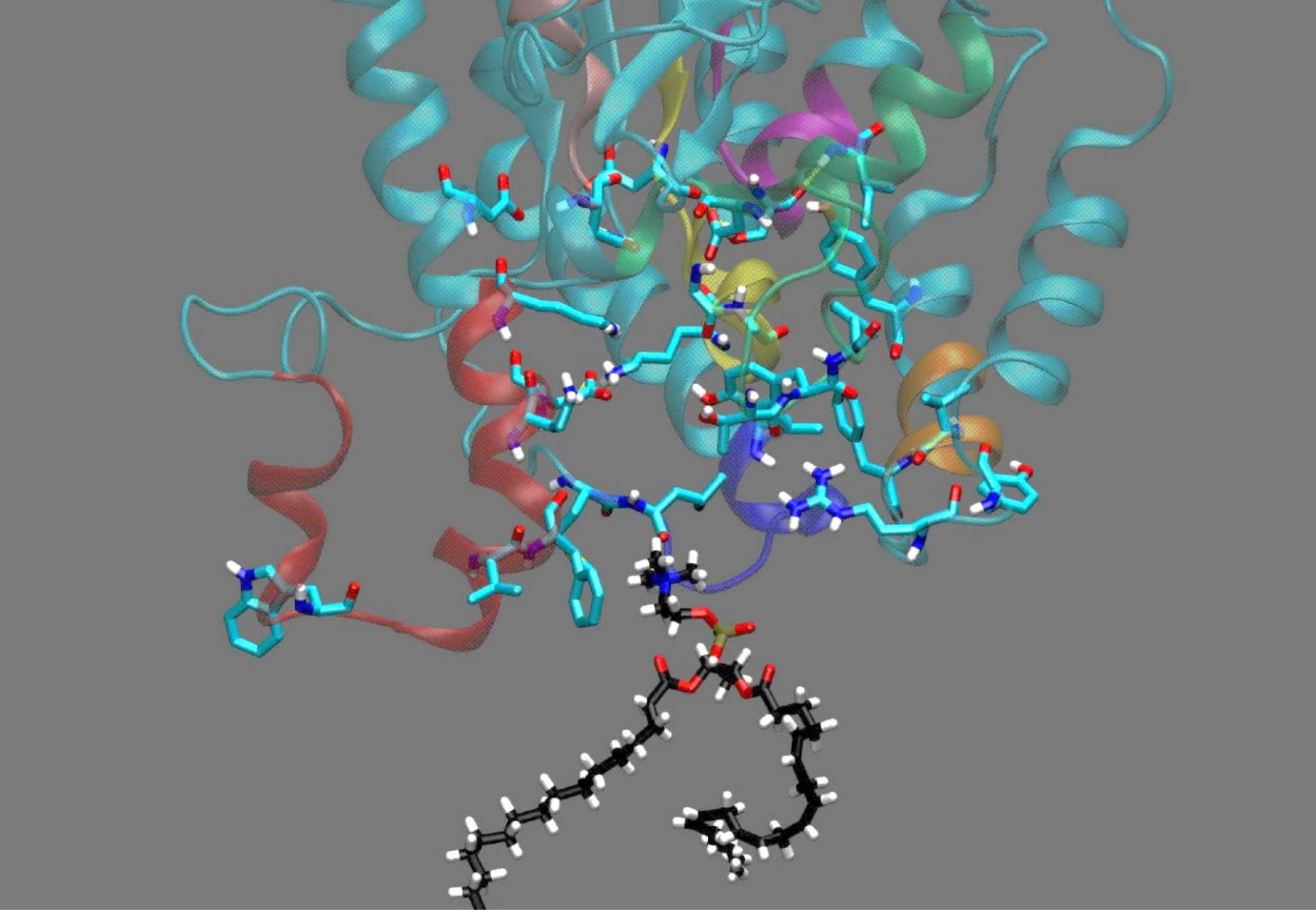

LIPID MEDIATORS IN HEALTH AND DISEASE II:

From The Cutting Edge–A Tribute to Edward Dennis

And

7TH INTERNATIONAL CONFERENCE ON PHOSPHOLIPASE A2 and LIPID MEDIATORS:

From Bench To Translational Medicine

Honorary Chair: Nobel Laureate Bengt Samuelsson

La Jolla, California May 19-20, 2016

http://www.medschool.lsuhsc.edu/neuroscience/LipidMediatorsPLA2-2016/

Steered molecular dynamics simulation of Group VIA Ca^{2+} - independent phospholipase A_2 (PLA_2) embedded in a bilayer membrane composed mainly of 1-palmitoyl, 2-oleoyl phosphatidycholine (POPC) extracting and pulling a 1-palmitoyl, 2-archidonyl phosphatidylcholine (PAPC) into its binding pocket in the active site.

[For movies of this simulation, see **Mouchlis VD, Bucher, D, McCammon, JA, Dennia EA (2015) Membranes serve as allosteric activators of phospholipase A_2 enabling it to extract, bind, and hydrolyze phospholipid substrates, *Proc Natl Acad Sci U S A*, 112, E516-25.]**

WELCOME

I would like to welcome all of the participants of the Lipid Mediators in Health and Disease II: From The Cutting Edge, A Tribute to Edward Dennis, and the 7th International Conference on Phospholipase A2 and Lipid Mediators: From Bench To Translational Medicine. This conference follows upon the very successful meeting led by Professor Jesper Z. Haeggström at the Karolinska Institutet, Nobel Forum, Stockholm, Sweden, on August 27-29, 2014, where Nobel Laureate Professor Bengt Samuelsson was honored.

Lipids serve a myriad of essential functions in cell signaling, cell organization, energy metabolism, and overall homeostasis. They are also precursors for the biosynthesis of potent chemical mediators of the immune, nervous, and endocrine systems. Lipids are central mediators of paracrine and autocrine signaling pathways and networks with critical roles in health and the major diseases of our times. Phospholipase A_2 is the key enzyme that initiates the inflammatory cascade by the release of arachidonic acid to generate numerous lipid mediators, including eicosanoids and docosanoids. Other enzymes generate endocannabinoids, platelet activating factor, sphingosines, and steroid hormones. Numerous successful drugs have emanated from insights into the role of these signaling cascades in pathogenesis.

The field of lipid mediators is vibrant, as attested to in this conference by the lectures and posters presented that are relevant to fundamental biology as well as to clinical research and therapeutic opportunities. The mission of this conference is to bring together the world's leading experts on cutting-edge topics, exchange new concepts and advances, as well as identify new paths and future strategies.

I want to thank, in a very special way, the members of the organizing committee, as well as the speakers and chairpersons for the contributions they already made toward this conference. I would especially like to thank the sponsors, who saw the worthiness of this conference, for their contributions and support.

And finally I would like to thank Edward Dennis, for whom this conference is paying tribute, for all of his remarkable contributions to the field of lipids.

With wishes for a memorable scientific meeting!

Nicolas G. Bazan, MD, PhD
Conference Chair and Organizer

LIPID MEDIATORS IN HEALTH AND DISEASE II:

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From Bench To Translational Medicine

Honorary Chair: Nobel Laureate Dr. Bengt Samuelsson
(Karolinska Institutet, Stockholm, Sweden)

Nicolas G. Bazan, MD, PhD, Louisiana State University Health
New Orleans, School of Medicine (New Orleans, LA, USA), Conference Chair and Organizer

Jerold Chun, MD, PhD, The Scripps Research Institute,
(La Jolla, CA, USA)

Jesper Z. Haeggström, MD, PhD, Karolinska Institutet
(Stockholm, Sweden)

Timothy Hla, PhD, Weill Cornell Medical College,
(New York, NY, USA)

Charles N. Serhan, PhD, DSc, Harvard Medical School
(Boston, MA, USA)

Takao Shimizu, MD, PhD, University of Tokyo,
(Tokyo Japan)

Venue: Scripps Forum
University of California, San Diego
La Jolla, California

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PROGRAM
SCRIPPS SEASIDE FORUM
LA JOLLA, CALIFORNIA, MAY 19-20, 2016

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Edward A. Dennis' Contributions to Science

Ed and his laboratory have made fundamental contributions to several aspects of the phospholipase A_2 (PLA_2) superfamily over the last 45 years. His first major contribution was his hypothesis of "surface dilution kinetics" in the early 1970s. This concept interprets structural and mechanistic studies on PLA_2 and other enzymes acting on membranes and other lipid-water interfaces. As his understanding of phospholipases advanced, he realized that lipids released by these enzymes are information-containing signaling molecules. In the 1980s, he recognized that phospholipase A_2 regulates the generation of precursors for the biosynthesis of eicosanoids and other bioactive lipid mediators of inflammation underlying disease progression.

When Ed started his independent faculty position at the University of California, San Diego in 1970, the central role of lipids in energy storage and metabolism was central in biology, and the structural role of lipids in biological membranes was assumed. At the time, the scientific community was focused on nucleic acids, proteins, and carbohydrates as information-containing molecules. Ed hypothesized that the enzymes that act on lipid substrates residing in or on membranes and micelles have important signaling roles and display unique modes of action differing from those acting on water soluble substrates. This led him to create the concept of "surface dilution kinetics" in 1973. Then, his laboratory hypothesized that PLA_2 contains allosteric activator sites for specific phospholipids based on observing activation of PLA_2 by certain specific phospholipids. Through NMR studies and x-ray crystallography, he could later identify the specific site on PLA_2 responsible for the activation.

During the last decade, his laboratory developed the application of deuterium exchange mass spectrometry (DXMS) to further understand the nature of interfacial activation for enzymes acting on membranes and micelles. This led him to an increased use of molecular dynamic approaches to propose and prove the allosteric activation of PLA_2 by membranes. Most recently his lab determined the catalytic cycle of two different human PLA_2s, namely $cPLA_2$ and $iPLA_2$, which were only purified in the early 1990s. Especially notable was the purification by his lab of the Group VIA $iPLA_2$ reported in 1994. His lab also introduced computer-aided techniques guided by DXMS for studying membrane interactions allowing for the creation of structural complexes of each enzyme with a single phospholipid substrate molecule. Simulations of the enzyme–substrate-membrane system revealed important information about the mechanisms by which these enzymes associate with the membrane and then extract and bind their phospholipid substrate. Most

strikingly, his laboratory demonstrated that the membrane acts as an allosteric ligand that binds the enzyme's interfacial surface, shifting its conformation from a closed (inactive) state in water to an open (active) state at the membrane interface; their simulation movies provide the first detailed picture of how these enzymes work.

Ed's laboratory also characterized cellular lipid signaling of Toll-like (TLR) and purinergic receptors and discovered their "synergy" in endotoxin stimulated macrophages as models for bacterial inflammation and infection, and they applied this approach to determining the course of infection-induced inflammation in Lyme disease. He also applied this approach to influenza virus infection where they found novel eicosanoid mediators including anti-inflammatory mediators that differentiate the pathogenicity of influenza strains in mouse and in human lavages.

His laboratory studied prostaglandins and isoprostanes in human plasma as markers of oxidation and disease. Besides spearheading the development of the overall lipidomics field, they also developed one of today's most sophisticated lipidomics analysis to follow over 200 eicosanoids, whose production is initiated by PLA_2, as well as novel techniques for phospholipid and lysophospholipid molecular species analysis. Recent experiments comparing various primary macrophages with cell lines have resulted in the first quantitative picture and integrated description of the fluxes of eicosanoids in cells over time and has advanced our understanding of the inflammatory response. Lipidomic analysis of cells supplemented with small amounts of the omega-3 fatty acids EPA or DHA provides information on the overall effects of EPA and DHA on the inflammatory eicosadomes and their mechanism of action, especially how they inhibit COX-1 and COX-2 facilitating the shunting of arachidonate to LOX in cells.

Inflammatory hyperalgesia and various forms of pain induce essential bioactive lipid production in the spinal cord and spinal fluid. Lipidomic analysis has revealed the production of bioactive eicosanoids including the novel role of spinal 12-lipoxygenase-derived hepoxilins A3 and B3 in inflammatory hyperalgesia which activate TRPV1 and TRPA1 receptors. His laboratory showed that intrathecal administration of these hepoxilins induce hyperalgesia in rats. The specific 12-lipoxygenase enzyme responsible for the generation of hepoxilins has also been identified by his laboratory as well the particular glial cell source in the spinal cord. Ed's results demonstrate the utility of a comprehensive lipidomics approach to identify potential contributors to disease pathology and should facilitate the development of more precisely-targeted treatment strategies.

