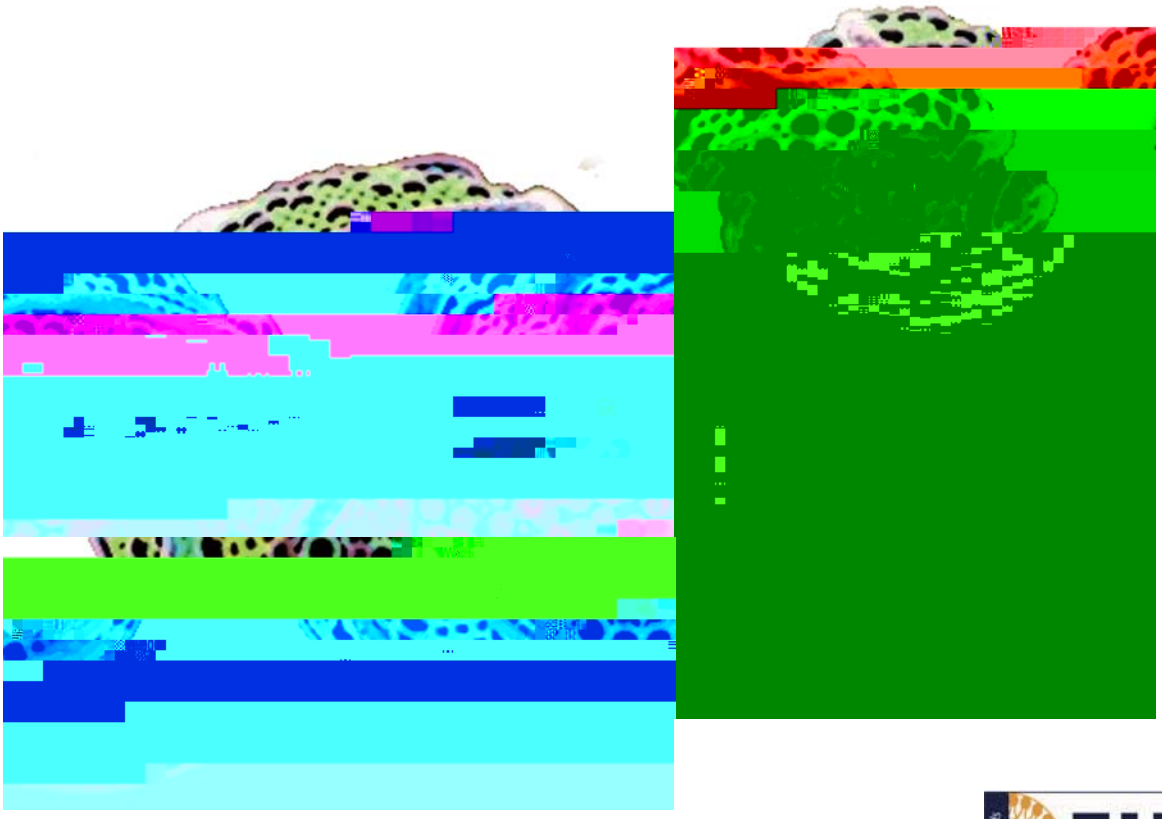
March 1-4, 2011

Napa Valley, California

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

DEUEL CONFERENCE ON LIPID



DEUEL Conference on Lipids

Thank You to Our

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2011 D C L , M 1-4, 2011
Silverado Resort, Napa Valley, California

CHEDULE

Wednesday, March 2

Wed e da , Ma c 2, 8:30 AM 12:00 PM

Session Chair: Jay Horton

1 O , M I R

8:30-9:15 "Surviving Starvation: Essential Role of the Ghrelin-Growth Hormone Axis"
J L. G , *U i e i f Te a S e e* , Dallas, TX

9:15-10:00 "Surviving Starvation: Essential Role of the Ghrelin-Growth Hormone Axis"
M .B , *U i e i f Te a S e e* , Dallas, TX

10:00-10:20 Co□ee Break

10:20-11:00 "Regulation and Function of Adipose Lipolysis"
H , *U i e i f Ca if ia*, Berkeley, CA

11:00-11:40 "New Insights Regarding the Structure and Function of GPIHBP1, an Endothelial Cell Protein Required for Lipolysis"
A B , *U i e i f Ca if ia*, Los Angeles, CA

11:40-12:00 "Ubxd8, a Sensor for Unsaturated Fatty Acids, Regulates Cellular Responses to Fatty Acids"
J , *U i e i f Te a S e e Medica Ce e* , Dallas, TX

Wed e da , Ma c 2, 7:30 8:30 PM

Session Chair: Jay Heinecke

H L

"Oxysterol Regulation of Macrophage Gene Expression",
C G , *U i e i f Ca if ia*, San Diego, CA
R P

Thursday, March 3

T da , Ma c 3, 8:30 AM 12:00 PM

Session Chair: Jay Horton

2 B

8:30-9:10 "Exploring in□ammatory links between obesity and type 2 diabetes"
A , *U i e i f Mic iga* , Ann Arbor, MI

9:10-9:50 "Evolutionary Conservation and Adaptation in the Mechanisms that Regulate SREBP Action"
O , *Sa f d-B a Medica Re ea c I i e*, Orlando, FL

9:50-10:20 Co□ee Break

10:20-11:00 "PNPLA3 to Pâté"
H H , *U i e i f Te a S e e* , Dallas, TX

11:00-11:40

J L R L

Introduction to the lecture - Steve Young, University of California, Los Angeles, CA
"A Mouse Resource for Systems Genetics: Application to Atherosclerosis"
J L , *U i e i f Ca if ia*, Los Angeles , CA

CHEDULE

1
Ubxd8, a Sensor for Unsaturated Fatty Acids, Regulates Cellular Responses to Fatty Acids

Jin Ye, Joon No Lee, Hyeonwoo Kim, and Hongbing Yao

Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX

Abstract:

n mammalian cells, fatty acids (FAs) are required for the synthesis of the phospholipid components of membranes and generation of energy. However, overaccumulation of FAs is toxic. When FAs accumulate in cells, they inhibit their own synthesis and enhance the incorporation of excess FAs into triglycerides (TGs) that are stored in lipid droplets. These regulatory functions are carried out by unsaturated but not saturated FAs. Here, we report that Ubxd8 is a sensor for unsaturated FAs that regulate cellular responses to FAs. In cells depleted of FAs, Ubxd8 binds to Insig-1, a reaction leads to proteasomal degradation of Insig-1. Inasmuch as Insig-1 inhibits proteolytic activation of sterol-regulatory element-binding protein (SREBP)-1, a transcription factor that activates all genes involved in FA synthesis, this reaction stimulates FA synthesis by promoting cleavage of SREBP-1. Ubxd8 also blocks TG synthesis by limiting the conversion of diacylglycerols (DAGs) to TGs in these cells as well. Thus, in cells deprived of FAs, the concerted regulatory actions of Ubxd8 make FAs available for incorporation into phospholipids by limiting their diversion into TGs. When long chain unsaturated FAs are supplied externally, these FAs change the structure of Ubxd8, promoting its polymerization, and inhibiting its activity. Consequently, Insig-1 is dissociated from Ubxd8 and stabilized so that FA synthesis is inhibited. Inhibition in TG synthesis is also relieved in these cells so that excess exogenous FAs are incorporated into TGs and stored in lipid droplets. Unlike unsaturated FAs, saturated FAs do not alter the structure of Ubxd8. As a result, saturated FAs are unable to inactivate Ubxd8 so that these FAs are channeled primarily into DAGs instead of TGs. Inasmuch as accumulation of DAGs is responsible for the development of insulin resistance, our studies suggest that Ubxd8 could be a novel drug target to relieve insulin resistance caused by excessive saturated FAs.

2

miR-33a/b contributes to the regulation of fatty acid metabolism and insulin signaling

Leigh Goedeke1, Alberto Davalos1, Cristina Ramirez-Hidalgo1, Peter Smibert2, Nikhil Warrier1, Ursula Andreo1, Daniel Cirera-Salinas1, 3, Katey Rayner1, Enric Esplugues3, 4, Edward Fisher1, Kathryn Moore1, Yajaira Suarez1, Eric Lai2, and Carlos Fernandez-Hernando1

1Department of Medicine and Cell Biology, New York University School of Medicine, New York, NY; 2Department of Developmental Biology, Sloan-Kettering Institute, New York, NY; 3German Rheumatism Research Center (DRFZ), a Leibniz Institute, Berlin, Germany; 4Department of Immunobiology, Yale University School of Medicine, New Haven, CT

Abstract:

Cellular imbalances of cholesterol and fatty acid metabolism result in pathological processes, including atherosclerosis and metabolic syndrome. Recent work from our group and others has shown that the intronic microRNAs (miRNAs), hsa-miR-33a and hsa-miR-33b, are located within the sterol-regulatory element-binding protein (SREBP) 2 and 1 genes, respectively, and regulate cholesterol homeostasis in concert with the their host genes. Here, we show that miR-33a/b also regulate genes involved in fatty acid metabolism and insulin signaling. miR-33a/b target key enzymes involved in the regulation of fatty acid oxidation, including CROT, CPT1a, HADHB, SIRT6 and AMPKα. Moreover, miR-33a/b also target the insulin receptor substrate 2 (IRS2), an essential component of the insulin-signaling pathway in the liver. Overexpression of miR-33a/b reduces both fatty acid oxidation and insulin signaling in hepatic cell lines, whereas inhibition of endogenous miR-33a/b increases these two metabolic pathways. Together, these data establish that miR-33a/b regulate pathways controlling three of the risk factors of metabolic syndrome, namely, levels of HDL, triglycerides, and insulin signaling, and suggest that inhibitors of miR-33a/b may be useful in the treatment of this growing health concern.

3

miR-758 Regulates Cholesterol E□ux through Posttranscriptional Repression of ABCA1

Cristina Ramírez-Hidalgo, Leigh Goedeke, Alberto Dávalos, Yajaira Suárez, and Carlos Fernández-Hernando

Departments of Medicine and Cell Biology, New York University School of Medicine, New York, NY

Abstract:

The ATP-binding cassette transporter A1 (ABCA1) is a major regulator of macrophage cholesterol e□ux and protects cells from excess of intracellular cholesterol accumulation. The mechanism involved in posttranscriptional regulation of ABCA1 is poorly understood. Thus, here we investigate the potential contribution of microRNAs to regulate ABCA1 and macrophage cholesterol e□ux posttranscriptionally. Based on an unbiased genome-wide screen of microRNA modulated by excess of cholesterol and quantitative real-time revers7(thr)hdulat(APCR,0(e r)9.8(e)-(ts c)5on□ e□)]T 61823511

4

Angptl4 Protects against Severe Proin□ammatory E□

5

Identi□cation of Compounds Reducing the Expression of Proprotein Convertase Subtilisin-like/Kexin Type 9 (PCSK9) as Therapy in the Treatment of Hypercholesterolemia

Dong-Kook Min1, 2, Hyun-Sook Lee1, 3, Chan-Ju Lee1, 2, and Sahng Wook Park1, 2

1Department of Biochemistry and Molecular Biology, 2Center for Chronic Metabolic Diseases, Brain Korea 21 Project, 3Bio-Medical Science Institute, Yonsei University College of Medicine, Seoul, Korea

Abstract:

roprotein convertase subtilisin/kexin type 9 (PCSK9), the ninth member of subtilisin serine protease, promotes the degradation of the LDL receptor, thereby increasing the plasma concentration of LDL-cholesterol. Several gain-of-function mutations of PCSK9 have been reported to cause a form of autosomal dominant hypercholesterolemia, whereas loss-of-function mutations cause hypocholesterolemia associated with a low incidence of coronary heart disease. These recent studies strongly suggest that inhibition of PCSK9 action is a potent therapeutic target of treatment of hypercholesterolemia. To inhibit PCSK9 action, we focused on screening the chemical library for identi□cation of compounds that reduce the amount of PCSK9 with a reciprocal increase in that of the LDL receptor. We selected a set of chemicals that have the core sca□old structure. The decrease in the amount of PCSK9 protein by these chemicals is supposed to be achieved at the transcriptional level of the PCSK9 gene. They increased uptake of □uorescence-labeled LDL particles in HepG2 cells. These bene□cial e□ects of increasing the uptake of LDL particles suggest that these chemicals could be implicated as a therapeutic modality to treat hypercholesterolemia. Evaluation of functionality in vivo is required for further study.

