: 5034942007
Email: duellb@ohsu.edu

Ruth Duffy
Merck Research Labs
2015 Galloping Hill Rd.
K-15-C4/4600
Kenilworth , NJ
USA
07033
Telephone: 9087403280
Email: ruth.duffy@spcorp.com

Peter Edwards
UCLA
Box951737, BSRB#310
Los Angeles , CA
USA
90095
Telephone: 3102063717
Email: pedwards@mednet.ucla.edu

Nikla Emambokus
Cell Press
5th Floor - 600 Technology Square
Cambridge , MA
USA
02139
Telephone: 6173972851
Email: nemambokus@cell.com

Sandra Erickson
UCSF and VAMCSF
VAMC-111F
4150 Clement
San Francisco , CA
USA
94121
Telephone: 4157502005
Email: sandra.kerickson@ucsf.edu

Jeffrey Esko
University of California, San Diego
9500 Gilman Dr MC 0687
La Jolla , CA
USA
92093
Telephone: 8588221100
Email: jesko@ucsd.edu

Longhou Fang
UC at San Diego
9500 Gilman Dr, MC 0682
La Jolla , CA
USA
92093
Telephone: 8585346738
Email: lofang@ucsd.edu

Robert Farese, Jr.
J. David Gladstone Institutes
1650 Owens Street
San Francisco , CA
USA
94158
Telephone: 4157342000
Email: bfarese@gladstone.ucsf.edu

Edward Fisher
NYU School of Medicine
Smilow 8
522 First Avenue
New York , NY
USA
10016
Telephone: 2122636631
Email: edward.fisher@nyumc.org

Erin Foley
University of California San Diego
9500 Gilman Dr.
MC 0687
La Jolla, CA
USA
92093
Telephone: 8588221102
Email: efoley@ucsd.edu

Loren Fong
UCLA
695 Charles Young Dr. South
Gonda Bldg., Rm 4524
los angeles, CA
USA
90095
Telephone: 3102674380
Email: lfong@mednet.ucla.edu

Philip Frost
UCSF
151 Tenth Avenue
San Francisco, CA
USA
94118
Telephone: 4156732241
Email: philip.frost@ucsf.edu

Feng Gao
UC Davis
3135 Meyer Hall
One Shields Avenue
Davis, CA
USA
95616
Telephone: 5104283885
Email: fgao@chori.org

Ricardo Garcia
Bristol-Myers Squibb
311 Pennington-Rocky Hill Rd.
Pennington, NJ
USA
08534
Telephone: 6098183324
Email: ricardo.garcia@bms.com

Barbara Gordon
ASBMB
9650 Rockville Pike
Bethesda, MD
USA
20184
Telephone: 3016347880
Email: bgordon@asbmb.org

Daniel Halperin
UCLA
675 Charles E. Young Dr. South
MRL 6629
Los Angeles, CA
USA
90024
Telephone: 3102064622
Email: dannyhalperin@gmail.com

Robert Hamilton
UCSF Medical School
8 Blacklog Rd.
Kentfield, CA
USA
94904
Telephone: 4154610607
Email: robert.hamilton.jr@ucsf.edu

Richard Havel
University of California San Francisco
513 Parnassus Ave
Box 0130
San Francisco, CA
USA
94143
Telephone: 4144769559
Email: richard.havel@ucsf.edu

Jay Heinecke
University of Washington
815 Mercer Street
Seattle, WA
USA
98195-8055
Telephone: 2065433470
Email: heinecke@u.washington.edu

Joachim Herz
UT Southwestern
5323 Harry Hines Blvd
Dallas, TX
USA
75390
Telephone: 2146485633
Email: joachim.herz@utsouthwestern.edu

Cynthia Hong
University of California, Los Angeles
675 Charles Young Drive South
MRL-6619
Los Angeles, CA
USA
90049
Telephone: 3102064622
Email: chong@mednet.ucla.edu

Jay Horton
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX
USA
75390-9046
Telephone: 2146489677
Email: jay.horton@utsouthwestern.edu

Brian Hubbard
Merck & Co., Inc
126 E Lincoln Avenue
RY80T-A185
Rahway , NJ
USA
07065
Telephone: 7325947556
Email: patti_gregory@merck.com