Recently Ed's laboratory demonstrated that PLA_2 regulates "eicosanoid class switching" during inflammasome activation. Initiation and resolution of inflammation are tightly connected processes. Lipoxins (LX) are pro-resolution lipid mediators that inhibit phlogistic neutrophil recruitment and promote wound-healing by macrophage recruitment via potent and specific signaling through the LXA4 receptor (ALX). His laboratory demonstrated that lipoxins are generated as a consequence of sequential activation of the toll-like receptor 4 (TLR4), a receptor for endotoxin, and P2X7, a purinergic receptor for extracellular ATP. Initial activation of TLR4 results in accumulation of the COX2-

derived lipoxin precursor 15-HETE in esterified form within membrane phospholipids, which can be enhanced by aspirin. Subsequent activation of P2X7 results in efficient hydrolysis of 15-HETE from membrane phospholipids by $cPLA_2$, and its conversion to bioactive lipoxins by 5-LOX. His laboratory's results demonstrate how a single immune cell can store a pro-resolving lipid precursor and then release it for bioactive maturation and secretion, conceptually similar to the production and inflammasome-dependent maturation of the pro-inflammatory IL-1 family of cytokines. This study led them to discover a "dual" mode of action of aspirin, besides its inhibition of prostaglandin production, and that it promotes pro-resolution eicosanoids.

Ed's academic leadership has been outstanding on many fronts. He initiated, organized and led the LIPID MAPS Consortium. This effort contributed to the emergence of the lipidomics field, recognizing that bioactive lipids are central to human physiology and metabolism and key mediators of health and disease as we enter a new era of biomarkers and personalized medicine. The largest number of distinct molecular species in cellular metabolism lies in the lipids where tens of thousands of distinct molecular species exist. Lipid Maps developed novel liquid chromatographic-mass spectrometric (LC/MS)-based lipidomic techniques termed "CLASS" and applied this approach to the overall "omics" analysis of some 500 lipid species in immunologically-activated macrophages, integrating transcriptomics, proteomics, and metabolomics of lipid metabolites. Human plasma was also profiled to quantify some 600 distinct lipid molecular species present across all mammalian lipid categories, and this has important implications for the future of clinical medicine and the understanding of the mechanisms of disease.

Nicolas G. Bazan, MD, PhD
Conference Chair and Organizer

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OVERALL PROGRAM

Thursday, May 19 7:00-7:50 am - Breakfast, Registration and Poster set-up 8:00-8:55 am - Welcome and Introductions - Nicolas G. Bazan

Keynote Lecture

- **Bengt Samuelsson - Role of Basic Science in the Development of New Medicines: Examples from the Eicosanoid Field**

8:55-10:10 am - Session 1: **Inflammation and Oxidized Lipids**
Chairpersons: Michel Lagarde and Ken Honn

- K. Frank Austen - LTE_4 stimulation of GPR99 on respiratory epithelial cells regulates mucin release
- Bruce Levy - Specialized pro-resolving mediators in lung infection
- Christopher Glass - Genomics and lipidomics of macrophage activation

10:10–10:30 am - Coffee break

10:40-11:55 am - Session 2: Sphingolipid Biology and Disease
Chairpersons: Gabor Tigyi and Carlo Patrono

- Jason Cyster - Lipid mediators as guides and regulators of adaptive immunity
- Tim Hla - Vascular and immuno-biology of sphingosine-1-phosphate signaling
- Richard Proia - Bioluminescence imaging of sphingosine-1-phosphate G protein-coupled receptor activation in living mice

11:55–12:05 pm - Group Photo
12:05-1:20 pm - Lunch and Posters

1:30-2:45 pm - Session 3: Diversity of Enzymes: Molecular Mechanisms and Biological Function Chairpersons: Bill Smith and Takao Shimizu

2016 Journal of Lipid Research Lecture

- **Jesper Z. Haeggström - Structure and function of enzymes in the leukotriene cascade**
  - Jesus Balsinde - Phospholipase A_2-driven phospholipid metabolism during phagocytosis
  - Sasanka Ramanadham - $iPLA_2b$ and type 1 diabetes

2:45-4:00 pm - Session 4: Inflammation and Resolution
Chairpersons: Tony Yaksh and Karsten Gronert

- Ben Cravatt - Mapping lipid pathways in human biology and disease
- Charles N. Serhan - Novel mediators and mechanisms in infectious inflammation resolution
- Nicolas Bazan - Molecular principles of cellular DHA uptake, cell function and disease

4:00–4:20 pm - Coffee break

4:25-5:40 pm - Session 5: Lipids, Membranes, and Disease
Chairpersons: George Carman and George Kokotos

- Robert Murphy - Metabolism of maresin 1 by human polymorphonuclear leukocytes
- Gérard Lambeau - PLA_2R1, a puzzling and multifunctional receptor: from discovery to possible functions
- Mary Roberts - Bacterial phospholipase virulence factors – from phospholipid binding to modulating the target defense response

5:40-6:30 pm - Lightning talks selected from posters
Chairpersons: Charles N. Serhan and Jerold Chun

1. **2016 Journal of Lipid Research Junior Investigator Award - Lipoxin A4 and Lipoxin B4 attenuate adipose tissue inflammation in obese patients** – Emma Börgeson, Ville Wallenius, Per Björklund, Marianne Quiding-Järbrink, Kumar Sharma, Catherine Godson (Institute of Clinical Sciences, Department of Gastrosurgical Research and Education and Diabetes Complications Research Centre, School of Medicine and Medical Sciences, Conway Institute, University College Dublin, England)
2. **APOE4 genotype dependent deficits in DHA containing phospholipids and DHA transporters in the cerebrovasculature of Alzheimer's disease patients -** Laila Abdullah**,** James E. Evans, Ben Shackleton, Joseph O. Ojo, Thinh Nguyen, Jon Reed, Michael Mullan, Fiona Crawford and Corbin Bachmeier (Roskamp Institute, Sarasota, FL)
3. **Adipose prostaglandin D2 enhances body weight gain and suppresses lipolysis through DP2 receptors** - Ko Fujimori, Eri Wakai, Kosuke Aritake, Yo Oishi, Nanae Nagata, Fumio Amano, Michael Lazarus, and Yoshihiro Urade (Osaka University of Pharmaceutical Sciences and Osaka Bioscience Institute, Osaka, Japan)
4. **MGST2-generated LTC4 is the major mediator of stress-triggered DNA damage** - Efrat Dvash, Adi Katov and Menachem Rubinstein (Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel)
5. **APOE ε4 increases the ratio of serum phospholipid arachidonic acid to docosahexaenoic acid and aids in the identification of individuals with preclinical Alzheimer 's disease** - James E. Evans, Laila Abdullah, Tanja Emmerich, Thinh Nguyen, Gogce Crynen, Ben Shackleton, Jon Reed, Andrew P. Keegan, Cheryl Luis, Leon Tai, Mary J. LaDu, Michael Mullan, Fiona Crawford and Corbin Bachmeier (Roskamp Institute, Sarasota, LA)
6. **Pigment Epithelium- Derived Factor (PEDF) regulation of docosanoid-mediated signaling enhances corneal nerve regeneration by targeting neurotrophins, semaphorins, and regeneration associated genes (RAGs)** - Thang Luong Pham, Azucena Kakazu, Jiucheng He, Haydee H.P. Bazan (Louisiana State University Health New Orleans, Neuroscience Center of Excellence, New Orleans, LA)

7. **Subcellular localization of a 2-arachidonoyl glycerol signaling cassette in developing retinal ganglion cell axons is consistent with formation of hotspots** - David T. Stark, Joseph Caprioli (Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA)
8. **Normalizing Membrane Phospholipid Derangement from Epigenetic Insults in Neurological Disease with Lipids and Resolvins** – Patricia C. Kane, Shideh Pouria, Annette L. Cartaxo, Kristine Gedroic, Damien Downing, Thomas Wnorowski, Edward Kane, Mark O'Neal Speight (Director, NeuroLipid Research Foundation, Millville, New Jersey, USA)

Friday, May 20 7:00 to 7:50am - Breakfast

8:00-9:55 am - Session 6: Phospholipases and Lipid Signaling
Chairpersons: Nicolas G. Bazan and Alan Brash

- **Welcome Chancellor UC San Diego; Dr. Pradeep K. Khosla**

- Edward A. Dennis - Phospholipase A_2 and Lipid Mediators
- Shuh Narumiya - Prostaglandins and immune inflammation
- John Burke - Structural and dynamic studies of phosphoinositide signaling enzymes in health and disease
- Larry Marnett - Modulation of endocannabinoid metabolism by COX-2

9:55-10:15 am - Coffee break

10:20-11:35 am - Session 7: Inflammation and Obesity
Chairpersons: Jesper Z. Haeggström and Andreas Plückthun

- Michael Karin - From inflammation to immunity: Understanding cancer and improving its treatment
- Yasuhito Shrai - Function of diacylglycerol kinase
- Dennis Vance - The unexpected role of phospholipid methylation in diabetes and obesity

11:35 am–12:50 pm - Session 8: Phospholipid Signaling
Chairpersons: Robert E. Anderson and Jean Vance

- Richard Phipps - Resolvins in airway inflammation: An effective therapy for chronic obstructive pulmonary disease?
- Jack Dixon - A novel family of secretory kinases
- Makoto Murakami - Novel roles of the phospholipase A2 family in metabolic regulation

12:50-1:50 pm - Lunch and Posters

1:55-2:45 pm - Session 9: Lysolipids as Mediators of Disease
Chairpersons: Suzanne E. Barbour and Joan Clària

- Sarah Spiegel - Sphingosine-1-phosphate rheostat
- Junken Aoki - ATX-LPA1 axis contributes to proliferation of chondrocytes by regulating fibronectin assembly leading to proper cartilage formation

2:45-3:35 pm - Session 10: Phospholipids and Lysolipids in Disease
Chairpersons: Tim Hla and Sophie Layé

- Jerold Chun - Diseases involving lysophosphatidic acid (LPA) or sphingosine 1-phosphate (S1P) receptor signaling
- Joan Heller Brown - Sphingosine 1-phosphate signaling in inflammation and disease

3:35-4:00 pm - Coffee break

4:00-5:15 pm - Session 11: New Frontiers

Chairpersons: Marianne Schultzberg and Nicos A. Petasis

- Takao Shimizu - Mechanism of glycerophospholipid diversity and its biological consequence
- Hiroyuki Arai - Cellular responses to loading with excess SFAs or PUFAs
- Jean-Pierre Changeux - Lipids as allosteric modulates of ligand-gated ion channels

5:15-5:45 pm - Concluding Session

Nicolas G. Bazan, Jerold Chun, Jesper Z. Haeggström, Tim Hla, Charles N. Serhan, and Takao Shimizu

THURSDAY, MAY 19

7:00-7:50 am - Breakfast, Registration and Poster set-up

8:00-8:55 am - Welcome and Introductions - Nicolas G. Bazan

Keynote Lecture

- **Bengt Samuelsson - Role of Basic Science in the Development of New Medicines: Examples from the Eicosanoid Field**

Keynote Speaker

Bengt Samuelsson

Professor of Physiological Chemistry
Department of Medical Biochemistry and Biophysics
Karolinska Institute, Stockholm, Sweden

Abstract: Basic science plays an important role in the development of health care. In the area of eicosanoids, there are many examples of how studies of structure and function of small molecules, as well as proteins and genes, have led to new therapeutic agents for treatment of a variety of diseases. In most of the cases, the discoveries have resulted in the recognition of novel therapeutic targets amenable to modulation by small molecules. However, there are also examples in which the molecular mechanism of actions of drugs, discovered by phenotypic screening, have been elucidated. The majority of the examples consist of approved drugs; however, in some cases, ongoing developments of potential therapeutics will be discussed.