* This work was supported by National Research Foundation of Korea (NRF) Grants 2010-0028363 and 2010-0026376 funded by the Korean government (MEST).

6

Patterns and Associations of LDL during and after Pregnancy

Donald Tanyanyiwa1, David Marais2, Sheena Jones2, and Pam Byrnes2

1Chris Hani Baragwanath Hospital, Division of Chemical Pathology, Johannesburg, South Africa; 2University of Cape Town, Faculty of Health Sciences, Cape Town, South Africa

Abstract:

he aim of this study was to report the prevalence of various species of LDL in pregnancy and the association of LDL species with triglyceride concentration and apolipoprotein E (apoE) genotype. 595 women were studied at antenatal clinics, after obtaining informed consent and excluding women with diabetes. Blood for lipids and lipoproteins was taken during and at least 6 weeks after pregnancy. Nondenaturing gradient gel electrophoresis was employed to classify LDL species into ve categories named A, AI, I, IB, and B in decreasing sizes. Genotyping of apoE was done by polymerase chain reaction. Statistical analyses were done by nonparametric t tests and contingency tables; signi- cance was taken as $p < 0.0001$. The total cholesterol was signi cantly higher during pregnancy, 4.1 median (4.1-4.3 95% con dence interval) and 3.6 (3.5-3.6) (5 mmol/liter) and severe (>15 mmol/liter) hypertriglyceridemia occurred in 0.7 and 0.6% during pregnancy but was observed in the GGE of the 15 subjects with apoE 2/2 status. A relationship between hypertriglyceridemia and LDL species was observed.

7

Impact of Diabetes-associated LDL on Mitochondrial Respiration in Vascular Endothelial Cells

Garry Shen, Ganesh Sangle, Xueping Xie, and Subir Roy Chowdhury

University of Manitoba,Winnipeg, MB, Canada

Abstract:

Cardiovascular disease is the predominant cause of death in diabetic patients. Oxidative stress and endothelial dysfunction have been detected in vasculature of diabetic patients or animal models. Hyperglycemia and dyslipoproteinemia are biochemical markers for diabetes. Elevated levels of glycated LDL (gLDL) and oxidized LDL (oLDL) were frequently detected in diabetic patients. Our group reported that gLDL and oLDL increased the generation of reactive oxygen species (ROS) from vascular endothelial cells (EC). The present study demonstrated that gLDL and oLDL reduced oxygen consumption in mitochondrial electron transfer chain (mETC) Complex I and IV in porcine aortic EC. Treatment with gLDL or oLDL reduced mitochondrial membrane potential in EC, and inhibited the activities of NADH dehydrogenase (ND, Complex I), succinate cytochrome c reductase (Complex II), ubiquinol cytochrome c reductase (Complex III), and cytochrome c oxidase (Complex IV) in EC. Abundanced of ND1 and cytochrome b (a subunit of Complex III enzyme) in EC were reduced following incubation with gLDL or oLDL. Treatment with gLDL or oLDL increased the abundance of ROS-associated with mitochondria in EC detected using immunohistochemistry and confocal microscopy. The results suggest that diabetes-associated LDL may inhibit activities of mETC enzymes through reducing abundances of multiple subunits in mETC enzymes, which was associated with increase of ROS in mitochondria of EC. Impairment in mitochondrial respiration in EC induced by diabetes-associated LDL may contribute to oxidative stress and endothelial dysfunction in vasculature of diabetes.

8

Adnectin Proprotein Convertase Subtilisin-like/Kexin Type 9 (PCSK9) Antagonists Inhibit PCSK9 Function and Rapidly Reduce LDL-C in hPCSK9 Transgenic Mice and Cynomolgus Monkeys

Rex Parker1 and Tracy Mitchell2

1Bristol-Myers Squibb R & D, Princeton, NJ; 2Adnexus, a Bristol-Myers Squibb R & D Company, Waltham, MA

Abstract:

Adnectins are 12-kDa proteins derived from the 10th type 3 domain of human fibronectin. We use mRNA display to engineer Adnectins to bind pharmaceutical targets with high affinity and specificity and express and purify the Adnectin proteins from Escherichia coli. Using these techniques, we identified potent Adnectins that bind PCSK9 and antagonize PCSK9/EGFA (LDLR) interactions. These Adnectins were optimized for high affinity, biophysical properties, and low in silico immunogenicity. Adnectin 1 (ADN1) bound PCSK9 with KD <1 nM (human) and ~10 nM (cynomolgus) by SPR and did not bind mouse PCSK9 appreciably. ADN1 competitively displaced EGFA in FRET-based assays and inhibited PCSK9 activity in cell-based LDLR functional assays, with EC50 values consistent with the law of mass action for human and cyno PCSK9 (i.e., EC50 related to KD and target concentration in the assays). In a hypercholesterolemic, hyperexpressing transgenic hPCSK9 mouse model (from UT-SW), PEGylated ADN1 (ADN1-PEG given i.p.) reduced TC and LDL-C by ~35% within 3 h as free PCSK9 levels fell to near-zero and liver LDLR increased ~2-fold. In a genomic transgenic hPCSK9 mouse (BMS) expressing normal hPCSK9 levels, ADN1-PEG (i.p.) reduced free circulating hPCSK9 to near-zero within 30 min with EC50 ~0.01 mg/kg (i.p.), whereas total plasma hPCSK9 levels rose ~2-fold by 48 h. In normal cynomolgus monkeys, ADN1-PEG (5 mg/kg, i.v. or s.c.) rapidly reduced LDL-C and free PCSK9 in a dose-dependent manner, whereas other lipids were unaffected. LDL-C decreased ~50% within 48 h and returned to base line by 3 weeks, mirroring the free PCSK9 profile. Plasma total PCSK9 levels rose 3-5-fold and returned to base line by 3 weeks, suggesting that liver LDLR binding and endocytosis is a key physiological route of clearance for circulating PCSK9. These studies indicate that PCSK9 Adnectins are potent and effective PCSK9 antagonists in vitro and in vivo and demonstrate the dynamic role of circulating PCSK9 in LDL metabolism.

10

Apolipoprotein E Mediates Enhanced Plasma Cholesterol Clearance by Low Dose Streptococcal Serum Opacity Factor via Hepatic LDL Receptors in Vivo

Corina Rosales1, Daming Tang1, Baiba Gillard1, Harry Courtney2, and Henry Pownall

1Department of Medicine, Baylor College of Medicine, Houston, TX; 2Veterans A□airs Medical Center and Department of Medicine, University of Tennessee Health Science Center, Memphis, TN

Abstract:

erum opacity factor (SOF), a virulence determinant produced by the group A streptococcus, Streptococcus pyogenes, opaci□es human serum and is expressed by approximately half of the clinical isolates of S. pyogenes, an important human pathogen that causes pharyngitis, tonsilitis, impetigo, necrotizing fasciitis, and toxic shock syndrome. SOF opaci□es serum by disrupting HDL, its exclusive target, and forming a large cholesteryl ester-rich microemulsion (CERM; r ~100-200 nm), lipid-free (LF) apolipoprotein (apo)A-I and small neo-HDL that are cholesterol-poor and phospholipid-rich. The CERM contains apoE and its heterodimer with apoA-II as its sole proteins and the neutral lipids of ~400,000 HDL particles. Given the occurrence of apoE on the CERM, we tested the hypothesis that rSOF injection into mice would reduce total plasma cholesterol clearance via apoE-dependent hepatic LDL receptors (LDLR). rSOF (4 µg) injection into wild-type C57BL mice forms neo-HDL, CERM, and LF apoA-I, as observed in vitro, and reduced plasma total cholesterol (–43%, t1/2 = 44 ± 18 min) whereas control saline injections had a negligible e□ect. Similar experiments with apoE–/– and LDLR–/– mice, respectively, reduced plasma total cholesterol ~0 and 9%. rSOF is potent; injection of 0.18 µg of rSOF produces 50% of maximum reduction of plasma cholesterol 3 h after injection, corresponding to a ~0.5-mg human dose. Most cholesterol is cleared hepatically (>99%), with rSOF treatment increasing clearance by 65%. We conclude that intravenous injection of rSOF into mice forms a CERM that is readily cleared via hepatic LDLR that recognize apoE. Therapies based on the rSOF reaction have the potential to atheroprotect via enhanced reverse cholesterol transport.

12

Reactive Oxygen Species Are Implicated in the Mitogenic E□ect of Ceramide 1-Phosphate

Antonio Gomez-Munoz, Lide Arana, Alberto Ouro, and Patricia Gangoiti

University of the Basque Country, Bilbao, Spain

Abstract:

e reported previously that ceramide 1-phosphate (C1P) is mitogenic and antiapoptotic in macrophages. Major pathways involved in the stimulation of cell proliferation by C1P include mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinases (ERK1/2), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB, or Akt), c-Jun N-terminal kinase (JNK), and protein kinase C- . Here, we demonstrate that C1P induces reactive oxygen species (ROS) production through a mechanism involving NADPH oxidase activation. C1P-stimulated ROS generation was inhibited by apocynin, a potent NADPH oxidase inhibitor, and by the cell-permeable ROS scavenger N-acetylcysteine (NAC). In addition, C1P-stimulated ROS production was blocked by the protein kinase C (PKC) inhibitor Go6976, the PKC- inhibitor rottlerin, and by long term treatment with phorbol esters. Interestingly, a speci□c cytosolic phospholipase A2- inhibitor also blocked C1P-stimulated ROS production, and all of the ROS inhibitors blocked C1P-stimulated macrophage proliferation, suggesting that ROS are implicated in the mitogenic e□ect of C1P in macrophages.

14

Targeted Disruption of the Idol Gene Alters Cellular Regulation of the LDL Receptor by Sterols and LXR Agonists

Elena Scotti1, 2, 6, Cynthia Hong1, 2, Yuko Yoshinaga5, Yiping Tu4, Yan Hu4, Noam Zelcer1, 2, Rima Boyadjian1, 2, Pieter J. de Jong5, Stephen G. Young3, 4, Loren Fong4, and Peter Tontonoz1, 2

1Howard Hughes Medical Institute, 2Department of Pathology and Laboratory Medicine, 3Department of Human Genetics, 4Department of Medicine, UCLA, Los Angeles, CA; 5Children's Hospital Oakland Research Institute, Oakland, CA; 6Dipartimento di Scienze Farmacologiche, Università degli Studi di Milano, Milan, Italy

Abstract:

reviously, we identi□ed the E3 ubiquitin ligase Idol (inducible degrader of the LDL receptor) as a post-transcriptional regulator of the LDLR pathway. Idol stimulates LDLR degradation through ubiquitination of its C-terminal domain, thereby limiting cholesterol uptake. Here, we report the generation and characterization of mouse embryonic stem cells homozygous for a null mutation in the Idol gene. Cells lacking Idol exhibit markedly elevated levels of LDLR protein and increased rates of LDL degradation. Furthermore, despite an intact SREBP pathway, Idol-null cells exhibit an altered response to multiple regulators of sterol metabolism, including serum, oxysterols, and synthetic LXR agonists. The ability of oxysterols and lipoprotein-containing serum to suppress LDLR protein levels is reduced, and the time course of suppression is delayed, in cells lacking Idol. LXR ligands have no e□ect on LDLR levels in Idol-null cells, indicating that Idol is required for LXR-dependent inhibition of the identi□

15

Improved Sensitivity to Ezetimibe and Rosuvastatin following siRNA-mediated Knockdown of Proprotein Convertase Subtilisin-like/Kexin Type 9 (PCSK9) in Mice

Brandon Ason1, Samnang Tep1, Harry Davis Jr.2, Yiming Xu2, Glen Tetzlo□2, Beverly Galinski1, Ferdie Soriano1, Natalya Dubinina1, Lei Zhu3, Alice Stefanni2, Kenny Wong2, Marija Tadin-Strapps1, Steven Bartz1, Brian Hubbard2, Mollie Ranalletta2, Alan Sachs1, Mike Flanagan1, Alison Strack2, and Nelly Kuklin1

1Sirna Therapeutics/Merck & Co. Inc., San Francisco, CA; 2Department of Cardiovascular and Metabolic Disease Research, 3Department of Genetically Engineered Models, Merck Research Laboratories, Rahway, NJ

Abstract:

Elevated LDL cholesterol (LDL-c) is a risk factor for cardiovascular disease. Current treatments that reduce circulating LDL-c elevate serum PCSK9 (proprotein convertase subtilisin/kexin type 9a) in patients, which may attenuate their e□cacy by reducing the amount of LDL-c cleared from circulation. Using mice engineered to exhibit a human-like lipid pro□

16

17

HDL Is an Important Source for Hepatic Phosphatidylcholine and Triacylglycerol

Jelske van der Veen and Dennis Vance

Department of Biochemistry, University of Alberta, Edmonton, AB, Canada

Abstract:

Hepatic phosphatidylcholine (PC) is synthesized via the CDP-choline pathway, controlled by the activity of CTP:phosphocholine cytidylyltransferase (CT), and via sequential methylation of phosphatidylethanolamine through the action of phosphatidylethanolamine N-methyltransferase (PEMT). The liver can also obtain PC by uptake of circulating lipoproteins. In mice, the majority of circulating PC is associated with HDL. The current study has quantitated the importance of hepatic uptake of HDL-PC in vivo as well as its subsequent metabolism. We intravenously injected PEMT–/–, liver-specific CTα–/–, and their wild-type control mice with [3H]PC-labeled HDL. Hepatic uptake of HDL-PC was about 10 μmol/day in all mouse models, which is of the same order as hepatic de novo PC synthesis. In agreement, specific activities of PC in plasma and liver indicated that 50% of hepatic PC is derived from the circulation. Surprisingly, neither the absolute uptake of HDL-PC nor its relative contribution to total hepatic PC is affected by PEMT or CTα deficiency. Analysis of 3H radiolabel in the different lipid fractions of the liver showed that 33% of HDL-derived PC was converted into triacylglycerols. This process was unaffected in liver-specific Ctα–/– mice but increased to 49% in mice lacking PEMT. Importantly, approximately 65% of the total hepatic pool of triacylglycerol appears to be derived from PC. These data clearly show the quantitative importance of HDL-PC to the hepatic pool of PC as well as its significance as a precursor for hepatic triacylglycerol.

18

AB RAC

19

X-ray Crystal Structure of Proprotein Convertase Subtilisin-like/ Kexin Type 9 (PCSK9) in Complex with the LDL Receptor

Andrew Schumacher1, Jun Li1, Eric Hampton1, Julie-Ann Gavigan1, Waan-Jeng Huang2, David Yowe2, Sabine Geisse3, Jennifer Harris1, Scott Lesley1, and Glen Spraggon1

1Genomics Institute, Novartis Research Foundation, San Diego, CA; 2Novartis Institutes for Biomedical Research, Cambridge, MA; 3Novartis Institutes for Biomedical Research, Basel, Switzerland

Abstract:

20

Cardiac Dysfunction and Aberrant Phosphatidate Metabolism in the Lipin-1-de□cient Mouse

Bernard Kok1, Petra Kienesberger2, Jason Dyck2, and David Brindley1

1Signal Transduction Research Group, Department of Biochemistry, 2Cardiovascular Research Centre, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

Abstract:

he heart uses diverse substrates to produce energy, but when substrate utilization becomes in□exible, heart function inevitably deteriorates. For example, there are increased fatty acid (FA) oxidation and triglyceride (TG) levels in diabetes, which are associated with cardiac dysfunction. We are studying how the heart might coordinate the control of TG synthesis and FA oxidation through lipin-1. This protein provides the major cardiac phosphatidate phosphatase (PAP) activity, which is essential for synthesizing TG. Lipin-1 also acts with PGC-1α and PPARα to increase expression of FA oxidation genes. Despite the importance of lipin-1, little is known about its role in the heart. We hypothesize that lipin-1 de□ciency in fatty liver dystrophy (□d) mouse hearts would cause dysfunction due to decreased capabilities to esterify or oxidize FAs. Echocardiographic studies revealed cardiac dysfunction, speci□cally decreased ejection fraction and fractional shortening. We then measured FA esteri□cation and oxidation in ex vivo working perfused □d hearts. Surprisingly, □d hearts perfused with radiolabeled oleate have TG accumulation rates similar to those of controls. Decreased TG lipolysis due to decreased HSL activation and ATGL levels, in combination with decreased TG synthesis due to reduced PAP activities (20% of controls), explain this result. Rates of FA and glucose oxidation were not signi□cantly di□

21

Control of One-carbon Cycle Genes by SREBP-1 Links S-Adenosylmethionine Production, Phosphatidylcholine Biosynthesis, and Hepatic Lipogenesis

Amy Walker1, Rene Jacobs2, Jennifer Watts3, Veerle Rottiers1, Karen Jiang1, Deirdre Finnegan1, Toshi Shioda1, Malene Hansen4, Lorissa Niebergall2, Dennis Vance2, Anne Hart1, and Anders Naar1

1Massachusetts General Hospital Cancer Center, Boston, MA; 2Department of Agricultural, Food, and Nutritional Science, University of Alberta, Edmonton, AB, Canada; 3School of Molecular Biosciences, Washington State University, Pullman, WA; 4Sanford-Burnham Medical Research Institute, La Jolla, CA

Abstract:

Altered methionine/1-carbon cycle (1CC) metabolism has been linked to elevated hepatic lipogenesis and the development of liver steatosis; however, the mechanisms are unclear. We have found that the sterol regulatory element-binding protein-1 (SREBP-1), a transcriptional activator of fatty acid and phospholipid biosynthesis, also controls the expression of 1CC genes in Caenorhabditis elegans and mammals and in□uences the levels of the key 1CC product S-adenosylmethionine (SAMe), the major cellular methyl donor. SAMe is important for production of the membrane phospholipid phosphatidylcholine (PC), and we □nd that blocking SAMe production or PC biogenesis in C. elegans, mouse liver, and human cells causes depletion of PC and induces SREBP-1-dependent lipogenic transcription and accumulation of lipid droplets. In addition, we □nd that in HepG2 cells, blocking SAMe or PC production promotes loss of Golgi-speci□c localization of the SREBP-activating Site-1 and Site-2 proteases. This suggests that similar to brefeldin A-induced SREBP activation, reduction of PC lev

24

AB RAC

27

Cholesteryl Ester Transfer Protein Inhibition by Anacetrapib Results in Increased HDL and Bulk Cholesterol Excretion in Syrian Golden Hamsters

28

Myeloid-speci□c Estrogen Receptor- De□ciency Impairs Metabolic Homeostasis and Accelerates Atherosclerotic Lesion Development

Brian Drew1, Vicent Ribas1, Jamie Le1, Teo Soleymani1, Pedram Daraei1, Daniel Sitz1, Darren Henstridge2, Mark Febbraio2, Sylvia Hewitt3, Kenneth Korach3, and Andrea Hevener1

1UCLA, Los Angeles, CA; 2Baker IDI Heart & Diabetes Institute, Melbourne, Australia; 3NIEHS, National Institutes of Health, Research Triangle Park, NC

Abstract:

Estrogen receptor- (ER-) is readily expressed in macrophages and other immune cells, which are shown to exert dramatic e□ects on whole body glucose homeostasis and atherosclerosis development. Here, we investigated the impact of ER- expression on macrophage function to determine whether hematopoietic or myeloid cell-speci□c ER- deletion promotes obesity-induced insulin resistance. Mice harboring a hematopoietic or myeloid cell-speci□c deletion of Esr1 exhibit altered circulating adipokine levels, glucose intolerance, muscle insulin resistance, and increased adipose tissue mass. A similar obese phenotype and increased atherosclerotic lesion area were observed in LDL receptor (LDLR) knock-out mice transplanted with Esr1–/– bone marrow. In isolated macrophages, we □nd that ER- is necessary for the maintenance of oxidative metabolism, IL-4-mediated induction of alternative activation, and phagocytic capacity in response to oxidized LDL and lipopolysaccharide. In addition, we found that ER- is an important and direct regulator of macrophage transglutaminase 2 expression, a potent atheroprotective multifunctional enzyme. Taken together, our □ndings suggest that diminished ER- expression in hematopoietic/myeloid cells is causal for aspects of the metabolic syndrome and accelerates the development of atherosclerosis.

29

Structural and Functional Characterization of Spot 14

Chai-Wan Kim1, Christopher Colbert2, Young-Ah Moon1, William Mckean1, Hyock Kwon2, Johann Deisenhofer2, and Jay Horton

1Department of Molecular Genetics, 2Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX

Abstract:

pot14 (S14) is highly expressed in liver and is regulated by SREBP-1c, a transcription factor that activates all genes involved in fatty acid synthesis. S14 knock-out mice manifest decreased rates of fatty acid synthesis in mammary glands and increased rates of fatty acid synthesis in liver. The mechanism for the ability of S14 to modulate lipogenesis has not been elucidated. In a □rst step in further de□ning the function and mechanism of S14 action, we have determined the crystal structure of S14 to 2.65 Å. Additional biochemical studies reveal that S14 forms a heterodimer with MIG12, the only protein in the genome that shares signi□cant homology with S14. MIG12 can bind acetyl-CoA carbox-

30

Evaluating Hepatic Steatosis as a Risk Factor for 70% Partial Hepatectomy

Ji Ling1, Rene Jacobs3, Lin-Fu Zhu2, Todd Chaba4, Dennis Vance1

1Department of Biochemistry, 2Department of Surgery, 3Department of Agriculture, Food, and Nutritional Science, 4Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada

Abstract:

he process of liver regeneration is important for increasing the success rate of small-for-size liver transplants, grafts, and resections. A major risk factor for liver surgery is hepatic steatosis, which has been shown to increase the occurrence of postoperative morbidity and mortality. Hepatic steatosis is related to wide spectrum of diseases including obesity and diabetes. With the increasing prevalence of these diseases in the Western population today, it becomes important to perfect the current evaluation methods of livers slated for surgery and to develop therapies to improve the postoperative outcome in patients with hepatic steatosis. We used mice models of hepatic steatosis to answer these questions. Mice de□cient in phosphatidylethanolamine N-methyl transferase (PEMT) and mice de□cient speci□cally in hepatic phosphocholine cytidylyltransferase α (LCT-α) were fed a high fat diet for various lengths of time to stimulate varying grades of steatosis. 70% partial hepatectomy (PH) was then performed in these mice, and postoperative survival was monitored. Interestingly, we found the ratio of hepatic phosphatidylcholine (PC) to phosphatidylethanolamine (PE) to have a much higher correlation to the rate of survival after surgery than hepatic triacylglycerol (TG) levels. Histopathological evaluation further suggests that in□ammation more than steatosis may increase the risk of post-PH mortality. Finally, supplementation of additional choline to the diet in already steatotic PEMT-de□cient mice improved survival rate, decreased in□ammation, and increased hepatic PC:PE ratio but did not affect hepatic TG levels. In conclusion, other factors in addition to hepatic steatosis need to be considered in determining the risk of post-surgery complications. Furthermore, choline supplementation may be a viable therapy to improve liver regeneration in instances of elevated in□ammation or PEMT and choline de□ciency.

31

Syndecan-1 Shedding Reduces Clearance of Triglyceride-rich Lipoproteins by Human Hepatocytes and Causes Hypertriglyceridemia

Yiping Deng1, 2, Erin Foley1, Jon Gonzales1, Philip Gordts1, and Je□rey Esko1

1Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, CA; 2Key Laboratory of Pathobiology, Jilin University, Changchun, China

Abstract:

he heparan sulfate proteoglycan syndecan-1 mediates hepatic clearance of triglyceride-rich lipoproteins in mice based on systemic deletion of Sdc1 and hepatocyte-speci□c inactivation of heparan sulfate biosynthesis (MacArthur et al. (2007) J. Clin. Invest. 117, 153-164; Stanford et al. (2009) J. Clin. Invest. 119, 3236-3245; Stanford et al. (2010) J. Biol. Chem. 285, 286-294). Here, we show that syndecan-1 is expressed on primary human hepatocytes and Hep3B human hepatoma cells and can mediate binding and uptake of VLDL, based on heparin lyase inhibition and small interfering RNA (siRNA) directed against SDC1. We also show that syndecan-1 is spontaneously shed from primary human and murine hepatocytes and Hep3B cells. In human cells, syndecan-1 shedding was induced with phorbol myristic acid (PMA), resulting in 70-75% reduction of syndecan-1 expression on the cell surface and accumulation of syndecan-1 ectodomains in the medium. Shedding occurred through a protein kinase C-dependent activation of ADAM-17 (a disintegrin and metalloproteinase-17) based on pharmacological inhibition studies and siRNA-mediated silencing. PMA stimulation signi□cantly decreased diD-VLDL binding. Furthermore, the shed syndecan-1 ectodomains bound to VLDL based on an assay in which association of VLDL with 35S-labeled ectodomains caused a decrease in the buoyant density of the proteoglycan. Induction of Sdc1 shedding in mice by injection of lipopolysaccharide resulted in loss of hepatic Sdc1, accumulation of ectodomains in the plasma, and hypertriglyceridemia. Thus, shedding of syndecan-1 provides a mechanism that might explain hypertriglyceridemia in patients with sepsis or in patients undergoing therapeutic regimens that result in idiopathic hyperlipidemia.