Ayaka Ito
Mac Donald Research Lab
675 Charles Young Dr. S.
MRL#6629
Los Angeles, CA
USA
90095-1662
Telephone: 3102064622
Email: AIto@mednet.ucla.edu

C. Ronald Kahn
Joslin Diabetes Center
One Joslin Place
Boston, MA
USA
02215
Telephone: 6177322635
Email: c.ronald.kahn@joslin.harvard.edu

John Kane
UCSF
1312 HSE, 513 Parnassus Ave
San Francisco, CA
USA
94143-0130
Telephone: 415476151
Email: john.kane@ucsf.edu

Jenny Kanter
University of Washington
815 Mercer St
Seattle, WA
USA
98109
Telephone: 2066163551
Email: jenka@uw.edu

Milka Koupenova-Zamor
Boston University School of Medicine
715 Albany street,W-520
Boston, MA
USA
02118
Telephone: 6176385095
Email: milka@bu.edu

Fredric Kraemer
Stanofrd University
Division of Endocrinology, S-025
Stanford, CA
USA
94305-5103
Telephone: 6507236054
Email: fbk@stanford.edu

Mary Malloy
UCSF
505 Parnassus Ave. Room 1310 HSE
San Francisco, CA
USA
94143-0130
Telephone: 4154762754
Email: mary.malloy@ucsf.edu

David Mangelsdorf
University of Texas Southwestern Medical Center
6001 Forest Park Road, ND9.124
Dallas, TX
USA
75390
Telephone: 2146455917
Email: davo.mango@utsouthwestern.edu

Marisa Medina
Children"s Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA
USA
94609
Telephone: 5104283885
Email: mwmedina@chori.org

Yury Miller
UCSD
9500 Gilman Dr
La Jolla, CA
USA
92093
Telephone: 8588225771
Email: yumiller@ucsd.edu

Yale Mitchel
Merck
PO BOX 2000 (RY 34-a228)
126 E. LINCOLN AVENUE
Rahway, NJ
USA
07065
Telephone: 7325944167
Email: Yale_mitchel@merck.com

Neha Molina
Abbott Global Pharmaceutical Research and Development
Neha.molina@abbott.com
99 Lamplighter,
Irvine, CA 92620
Telephone: 9496977531
Neha.molina@abbott.com

Kathryn Moore
New York University Medical Center
522 First Avenue
Smilow 705
New York , NY
USA
10016
Telephone: 2122639259
Email: kathryn.moore@nyumc.org

David Neff
6260 Timberview
East Lansing, MI
USA
48823
Telephone: 5172901079
Fax: 5173395489

Christopher Newgard
Duke University
4321 Medical Park Drive, Ste. 200
Durham, NC
USA
27704
Telephone: 9196686059
Email: newga002@mc.duke.edu

Barry Noble
Merck Pharmaceauticals
351 N. Sumneytown Pike
UG4B-65
North Wale, PA
USA
19454
Telephone: 2673059535
Email: r_barry_noble@merck.com

Kris Norenberg
AstraZeneca
646 Alex Way
Encinitas, CA
USA
92024
Telephone: 7609441305
Email: kris.norenberg@astrazeneca.com

Michael Oda
Children's Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA
94609-1673
USA
Telephone: 5104507652
Email: moda@chori.org

Jerrold Olefsky
University of California, San Diego
Department of Medicine (0673)
9500 Gilman Drive
La Jolla, CA
USA
92093-0673
Telephone: 8585346651
Email: jolefsky@ucsd.edu

Daniel Ory
Washington University
Box 8086
660 S. Euclid Ave.
St. Louis, MO
USA
63110
Telephone: 3143628737
Email: dory@wustl.edu

Lale Ozcan
Columbia Univeristy
630 West 168th Street PH:9-405
New York , NY
USA
Telephone: 2123055669
Email: lo2192@columbia.edu

Jianqiu Pan
Summit Hospital
430 hawthorne ave
Oakland, CA
USA
94801
Telephone: 4158168440
Email: jianqiup@yahoo.com

Meihui Pan
Novartis
100 Tech Square, Rm 6401
Cambridge , MA
USA
02139
Telephone: 6178717336
Email: meihui.pan@novartis.com