Bio: Dr. Bengt Samuelsson received his Doctor of Medical Science degree in biochemistry and later, his M.D. degree, from the Karolinska Institute. He spent a year as a research fellow in the Department of Chemistry at Harvard University, Cambridge, Mass., USA. In 1972, Dr. Samuelsson was appointed professor at the Karolinska Institute. In 1973 – 1983, he was Chairman of the Department of Chemistry; in 1978 – 1983, Dean of the Medical Faculty and in 1983 – 1995, President of the Karolinska Institute.

In 1985 – 1988, he was a member of the Swedish Government Research Advisory Board and in 1987 – 1990, a member of the Swedish National Commission on Health Policy. Dr. Samuelsson has been a member of the Nobel Assembly and the Nobel Committee for Physiology or Medicine at the Karolinska Institute and in 1993 – 2005, he was Chairman of the Nobel Foundation in Stockholm.

In 1994 – 1997, Dr. Samuelsson was a member of the European Science and Technology Assembly (ESTA) and in 1995 – 1997, a special advisor to the Commissioner for Research and Education in the European Commission.

THURSDAY, MAY 19

8:55-10:10 am - Session 1: **Inflammation and Oxidized Lipids**

Chairpersons: Michel Lagarde and Ken Honn

- K. Frank Austen - LTE_4 stimulation of GPR99 on respiratory epithelial cells regulates mucin release
- Bruce Levy - Specialized pro-resolving mediators in lung infection
- Christopher Glass - Genomics and lipidomics of macrophage activation

10:10–10:30 am - Coffee break

Michel Lagarde

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michel.lagarde@insalyon.fr

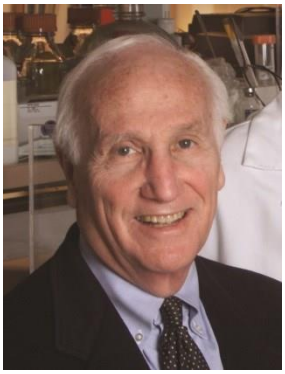
Bio: Michel Lagarde is a university Professor Emeritus at INSA-Lyon (Lyon University). Former research scientist at Pasteur Institute, then at Inserm, he has been director of an Inserm research unit, and he taught biochemistry and molecular biology at the BioSciences Department of INSA-Lyon for 25 years. He founded the Institute for Multidisciplinary Biochemistry of Lipids (IMBL), and its Lipidomics platform, that he chaired for 10 years. He has been president of several scientific societies dedicated to lipids (GERLI, ICBL and ISSFAL). He is co-author of around 500 articles according to the web of science (H factor 47). His research concerns membrane lipids and lipid mediators, especially oxygenated metabolites of polyunsaturated fatty acids of nutritional interest, in the frame of aging and diabetes mellitus.

Kenneth V. Honn

Distinguished Professor and Director, Bioactive Lipids Research Program
Wayne State University

http://cancerbiology.med.wayne.edu/index.php

Bio: Kenneth Honn, Ph.D., is a Distinguished Professor in the Wayne State University School of Medicine's Departments of Pathology and Oncology and an adjunct professor in the WSU Department of Chemistry. He is director of the Bioactive Lipids Research Program and serves as a member of the Cancer Biology Graduate Program and of the Barbara Ann Karmanos Cancer Institute. He is the founding member and president of the Eicosanoid Research Foundation and chairman of the International Conference on Bioactive Lipids in Cancer, Inflammation and Related Diseases, a biennial international conference he initiated in 1989. Dr. Honn received his Ph.D. in endocrinology from Wayne State University in 1977. With more than 30 years of experience in the fields of cancer, inflammation and bioactive lipids, his laboratory focuses on bioactive lipids and integrin receptors and the role they play in various aspects of tumor progression, namely, cell growth and apoptosis, angiogenesis and tumor cell matrix interactions. Dr. Honn's lab concentrates on lipoxygenases, and in particular 12-lipoxygenase and its metabolic product 12(*S*)HETE. In addition to his research on bioactive lipids in tumor progression, he has collaborated with scientists at the Perinatology Research Branch of the National Institutes of Health for the past four years, studying the role of lipids in human parturition, in particular, their role in preterm labor and term labor. Research efforts in Dr. Honn's laboratory have directly led to six clinical trials, and he holds 17 U.S. patents, seven of which are based on the generation of novel chemo-therapeutic/radiation sensitizing compounds. Dr. Honn is the author of more than 300 published works. He has had continuous external funding with more than 50 grants totaling in excess of $25 million. He has and continues to serve on numerous study sections, reviewing grants for the National Cancer Institute and the Department of Defense, and he provides consultation to pharmaceutical companies. Dr. Honn is a member of the editorial boards of 12 scientific journals and is co-Editor-in-Chief of *Cancer and Metastasis Reviews*.



K. Frank Austen

AstraZeneca Professor of Respiratory and Inflammatory Diseases
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and Women's Hospital

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LTE_4 stimulation of GPR99 on respiratory epithelial cells regulates mucin release

Abstract: Among the leukotriene C_4 synthase (LTC_4S) derived cysteinyl leukotrienes (cysLTs), the most stable LTE_4 is detected in the biologic fluids of patients with asthma exacerbations. Although LTE was similar in potency to LTC_4 and LTD_4 in eliciting cutaneous vascular leak, it was a hundred-fold less potent in causing airflow obstruction on inhalation in normal subjects. In contrast, studies in the literature show that with inhalation in asthmatic subjects LTE_4 was as potent as LTC_4 and LTD_4 implying a phenotypic mechanism for its action. Intranasal injection of WT mice with the mold allergen, Alternaria alternate, elicited goblet cell mucin release, a response which was fully abrogated by a respective deficiency of LTC_4S, GPR99, or mast cells but not by deficiency of the classical receptors, $CysLT_1R$ or $CysLT_2R$. Mucin release to i.n. LTE_4 was robust in WT mice and absent in the LTC_4S deficient strain and in the GPR99 deficient strain despite the presence of the classical receptors establishing GPR99 as a 3rd receptor ($CysLT_3R$).

Bio: K. Frank Austen, M.D. received his medical degree from Harvard Medical School followed by medicine residency and chief residency at Massachusetts General Hospital and postdoctoral fellowships at Walter Reed Army Institute of Research, National Institute for Medical Research (London UK), and Johns Hopkins Department of Microbiology. He then joined the faculty of the Harvard Medical School (HMS) at the Massachusetts General Hospital, initially in Infectious Diseases and then as Chief of Pulmonary. He subsequently moved to the Robert B. Brigham Hospital as Physician-in-Chief and Chairman of a new HMS Department of Medicine entirely focused on Rheumatology, Allergy and Immunology. He is currently the AstraZeneca Professor of Respiratory and Inflammatory Diseases at HMS in the Division of Rheumatology, Immunology and Allergy of the Department of Medicine at the Brigham and Women's Hospital.

Dr. Austen is the recipient of numerous medical awards including election to the American Society of Clinical Investigation, the American Academy of Arts and Sciences, the National Academy of Sciences (USA), the Royal Society (UK), and the Association of American Physicians, which chose him as the recipient of the prestigious George M. Kober Medal. Dr. Austen served as President of the American Association of Immunologist, the American Academy of Allergy Asthma and Immunology, and the American Association of Physicians. He has received honorary doctorates from the University of Paris, Hofstra University, Akron University and Amherst College. He has provided numerous named lectures and is currently on the editorial boards of the *Journal of Experimental Medicine* and *Advances in Immunology.* He has served as the mentor for many pre- and postdoctoral research-trainees, who themselves have gone on to distinguished careers in medicine and medical research.

Dr. Austen has focused his basic science and clinical research skills on the immune basis of inflammatory diseases. He is particularly well known for his seminal investigations of the role of mast cells and their production of proteases, the integrated function of the cysteinyl leukotrienes and their receptors in bronchial asthma and the importance of the amplification loop in mediating the functions of the complement system. On the occasion of his 80th birthday in 2007, the K. Frank Austen Visiting Professorship was established to recognize Dr. Austen's scholarly accomplishments, mentorship of many established leaders in his field, and initiation of the Division of Rheumatology, Immunology and Allergy.

Bruce D. Levy

Parker B. Francis Professor of Medicine, Harvard Medical School
Chief, Division of Pulmonary and Critical Care Medicine
Medical Director, The Lung Center and co-Director, Lung Research Center
Brigham and Women's Hospital

http://levylab.bwh.harvard.edu/

Specialized Pro-Resolving Mediators in Lung Infection

Abstract: Acute lung inflammation is fundamentally important to host defense, but chronic or excessive inflammation can lead to several important diseases. The resolution of inflammation is an active process that is directed, in part, by specialized pro-resolving mediators that are enzymatically derived from polyunsaturated fatty acids. In health, cell-cell interactions at the onset of acute inflammation establish biosynthetic circuits for these pro-resolving mediators, including the omega-3 fatty acid-derived resolvins, protectins and maresins, which serve as agonists to orchestrate a return of the inflamed tissue to homeostasis. Understanding the cellular and molecular mechanisms for pro-resolving mediators in catabasis is providing new insights into lung tissue responses for resolution of inflammation in health, in response to infection and the pathophysiology of disease; as well as opportunities for therapeutic intervention. E-series and D-series resolvins are enzymatically derived from the essential omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, respectively. Protectin D1 and maresin 1 (MaR1) are also derived from DHA. Relevant to lung inflammation, specialized pro-resolving mediators are generated in lung. Receptors for LXA_4 and RvD1 (ALX/FPR2) and for RvE1 (CMKLR1) are expressed in lung and are dynamically regulated with lung inflammation. Evidence will be presented for cellular and molecular mechanisms for representative specialized pro-resolving mediators in their protective actions in the regulation of pathogen-initiated lung inflammation and host defense.

Bio: Dr. Bruce D. Levy received his B.A. degree from the University Of Pennsylvania and his M.D. degree from the University Of Pennsylvania School Of Medicine. He performed his clinical training in internal medicine at Brigham and Women's Hospital (BWH). After training in the Harvard joint fellowship program in pulmonary and critical care medicine, he returned to BWH to be a chief medical resident. His postdoctoral research training was in the laboratory of Professor Charles N. Serhan also at BWH. Since then, Dr. Levy has been a physician-scientist in the Pulmonary and Critical Care Medicine Division at BWH where he now serves as the Chief of the Pulmonary and Critical Care Medicine Division of the Department of Internal Medicine as well as the medical director of the BWH Lung Center and its companion Lung Research Center in the Brigham Research Institute. He is the Parker B. Francis Professor of Medicine at Harvard Medical School and serves as a teacher of medical students, residents and fellows. His specific areas of research interest are in endogenous mechanisms for the resolution of acute lung inflammation and injury. His laboratory works to identify natural small molecule regulators of the severity and duration of innate and adaptive immune responses in the lung. He has authored over 150 publications. Dr. Levy is a Fellow of the American College of Physicians and an elected member of the ASCI, AAP and Interurban Clinical Club. He is the former Chair of the Program Committee for the Allergy, Immunology and Inflammation Assembly of the American Thoracic Society. He is the former Associate Editor of the *American Journal of Respiratory and Critical Care Medicine* and currently serves as an Associate Editor for the *New England Journal of Medicine* and Section Editor for the *Journal of Immunology*. He is a member of the Lung Cellular and Molecular Immunology Study Section of the NIH.

Christopher K. Glass

Professor, University of California San Diego Department of Cellular & Molecular Medicine
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Genomics and lipidomics of macrophage activation

Abstract: Macrophages reside in all tissues of the body and play important roles as sentinels of infection and injury. In addition, macrophages assume distinct roles in different tissue environments that can contribute to normal homeostasis or promote disease. Important examples of pathogenic roles of macrophages are provided by macrophage foam cells of atherosclerotic lesions and inflammatory adipose tissue macrophages observed in the context of obesity and type 2 diabetes. Integration of genomic and lipidomic data provide evidence for important roles of macrophages as endogenous sources of anti-inflammatory fatty acids that include EPA, DHA and 9Z-palmitoleic acid. Generation of these fatty acids is under positive transcriptional control by Liver X Receptors in response to endogenous LXR agonists that include desmosterol. Unexpectedly, we find evidence for important roles of SREBP1 in driving the synthesis of anti-inflammatory fatty acids at late time points after macrophage activation in response to Kdo2 lipid A, a potent agonist of TLR4. Genetic deletion of SREBP1 results in diminished production of anti-inflammatory fatty acids and prolonged expression of a subset of pro-inflammatory cytokines and chemokines. These observations suggest that SREBP1 functions as part of a cell autonomous negative feedback loop to restore gene expression to a basal state during the resolution phase of inflammation.