32

CD36 and SR-A Contribute Similarly and Independently to Nonalcoholic Steatohepatitis in Hyperlipidemic Mice

Veerle Bieghs1, Fons Verheyen1, Patrick van Gorp1, Tim Hendrikx1, Kristiaan Wouters2, Dieter Lütjohann3, Marion Gijbels1, Maria Febbraio5, Christoph Binder4, Marten Hofker6, and Ronit Shiri-Sverdlov1

1Maastricht University Medical Center, Maastricht, The Netherlands; 2Université Lille Nord de France, Institut Pasteur de Lille , Lille, France; 3Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn, Germany; 4Medical University of Vienna, Vienna, Austria; 5Lerner Research Institute, Cleveland, OH; 6University Medical Center Groningen, Groningen, The Netherlands

Abstract:

he major feature of nonalcoholic steatohepatitis (NASH) is hepatic lipid accumulation in combination with in□ammation, which can further progress into □brosis and cirrhosis. Recently, we demonstrated that combined deletion of the two main scavenger receptors, CD36 and macrophage scavenger receptor 1 (MSR1), which are important for the uptake of modi□ed cholesterol-rich lipoproteins, reduced the initiation and progression of NASH. So far, the individual contributions of these receptors to NASH and the intracellular mechanisms by which they contribute to in□ammation have not been established. We hypothesize that CD36 and MSR1 contribute similarly and independently to the progression of diet-induced NASH. Ldlr–/– mice were lethally irradiated and transplanted with wild-type (WT), Cd36–/–, or Msr1–/– bone marrow and fed a Western diet for 3 months. Results showed that Cd36–/– and Msr1–/– transplanted (tp) mice showenths≈ET≈/G2duct-.1(c)5. Resa(in□)]T1ah(l-ra) micwro–/–,

33

Ezetimibe Exacerbates the Hypertriglyceridemia in Gpihbp1–/– Mice

Michael Weinstein, Anne Beigneux, Loren Fong, and Stephen Young

UCLA, Los Angeles, CA

Abstract:

Adult GPIHBP1-de□cient mice (Gpihbp1–/–) have severe hypertriglyceridemia; however, the plasma triglyceride

34

Identi□cation of Ubxd8 Protein as a Sensor for Unsaturated Fatty Acids and Regulator of Triglyceride Synthesis

Joon No Lee1, Hyeonwoo Kim1, Hongbing Yao1, Kayson Weng2, and Jin Ye1

1Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX; 2Department of Chemistry and Biochemistry, University of Texas, Austin, TX

Abstract:

atty acids (FAs) are essential for cell survival, yet their overaccumulation causes lipotoxicity. To prevent lipotoxicity, cells store excess FAs as triglycerides (TGs). In cultured cells, TG synthesis is activated by excess unsaturated but not saturated FAs. Here, we identify Ubxd8 as a sensor for unsaturated FAs and regulator of TG synthesis. In cultured cells depleted of FAs, Ubxd8 inhibits TG synthesis by blocking conversion of diacylglycerols (DAGs) to TGs. Excess unsaturated but not saturated FAs relieve this inhibition. As a result, unsaturated FAs are incorporated into TGs, whereas saturated FAs are incorporated into DAGs. In vitro, unsaturated but not saturated FAs alter the structure of puri□ed

35

Loss of ABCG1 Elicits a Natural Immune Response That May Protect from Atherosclerosis

Elizabeth Tarling1, Joseph Witztum2, Angel Baldan1, 3, and Peter Edwards1

1Departments of Biological Chemistry and Medicine, UCLA, Los Angeles, CA; Department of Medicine, University of California at San Diego, La Jolla, CA; 3Edward A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University, St. Louis, MO

Abstract:

he oxidation of LDL, a key event in the pathogenesis of atherosclerosis, generates multiple oxidation-speci□c neoepitopes, including malondialdehyde-modi□ed (MDA-modi□ed) LDL (MDA-LDL), and the phosphorylcholine (PC) head group of oxidized phospholipids (oxPL). These epitopes are recognized by natural germ line IgM antibodies that are secreted by B cells. We previously showed that mice lacking the ABC transporter, ABCG1, display signs of severe in□ammation in the lungs, associated with the accumulation of lipid-laden foam cells and cholesterol crystals, which are also characteristic of atherosclerotic lesions. We

36

Functional and Dysfunctional Structures of Apolipoprotein A-I in HDL

Jens Lagerstedt1, Giorgio Cavigiolio2, Megan Cochran4, Jitka Petrlova1, Angela Monterrubio4, Madhu Budamagunta3, Annika Axelsson1, Ioanna Pagani2, Linda Roberts4, John Voss3, and Michael Oda2

1Department of Experimental Medical Science, Lund University, Lund, Sweden; 2Children's Hospital Oakland Research Institute, Oakland, CA; 3Department of Biochemistry and Molecular Medicine, University of California, Davis, CA; 4Department of Chemistry, California State University, Sacramento, CA

Abstract:

Apolipoprotein A-I (apoA-I) is the major protein component of HDLs and a critical element in vascular health. The three-dimensional organization of this exchangeable lipoprotein is highly □exible and includes several structural subspecies that vary in oligomeric state and lipidation pro□le. We have previously used electron paramagnetic resonance (EPR) spectroscopy to describe the structural organization of the N-terminal domain of apoA-I in the lipid-free state (Lagerstedt et al. (2007) J. Biol. Chem. 282, 9143-9149). Here, we report on the structure of residues 6-98 on 9.6-nm rHDL and, at select sites, on 7.8- and 8.4-nm rHDL. Our analyses of 9.6-nm rHDL reveal a secondary structure composed of random coil and β-strand positioned between two α-helices. Further, we have identi□ed N-terminal residues important in apoA-I structural rearrangement that occur in response to changes in HDL lipid cargo and particle size. The structural conversion of this region in initial lipid loading will be discussed. In addition to functional apoA-I, several variants of apoA-I have been shown to form tissue-speci□c amyloid deposits in vivo. We previously characterized the N-terminal G26R variant, which possesses decreased stability and increased -structure typical of amyloid proteins (Lagerstedt et al. (2007) Biochemistry 46, 9693-9699). Currently, we are analyzing the structural properties of the C-terminal amyloid variant L178H (associated with cardiac and larynx amyloidosis) which, in similarity to G26R, exhibits decreased stability and an altered conformation. However, in contrast to G26R, the L178H variant acquires helical structure upon □bril formation and may thus represent a novel aggregation pathway.

37

Anacetrapib Stimulates Macrophage-to-feces Reverse Cholesterol Transport in the Dyslipidemic Syrian Golden Hamster

Douglas Johns1, Francois Briand2, Jose Castro-Perez1, Thierry Sulpice2, and Brian Hubbard1

1Department of Cardiovascular Diseases-Atherosclerosis, Merck Research Laboratories, Rahway NJ; 2Physiogenex, S.A.S., Prologue Biotech, Labege-Innopole cedex, France

Abstract:

Cholesteryl ester transfer protein (CETP) mediates transfer of cholesteryl ester and triglyceride between HDL and

38

Characterization of Proprotein Convertase Subtilisin-like/Kexin Type 9 (PCSK9) Secretion Mutant S462P: Fate of the Protein

Xi Ai1, Sookhee Ha2, Oksana Palyha1, Douglas Wisniewski3, Paul Fischer3, Ronald Painter3, Marina Ichetovkin1, Jing Xiao1, Jennifer Baysarowich3, Anka Ehrhardt3, Michael Kavana3, Brian Hubbard1, and Alison Strack1

1Department of Atherosclerosis, 2Department of Chemistry Modeling and Informatics, 3Department of in Vitro Pharmacology, Merck Research Laboratories, Rahway, NJ

Abstract:

roprotein convertase subtilisin-like/kexin type 9 (PCSK9) is an attractive target for treatment of dyslipidemia. It secretes and binds to LDL receptors (LDLRs) and subsequently directs the LDLR to lysosomes for degradation in the liver, therefore controlling the level of LDL in plasma. Various naturally occurring PCSK9 gain-of-function (GOF) or loss-of-function (LOF) mutants have been identi□ed. Among them, S462P, a LOF mutant, is defective on PCSK9 secretion. In the current study, we investigated the possible mechanism of action of the S462P mutant utilizing biochemistry and imaging approaches as well as protein modeling tools. Stable cell lines expressing wild-type PCSK9, S462P, or S462A mutant were established in HEK293 cells. S462 is located in the loop of the C-terminal domain that interfaces with the catalytic domain. The side chain OH of Ser-462 appears to stabilize the local region via hydrogen bonds to the backbone NH of Ala-522 and backbone C=O of Ala-423. Mutation of Ser to Pro would eliminate those two strong hydrogen bonds and introduce a bulky Pro ring that may cause misfolding; mutation of Ser to Ala also causes elimination of hydrogen bonds; however, sterically it may be possible to maintain the folding structure. Quantitative Western blotting revealed that the S462P mutant is cleaved to the same extent as the wild-type and S462A mutant; however, most S462P protein stayed in the cytosol; only a small amount is secreted. Imaging analysis indicated that the S462P protein is mostly trapped in the endoplasmic reticulum during protein tra□cking. Protein puri□ed from the medium showed in vitro functional activity similar to that of the wild-type PCSK9. Di□culty in purifying the active form of protein from the cell lysate suggests improper folding. Further characterization is ongoing to investigate markers of endoplasmic reticulum stress in association with S462P-containing HEK293 cells.

39

Measuring the E□ect of the Membrane Environment on Choles-

40

Evidence for Nondetectable Cholesteryl Ester Transfer Protein Expression in Parenchymal Cells of Human Liver and Adipose Tissues using Immunohistochemistry

Douglas Johns, Emmanuel Zycband, Vivenne Mendoza, Pan Yi, Shilpa Pandit, Jing Li, Brian Hubbard, and Yonghua Zhu

Department of Cardiovascular Diseases-Atherosclerosis, Merck Research Laboratories, Rahway NJ

Abstract:

Cholesteryl ester transfer protein (CETP) mediates transfer of cholesteryl ester and triglyceride between HDLs and LDLs and currently is a target for dyslipidemia and coronary artery disease. Although CETP is known to circulate in plasma, historically the study of tissue distribution of CETP expression is limited to studies examining mRNA measurement in in vitro systems. Such studies suggested that nonhuman primate CETP mRNA expression in the liver occurs in nonparenchymal (nonhepatocyte) cells. In the current study, we sought to determine the cell type responsible for CETP expression in human liver and adipose tissue, using immunohistochemical methods. Immunohistochemistry was performed using three speci□c mouse anti-human CETP monoclonal antibodies, TP1, TP2, and TP20, which recognize di□erent segments of human CETP. In normal human liver, CETP was expressed in nonparenchymal cells of the liver sinusoid, whereas no CETP was found in parenchymal cells and biliary epithelial cells. Double immuno□uorescence staining demonstrated that CETP-expressing cells were co-localized with CD68, a macrophage/Kup□er cell marker, in the liver. In human adipose tissue, CETP expression was not detected in adipocytes but rather in stromal cells, although additional studies are required to identify the type of stromal cell. These studies describe the in situ expression pattern for CETP in human liver and adipose tissue. Once the location of CETP tissue expression is determined, future studies may focus on the role of resident tissue CETP activity and its contribution to cholesterol homeostasis both under normal and diseased states.