John Parks
Wake Forest University Health Sciences
Medical Center Blvd
Winston-Salem, NC
USA
27157
Telephone: 3367162145
Email: jparks@wfubmc.edu

Robert Phair
1016 Dartmouth Ln
Los Altos, CA
USA
94024

Paul Pilch
Boston University Medical School
715 Albany St.
Boston, MA
USA
02118
Telephone: 6176384044
Email: ppilch@bu.edu

Steve Pinkosky
Esperion Therapeutics
46701 Commerce Center Drive
Plymouth, MI
USA
48170
Telephone: 7348624851
Email: ksmirnov@esperion.com

Jorge Plutzky
Brigham and Women's Hospital
77 Avenue Louis Pasteur
NRB 742
Boston, MA
USA
02115
Telephone: 6175254360
Email: jplutzky@rics.bwh.harvard.edu

Matthew Potthoff
University of Texas Southwestern Medical Center
6000 Harry Hines Blvd
ND9.504A
Dallas, TX
USA
75390
Telephone: 2146456054
Email: matthew.potthoff@utsouthwestern.edu

Clive Pullinger
UCSF
513 Parnassus Avenue
HSE1304, Box 0130
San Francisco, CA
USA
94143
Telephone: 4154765938
Email: clive.pullinger@ucsf.edu

Daniel Rader
University of Pennsylvania
654 BRBII/III
421 Curie Blvd.
Philadelphia, PA
USA
19104
Telephone: 2155734176
Email: rader@mail.med.upenn.edu

Katey Rayner
New York University School of Medicine
522 First Avenue
Smilow 707
New York, NY
USA
10016
Telephone: 2122639496
Email: katey.rayner@nyumc.org

Donna Reichart
UC San Diego
9500 Gilman Drive, MC 0651
GPL CMMW Room 219
La Jolla, CA
USA
92093-0651
Telephone: 8588225664
Email: dreichart@ucsd.edu

Muredach Reilly
University of Pennsylvania
421 Curie Blvd
609 BRB II/III
Philadelphia, PA
USA
19104
Telephone: 2155731214
Email: muredach@mail.med.upenn.edu

Karen Reue
UCLA
6506A Gonda
695 Charles E. Young Drive South
Los Angeles, CA
USA
90095
Telephone: 3107945631
Email: reuek@ucla.edu

Jean-Marc Schwarz
UCSF/Touro University
1310 Johnson Lane
Mare Island
Vallejo, CA
USA
94592
Telephone: 7076385456
Email: jschwarz@medsfgh.ucsf.edu

Elena Scotti
UCLA
675 Charles E.Young DR.S.
Los Angeles, CA
USA
90095
Telephone: 3102064622
Email: escotti@mednet.ucla.edu

Randy Seeley
University of Cincinnati
2170 E. Gailbraith Rd
Metabolic Diseases Institute
Cincinnati, OH
USA
45237
Telephone: 5135586664
Email: randy.seeley@uc.edu

Wen-Jun Shen
Stanford University/VAPAHCS
3801 Miranda Ave.
Palo Alto, CA
USA
94304
Telephone: 6504935000
Email: wenjun@stanford.edu

Mark Sleeman
Regeneron Pharmaceuticals Inc
777 Old Saw Mill River Road
Tarrytown, NY
USA
10591
Telephone: 9143457971
Email: mark.sleeman@regeneron.com

Ira Tabas
Columbia University Medical Center
630 West 168th Street
New York , NY
USA
10032
Telephone: 2123059430
Email: iat1@columbia.edu

Elizabeth Tarling
UCLA
675 Charles E Young Drive South
MRL 3230
Los Angeles, CA
USA
90024
Telephone: 3102068383
Email: etarling@mednet.ucla.edu

Peter Tobias
The Scripps Research Institute
10550 N. Torrey Pines Rd.
La Jolla, CA
USA
92037
Telephone: 8587848215
Email: tobias@scripps.edu

Peter Tontonoz
UCLA
675 Charles Young Dr.
MRL 6-770
Los Angeles, CA
USA
90095
Telephone: 3102064546
Email: ptontonoz@mednet.ucla.edu

Diane Tribble
ISIS Pharmaceuticals, Inc
1896 Rutherford Rd
Carlsbad , CA
USA
92008
Telephone: 7606032727
Email: dtribble@isisph.com