Bio: Dr. Glass received M.D. and Ph.D. degrees from UC San Diego and performed internship and residency training in Internal Medicine at Brigham and Women's Hospital. He returned to UC San Diego for fellowship training in Endocrinology and Metabolism and then joined the UC San Diego faculty. He is currently Professor of Medicine and Cellular and Molecular Medicine at UC San Diego. Dr. Glass has had a long-standing interest in elucidating the molecular mechanisms by which sequence specific transcription factors, co-activators and co-repressors regulate the development and function of macrophages in the context of metabolic and neurodegenerative disease. His most recent studies have used a combination of genomics and lipidomics to define molecular mechanisms specifying macrophage phenotypes. Dr. Glass' laboratory is currently applying these approaches to understand pathological programs of macrophage gene expression that promote the development of atherosclerosis, diabetes, cancer and other chronic inflammatory diseases. He has authored more than 250 primary research articles and more than 80 invited reviews. Dr. Glass' national service includes chairing the NIH Molecular and Cellular Endocrinology Study Section and serving as a member of the NIDDK Council. He is an elected member of the American Association of Physicians, the American Academy of Arts and Sciences, and the National Academy of Medicine.

THURSDAY, MAY 19

10:40-11:55 am - Session 2: Sphingolipid Biology and Disease

Chairpersons: Gabor Tigyi and Carlo Patrono

- Jason Cyster - Lipid mediators as guides and regulators of adaptive immunity
- Tim Hla - Vascular and immuno-biology of sphingosine-1-phosphate signaling
- Richard Proia - Bioluminescence imaging of sphingosine-1phosphate G protein-coupled receptor activation in living mice

11:55–12:05 pm - Group Photo

12:05-1:20 pm - Lunch and Posters

Gabor J. Tigyi

Professor of Physiology
University of Tennessee Health Science Center, Memphis

http://www.uthsc.edu/physiology/faculty/gtigyi.php/gtigyi@uthsc.edu

Bio: Dr. Tigyi's research is aimed at elucidating the structure and function as well as the signal transduction mechanism of a family of endogenous phospholipids with growth factor-like properties. Dr. Tigyi has shown that serum contains a set of lipid factors that are the major source of mitogenic stimuli present in serum. The best characterized member of this group of lipid mediators is lysophosphatidic acid (LPA). Dr. Tigyi's group has determined the ligand-binding pocket for the EDG family of sphingosine-1-phosphate receptors and LPA receptors. Dr. Tigyi's group has made pioneering contributions to the current understanding of the pharmacology of phospholipid growth factors and developed several new ligands. His recent research focuses on the role of the lysophospholipase D/autotaxin that plays a role in cancer metastasis and therapeutic resistance. He has coauthors over 200 peer-reviewed research papers. He is elected member of the Hungarian Academy of Sciences Budapest and the European Academy of Sciences Paris. He serves on several editorial board including that of Progress in Lipid Research and BBA Cellular and Molecular Biology of Lipids.

Carlo Patrono

Professor of Pharmacology
Department of Pharmacology
Catholic University School of Medicine Rome, Italy

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Bio: Carlo Patrono received his M.D. degree from the Catholic University School of Medicine in Rome, Italy, and trained as a Postdoctoral Fellow in New York with the late Solomon Berson and Nobel Laureate Rosalyn Yalow. Dr. Patrono's main research interest is in the study of platelet activation and inhibition in atherothrombosis and colorectal cancer. His research has characterized the human pharmacology of aspirin as an inhibitor of platelet COX-1 and provided the basis for the development of low-dose aspirin as an antithrombotic agent. During the past decade Dr. Patrono contributed to characterizing the human pharmacology of COX-2 inhibitors and evaluating their cardiovascular effects in different clinical settings. He serves on the editorial board of the American Heart Association's Journals, *Circulation* and *Arteriosclerosis, Thrombosis, and Vascular Biology,* and is a Section Editor of the *Journal of the American College of Cardiology.*

He is a member of the scientific advisory boards of the Dutch Heart Foundation, William Harvey Research Institute, and International Aspirin Foundation. He has been elected to membership in scientific societies, including the Association of American Physicians, the Royal College of Physicians, the European Society of Cardiology, the Academia Europaea and the Accademia Nazionale dei Lincei.

He has received the Alexander B. Gutman award from the Mount Sinai School of Medicine, the Distinguished Award in Neuroscience from the Louisiana State University, the 1998 International Aspirin® Award from Bayer AG, the 2007 John Vane Award from the William Harvey Research Institute of the University of London, the 2011 Outstanding Achievement Award of the Eicosanoid Research Foundation, the 2013 Grand Prix Scientifique of the Institut de France, and the 2013 Lifetime Achievement Award of the European Association for Clinical Pharmacology and Therapeutics.

Dr. Patrono has published over 220 research articles with over 40,000 citations and an *h* index of 90.

Jason G. Cyster

Professor; HHMI Investigator
University of California, San Francisco
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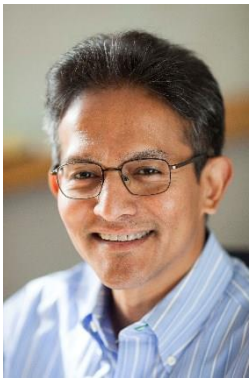
Lipid mediators as guides and regulators of adaptive immunity

Abstract: Lymphocyte migration in and out of lymphoid organs is essential for immune surveillance and effector function. Sphingosine-1-phosphate (S1P) is abundant in blood and lymph and acts on lymphocyte S1PR1 (and S1PR5) to promote egress from lymphoid organs. Once in circulatory fluids, lymphocytes rapidly downregulate S1PR1 in a GRK2-dependent manner and this allows them to overcome their attraction for blood and re-enter tissues. As well as acting at egress sites, S1P controls cell behavior within lymphoid organs. Inside the spleen, marginal zone (MZ) B cells shuttle between the blood exposed MZ and the adjacent B cell follicle ferrying antigens. Movement from follicle to MZ occurs in an S1P-S1PR1 dependent manner. In lymphoid tissues responding to immunization, germinal centers (GC) form and B cell confinement to these sites of antibody affinity maturation depends on S1P inhibiting their migration by acting on the G13-coupled S1PR2 receptor. This confinement pathway is mutated in GC B cell diffuse large B cell lymphoma (DLBCL) and we have found that dissemination of G13-deficient GC B cells is promoted by S1PR3. Most recently, we have found that innate T cell interaction with subcapsular sinus macrophages in lymph nodes is promoted by S1P-S1PR1. These interactions help promote lymph node barrier immunity. Supported by HHMI and NIH grants RO1-AI074847 and RO1-AI045073.

Bio: Jason Cyster is a Professor in the Department of Microbiology and Immunology at the University of California, San Francisco. Cyster is an Immunologist recognized for his work on the cues guiding immune cell movements in lymphoid organs and for defining the mechanism of lymphocyte egress from tissues. He is also known for his use of real-time 2-photon microscopy to study immune cell migration and interaction dynamics within tissues during antibody responses. Cyster was born in Western Australia and grew up on a cattle farm in the south of the state. He graduated from the University of Western Australia with a degree in Biochemistry and Microbiology and from the University of Oxford with a D.Phil. in Immunology in 1992. He was a postdoctoral fellow in immunology at Stanford University School of Medicine and he joined the faculty at the University of California, San Francisco in 1995.



Timothy Hla

Professor of Pathology and Laboratory Medicine and of Neuroscience
Director, Center for Vascular Biology
Weill Cornell Medical College, Cornell University
http://weill.cornell.edu/vascularbiology/

Vascular and Immuno-Biology of Sphingosine-1-phosphate Signaling

Abstract: Although originally thought as an intracellular second messenger, work over the past two decades have shown that sphingosine 1-phosphate (S1P) acts primarily as an extracellular lipid mediator. Our laboratory cloned the first S1P receptor as an orphan G protein-coupled receptor (GPCR) from vascular endothelial cells in 1990 and de-orphaned in 1998. Some of the well-studied actions of S1P include its essential roles in vascular development, immune cell trafficking and neuronal development. Inhibition of GPCR-dependent S1P signaling results in therapeutic efficacy in the autoimmune disease of remitting, relapsing multiple sclerosis (RRMS). We recently discovered that the majority (~65%) of plasma S1P is chaperoned by HDL-bound Apolipoprotein M. Plasma S1P is essential for lymphocyte trafficking. This talk will discuss the role of chaperone-dependent signaling of HDL-bound Apolipoprotein M. Our recent studies suggest that HDL-bound S1P acts as a biased agonist to suppress vascular inflammation and restore endothelial function. In the immune system, HDL-bound S1P is dispensable for immune cell trafficking but suppresses lymphopoiesis and neuroinflammation in mouse models. Better understanding of fundamental biochemical principles involved in S1P signaling may aid in the development of novel therapeutic principles in vascular and immunological diseases. *The work was supported by grants from the NIH and the Fondation Leducq transatlantic network program.*

Bio: Tim Hla trained with J. Martyn Bailey at the George Washington University for his Ph.D. degree in Biochemistry and received postdoctoral training in Vascular Biology with Thomas Maciag at the American Red Cross Holland Laboratories in Rockville, Maryland. He was recruited as a staff scientist at the Red Cross, moved to University of Connecticut School of Medicine as an Associate Professor and subsequently promoted to Professor of Cell Biology, Genetics and Developmental Biology and the Director of Center for Vascular Biology. In 2009, he moved to Weill Cornell Medical College, Cornell University as Professor of Pathology and Laboratory Medicine and the Director of Center for Vascular Biology. He cloned the human cyclooxygenase-2, and characterized the regulation and functions of this enzyme in angiogenesis, cancer biology and chronic inflammatory diseases. He also cloned and de-orphaned the first sphingosine 1phosphate (S1P) receptor. His lab contributed to the areas of S1P biology, angiogenesis and disease mechanisms. Moreover, the discovery of the S1P receptor paved the way for the development of the first S1P receptor-targeted drug as an oral medication to treat multiple sclerosis. He served in numerous national and international peer review committees and organized international meetings in lipid signaling and vascular biology. For his scientific contributions, he received several honors, including the NIH MERIT award, established investigator award of the AHA, honorary membership of the Japanese Biochemical Society, outstanding investigator award from the eicosanoid research foundation and the degree of Doctor of Medicine (honoris causa) from the Goethe University, Frankfurt, Germany.

Richard L. Proia

Chief, Genetics of Development and Disease Branch
National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

http://irp.nih.gov/pi/richard-proia

Bioluminescence imaging of sphingosine-1-phosphate G proteincoupled receptor activation in living mice

Abstract: The G protein coupled receptor (GPCR), S1P1, is activated by sphingosine-1-phosphate, a bioactive lipid produced during sphingolipid metabolism. S1P1 mediated signaling has key functions within the vascular and immune systems and is also involved in pathologic processes, including autoimmunity and inflammation. Pharmacologic targeting of S1P1 has led to an effective treatment for patients with remitting-relapsing multiple sclerosis with the S1P receptor active compound, FTY720.

A major limitation in our understanding of the *in vivo* biology of S1P signaling comes from the inability to determine the precise cellular sites and timing of signaling events. The ability to visualize S1P receptor signaling *in vivo* would be a powerful means to unravel the complexities of the biological responses that are induced by the S1P signaling pathway. We have previously established a Tango mouse model by genetically embedding a synthetic signaling pathway that is able to record cellular S1P1 receptor-activation events.

We have now developed a second, complementary mouse model in which S1P1 activation can be detected by bioluminescence imaging in live mice. These imaging strategies can be used for S1P1, or applied to other GPCRs, to investigate receptor activation dynamics in normal and disease contexts.

Bio: Dr. Richard Proia obtained his B.S. degree from Bates College and Ph.D. degree in Immunology from the University of Texas Southwestern Medical Center. During his postdoctoral studies, under the supervision of Elizabeth F. Neufeld at NIH, he began the cloning of the lysosomal β-hexosamindase genes that underlie Tay-Sachs and Sandhoff diseases. He established mouse models of several sphingolipid storage diseases that have been pivotal for the understanding of pathogenic mechanisms and for the development of therapies. His genetic studies of sphingolipid metabolism and signaling in mice have helped clarify sphingolipid function *in vivo* and their role in disease. His laboratory is currently developing methods to image sphingolipid signaling *in vivo*.