42

Proprotein Convertase Subtilisin-like/Kexin Type 9 (PCSK9)-mediated Regulation of LDL Receptor in the Mouse Enterocyte

Alison Strack, Jing Xiao, Sheng-Ping Wang, Paul Fischer, Anka Ehrhardt, Yan Cui, Yonghua Zhu, Denise Milot, Liwen Zhang, and Brian Hubbard

Merck Research Laboratories, Rahway, NJ

Abstract:

roprotein convertase subtilisin-like/kexin type 9 (PCSK9) has been demonstrated by others to be present in the gut as well as in the liver. We examined the role of PCSK9 on LDL receptor regulation in the mouse small intestine. First, we studied immunohistochemical examination of the ileum in the wild-type C57BL/6 mouse and the PCSK9–/– mice. In the normal, wild-type mouse, the LDLR is localized predominantly on the basolateral membrane. In the PCSK9–/– mouse, a signi

43

E□ect of Anacetrapib Treatment on HDL Function: Anti-in□amma-tory Response on Endothelial Cells and Promoting -Cell Func-tion

Seongah Han1, Yue Feng2, Paul Fisher3, Lauretta LeVoci1, Kathleen Bierilo1, Mihajlo Krsmanovic1, Sheng-Ping Wang1, Yun-Ping Zhou2, Anka Ehrhardt3, Douglas Johns1, Brian Hubbard1, and Timothy Fisher1

1Department of Cardiovascular Diseases, 2Department of Diabetes, 3Department of in Vitro Pharmacology, Merck Research Laboratories, Rahway, NJ

Abstract:

DL cholesterol levels are inversely related to the development of coronary heart disease. Cholesteryl ester trans-fer protein (CETP) is a plasma protein that facilitates the transport of cholesteryl esters from HDL to apoB-containing lipoproteins. Thus, CETP inhibition has been identi□ed as a potential strategy of raising HDL cholesterol levels for the treatment of atherosclerotic vascular disease. Recent studies suggest a number of potential atheroprotective func-tions of HDL. The objective of this study was to evaluate two potential aspects of HDL: anti-in□ammatory e□ects on endothelial cells and improving pancreatic β-cell function. Speci□cally, we wanted to determine whether CETP inhib-itor-treated HDL maintains proper function. Human, hamster, and anacetrapib-treated hamster HDL samples were isolated by ultracentrifugation, and their ability to suppress endothelial in□ammation and promote β-cell function was determined. HDL demonstrated anti-in□ammatory e□ects of reducing expression of cell adhesion molecules in human artery endothelial cells (HAEC). Both human and hamster HDL inhibited TNFα-induced expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. Moreover, HDL from anacetrapib-treated hamsters maintained the ability to suppress in□ammatory responses in HAEC. The e□ect of HDL to promote insulin secretion was tested using primary β-cells. HDL increased glucose-stimulated insulin secretion by both hamster and human islets. These studies demonstrate that anacetrapib treatment maintains the potent ability of HDL to suppress an endothelial cell in□ammatory response. In addition, both human and hamster HDL promoted β-cell function. Additional studies to determine the e□ect of anacetrapib treatment on the ability of HDL to promote β-cell function are currently ongoing. The present studies indicate that anacetrapib treatment maintains proper HDL function.

44

Coordinately Regulated Alternative Splicing of Genes Involved in Cholesterol Biosynthesis and Uptake

Marisa Medina1, Feng Gao1, Devesh Naidoo1, Lawrence Rudel2, Ryan Temel2, Allison McDaniel2, Stephanie Marshall2, and Ronald Krauss1

1Children's Hospital Oakland Research Institute, Oakland, CA; 2Wake Forest University Health Sciences, Winston-Salem, NC

Abstract:

enes involved in cholesterol biosynthesis and uptake are transcriptionally regulated in response to cellular sterol content in a coordinated manner. A number of these genes, including 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and LDL receptor (LDLR), have been reported to undergo alternative splicing in a manner that results in reductions of enzyme or protein activity. Here, we demonstrate that cellular sterol depletion suppresses, and sterol loading induces, alternative splicing of multiple genes involved in the maintenance of cholesterol homeostasis including HMGCR and LDLR, the key regulators of cellular cholesterol biosynthesis and uptake, respectively. These changes were observed in both in vitro studies of the HepG2 human hepatoma-derived cell line, as well as in vivo studies of St. Kitts vervets. These e□ects are mediated in part by sterol regulation of polypyrimidine tract-binding protein 1 (PTBP1) because knockdown of PTBP1 eliminates sterol-induced changes in alternative splicing of several of these genes. Single-nucleotide polymorphisms (SNPs) that in□uence HMGCR and LDLR alternative splicing (rs3846662 and rs688, respectively), have been associated with variation in plasma LDL-cholesterol levels. Sterol-induced changes in alternative splicing are blunted in carriers of the minor alleles for each of these SNPs, indicating an interaction between genetic and nongenetic regulation of this process. Our results implicate alternative splicing as a novel mechanism of enhancing the robust transcriptional response to conditions of cellular cholesterol depletion or accumulation. Thus, coordinated regulation of alternative splicing may contribute to cellular cholesterol homeostasis as well as plasma LDL levels.

45

Does VLDL or Chylomicron Secretion Contribute to Lowered Plasma Lipids in Apolipoprotein A-IV Knock-out Animals?

Alison Kohan, Fei Wang, Xiaoming Li, and Patrick Tso

University of Cincinnati, Cincinnati OH

Abstract:

Many functions have been attributed to intestinal apolipoprotein A-IV (apoA-IV), an intestinally derived apolipoprotein secreted in response to fat in the diet, including its role as an antioxidant, an anti-inflammatory factor, and a mediator of reverse-cholesterol transport. Although these are important functions of apoA-IV, these are also ascribed to other apolipoproteins. We have demonstrated that apoA-IV plays a role in mediating triglyceride (TG) and cholesterol homeostasis in plasma. Loss of apoA-IV causes a significant decrease in plasma lipid levels in mice maintained on a chow diet, confirming the findings of Breslow et al. (1997). Further, apoA-IV knock-out mice are resistant to high fat diet-induced increases in plasma TG and cholesterol. The lowered plasma lipids in apoA-IV knock-out mice are not due to differences in body weight, because apoA-IV knock-out and wild-type animals have comparable body weights. Additionally, apoA-IV knock-out mice have a total fat mass to body weight ratio that is comparable to that of wild-type mice on the same diet. Loss of apoA-IV does not cause mice to develop fatty liver on chow, low fat, or high fat diets. Finally, apoA-IV knock-out mice do not have altered TG-rich lipoprotein secretion from the liver. This function for intestinally derived apoA-IV strongly suggests that apoA-IV plays a previously unknown role in the regulation of plasma lipid levels. We have recently determined that the loss of apoA-IV does not affect absorption of TG or cholesterol from the intestine into lymph. Whether apoA-IV affects chylomicron metabolism is the focus of ongoing experiments.

46

E□ects of Small Interfering RNA-mediated Hepatic Glucagon Receptor Inhibition on Glucose and Lipid Metabolism in db/db Mice

Seongah Han1, Taro Akiyama2, Hong-ping Guan2, Beth Murphy3, Walter Strapps4, Brian Hubbard1, Cai Li2, and Jing Li1

1Department of Cardiovascular Diseases, 2Department of Diabetes, 3Department of Central Pharmacology, Merck Research Laboratories, Rahway, NJ; 4Sirna Lead Development, Sirna Therapeutics, San Francisco, CA

Abstract:

epatic glucose overproduction is one of the major characteristics of type 2 diabetes. Glucagon is a key regulator for glucose homeostasis. Inhibition of glucagon activity by inhibition of glucagon receptor (GCGR) has been considered as one of the therapeutic strategies for the treatment of diabetes mellitus. To study the e□ects of hepatic GCGR inhibition on glucose metabolism in a diabetic mouse model, small interfering RNA (siRNA) targeting GCGR was introduced to db/db mice by tail vein injection. Knocking down of GCGR reduced plasma glucose levels but also increased plasma cholesterol levels. Hepatic lipid contents in si-GCGR-treated animals were also increased. Detailed lipid analysis showed that increased plasma cholesterol was due to an increase of LDL, but VLDL or HDL fractions were not changed. Taqman analysis of liver samples indicated that the mRNA expression levels of gluconeogenic genes were reduced, whereas the mRNA levels of the genes associated with fatty acid and cholesterol biosynthesis were increased in si-GCGR-treated mice. Because alterations in glucagon levels have been associated with changes in serum lipid levels, these □ndings provided additional insight on the role of GCGR in hepatic glucose output. Additional studies around lipid synthesis and clearance in these siRNA-treated mice are currently ongoing. Further understanding of glucagon/GCGR e□ects in glucose and lipid metabolism could lead to the identi□cation of novel therapeutic strategies to treat hyperglycemia without causing lipid abnormalities.

47

Insights into Triglyceride-rich Lipoprotein Assembly from Drop Tensiometry

Matthew Mitsche and Donald Small

Boston University, Boston, MA

Abstract:

Apolipoprotein B-100 (apoB) is the principal protein component of LDL, commonly known as "bad cholesterol." The N-terminal ~1,000 amino acids of apoB, called the βa1 superdomain, co-translationally recruit neutral lipids for the assembly of triglyceride-rich lipoproteins. The βa1 superdomain contains four subdomains and is predicted to interact directly with lipids while retaining its tertiary structure. Using drop tensiometry, we examined the interfacial properties of the second and third domains, called the -helical (amino acids 316-636) and C-sheet (amino acids 636-787) domains, and their subdomains to establish their structure-function relationship at a hydrophobic interface. We studied the adsorption, stress response, viscoelasticity, exchangeability, and pressure-area relationship at both a TO/W and TO/POPC/W interface. The -helical domain spontaneously adsorbs to a TO/W interface and forms a viscoelastic surface. It is anchored to the surface by helix 6 and remodels on the surface as a function of surface pressure. The C-sheet forms an elastic lm on a TO/W interface and is irreversibly anchored to a lipid surface, which is consistent with the behavior of an amphipathic β-sheet. The exclusion pressure at a TO/POPC/W interface of the -helical domain is 22 ± 1.5 mN/m, whereas the C-sheet is ~17 ± 1 mN/m. When both domains are adsorbed together to the surface, the C-sheet shields a portion of the -helical domain from the surface, which may retain its globular structure. We used these as well as other insights to develop a molecular level model of co-translational triglyceride recruitment by apoB.

48

Birth of Lipid Droplets: A Mammalian System for Induced Lipid Droplet Formation

Joel Haas1, 2, Charles Harris1, 3, Caroline Mrejen1, and Robert Farese, Jr.1, 2, 3

1Gladstone Institute of Cardiovascular Disease, San Francisco, CA; 2Department of Biochemistry and Biophysics, 3Department of Medicine, University of California, San Francisco, CA

Abstract:

he lipid droplet (LD) is a dynamic and ubiquitous organelle that is central to cellular energy homeostasis. Despite their importance, almost nothing is known about how LDs form. The working model suggests that neutral lipids (sterol esters and triacylglycerols) coalesce locally in subdomains of the endoplasmic reticulum (ER) bilayer. These collections of neutral lipids then separate from the ER and localize to the cytosol where they are coated by a phospholipid monolayer and a number of speci□c proteins. This model raises two key questions: (1) What cellular components organize sites of LD formation? (2) How is the LD monolayer separated from a bilayer while maintaining is iT*≈8Js

49

CYP27: A Novel Player in Diet-induced Nonalcoholic Steatohepatitis

Veerle Bieghs1, Patrick van Gorp1, Tim Hendrikx1, Fons Verheyen1, Marion Gijbels1, Eran Leitersdorf2, Marten Hofker3, Dieter Lütjohann4, and Ronit Shiri-Sverdlov1

1Maastricht University Medical Center, Maastricht, The Netherlands; 2Hebrew University Medical School, Jerusalem,

51

Apolipoprotein E Reduces Atherosclerosis Independently of Lowering Plasma Cholesterol by Suppressing In□ammation in Circulating Leukocytes and Vascular Endothelium

Robert Ra□ai1, 2, Nathalie Gaudreault1, 2, Nikit Kumar1, Jessica Posada1, Soledad de Mochel1, Delphine Eberle1, 2, Kyle Stephens1, Roy Kim1, Matthew Harms1, Amy Johnson1, Victor Olivas1, Louis Messina3, and Joseph Rapp1, 2

1Veterans A□airs Medical Center, San Francisco, CA; 2Department of Surgery, University of California, San Francisco, CA; 3Department of Surgery, University of Massachusetts, Worcester, MA

Abstract:

e sought to investigate mechanisms by which apolipoprotein (apoE) E can suppress atherosclerosis beyond reducing plasma cholesterol. To this end, we bred hypomorphic apoE (Apoeh/h) mice to Ldlr–/– mice to derive Apoeh/hLdlr–/– mice. When fed a chow diet, Apoeh/hLdlr–/– mice displayed plasma cholesterol levels that were similar to those of chow-fed Apoe–/–Ldlr–/– mice (597.5 ± 24.3 mg/dl vs. 662.4 ± 26.4 mg/dl, respectively), despite accumulating 4-fold more plasma apoE than wild-type mice. By 20 weeks of age, Apoeh/hLdlr–/– mice developed ~4-fold less Oil Red O- and ~3-fold less macrophage-positive surface area in the aortic root than Apoe–/–Ldlr–/– mice. Apoeh/hLdlr–/– mice displayed reduced endothelial activation, with reduced expression of ICAM-1 (1.28-fold less), PECAM-1 (4.5-fold less), and JAM-A (11-fold less) as assessed by confocal microscopy of en face preparations of the aortic arch derived from 14-week-old mice of both groups. By 20 weeks of age, Apoeh/hLdlr–/– mice displayed 30% fewer circulating blood leukocytes and 10% fewer proin□ammatory Ly6C-hi monocytes. They also displayed .2(yt)25er proin.8352 0 T0yt

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52

Lipoprotein Sizing Comparison among Di□erent Analytical Platforms: Is There a Technique That Fits All?