Lynn Ulatowski
Case Western Reserve University
School of Medicne Dept of Nutrition
2109 Adelbert Rd RT 600B
Cleveland, OH
USA
44106
Telephone: 2167028434
Email: lmu@po.cwru.edu

Tomas Vaisar
University of Washington
815 Mercer Street
Box 358055
Seattle, WA
USA
98195-8055
Telephone: 2066164972
Email: tvaisar@u.washington.edu

Thomas Vallim
UCLA
10966 Rochester Avenue
Apt 1D
Los Angeles, CA
USA
90024
Telephone: 3102068383
Email: tvallim@mednet.ucla.edu

Janine van Gils
New York University Medical Center
522 First Avenue, Smilow 707
New York, NY
USA
10016
Telephone: 2122639496
Email: janine.vangils@nyumc.org

Jean Vance
University of Alberta
328 HMRC, University of Alberta
Edmonton, AB
Canada
T6G 2S2
Telephone: 780492725
Email: jean.vance@ualberta.ca

Dennis Vance
University of Alberta
328 HMRC
Edmonton, AB
Canada
T6G 2S2
Telephone: 7804928286
Email: dennis.vance@ualberta.ca

Murielle Veniant
Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA
USA
91320
Telephone: 8054478009
Email: mveniant@amgen.com

Claudio Villanueva
UCLA
675 Charles E. Young Dr. S., MRL6629
Los Angeles, CA
USA
90095
Telephone: 3102064622
Email: cvillanueva@mednet.ucla.edu

Constance Voss
University of California Los Angeles
650 Charles E. Young Dr. South
A2-237 CHS Bldg.
Los Angeles, CA
USA
90095
Telephone: 3108259422
Email: cvoss@mednet.ucla.edu

Rosemary Walzem
Texas A&M University
2800 Longmire
Number 19
College Station, TX
USA
77845
Telephone: 9795750795
Email: rwalzem@poultry.tamu.edu

Steven Watkins
Tethys Bioscience, Inc.
3410 Industrial Blvd., Suite 103
Sacramento, CA
USA
95691
Telephone: 9163717974
Email: swatkins@tethysbio.com

Michael Weinstein
University of California, Los Angeles
695 Charles E. Young Dr
Gonda 4524
Los Angeles, CA
USA
90095
Telephone: 3102674380
Email: mweinste@ucla.edu

Cheryl Wellngton
University of British Columbia
980 West 28th Avenue
Vancouver, BC
Canada
V5S 4H$
Telephone: 6048752000
Email: cheryl@cmmt.ubc.ca

Philipp Wiesner
UCSD
9500 Gilman Drive
La Jolla, CA
USA
92093
Telephone: 8585344407
Email: pwiesner@ucsd.edu

Joseph Witztum
University California, San Diego
Biomedical Science Building,MC 0682
9500 Gilman Drive
La Jolla, CA
USA
92093
Telephone: 8585344347
Email: jwitztum@ucsd.edu

Kevin Wroblewski
UCLA
675 Charles E. Young Dr. S.
MRL 6629
Los Angeles, CA
USA
90095
Telephone: 3102064622
Email: wrobo85@ucla.edu

Lorraine Young
UCLA
Box 956957, 200 Med Plaza #450
Los Angeles, CA
USA
90095
Telephone: 3109173376
Email: lcyoung@mednet.ucla.edu

Stephen Young
UCLA
650 Charles E. Young Drive South
BH-307 CHS
Los Angeles, CA
USA
90095
Telephone: 3108254934
Email: sgyoung@mednet.ucla.edu

Li Zhang
UCLA
11423 Ohio Ave Apt 5
Los Angeles, CA
USA
90025
Telephone: 3102064622
Email: lizhang@mednet.ucla.edu

Mingyue Zhou
Amgen Inc.
1120 Veterans Blvd
San Francisco, CA
USA
94545
Telephone: 6502442280
Email: mzhou@amgen.com

Notes

SILVERADO.
NAPA VALLEY

Save the Date

2011 DEUEL Conference on Lipids
March 1 – 4, 2011

Silverado Resort, Napa Valley

2010 DEUEL Conference on Lipids
March 2-5, 2010
Dana Point, California