THURSDAY, MAY 19

1:30-2:45 pm - Session 3: Diversity of Enzymes: Molecular Mechanisms and Biological Function

Chairpersons: Bill Smith and Takao Shimizu

2016 Journal of Lipid Research Lecture
Jesper Z. Haeggström - Structure and function of enzymes in the leukotriene cascade

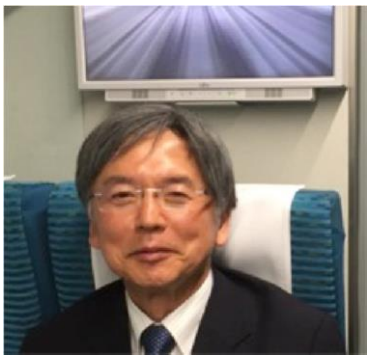
- Jesus Balsinde - Phospholipase A_2-driven phospholipid metabolism during phagocytosis
- Sasanka Ramanadham - iPLA$_2$b and type 1 diabetes

William L. Smith

Professor, Department of Biological Chemistry University of Michigan Medical School

https://medicine.umich.edu/dept/biochem/william-smith-phd

Bio: William L. Smith received his B.A. in Chemistry from the University of Colorado (1967) and his Ph.D. in Biological Chemistry from the University of Michigan (1971). After postdoctoral training in Biochemistry at the University of California, Berkeley, he spent a year as a Senior Scientist at Mead Johnson Company and then joined the faculty in Biochemistry at Michigan State University in 1975. He was Chair of Biochemistry and Molecular Biology at MSU from 1994-2003 and was named a University Distinguished Professor in 2001. Dr. Smith moved to the University of Michigan in 2003 as Minor J. Coon Professor and served as Chair of Biological Chemistry from 2003-2013. His research interests are in eicosanoid biochemistry and pharmacology where he has contributed to our understanding of how cyclooxygenases and other prostaglandin biosynthetic enzymes function. He is the author of some 200 publications. Dr. Smith has been a recipient of both the Avanti Award (2004) and the William C. Rose Award (2006) from the American Society of Biochemistry and Molecular Biology. He was the 2012 recipient of the Distinguished Faculty Lectureship Award in Biomedical Research from the University of Michigan Medical School. Dr. Smith has trained some 60 graduate students and fellows and mentored many junior faculty. He served as an Associate Editor of the *Journal of Biological Chemistry* from 2000-2014. He currently serves as co-Editor-in-Chief of the *Journal of Lipid Research*.



Takao Shimizu, M.D, Ph.D.

Professor, Department of Biochemistry and Molecular Biology
Faculty of Medicine
The University of Tokyo
Director, National Center for Global Health and Medicine, Tokyo Japan

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Mechanism of glycerophospholipid diversity and its biological consequence

Abstract: Membrane glycerosphospholipids are structurally diverse and fatty acid composition is asymmetry in terms of *sn*-1 and *sn*-2. The mechanism of such diverse structures and their outcomes in both physiology and pathology attract much attention. We have identified several key molecules in AGPAT and MBOAT family, and proposed a preliminary concept how fatty acids are incorporated into a glycerol backbone (1. 2). By genetic editing of individual enzymes in cells and mice, we are now confirming the concept at least partly. This work also provides genetic evidence of membrane diversity in various biological processes. The work is supported by JSPS of MEXT, Japan. Department at the University of Tokyo is funded by Shimadzu Co., & ONO Pharmaceutica. *Ref*.. 1. Harayama, T. *et al*. *Cell Metabolism* 20, 295-305, 2014. Hashidate-Yoshida, T. *et al*. *eLife* 2015;e06328.

Bio: TS graduated from the Medical School at the University of Tokyo in 1973. After 2 year clinical training, he had postdoc experience at Kyoto University (O. Hayaishi) and Karolinska Institutet (B. Samuelsson). He became an associate professor at the University of Tokyo in 1984, and full professor of Biochemistry in 1991. He has been working on enzymes and receptors of various lipid mediators (PLA_2, lipoxygenase, LTA4 hydrolase, receptors for PAF, LTB4 and lysophosphatidic acid (LPA4)). Since 2003, he initiated lipidomics program at the University of Tokyo, and studies extensively glycerophospholipid structure and function. Served Editorial Board for JBC for 18 years, authored >400 papers, and worked for medical researcher training.

Jesper Z. Haeggström

Professor of Molecular Eicosanoid Research
Director of the Cardiovascular Program Division
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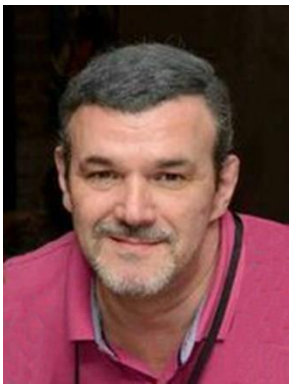
Structure and function of enzymes in the leukotriene cascade

Abstract: Leukotrienes (LT) are formed along the 5-lipoxygenase pathway of arachidonic acid metabolism and involves the highly unstable intermediate LTA_4, which may either be enzymatically hydrolyzed by LTA_4 hydrolase (LTA4H), into the chemotaxin LTB_4 or conjugated with glutathione by a specific synthase (LTC4S) to produce the spasmogenic agent LTC_4, which together with the cleavage products LTD_4 and LTE_4, constitute “slow reacting substance of anaphylaxis” (SRS). LTC4S is a member of the MAPEG superfamily of integral membrane proteins, which also includes, FLAP, mPGES-1, MGST2, and MGST3. Due to their powerful biological activities, leukotrienes are implicated in several human pathologies, in particular asthma and cardiovascular diseases. Here, recent advances in our understanding of the biochemistry and structure biology of enzymes in the leukotriene cascade will be discussed. The work was supported by the Swedish Medical Research Council, NovoNordisk Foundation, and a Distinguished Professor Award from the Karolinska Institutet.

Bio: Jesper Z. Haeggström received his MD and completed a BA at Uppsala University in 1981. After practice as a general physician he moved to Stockholm and began his post-graduate training under the supervision of Nobel Laureate, Professor Bengt Samuelsson. He received his PhD in 1988, carried out his post-doctoral training in molecular biology and protein chemistry, and became associate professor at Karolinska Institute in 1991. In 1999, Dr. Haeggström received a position as ”Karolinska Institute Senior Investigator”, and in the following year he became full professor, head of Division Physiological Chemistry 2, and is currently acting chairman of the Department of Medical Biochemistry and Biophysics. Since 2001, he has lead several major international research consortia in the field of eicosanoids and is director of the Cardiovascular Program (CVP). In 2007, Jesper Z. Haeggström was awarded the Bert L. Valle Visiting Professorship” at Harvard Medical School, Boston, in 2008 he was elected member of the Nobel Assembly, and in 2009 he received a Distinguished Professor Award from Karolinska Institute. Since 2015, Jesper Z. Haeggström is an adjunct member of the Nobel Committee for Physiology or Medicine.



Jesús Balsinde

Institute of Molecular Biology and Genetics (CSIC & CIBERDEM), University of Valladolid School of Medicine. Valladolid, Spain
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PHOSPHOLIPASE A_2-DRIVEN PHOSPHOLIPID METABOLISM DURING PHAGOCYTOSIS

Abstract: Phospholipase A_2s generate lipid mediators that constitute an important component of the integrated response of macrophages to stimuli of the innate immune response. Because these cells contain multiple phospholipase A_2 forms, the challenge is to elucidate the roles that each of these forms plays in regulating normal cellular processes and in disease pathogenesis. A major issue is to precisely determine the phospholipid substrates that these enzymes use for generating lipid mediators. There is compelling evidence that group IVA cytosolic phospholipase A_2 (cPLA$_2\alpha$) targets arachidonic acid–containing phospholipids but the role of the other cytosolic enzyme present in macrophages, the Ca^{2+}-independent group VIA phospholipase A_2 (iPLA$_2\beta$) has not been clearly defined. We applied mass spectrometry–based lipid profiling to study the substrate specificities of these two enzymes during inflammatory activation of macrophages with yeast-derived zymosan, a phagocytosable particle. Using selective inhibitors, we find that, contrary to cPLA$_2\alpha$, iPLA$_2\beta$ spares arachidonate-containing phospholipids and hydrolyzes only those that do not contain arachidonate, in particular choline phospholipids containing palmitic acid at the sn-1 position. This in turn results in the liberation of palmitoleic acid, which is incorporated into inositol lipids. The biological significance of this novel iPLA$_2\beta$-driven pathway will be discussed.

This work was supported by the Spanish Ministry of Science and Education and the Spanish National Network on Diabetes and Associated Metabolic Disorders (CIBERDEM). Key words: Phospholipase A_2; Arachidonic Acid; Palmitoleic Acid.

Bio: Jesús Balsinde is a Spanish Research Council Distinguished Professor of Biology and Biomedicine at the University of Valladolid, School of Medicine. He received an MS in Chemistry and Biochemistry and a PhD in Biochemistry and Molecular Biology from Complutense University of Madrid, and received postdoctoral training at the University of California, San Diego. He moved to the University of Valladolid in 2000. His research focuses on applying mass spectrometry-based lipidomics approaches to the study of the innate immune response in humans and murine animal systems. Particular emphasis is placed on the search for stimulus-specific lipid activation markers whose metabolic pathways of synthesis can provide targets for pharmacological intervention. The phospholipase A_2 family of enzymes and the routes for phospholipid fatty incorporation and remodeling are also long standing interests. His work has been supported by state and regional founding agencies, charities, private foundations and the industry and he is past and present member of various editorial and scientific boards and grant review panels.

Sasanka Ramanadham

Professor, Cell Developmental, and Integrative Biology; Senior Scientist, Comprehensive Diabetes Center; Associate Director, β-Cell Morphology Resource**,** University of Alabama at Birmingham

http://www.uab.edu/medicine/diabetes/faculty/faculty-bios/186-sasankaramanadham

IPLA$_2$ and Type 1 Diabetes

Abstract: Type 1 diabetes results (T1D) from autoimmune destruction of β-cells, as a consequence of islet infiltration by leukocytes and triggering of inflammatory sequelae. Less understood is the role lipid signals generated by β-cells play in this process. Earlier studies revealed that metabolites of arachidonic acid generated in the absence of Ca^{2+} during ER stress contributed to insulinoma cell apoptosis and that products of group VIA Ca^{2+}-independent phospholipase A_2 (iPLA$_2$β) activation contribute to Fas-induced U937 apoptosis. These observations gave us reason to examine the potential role of iPLA$_2$β in β-cell apoptosis. Cytosol-associated iPLA$_2$β is part of a diverse family of PLA$_2$s, which hydrolyze the *sn*-2 substituent from membrane phospholipids to release a free fatty acid and a lysolipid. In the islet, iPLA$_2$β is localized predominantly in β-cells and β-cell subcellular membranes are enriched in arachidonic acid. Thus, activation of iPLA$_2$β can lead to accumulation of this fatty acid and its subsequent metabolism by cyclo (COX) - and lipo-oxygenases (LO) to numerous bioactive lipids, or eicosanoids. Several factors including ER stress, reactive oxygen species (ROS) and NF-βB participate in cytokine-mediated β-cell destruction. We find that ER stress induces iPLA$_2$β, and that iPLA$_2$β activation exacerbates the unfolded protein response and favors alternative splicing of Bcl-x away from anti-apoptotic Bcl-x (L). Of note, LO products contribute to ER stress, ROS generation, activation of inflammatory factor NF-κB, and alternative splicing. Our studies with cultured β-cell lines, and rodent and human islets reveal that iPLA$_2$β-derived lipids contribute to β-cell apoptosis due to ER stress and proinflammatory cytokines. Supporting a role for iPLA$_2$β derived lipids in diabetes development, Akita (ER stress model of diabetes) β-cell apoptosis is inhibited by iPLA$_2$β knockdown and diabetes incidence in NOD (autoimmune model of diabetes) mice is reduced with administration of an iPLA$_2$β-selective inhibitor. Our current studies are aimed at understanding the concerted roles of iPLA$_2$β-derived lipids, ER stress, and inflammatory signals in promoting β-cell apoptosis, in the context of T1D development.