Jose Castro-Perez, Timothy Fisher, Kathy Bierilo, Lyndon Mitnaul, Douglas Johns, Thomas Roddy, and Brian Hubbard

Department of Atherosclerosis Research, Merck Research Laboratories, Rahway, NJ

Abstract:

ecently, there has been much discussion as to which analytical platform is the most appropriate for lipoprotein sizing/measurement. Because the outputs from these measurements are routinely used for the diagnosis and management of hypercholesterolemia and coronary cardiovascular events, this has been a very hot topic in the cardiovascular disease arena. Di□erent methods have been utilized for the measurement of lipoproteins such as ultracentrifugation (UC), vertical autopro□

53

Systems Genetics-based Approach to Study Obesity in Mice

Brian Parks, Margarete Mehrabian, Elizabeth Nam, Brian Bennett, and Aldons Lusis

UCLA, Los Angeles, CA

Abstract:

besity is a polygenic disease with a complex etiology involving multiple genetic and environmental factors. In addition to these factors, recent studies have highlighted important roles for both the immune system and the microbiome in contributing to obesity in humans and mice. To understand the complex molecular interactions contributing to obesity we are using a powerful systems genetics resource, the Hybrid Mouse Diversity Panel (HMDP), which enables high resolution genetic mapping and integration of multiple high-throughput "-omics" data sets, such as transcriptomics and metabolomics. The HMDP is composed of commercially available, classical, and recombinant inbred strains of mice (~100 strains total), which takes advantage of common genetic variations that exists among inbred mice strains. Obesity will be assessed in mice fed a high fat or normal chow diet for 8 weeks (starting at 8 weeks of age), followed by extensive phenotyping (body weight, lean/fat mass, plasma lipids, etc.). To address immune system and microbiota contributions to obesity we are performing high throughput ow cytometry analysis of lymphoid and myeloid cell types in the periphery and within visceral adipose tissue. Gut microbial diversity is being measured using 454 pyrosequencing, which enables precise determination of the microbial community. Data collected thus far show robust weight gain with a high fat diet and signi cant strain variation for all traits measured. Collectively, these data will provide the rst comprehensive analysis of gene by environmental interactions contributing to obesity across multiple scales of biology (DNA, RNA, protein, metabolites, microbiota) and will allow the dissection of complex interactions in obese and lean settings.

56

E□ects of Postprandial Triglyceride-rich Lipoprotein Lipolysis Products on Kidney Injury

57

LDL-c Lowering in Rhesus Monkeys by Subcutaneous Administration of a Monoclonal Anti-proprotein Convertase Subtilisin-like/Kexin Type 9 (PCSK9) Antibody

Daniël Blom1, Ayesha Sitlani3, Marina Ichetovkin1, Neil Geoghagen1, Doug Johns1, Sheng-ping Wang1, Ray Rosa1, Vivienne Mendoza1, Yan Ni1, Shilpa Pandit1, Liwen Zhang1, Weirong Wang4, Jeanette Roman5, Wolfgang Seghezzi3, Melinda Marian3, Brittany Paporello3, Harry Davis2, Joe Hedrick, Jon Condra, Diane Hollenbaugh, Andy Plump1, and Brian Hubbard1

1Department of Cardiovascular Diseases, 2Department of in Vivo Pharmacology, Merck Research Laboratories, Rahway, NJ; 3Biologics Research, Palo Alto, CA, Union, NJ, and Rahway, NJ; 4Development DMPK, West Point, PA; 5Vaccine Analytical Development, West Point, PA

Abstract:

roprotein convertase subtilisin-like/kexin type 9 (PCSK9) has recently emerged as a major regulator of plasma LDL cholesterol (LDL-c) and consequently as a promising therapeutic target for treating coronary heart disease (CHD) (1-4). Inhibitors of the cell surface PCSK9-LDLR interaction are expected to enhance LDL-c clearance and lower circulating levels of LDL-c. Several lines of preclinical and clinical data validate the development of an anti-PCSK9 monoclonal antibody (mAb) as an e□ective therapeutic agent for LDL-c lowering in the clinic (5-8). We identi□ed a human monoclonal antibody (mAb8) that binds to human, murine, and Rhesus PCSK9 with low nanomolar a□nity (6.8, 2.8, and 2.2 nM, respectively) and that potently inhibits the PCSK9 functional e□ects in a HepG2 cell-based LDL-c uptake assay (EC50: 9 nM). mAb8 e□ciently lowered LDL-c in CETP/LDLR+/– mice upon administration of a single, 3 mpk dose (>20% for 5 days). E□cient lowering of plasma LDL-c (>25%) was also obtained by subcutaneous administration of 1 mpk mAb8 in Rhesus monkeys, which lasted for 45 days. A subsequent study in normal Rhesus monkeys showed a shorter duration of action for this mAb, in the same dosing paradigm. Analysis of LDL-c levels showed di□erences in base-line levels in these Rhesus monkeys that correlated with the duration of LDL-c lowering caused by mAb8. Our results show e□cacy of the monoclonal antibody mAb8 in Rhesus monkeys and suggest that base-line LDL-c levels may be of importance for the duration of e□cacy.

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DEUEL B M

C

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

M

Ira A. Tabas, M.D., Ph.D. (Chair, 2010)
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

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 Ge□en 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

John S. Parks (2015)
Department of Pathology/ Section on Lipid Sciences
Lipid Sciences Research Program
Richard H. Dean Biomedical Research Bld, Rm 333
Wake Forest University Health Sciences
Medical Center Blvd
Winston-Salem, NC 27157
Tel: 336-716-2145
Fax: 336-716-6279
Email: jparks@wfubmc.edu

Kathryn J. Moore (2015)
Associate Professor of Medicine
The Leon H. Charney Division of Cardiology Marc and Ruti Bell Program in Vascular Biology
New York University Medical Center
522 First Avenue, Smilow 705
New York, NY 10016
Tel.: 212-263-9259
Fax: 212-263-9115
Email: kathryn.moore@nyumc.org

Tim Osborne (2015)
Professor and Director of Metabolic Signaling and Disease
Sanford-Burnham Medical
Research Institute
6400 Sanger Rd
Orlando, FL 32827
Tel.: 407-745-2098
Fax: 407-745-2001
Email: tosborne@burnham.org

Daniel J. Rader (2015)
University of Pennsylvania
654 BRBII/III
421 Curie Blvd.
Philadelphia, PA 19104
Tel.: 215-573-4176
Fax: 215-573-8606
Email: rader@mail.med.upenn.edu

Guoqing Cao(2015)
Lilly Research Laboratories
359 Merrill Street
Indianapolis, IN 46285
Tel.: 317-433-3535
Fax: 317-433-2815
Email: guoqing_cao@lilly.com

/F
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

L A
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

P C C
Jay Heinecke, M.D. (Co-Chair, 2011)
University of Washington
Department of Medicine
HSB BB512, Box 356426
1959 NE Paci□c Street
Seattle, WA 98195
Tel: (206) 543-3158
FAX: (206) 685-3781
Email: heinecke@u.washington.edu

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

Karin Bornfeldt (2012)
Department of Pathology
Room E-501, Health Sciences Bldg.
University of Washington
University of el(tmw(8a(Unso p4(Uni0-9J≈T*≈8 Tc≈06u61006 s1 Tc≈-.0001 Tw≈[(Email: ja)85h(ja)85h(ja)8ohQy of0 TcTc≈0 Tw(elBBBBB5cr)1)-9(yilT*≈

C A

Xi Ai
Merck Research Laboratory
RY80T-100
126 E. Lincoln Ave.
Rahway, NJ
USA
07065
ph: 7325942286
e: xi_ai@merck.com

Alfred Alberts
Merck (retired)
156 Brewster Rd.
Wycko□, NJ
USA
07481
ph: 2016708330
e: aalberts@optonline.net

Louis Alvarez
Merck
437 Marshall Road
Southlake, TX
USA
76092
ph: 6023500799
e: louis_alvarez@merck.com

Teddi Anderson-Curry
Merck
167 Hillview Dr.
Vacaville, CA
USA
95688
ph: 7072914320
e: teddi_anderson_curry@merck.com

Jesus Araujo
University of California, Los Angeles
10833 Le Conte Avenue
Los Angeles, CA
USA
90066
ph: 3108253222
e: JAraujo@mednet.ucla.edu

Brandon Ason
Sirna Therapeutics/ Merck & Co. Inc.
1700 Owens St., 4th Flr.
San Francisco, CA
USA
94131
ph: 4158148418
e: brandon_ason@merck.com

Salman Azhar
VA Palo Alto Health Care System
GRECC, Bldg. 4
3801 Miranda Ave., MC 182-B
Palo Alto, CA
USA
94304-1207
ph: 6508583933
e: salman.azhar@med.va.gov

Simon Beaven
UCLA
10833 Le Conte Ave.
CHS 44-138
Los Angeles, CA
USA
90095-1684
ph: 3108251568
e: sbeaven@mednet.ucla.edu

Anne Beigneux
UCLA
A2-237 Center for Health Sciences
650 Charles E. Young Drive South
Los Angeles, CA
USA
90095
ph: 3108259422
e: abeigneux@mednet.ucla.edu

Andre Bensadoun
Cornell University
Division of Nutritional Sciences
321 Savage Hall
Ithaca, NY
USA
14853-0001
ph: 6075929904
e: AB55@Cornell.edu

Steven Bensinger
UCLA School of Medicine
36-120 CHS
Box 951735
Los Angeles, CA
USA
90095-1435
ph: 3108259885
e: sbensinger@mednet.ucla.edu

Sudha Biddinger
Children's Hospital Boston
300 Longwood Ave.
Boston, MA
USA
02115
ph: 6179192864
e: sudha.biddinger@childrens.harvard.edu
Veerle Bieghs

Maastricht University
Universiteitssingel 50
Maastricht
Netherlands
6229ER
ph: 31433881697
e: v.bieghs@maastrichtuniversity.nl

Agata Bielska
Washington University School of Medicine
660 S. Euclid Ave.
Campus Box 8086
St. Louis, MO
USA
63110
ph: 3143628732
e: bielskaa@wusm.wustl.edu

Daniel Blom
Merck & Co, Inc
126 East Lincoln Avenue
RY80T-A100
Rahway, NJ
USA
07065
ph: 7325945002
e: daniel_blom@merck.com

Jan Borén
University of Gothenburg
Wallenberg Laboratory
Sahlgrenska University Hospital
Gothenburg
Sweden
41345
ph: 46313422949
e: jan.boren@wlab.gu.se

Karin Bornfeldt
University of Washington
815 Mercer Street, Box 358055
Seattle, WA
USA
98109-8055
ph: 2065431681
e: bornf@u.washington.edu

Francois Briand
Physiogenex
Rue Pierre et Marie Curie
Labege
France
31682
ph: 0561287048
e: f.briand@physiogenex.com

Michael Brown
Univ of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX
USA
75390-9046
ph: 2146482179
e: mike.brown@utsouthwestern.edu

Leona Calhoun
UT Southwestern Medical Center
5323 Harry Hines Blvd.
L5.260
Dallas, TX
USA
75390-9046
ph: 2146487849
e: leona.calhoun@utsouhtwestern.edu

Anna Calkin
University of California, Los Angeles
MacDonald Research Laboratories 6-629
675 Charles E Young Dr. S.
Los Angeles, CA
USA
90095
ph: 3102064622
e: acalkin@mednet.ucla.edu

Guoqing Cao
Eli Lilly and Company
Lilly Corporate Center DC 0520
Indianapolis, IN
USA
46285
ph: 3174333535
e: cao_guoqing@lilly.com

Jose Castro-Perez
Merck
162 E. Lincoln Ave.
Rahway, NJ
USA
07974
ph: 5516559535
e: jose_castro-perez@merck.com

Alan Chait
University of Washington
Mailstop 356426
1959 NE Paci□c
Seattle, WA
USA
98185
ph: 2063235536
e: achait@u.washington.edu

Arthur Charles
UCSF
44 Marie Street
Suasalito, CA
USA
94965
ph: 9493038208
e: macharle@uci.edu

Ann Chasson
Integrative Bioinformatics Inc
1016 Dartmouth Ln.
Los Altos, CA
USA
94024
ph: 6509386123
e: achasson@integrativebioinformatics.com

Jay Chat□eld
Merck
415 210th St. SE
Bothell, WA
USA
98021
ph: 2104458207
e: jay_chat□eld@merck.com

Luther Clark
Merck
RY34-A238
126 East Lincoln Avenue
Rahway, NJ
USA
07065-0900
ph: 7325945420
e: luther_clark@merck.com

Linda Curtiss
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA
USA
92037
ph: 8587848248
e: lcurtiss@scripps.edu

Geeta Datta
University of Alabama at Birmingham
1808 7th Ave. S.
BDB 640
Birmingham, AL
USA
35294
ph: 2059344023
e: gdatta@uab.edu

Brandon Davies
UCLA
10833 LeConte Ave.
A2-237 CHS
Los Angeles, CA
USA
90095
ph: 3102674675
e: bdavies@mednet.ucla.edu

Jean Davignon
IRCM
110 Pine Avenue West
Montreal, QC
Canada
H2W 1R7
ph: 5149875626
e: davignj@ircm.qc.ca

Russell DeBose-Boyd
Univ of Texas Southwestern Medical Ctr.
5323 Harry Hines Blvd.
Dallas, TX
USA
75390-9046
ph: 2146483467
e: russell.debose-boyd@utsouthwestern.edu

Diane Dell'Armo
Merck
7073 Valley Greens Circle
Carmel, CA
USA
93923
ph: 8316251688
e: diane_dellarmo@merck.com

Yiping Deng
UCSD
1087H, CMME, 9500 Gilman Dr.
San Diego, CA
USA
92093
ph: 8588221102
e: y3deng@ucsd.edu

Helen Dichek
University of Washington
1959 NE Paci□c St.
Seattle, WA
USA
98105
ph: 2062216360
e: hdichek@u.washington.edu

Hans Dieplinger
Innsbruck Medical University
Schoepfstrasse 41
Innsbruck
Austria
A-6020
ph: 43512900370570
e: hans.dieplinger@i-med.ac.at

Brian Drew
UCLA
Warren Hall Ste 24-130
900 Veteran Avenue
Los Angeles, CA
USA
90095
ph: 3107944982
e: bdrew@mednet.ucla.edu

Jennifer Dudman
Merck
2556 8th Ave. West
Seattle, WA
USA
98119
ph: 2068547279
e: jennifer_dudman@merck.com

Bart Duell
Oregon Health and Science University
3181 SW Sam Jackson Park Road, L465
Portland, OR
USA
97239
ph: 5034942007
e: duellb@ohsu.edu

Ruth Du□y
Merck Research Labs
126 E. Lincoln Ave.
RY-80Y-3D53
Rahway, NJ
USA
07065
ph: 7325940847
e: ruth.du□y@merck.com

Delphine Eberle
UCSF - VA Medical Center
Buiding 2, Room 410
4150 Clement Street
San Francisco, CA
USA
94121
ph: 4152214810
e: delphine.eberle@ucsfmedctr.org

Robert Eckel
University of Colorado, Denver
PO Box 6511, Mail Stop 8106
12801 East 17th Avenue
Aurora, CO
USA
80045
ph: 3037243923
e: Robert.Eckel@ucdenver.edu

Peter Edwards
University of California, Los Angeles
615 Charles E. Young Drive South
Box 951737 BSRB
Los Angeles, CA
USA
90095-1737
ph: 3102063717
e: pedwards@mednet.ucla.edu

Sandra Erickson
University of California, San Francisco
VAMC-111F
4150 Clement
San Francisco, CA
USA
94040
ph: 4157502005
e: sandra.kerickson@ucsf.edu

Je□rey Esko
University of California, San Diego
9500 Gilman Dr., Cmm. East
La Jolla, CA
USA
92093-0687
ph: 8588221100
e: jesko@ucsd.edu

Eugen Falk
Sano□-Aventis Deutschland GmbH
Industriepark Höchst
Building H825, Room 236
Frankfurt
Germany
65926
ph: 49693056260
e: eugen.falk@sano□-aventis.com

Robert Farese
J. David Gladstone Institute
1650 Owens St.
San Francisco, CA
USA
94158
ph: 4157342000
e: bfarese@gladstone.ucsf.edu

Andrew Feldhaus
Alder Biopharmaceuticals
11804 North Creek Parkway S.
Bothell, WA
USA
98011
ph: 4252052962
e: feldhaus@alderbio.com

Carlos Fernandez-Hernando
New York University School of Medicine
522 First Avenue, Smilow Research Building 703
New York, NY
USA
10016
ph: 2122639324
e: carlos.fernandez-hernando@nyumc.org

Erin Foley
University of California, San Diego
9500 Gilman Dr.
MC 0687
La Jolla, CA
USA
92093
ph: 8588221102
e: efoley@ucsd.edu
Loren Fong
UCLA
695 Charles E. Young Dr. South

Gonda Bldg., Rm 4524
Los Angeles, CA
USA
90095
ph: 3102674380
e: lfong@mednet.ucla.edu
Trudy Forte

Children's Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA
USA
94609
ph: 5104507610
e: tforte@chori.org

Gordon Francis
University of British Columbia
Rm 166, Burrard Bldg., St. Paul's Hospital
1081 Burrard St.
Vancouver, BC
Canada
V6Z 1Y6
ph: 6048069269
e: gordon.francis@hli.ubc.ca

Omar Francone
P□zer
Eastern Point Road
Groton, CT
USA
06340
ph: 8604414872
e: omar.l.francone@p□zer.com

Jacob Friedman
University of Colorado Denver Sch of Medicine
12801 E. 17th Ave.
PO Box 6511, MS 8106
Aurora, CO
USA
80045
ph: 3037243983
e: jed.friedman@ucdenver.edu

Philip Frost
UCSF
151 Tenth Avenue
San Francisco, CA
USA
4118
ph: 4156732241
e: philip.frost@ucsf.edu

Feng Gao
Children's Hospital Oakland Institute
5700 Martin Luther King Jr. Way
Oakland, CA
USA
94609
ph: 5105201510
e: fgao@chori.org

Leon Garcia-Martinez
Alder Biopharmaceuticals
11804 North Creek Parkway South
Bothell, WA
USA
98011
ph: 4252052932
e: garcia@alderbio.com

Robert Gerszten
Massachusetts General Hospital
149 13th Street
4th Floor
Charlestown, MA
USA
02129
ph: 6177248322
e: rgerszten@partners.org

Christopher GI CA

Seongah Han
Merck Research Laboratories
126 E. Lincoln Av., P.O. Box 2000
80T-A100
Rahway, NJ
USA
07065
ph: 7325946710
e: seongah_han@merck.com

Richard Havel
UC San Francisco School of Medicine
Cardiovascular Research Institute
513 Parnassus Ave., L1314
San Francisco, CA
USA
94143-0130
ph: 4154769559
e: richard.havel@ucsf.edu

Julie Hawkins
P□zer, Inc.
Eastern Point Rd.
Groton, CT
USA
06340
ph: 8604414235
e: julie.l.hawkins@p□zer.com

Jay Heinecke
University of Washington
UW-SLU
815 Mercer Box 358055
Seattle, WA
USA
98102
ph: 2065433470
e: heinecke@u.washington.edu

Joachim Herz
University of Texas-Southwestern Medical Ctr.
5323 Harry Hines Blvd.
Dallas, TX
USA
75390-9046
ph: 2146485633
e: Joachim.Herz@UTSouthwestern.edu

John Hill
St. Paul's Hosp & Univ of British Columbia
1081 Burrard St.
Vancouver, BC
Canada
V6Z 1Y6
ph: 6048068616
e: jshill@interchange.ubc.ca

Helen Hobbs
U of Texas Southwestern Medical Center
Dept Of Molecular Genetics
5323 Harry Hines Boulevard
Dallas, TX
USA
75390
ph: 2146486728
e: helen.hobbs@utsouthwestern.edu

Marten Hofker
University Medical Center Groningen
Antonius Deusinglaan 1 (IPC EA12)
Groningen
Netherlands
9713 AV
ph: 0031503635777
e: m.h.hofker@med.umcg.nl

Jay Horton
Univ of Texas Southwestern Medical Center
5323 Harry Hines Blvd
Mail Code 9046
Dallas, TX
USA
75390-9046
ph: 2146489677
e: jay.horton@utsouthwestern.edu

Ayaka Ito
University of California, Los Angeles
MRL 675 Charles Young Dr. S. MRL#6629
Los Angeles, CA
USA
90095-1662
ph: 3102064622
e: AIto@mednet.ucla.edu

Douglas Johns
Merck Research Laboratories
126 E. Lincoln Ave.
RY80T-A185
Rahway, NJ
USA
07065
ph: 7325943231
e: Douglas_Johns@merck.com

John Kane
UCSF
Box 0130, UCSF 513 Parnassus Ave. SF 94143
San Francisco, CA
USA
94143
ph: 4154761517
e: john.kane@ucsf.edu

Victor Khor
Stanford University
Building 4, Room C-302
3801 Miranda Ave.
Palo Alto, CA
USA
94304
ph: 6504935000
e: vkhor@stanford.edu

Chai-Wan Kim
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd.
L5-126
Dallas, TX
USA
75390
ph: 2146483614
e: chai-wan.kim@utsouthwestern.edu

Todd Kirchgessner
Bristol-Myers Squibb
PO Box 5400
Princeton, NJ
USA
08543
ph: 6098183262
e: todd.kirchgessner@bms.com

Robert Kisilevsky
Queen's University
Richardson Laboratory
88 Stuart Street
Kingston, ON
Canada
K7L 3N6
ph: 6135332820
e: kisilevsky@cli□.path.queensu.ca

Alison Kohan
University of Cincinnati
2180 E. Galbraith Rd.
Building A, Room 247
Cincinnati, OH
USA
45237
ph: 5135583816
e: alison.kohan@uc.edu

Bernard Kok
University of Alberta
357 Heritage Medical Research Centre
Edmonton, AB
Canada
T6G 2S2
ph: 7804924613
e: bkok@ualberta.ca

Fredric Kraemer
Stanford University School of Medicine
Division of Endocrinology, S025
Stanford, CA
USA
94305-5103
ph: 6507236054
e: fbk@stanford.edu

Jens Lagerstedt
Lund University
Biomedical Research Center Floor C12, Tornav 10
Lund
Sweden
S-22184
ph: 46462227241
e: jens.lagerstedt@med.lu.se

Joon No Lee
UT Southwestern Medical Center
5323 Harry Hines
Dallas, TX
USA
75390
ph: 2146483078
e: joon.lee@utsouthwestern.edu
Richard Lee
Isis Pharmaceuticals
1896 Rutherford Rd.
Carlsbad, CA
USA
92008
ph: 7606032793
e: rlee@isisph.com

Sang Hak Lee
UC San Diego
1080 Biomedical Sciences Building
9500 Gilman Dr.
La Jolla, CA
USA
0682
ph: 8587409448
e: shl094@ucsd.edu

Richard Lehner
University of Alberta
328 HMRC
Edmonton, AB
Canada
T6G 2S2
ph: 7804922963
e: richard.lehner@ualberta.ca