Bio: Dr. Sasanka Ramanadham received his B.Sc. in Biochemistry from McGill University in Montreal, Canada and his PhD in Pharmacology from Texas Tech University Health Sciences Center in Lubbock, TX. His thesis project examined the effects of diabetes on cardiovascular function. He then did his first postdoctoral fellowship with Dr. John McNeill in the Department of Pharmacology and Toxicology at The University of British Columbia in Vancouver, CANADA. There he continued studies of myocardial complications associated with diabetes using the working heart preparation. During that time, he also demonstrated the beneficial effects of vanadium compounds in reversing and preventing diabetes in animal models. Subsequently, he joined the lab of Dr. John Turk at Washington University School of Medicine in St. Louis, MO as a post-doctoral fellow and began his current path of understanding the role of lipid signaling in islet β-cell function and survival. These studies led to the identification in β-cells of a Ca^{2+}-independent phospholipase A_2 (iPLA$_2$β), which when hyper-activated triggers processes that lead to β-cell apoptosis. His current work is focused on understanding the role iPLA$_2$β may play in the onset and progression of β cell death associated with T1D. Dr. Ramanadham is currently Professor in the Department of Cell, Developmental, and Integrative Biology and Senior Scientist in the Comprehensive Diabetes Center at The University of Alabama at Birmingham. He has nearly 100 publications; is a member of ADA, APS, ACS, and ASBMB; is on the editorial board of AJP and JDRCM; and has served on multiple grant panels including for the NIH, ADA, and International Diabetes Organizations.

THURSDAY, MAY 19

2:45-4:00 pm - Session 4: Inflammation and Resolution

Chairpersons: Tony Yaksh and Karsten Gronert

- Ben Cravatt - Mapping lipid pathways in human biology and disease
- Charles N. Serhan - Novel mediators and mechanisms in infectious inflammation-resolution
- Nicolas Bazan - Molecular principles of cellular DHA uptake, cell function and disease

4:00–4:20 pm - Coffee break

Tony L. Yaksh

University College San Diego, School of Medicine
Department of Anesthesiology
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Bio: Dr. Tony L. Yaksh received his PhD from from Purdue University (1971) and has had academic appointments in Neurosurgery at the Mayo Clinic and, since 1989, in Anesthesiology and Pharmacology at the University of California San Diego. He has published extensively on the biology of pain processing in general and in the spinal cord in particular.

He served in the U.S. Army in the Biomedical Laboratory at Edgewood Arsenal, MD (1971-73), was a research scientist in the School of Pharmacy, University of Wisconsin (1973-76) and an Associate Research Scientist in the Anatomy Department at University College London with Pat Wall. (1976-77). He worked at the Mayo Clinic with Dr. Frederick Kerr at Rochester, MN, from 1977 to 1988, in Pharmacology and Neurosurgery where he rose to the rank of Consultant and Professor. Dr. Yaksh joined UCSD in 1988 as Professor and Vice Chairman for Research in the Department of Anesthesiology and Professor of Pharmacology. His research has been on the biology of pain processing. His work on the brain and spinal action of opiates and later adrenergic agonists, lipid mediators, capsaicinoids, COX inhibitors and calcium channel blockers outlined the complexity of spinal nociceptive processing and pointed to a variety of drug targets for spinal drug development. His studies have provided a basis for understanding the pharmacology of the spinal gating of pain information. He is an expert on issues related to spinal drug kinetics and the evaluation of the safety of spinal agents. He has published more than 780 papers and edited 6 texts. His work has garnered over 46,000 citations in over 26,000 papers. He has been a mentor to more than 100 postdoctoral fellows and trainees. He has been funded consistently by NIH since 1977 and twice has been a Javitz award recipient. Dr. Yaksh has received several honors and awards, including the Kerr Award from the American Pain Society, the Seldon Memorial Lecturer award from the International Anesthesia Research Society, the American Society of Anesthesiologists award for Excellence in Research, the Torsten Gordh lecturer award from the Swedish Society of Medicine, the Bonica Award from the International Association for the Study of Pain and the lifetime achievement award from the North American Neuromodulation Society.

Karsten Gronert

Professor, Vision Science
Infectious Diseases and Immunity
Chair, Vision Science Graduate Program
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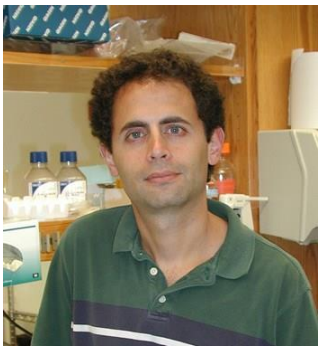
http://vision.berkeley.edu

Bio: Born in Germany, Karsten Gronert received his BS in biology with a minor in chemistry in 1987, and his MS in biology in 1990, from the University of Texas at El Paso. He obtained his PhD in cell physiology in 1995 from New Mexico State University and then moved to Boston for postdoctoral training in inflammation and molecular pharmacology at Harvard Medical School and Brigham and Women's Hospital under the mentorship of Charles Serhan. At Harvard Medical School he was promoted to Instructor in 1999 and Assistant Professor in 2002. He moved to New York Medical College in 2003, and in 2005 he was promoted to Associate Professor in Pharmacology and Ophthalmology. Karsten joined the University of California Berkeley Faculty in fall 2007. He was the Solon M. and Pearl A. Braff Chair in Clinical Optometric Science from 2008-2012 and currently is the Chair of the Vision Science Graduate Program. His NIH sponsored research is focused on defining the role of neutrophils and lipid mediators in the execution of healthy innate and adaptive immune responses and to define their sex-specific regulation. A particular emphasize of his research program are immune responses of the eye and developing therapeutic approaches to limit the consequence and progression of ocular injury and diseases. Karsten serves as a regular reviewer for National Institutes of Health study sections (NEI, NIDDK, NIGMS), the Department of Defense and for foundations. He is currently on the board of associate editors for Prostaglandins & Other Lipid Mediators and Eye & Contact Lens and a reviewer for numerous immunology, biochemistry and pathology journals. In 2012 he received the Deans Award from Louisiana State University, Neuroscience Center of Excellence.



Benjamin F. Cravatt

Professor and Chair of the Department of Chemical Physiology at The Scripps Research Institute

cravatt@scripps.edu

Mapping Lipid Pathways in Human Biology and Disease

Abstract: Lipids play critical roles in the mammalian nervous system, serving as both signaling molecules and building blocks for specialized subcellular structures. The metabolic pathways that control brain lipids remain, for the most part, poorly characterized. Here, I will discuss our lab's efforts to combine chemical proteomic and human genetic information to map lipid pathways that contribute to human neurological disorders. These studies have led to the discovery of lipid pathways that regulate neuro-immune crosstalk, as well as those regulated by noncanonical enzymes that we have deorphanized using activity-based proteomic methods.

Bio: Dr. Cravatt is a Professor and Chair of the Department of Chemical Physiology at The Scripps Research Institute. His research group is interested in understanding the roles that enzymes play in physiological and pathological processes, especially as pertains to the nervous system and cancer. Dr. Cravatt obtained his undergraduate education at Stanford University, receiving a B.S. in the Biological Sciences and a B.A. in History. He then received a Ph.D. from The Scripps Research Institute (TSRI) in 1996. Professor Cravatt joined the faculty at TSRI in 1997. Dr. Cravatt is a co-founder and scientific advisor of Activx Biosciences and Abide Therapeutics. His honors include a Searle Scholar Award, the Eli Lilly Award in Biological Chemistry, a Cope Scholar Award, the Protein Society Irving Sigal Young Investigator Award, the Tetrahedron Young Investigator Award in Bioorganic and Medicinal Chemistry, the ASBMB Merck Award, and membership in the National Academy of Sciences.

Charles Nicholas Serhan

Professor Harvard University and CET&RI Director BWH
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Novel Mediators and Mechanisms in Infectious Inflammation-Resolution

Abstract: Novel cellular mechanisms involved in the resolution of self–limited inflammation gave new n-3 pathways in host defense, tissue injury and nutrition (CN Serhan Nature 2014). Human milk contains nutrients and bioactive products relevant to infant development and immunological protection. Recently, we investigated the pro-resolving properties of milk using human milk lipid mediator isolates (HLMI) and determined their impact on resolution programs *in vivo* and with human macrophages. HLMI reduced maximum neutrophil numbers and shortened the resolution interval (R*i*; 50% neutrophil reduction) ~54% compared to mouse peritonitis. Using rigorous liquid-chromatography tandem-mass spectrometry (LC-MSMS)-based lipid mediator (LM) metabololipidomics, we demonstrated that human milk possesses a proresolving LM-SPM signature profile, containing specialized pro-resolving mediators (SPM; including resolvins, protectins, maresins and lipoxins) at bioactive levels (pico to nanomolar amounts) which enhance human macrophage efferocytosis and bacterial containment (Arnardottir et al Mucosal Immunol. 2015) . Specific SPM identified in human milk are the D-series resolvins, (e.g. Resolvin (Rv) D1, RvD2, RvD3, ATRvD3 and RvD4), Protectin (PD)1, Maresin (MaR)1, E-series resolvins (RvE1, RvE2 and RvE3) as well as lipoxins (LXA4 and LXB4). Of these milk SPM, RvD2 and MaR1 (50 ng/mouse) individually shortened R*i* ~75%. Human milk from mastitis gave higher LTB4 and prostanoids and lower SPM levels. These findings add to the growing evidence that human tissues produce SPM that function vivo. Moreover, human breast milk has pro-resolving actions via comprehensive LM-SPM profiling that uncover a potentially novel mechanism in maternal-infant imprinting.

Bio: Since 1995, Charles is Director of the Center for Experimental Therapeutics and Reperfusion Injury at BWH and endowed Gelman Professor of Anaesthesia (Biochemistry and Molecular Pharmacology) at Harvard Medical School and Professor of Oral Medicine, Infection and Immunity at Harvard School of Dental Medicine, Harvard University. He received the BS in Biochemistry Stony Brook University, NY, and doctorate in medical sciences from New York University School of Medicine. From 1981 to 1986, he was visiting scientist at the Karolinska Institutet and post-doctoral fellow with Professor Samuelsson (Nobel Laureate 1982). In 1986, he joined the faculty at Harvard and received an honorary degree from Harvard University in 1996. He also received the Honorary Degree of Doctor of Science, UCD, Ireland. Dr. Serhan was awarded an NIH MERIT Award and the 2004 Outstanding Scientist Award at BioDefense. He delivered the 2005 NIH Kreshover Lecture and received the Dart-NYU Biotechnology Outstanding Achievement Award. In 2008, he delivered the Sir John Vane Memorial Lecture and was awarded 2008 William Harvey Outstanding Scientist Medal. In 2010, he delivered the Kern Lecture and received the Society for Leukocyte Biology 2010 Bonazinga Award for "*SLB's highest honor*". Dr. Serhan was elected Fellow of AAAS 2011, delivered the Lawrence Tabak NIH-Lectureship for excellence in Oral Biology, 2011 American College of Rheumatology Hench (Nobel Laureate) Lecture awarded by Mayo Clinic Hench Society and gave the 2012 NIH/NCI Distinguished Lecture STARS in Nutrition and Cancer. He received the 2013 Oh Dang International Prize from Korean Pharmaceutical Society. In 2016, he received the IUBMB award and the 2016 Ross Prize in Molecular Medicine.