Robert Li
UT Southwestern
5323 Harry Hines Blvd.
Dallas, TX
USA
75390
ph: 2146487166
e: robert.li@utsouthwestern.edu
Ji Ling

University of Alberta
HMRC 320
University of Alberta
Edmonton, AB
Canada
T6G 2R3
ph: 7804927310
e: jil@ualberta.ca

Jingwen Liu
VA Palo Alto Health Care System (154P)
Bldg 4, Rm 2-237
3801 Miranda Ave.
Palo Alto, CA
USA
94304
ph: 6504935000
e: jingwen.liu@med.va.gov

Lijuan Liu
NIH
6701 Rockledge Dr.
Bethesda, MD
USA
20892
ph: 3014350582
e: lliu@mail.nih.gov

Aldons Lusis
University of California, Los Angeles
A2-237 CHS
Los Angeles, CA
USA
90095-1679
ph: 3108251359
e: jlusis@mednet.ucla.edu

Mary Malloy
UCSF
513 Parnassus Room 1312 HSE
San Francisco, CA
USA
94143-0130
ph: 4154762754
e: mary.malloy@ucsf.edu

Medha Manchekar
University of Alabama at Birmingham
1808 7th Avenue South
BDB 688
Birmingham, AL
USA
35294
ph: 2059340339
e: medha@uab.edu

Frits Mattijssen
Wageningen University
Dreijenlaan 2
Wageningen
Netherlands
6703 HA
ph: 0031317481100
e: frits.mattijssen@wur.nl

Gerard McGeehan
Vitae Pharmaceuticals
502 West O ce Center Drive
Fort Washington, PA
USA
19034
ph: 2154612005
e: gmcgeehan@vitaerx.com

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

Margarete Mehrabian
UCLA
6524 Gonda
Los Angeles, CA
USA
90095
ph: 3102060311
e: mehrabi.m@gmail.com

Nilamadhab Mishra
Wake Forest University School of Medicine
Medical Center Blvd.
Winston Salem, NC
USA
27157
ph: 3369183421
e: nmishra@wfubmc.edu

Yale Mitchel
Merck Research Labs
Merck and Co RY34-A228
PO Box 2000
Rahway, NJ
USA
07065
ph: 7325944147
e: yale_mitchel@merck.com

Matthew Mitsche
Boston University
700 Albany St. W330
Boston, MA
USA
2118
ph: 6176384013
e: mitsche@bu.edu

Young-Ah Moon
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX
USA
75206
ph: 2146485033
e: young-ah.moon@utsouthwestern.edu

Kathryn Moore
NYU School of Medicine
522 First Avenue
Smilow 705
New York, NY
USA
10016
ph: 2122639259
e: kathryn.moore@nyumc.org

David Ne
Merck
6260 Timber View Drive
East Lansing, MI
USA
48823
ph: 5172901079
e: david_ne@merck.com

Roger Newton
Esperion Therapeutics, Inc.
46701 Commerce Center Drive
Plymouth, MI
USA
48170
ph: 7348624841
e: rnewton@esperion.com

Kit Ng
UC Davis
5404 GBSF, 451 E. Health Science Dr.
Davis, CA
USA
95616
ph: 5307522182
e: kit.kennethng@gmail.com

Lorissa Niebergall
University of Alberta
116st & 85 Ave.
320 Heritage Medical Research Center
Edmonton, AB
Canada
T6G 2R3
ph: 7804927310
e: lorissa@ualberta.ca

Tomohiro Nishizawa
University of Washington
South Lake Union Campus, Rm. N231
815 Mercer Street
Seattle, WA
USA
98109
ph: 2063216285
e: tomohiron@eva.hi-ho.ne.jp

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

Eveline Oestreicher Stock
UCSF
505 Parnassus Ave., Box 0124
San Francisco, CA
USA
94143
ph: 4154762226
e: eveline.sf@gmail.com

Jerrold Olefsky
University of California, San Diego
Stein Clinical Research Building, Room 227
9500 Gilman Drive
San Diego, CA
USA
92093-0673
ph: 6195346651
e: jolefsky@ucsd.edu

Sven-Olof Olofsson
University of Goteborg
Dept. of Medicine
Sahlgrenska University Hospital
Goteborg
Sweden
SE-413 45
ph: 46313421956
e: sven-olof.olofsson@wlab.gu.se

Timothy Osborne
Sanford Burnham Medical Research Institute
6400 Sanger Rd.
Orlando, FL
USA
32827
ph: 4077452098
e: tfosborn@uci.edu

Sahng Wook Park
Yonsei University College of Medicine
134 Shinchon-dong, Seodaemoon-ku
Seoul
Korea
120752
ph: 82222281670
e: swpark64@yuhs.ac

Rex Parker
Bristol-Myers Squibb Pharmaceutical R & D
Hopewell 21.1208
311 Pennington-Rocky Hill Rd
Pennington, NJ
USA
08534
ph: 6098183252
e: rex.parker@bms.com

Brian Parks
UCLA
675 Charles E Young Dr.
MRL 3220
Los Angeles, CA
USA
90095-1679
ph: 3108251595
e: bparks@mednet.ucla.edu

John Parks
Wake Forest Univ School of Medicine
Medical Center Blvd.
Winston-Salem, NC
USA
27157-1040

Andrew Peterson
Genentech
1 DNA Way
South San Francisco, CA
USA
4080
ph: 6504673053
e: peterson.andrew@gene.com

Robert Phair
Integrative Bioinformatics Inc.
1016 Dartmouth Ln.
Los Altos, CA
USA
94024
ph: 6509386123
e: rphair@integrativebioinformatics.com

Andrew Plump
Merck Sharp & Dohme
126 E. Lincoln Ave.
RY80T-A185
Rahway, NJ
USA
07065
ph: 7325947556
e: patti_gregory@merck.com

Henry Pownall
Baylor College of Medicine
6565 Fannin
MS A-601
Houston, TX
USA
77030
ph: 7137984160
e: hpownall@bcm.edu

Clive Pullinger
UCSF
513 Parnassus Ave.
HSE 1304
San Francisco, CA
USA
94143-0130
ph: 4154765938
e: clive.pullinger@ucsf.edu

Xiaobing Qian
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY
USA
10591-6707
ph: 9143457765
e: bettyjean.tighe@regeneron.com

Robert Ra□ai
VA Medical Center San Francisco, UCSF
4150 Clement St. 151L
San Francisco, CA
USA
94121
ph: 4152214810
e: robert.ra□ai@ucsfmedctr.org

Cristina Ramirez-Hidalgo
NYU School of Medicine
522 First Avenue, Smilow 703
New York, NY
USA
10016
ph: 2122639242
e: Cristina.Ramirez@nyumc.org

Gwen Randolph
Mount Sinai School of Medicine
1425 Madison Ave.
Box 1496
New York, NY
USA
10029
ph: 2126598262
e: gwendalyn.randolph@mssm.edu

Shirya Rashid
McMaster University
David Braley Research Instiut
237 Barton St. East, Rm C4. 105
Hamilton, ON
Canada
L8L 2X2
ph: 9055212100
e: srashid@thrombosis.hhscr.org

Katey Rayner
New York University School of Medicine
522 First Avenue
Smilow 707
New York, NY
USA
10016
ph: 2122632235
e: katey.rayner@nyumc.org

Karen Reue
UCLA
David Ge□en School of Medicine at UCLA
695 Charles E. Young Dr. S.
Los Angeles, CA
USA
90095
ph: 3107945631
e: reuek@ucla.edu

Manuel Roqueta-Rivera
Sanford Burnham Medical Research Institute
10406 Falcon Parc Blvd. #302
Orlando, FL
USA
32832
ph: 2178410047
e: roqueta@sanfordburnham.org
Corina Rosales

Baylor College of Medicine
6565 Fannin, MS A-601
Houston, TX
USA
77030
ph: 7137984173
e: crosales@bcm.edu

John Rutledge
UC Davis
5404 GBSF
Davis, CA
USA
95618
ph: 9167343764
e: jcrutledge@gmail.com

Kerry Rye
Heart Research Institute
7 Eliza St., Newtown
Sydney
Australia
2042
ph: 61282088900
e: karye@ozemail.com.au

Alan Saltiel
ey J≈Tl

Jean-Marc Schwarz
UCSF/ Touro University
1632 Delaware Street
Berkeley, CA
USA
94703
ph: 4152065533
e: jschwarz@medsfgh.ucsf.edu

Margrit Schwarz
Amgen
1120 Veterans Blvd
South San Francisco, CA
USA
94080
ph: 6502442495
e: margrits@amgen.com

Elena Scotti
UCLA
675 Charles E. Young Dr. S.
MRL 6-629
Los Angeles, CA
USA
90095
ph: 3102064622
e: escotti@mednet.ucla.edu

Bei Shan
Amgen
1120 Veterans Blvd
South San Francisco, CA
USA
94080
ph: 6502442461
e: bshan@amgen.com

Walter Shaw
Avanti Polar Lipids, inc.
700 Industrial Park Dr.
Alabaster, AL
USA
35007-9105
ph: 2056632494
e: waltshaw@avantilipids.com

Adam Shaywitz
Amgen
1 Amgen Ctr Drive
38-3-A
Thousand Oaks, CA
USA
91320
ph: 8054471301
e: shaywitz@amgen.com

Garry Shen
University of Manitoba
835-715 McDermot Ave.
Winnipeg, MB
Canada
R3E 3P4
ph: 2047893816
e: gshen@ms.umanitoba.ca

Wen-Jun Shen
Stanford University
3801 Miranda Avenue
MS:154F
Palo Alto, CA
USA
94304
ph: 6504935000
e: wenjun@stanford.edu

Ronit Shiri-Sverdlov
Maastricht University
Universiteitssingel 50
Maastricht
Netherlands
6229ER
ph: 31433881746
e: r.sverdlov@maastrichtuniversity.nl

Aleem Siddiqui
University of California, San Diego
9500 Gilman Dr., 0711
Stein 409
La Jolla, CA
USA
92093
ph: 8588221750
e: asiddiqui@ucsd.edu

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

Friedrich Spener
University of Graz
Heirichstrasse 31
Graz
Austria
8010
ph: 433163805501
e: fritz.spener@uni-graz.at

Daniel Steinberg
University of California, San Diego
9500 Gilman Dr.
La Jolla, CA
USA
92093-0682
ph: 8585340569
e: dsteinberg@ucsd.edu

Alison Strack
Merck Research Labs
RY80T-B130
PO Box 2000
Rahway, NJ
USA
07065
ph: 7325948367
e: alison_strack@merck.com

Hei Sul
University of California, Berkeley
219 Morgan Hall
Berkeley, CA
USA
94720
ph: 5106423978
e: hsul@berkeley.edu

Meenakshi Sundaram
University of Ottawa
Room 4210, Roger Guindon Hall
451, Smyth Road
Ottawa, ON
Canada
K1H 8M5
ph: 6135625800
e: msundara@uottawa.ca

Gary Sweeney
Institut Pasteur Korea
Seoul
South Korea
ph: 8203180188002
e: gary@ip-korea.org

Ira Tabas
Columbia University
Department of Medicine, CUMC
630 W 168th St.
New York, NY
USA
10032-3702
ph: 2123059430
e: iat1@columbia.edu

Alan Tall
Columbia University
College of C and S
622 West 168th St, 8-401
New York, NY
USA
10032
ph: 2123059418
e: art1@columbia.edu

Chongren Tang
University of Washington
815 Mercer Street
Seattle, WA
USA
98109
ph: 2065433759

Jin Ye
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX
USA
75390
ph: 2146483461
e: jin.ye@utsouthwestern.edu

Stephen Young
University of California, Los Angeles
650 Charles E. Young Dr. S., BH-307 CHS Bldg.
Los Angeles, CA
USA
900951679
ph: 3108254934
e: sgyoung@mednet.ucla.edu

Liqing Yu
Wake Forest University Health Sciences
NRC Rm 226, Medical Center Blvd.
Winston-Salem, NC
USA
27157-1040
ph: 3367160920
e: lyu@wfubmc.edu

Li Zhang
UCLA
1718 High Vista Ave.
Palmdale, CA
USA
3550
ph: 3102064622
e: lizhang@mednet.ucla.edu

Youyan Zhang
Eli Lilly and Company
Lilly Corp Center, DC 0520
Indianapolis, IN
USA
46285
ph: 3174339471

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