Nicolas G. Bazan, MD, PhD

Professor and Director, Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, Louisiana

http://www.medschool.lsuhsc.edu/faculty/docs/Bazan_NG_033110_1.pdf

Molecular principles of docosahexaenoic acid (DHA) uptake, cell function and disease

Abstract: Molecular principles of cell survival in retina and brain need to be defined to ascertain their role in cell function, their impact on sight and cognition, and as a consequence, their potential significance in age-related macular degeneration (AMD) and Alzheimer's disease (AD). We found that in early onset of AD, DHA-derived neuroprotectin D1 (NPD1) synthesis is remarkably sluggish, resulting in a shortage of this mediator in human brain-memory areas (Lukiw WJ, *et al*. J Clin Invest. 2005;115:2774). DHA attains its highest concentrations in the body in photoreceptor cells (PRC) and in other parts of the central nervous system, where it is avidly retained and conserved. We began to identify necessary proteins required for DHA uptake and retention and, in this quest, found that the genetic ablation of the non-Gprotein seven transmembrane domain adiponectin receptor 1 (AdipoR1) is necessary for uptake and retention of DHA (Rice DS, et al. Nat Commun. 2015;6:6228). Interestingly, adiponectin (its cognate ligand) is not involved since adiponectin KO mice do not display a similar phenotype as that of mice with the deletion of AdipoR1. Thus we found that this receptor enables the synthesis of NPD1 that, in turn, modulates retinal pigment epithelial (RPE) cell and PRC protection against uncompensated oxidative stress. In addition, AdipoR1 provides DHA for its elongation to very long chain-polyunsaturated fatty acids (VLC-PUFAs; e.g., 38:6). These fatty acids become acylated in C1 of phosphatidylcholine molecular species, where DHA is acylated in C2. Deletion of AdipoR1 blunted the synthesis of these molecular species and severely attenuated the electroretinogram preceding photoreceptor degeneration. Overexpression of the receptor or its silencing in human RPE cells lead to increases or decreases, respectively, of cellular deuterium-labeled DHA. These findings indicate that AdipoR1 is a modulatory molecular switch for DHA uptake, retention, conservation and elongation, and for making available precursors for docosanoid mediators, such as NPD1, in PRC and RPE cells, thus sustaining PRC integrity and function. (Support by NIH EY005121, GM103340, and EENT Foundation).

Bio: MD, (Univ. Tucuman, Argentina); post-docs (Columbia Univ. P&S NY, and Harvard Medical School); faculty at Univ. of Toronto, Canada, and founder of the Institute of Biochemistry, Univ. of the South (1970); in New Orleans since 1981. A central theme of my laboratory is to understand early neuroinflammatory responses in neurodegenerative diseases, including Alzheimer's disease, ischemic stroke, epilepsy, and age-related macular degeneration. My laboratory has uncovered molecular principles of the retention/conservation of DHA and contributed to the understanding of cell survival signaling in retinal pigment epithelial (RPE) cells, photoreceptors and neurons. We contributed to the discovery of the cell survival mediator neuroprotectin D1 (NPD1), which is made on demand from DHA when disruptors of homeostasis evolve and the initial inflammatory response needs to be modulated/resolved to protect neural cell integrity. Our lab recently found gene-regulatory events, including stem cell niches as targets, which are modulated by docosanoids in a non-redundant fashion, critical for neuroinflammation resolution, and that also play a role in reuroprotection and neurorestoration.

THURSDAY, MAY 19

4:25-5:40 pm - Session 5: Lipids, Membranes, and Disease

Chairpersons: George Carman and George Kokotos

- Robert Murphy - Metabolism of maresin 1 by human polymorphonuclear leukocytes
- Gérard Lambeau - PLA_2R1, a puzzling and multifunctional receptor: from discovery to possible functions
- Mary Roberts - Bacterial phospholipase virulence factors – from phospholipid binding to modulating the target defense response

George Carman

Board of Governors Professor &
Distinguished Professor
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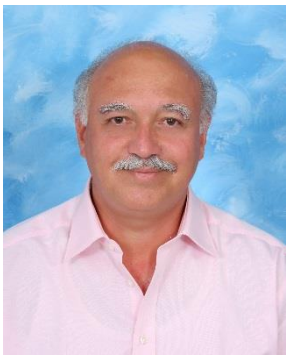
Bio: Dr. George M. Carman received his B.A. degree from William Paterson University, M.S. degree from Seton Hall University, and Ph.D. degree from the University of Massachusetts. His postdoctoral training was at the University of Texas Medical School in Houston. Dr. Carman's laboratory is recognized internationally for its work on the biochemical and molecular characterization of phospholipid metabolism/signaling in the yeast *Saccharomyces cerevisiae*. He has authored over 200 refereed publications and has written several review articles on phospholipid metabolism and on its regulation. Dr. Carman is a Fellow of the American Academy of Microbiology, and is the recipient of the American Society for Biochemistry and Molecular Biology (ASBMB) Avanti Award in Lipids, American Oil Chemists SocietySupelco/Nicholas Pelick Research Award, Selman A. Waksman Honorary Lectureship Award, the Faculty Mentor of the Year Award, the Rutgers University Board of Trustees Award for Excellence in Research, and the New Jersey Agricultural Experiment Station Research Excellence Award. He is a former chair and organizer of the Gordon Research Conference on Lipid Metabolism and the Keystone Symposium on Lipid Second Messengers, and served as chair of the ASBMB Program Planning Committee and the ASBMB Meetings Committee. He served as President of the Theobald Smith Society, the New Jersey branch of the American Society for Microbiology, and served on the Physiological Chemistry and the Biochemistry and Biophysics of Membranes Study Sections of the National Institutes of Health. He is a former Associate Editor of the Journal of Lipid Research and former Executive Editor of Biochimica et Biophysica Acta. Dr. Carman currently serves as an Associate Editor of the Journal of Biological Chemistry and Executive Editor of Analytical Biochemistry.



George Kokotos

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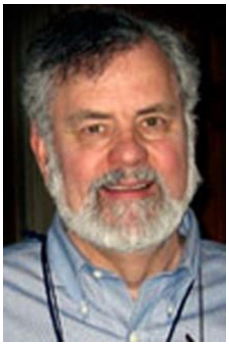
Bio: George Kokotos is the Chairman of the Department of Chemistry at the National and Kapodistrian University of Athens, Greece. He studied chemistry at the University of Athens where he also obtained his Ph.D. He then conducted postdoctoral work in the Department of Pharmaceutical and Biological Chemistry at the University of London. He has spent a sabbatical leave as a visiting Professor in the Department of Chemistry and Biochemistry at the University of California, San Diego. He has authored over 140 publications in peer-reviewed journals and edited two books on Bioactive Lipids and Lipases. He is also co-inventor of more than a dozen of patents. He is a member of the European Commitee, Division of Organic Chemistry (European Association of Chemical and Molecular Sciences, EuCheMS) and Member of the Editorial Board of “Current Organic Chemistry” and “Molecules”. His work includes the design and synthesis of lipolytic enzymes inhibitors.



Robert C. Murphy

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http://www.ucdenver.edu/academics/colleges/medicalschool/departments/Pharmacology/faculty/Pages/murphy.aspx:

Metabolism of Pro-Resolving mediators derived from DHA

With Ann-Charlotte Almstrand, Miguel Gijon
and Simona Zarini, and Robert C. Murphy

Abstract: The resolution of inflammation is a critical feature of human health. Recent evidence suggests that a series of lipids derived from polyunsaturated fatty acids such as docosahexaenoic acid can be converted in the body to biologically active compounds that assist in resolution of inflammation. Our current understanding of the pharmacologic cycle of lipid mediators involves biosynthesis, binding to receptor (protein target) as a signal, metabolic activation to terminate signal, then excretion of inactive metabolites. Initial metabolic studies were carried out to assess potential metabolism of one of the mediators derived from the macrophage, termed maresin or 7*R*,14*S*-dihydroxy-4*Z*,8*E*,10*E*,12*Z*,16*Z*,19*Z*-docosahexaenoic acid. The polymorphonuclear leukocyte was found to rapidly metabolize maresin into 5 different metabolites. These compounds were structurally characterized using mass spectrometric techniques including UV spectroscopy, LC-MS/MS and GC/MS. The metabolic inactivation of these lipids will be studied in mice to determine if in vivo biosynthesis of maresin can measured as metabolites excreted into urine.

Bio: Dr. Murphy received his PhD degree from MIT and postdoctoral training at Harvard Medical School. Dr. Murphy has maintained an active research laboratory (funded by the National Institutes of Health since 1972) and on the faculty of the University of Colorado Denver. During the past several decades, the techniques of mass spectrometry have enormously advanced and the application of these to lipid biochemistry as well. A considerable amount of his research effort has been focused on arachidonic acid metabolism by 5-lipoxygenase (leukotriene pathway), the structure elucidation of the primary leukotrienes, metabolites of leukotrienes, transcellular biosynthesis of eicosanoids, and more recently free radical products of lipid metabolism. To understand these events, mass spectrometry and ancillary techniques has been employed as a major bioanalytical tool to understand metabolism of eicosanoids and to understand their biosynthesis. He is former President of the American Society for Mass Spectrometry, Associate Editor of the Journal of Lipid Research He has published approximately 500 research papers and authored two monographs on the topic of lipid mass spectrometry.

Gérard Lambeau

Director of Research, Centre National de la Recherche Scientifique| (CNRS, France)
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PLA2R1, a puzzling and multifunctional receptor: from discovery to possible functions

Abstract: More than 2 decades ago, we discovered in rabbit skeletal muscle cells, a receptor that binds snake venom secreted phospholipases A_2 (sPLA$_2$s) with high affinities, up to 7 p.m. This M(muscle)-type receptor is now known as PLA$_2$R1. The cloned receptor is a 180 kDa type I transmembrane glycoprotein with a large extracellular portion consisting of multiple domains: an N-terminal cysteine–rich region, a fibronectin-like type II domain, a tandem repeat of 8 carbohydrate recognition domains containing the sPLA$_2$ binding site, and a short intracellular C-terminal region with an internalization motif but no obvious signaling pattern. PLA$_2$R1 belongs to the C-type lectin family and the macrophage mannose receptor, Endo-180 and DEC-205 are the closest paralogs. Despite a relatively large number of studies (>200 papers), the exact functions, endogenous ligands, signaling pathways, tissue distribution and regulation of expression of PLA$_2$R1 are still puzzling. The receptor is likely multifunctional, in line with its multiple domains, and its function(s) may vary according to species, depending on cellular expression and cognate ligands. PLA$_2$R1 may serve to counteract the biological effects of endogenous sPLA$_2$s (a function also found in snake serum) but also to bind other biomolecules including collagens, glycosylated proteins and even IgY in chicken, thereby serving roles in cell adhesion, protein transport or immune response. In this talk, I will briefly summarize our current knowledge on PLA$_2$R1, first in line with its possible function related to sPLA$_2$ binding and second in view of its more recent functions 1) in cellular senescence in the context of cancer and 2) in human kidney podocytes where PLA$_2$R1 serves as the major autoantigen of a rare but severe autoimmune kidney disease called membranous nephropathy (MN). Our most recent findings has dramatically changed diagnosis of MN and patient's care, although we still do not know the physiological function of PLA$_2$R1 in human kidney, and neither the role of sPLA$_2$s in MN nor the role of THSD7A, a second autoantigen that we identified in MN and that shares "puzzling similarities" with PLA$_2$R1.

Bio: Dr Gérard Lambeau received his M.S. and Ph.D. degrees from the University of Nice Sophia Antipolis (France). Dr Lambeau's laboratory is recognized for its work on the identification and molecular characterization of PLA$_2$ receptors and a family of secreted PLA$_2$s from venom and human/mouse tissues. Since 2006, he leads the team "Molecular physiopathology of PLA$_2$s and their mediators" at the Institute of Molecular and Cellular Pharmacology, UMR7275 CNRS and University of Nice Sophia Antipolis. He is actively involved in several national and international collaborations with academic laboratories and companies, with the aim to increase knowledge on PLA$_2$s and open new avenues towards PLA$_2$-based therapies. He has authored 128 original publications and review articles on sPLA$_2$s and PLA$_2$ receptors, and is the inventor of 15 patents. He is the recipient of the CNRS Bronze Medal Award, the Pierre Desnuelle Award of the French Academy of Sciences, and the LSUHSC Neuroscience Center of Excellence Award in recognition of its work on PLA$_2$s. He has more than 100 invited lectures and seminars and is the co-organizer of several national and international conferences. He is a member of the French society GERLI with focus on lipids and lipidomics.

Mary F. Roberts

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Bacterial phospholipase virulence factors – from phospholipid binding to modulating the target defense response

Abstract: The enzymatic activity of bacterial phosphatidylinositol-specific phospholipase C (PLC) enzymes contributes to the virulence of many Gram-positive pathogens. These amphitropic enzymes need to first bind to target cell membranes and then ferret out their very specific substrates (minor components in the surface). Using a variety of biophysical techniques we have quantified their transient binding to membranes and identified discrete binding sites for nonsubstrate phospholipids that allow processive catalysis of the enzyme. Models for membrane binding specificity and dynamics then provide insight on their mechanism of virulence. *L. monocytogenes* PI-PLC cleaves intracellular PI, which in turn depletes PI(3)P, and thus mediates autophagy avoidance. The substrates of extracellular PI-PLCs (GPI-anchored proteins) are in the outer leaflet of their target cells – a membrane rich in PC and sphingomyelin – and interactions with PC are key to stabilizing active forms of these enzymes. Release of GPI-anchored proteins alters the target cell's immune response. Supported by NIH grant GM60418.

Bio: Dr. Mary F. Roberts received her A. B. degree from Bryn Mawr College and her Ph. D. degree from Stanford University. Her postdoctoral training was at the University of Illinois in Urbana and then at the University of California, San Diego. At U.C.S.D. (in the Dennis laboratory) she experienced the joys of working with phospholipids as well as proteins. Her checkered career includes a stint at M.I.T. where she was both an Alfred P. Sloan Fellow and Dreyfus Teacher-Scholar awardee, and a more prolonged stay at Boston College where she expanded her work on phospholipases receiving the B.C. Distinguished Senior Research Award and election as an A.A.A.S. Fellow. She has 244 refereed publications and review articles covering diverse topics –recently a pseudo-metabolomic NMR project that started out identifying osmolytes in extremophiles and ended with discovering itaconic acid in macrophage-derived cells, characterizing phosphatidylcholine cation – amphitropic protein π binding motifs, and developing high resolution NMR field cycling relaxometry using the Redfield Spin-Spa to characterize membrane-protein dynamics and binding sites. She has served on N.S.F. and D.O.E. review panels as well as several N.I.H. Study Sections (BBCB, Physiological Chemistry, and BBM, acting as Chair for the latter two). She has been on the editorial board of *Journal of Biological Chemistry* and *Biochemical Journal* and co-chaired the ASBMB 2015 Annual Meeting.

THURSDAY, MAY

5:40-6:30 pm - Lightning talks selected from posters

Chairpersons: Charles N. Serhan and Jerold Chun

1. **2016 Journal of Lipid Research Junior Investigator Award - Lipoxin A4 and Lipoxin B4 attenuate adipose tissue inflammation in obese patients** – Emma Börgeson, Ville Wallenius, Per Björklund, Marianne Quiding-Järbrink, Kumar Sharma, Catherine Godson (Institute of Clinical Sciences, Department of Gastrosurgical Research and Education and Diabetes Complications Research Centre, School of Medicine and Medical Sciences, Conway Institute, University College Dublin, England)
2. **APOE4 genotype dependent deficits in DHA containing phospholipids and DHA transporters in the cerebrovasculature of Alzheimer's disease patients -** Laila Abdullah**,** James E. Evans, Ben Shackleton, Joseph O. Ojo, Thinh Nguyen, Jon Reed, Michael Mullan, Fiona Crawford and Corbin Bachmeier (Roskamp Institute, Sarasota, FL)
3. **Adipose prostaglandin D2 enhances body weight gain and suppresses lipolysis through DP2 receptors** - Ko Fujimori, Eri Wakai, Kosuke Aritake, Yo Oishi, Nanae Nagata, Fumio Amano, Michael Lazarus, and Yoshihiro Urade (Osaka University of Pharmaceutical Sciences and Osaka Bioscience Institute, Osaka, Japan)
4. **MGST2-generated LTC4 is the major mediator of stress-triggered DNA damage** - Efrat Dvash, Adi Katov and Menachem Rubinstein (Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel)
5. **APOE ε4 increases the ratio of serum phospholipid arachidonic acid to docosahexaenoic acid and aids in the identification of individuals with preclinical Alzheimer's Disease** - James E. Evans, Laila Abdullah, Tanja Emmerich, Thinh Nguyen, Gogce Crynen, Ben Shackleton, Jon Reed, Andrew P. Keegan, Cheryl Luis, Leon Tai, Mary J. LaDu, Michael Mullan, Fiona Crawford and Corbin Bachmeier (Roskamp Institute, Sarasota, LA)
6. **Pigment Epithelium- Derived Factor (PEDF) regulation of docosanoid-mediated signaling enhances corneal nerve regeneration by targeting neurotrophins, semaphorins, and regeneration associated genes (RAGs)** - Thang Luong Pham, Azucena Kakazu, Jiucheng He, Haydee H.P. Bazan (Louisiana State University Health New Orleans, Neuroscience Center of Excellence, New Orleans, LA)
7. **Subcellular localization of a 2-arachidonoyl glycerol signaling cassette in developing retinal ganglion cell axons is consistent with formation of hotspots** - David T. Stark, Joseph Caprioli (Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA)
8. **Normalizing Membrane Phospholipid Derangement from Epigenetic Insults in Neurological Disease with Lipids and Resolvins** – Patricia C. Kane, Shideh Pouria, Annette L. Cartaxo, Kristine Gedroic, Damien Downing, Thomas Wnorowski, Edward Kane, Mark O'Neal Speight (Director, NeuroLipid Research Foundation, Millville, New Jersey, USA)
9. **Maresin 1 modulates hypoxia-induced and lipotoxic ER stress in primary hepatocytes** – Bibiana Rius, Esther Titos, Cristina López-Vicario, A. Lopategi, Mireia Casulleras, José AlcarazQuiles, Joan Clària (Department of Biochemistry and Molecular Genetics, Hospital Clínic-IDIBAPS, Barcelona, Spain)
10. **Identification of Cyclooxygenase-related Enzymes in Bacteria** - Zahra Mashhadi, William E. Boeglin, and Alan R. Brash (Department of Pharmacology and the Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, TN, USA)

6:30–7:15pm – Reception 7:15-8:30 pm - Conference Dinner for all Registered Participant

Jerold Chun

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Diseases involving lysophosphatidic acid (LPA) or sphingosine 1-phosphate (S1P) receptor signaling

Abstract: Lysophospholipids (LPs) that are derived from cell membranes can act as extracellular signals by activating an enlarging family of G protein-coupled receptors (GPCRs) that now represent over 40% of known lipid GPCRs within the genome. Two major LPs are lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), however other LPs and their cognate receptors continue to be reported. The first cloned receptor was identified from brain, where many LP receptor subtypes are expressed and where they have diverse functions. Studies on genetic mutants of these receptors have identified not only normal biological effects but also relationships to diseases. Two examples will be discussed: multiple sclerosis (MS) – involving S1P1 – and hydrocephalus – involving LPA1. Receptor modulation of S1P1, along with other receptor subtypes, is the basis for the FDA-approved drug fingolimod (Gilenya). Current work is identifying new aspects of receptor mechanisms distinct from direct immunological actions that may be relevant to other forms of MS and related diseases. Hydrocephalus studies have identified roles for LPA1 signaling that may enable therapeutic intervention into what is currently an inadequately treated disorder. LP receptors thus have both biological and disease-related roles, which could be accessed for therapeutic benefit. Supported by the NIH (NS084398) and a grant from Novartis Pharmaceutical Corp.

Bio: Jerold Chun, MD, PhD, is Professor in the Department of Molecular and Cellular Neuroscience, Dorris Neuroscience Center, The Scripps Research Institute (TSRI). He is also Adjunct Professor in the Departments of Pharmacology and Neuroscience at the University of California at San Diego (UCSD) School of Medicine. He received his MD and PhD (Neuroscience) degrees through the Medical Scientist Training Program at Stanford University School of Medicine, trained as a Helen Hay Whitney Postdoctoral Fellow at the Whitehead Institute for Biomedical Research–Massachusetts Institute of Technology, then joined the faculty at the UCSD School of Medicine, where he became Professor of Pharmacology and Neurosciences and directed the Neurosciences Graduate Program. He subsequently became Department Head of Molecular Neuroscience at Merck Research Laboratories, and then returned to academia as Professor at TSRI and adjunct professor at UCSD.

He has made contributions to our understanding of lipid signaling, with an emphasis on the brain and its diseases. His laboratory identified the first lysophospholipid receptor – known as LPA1 – part of a growing class of lipid receptors mediating drug actions (e.g., Gilenya for Multiple Sclerosis) and implicated in other diseases including hydrocephalus, schizophrenia, and fibrosis. His lab also discovered that our brains are composed of genomically distinct cells – showing somatic genomic mosaicism – with both research fields currently being pursued in his laboratory. He has authored more than 250 scientific papers, is a member of multiple editorial, advisory, and review boards; and has received awards from the NIH, Alfred P. Sloan Foundation, The Klingenstein Fund, and The March of Dimes.

POSTER #1
2019 Journal of Lipid Research Junior Investigator Award
Lipoxin A_4 and Lipoxin B_4 attenuate adipose tissue inflammation in obese patients

Börgeson, Emma[1,4]; Wallenius, Ville[1]; Björklund, Per[1]; Quiding-Järbrink, Marianne[2]; Sharma, Kumar[3]; and Godson, Catherine[4]

[1] Institute of Clinical Sciences, Department of Gastrosurgical Research and Education; [2] Department of Microbiology and Immunology, Sahlgrenska Academy; University of Gothenburg, Sweden; [3] Center for Renal Translational Medicine, Department of Medicine, UC San Diego; [4] Diabetes Complications Research Centre, School of Medicine and Medical Sciences, Conway Institute, University College Dublin

Background: Visceral obesity and adipose inflammation is considered a driving force of systemic disease. Inflammatory resolution is actively regulated by specialized pro-resolving mediators (SPMs), such as the arachidonic acid derived Lipoxin A_4 (LXA_4) and Lipoxin B_4 (LXB_4). We recently demonstrated that LXA_4 attenuates obesity-induced adipose inflammation in mice, resulting in protection against liver and kidney disease (Börgeson *et al*, Cell Metabolism, 2015). The current study attempts to translate these findings from rodent to human pathophysiology.

Method: White adipose tissue explants were obtained from the greater omentum of obese (BMI 35-50), non-diabetic, bariatric surgery patients (n=4). The adipose tissue was incubated *ex vivo* with vehicle, LXA_4 (1 nM) or LXB_4 (1 nM) for 6 hours at 37˚C. Supernatant IL-6 and TNF-α levels were determined using ELISA, and tissue leukocytes were isolated and characterized by flow cytometry. Patients were recruited in accordance with the Helsinki Declaration; ClinicalTrials.gov #NCT02322073.

Results: In adipose explants from obese patients, lipoxins increased the percentage of $CD206^+$ M2 MΦs (LXA_4 +66%, LXB_4 +57%), although $CD11c^+$ expression on MΦs was not altered. Importantly, lipoxin treatment reduced TNF-α levels ($p<0.05$), which is a key functional response in promoting metabolic health. Lymphocyte $CD4^+$ and $CD8^+$ remained unaltered, although LXA_4 reduced $CD69^+$ expression, suggesting a less activated T-cell phenotype. Current experiments further delineate the molecular mechanisms involved in the lipoxin-mediated attenuation of adipose inflammation.

Conclusion: The data indicate that both LXA_4 and LXB_4 reduce obesity-induced inflammation in human adipose tissue. This encouraging proof of concept study suggests that lipoxins may have therapeutic potential in attenuating metabolic disease in humans.

Acknowledgment: EB is supported by the Swedish Research Council, Swedish Society for Medical Research (SSMF), Åke Wibergs Foundation, Konrad & Helfrid Johansson Foundation, Wilhelm & Martina Lundgrens foundation, Goljas memorial fund. KS is supported by the NIH and CG by Science Foundation Ireland.

POSTER #2

APOE4 genotype dependent deficits in DHA containing phospholipids and DHA transporters in the cerebrovasculature of Alzheimer's disease patients

Laila Abdullah[1], James E. Evans[1], Ben Shackleton[1], Joseph O. Ojo[1], Thinh Nguyen[1], Jon Reed[1], Michael Mullan[1], Fiona Crawford[1], and Corbin Bachmeier[1]

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Introduction: It has been proposed that the diminished capacity of the apoE4 protein to transport essential polyunsaturated fatty acids (PUFAs) that are required for the structural and functional maintenance and vascular integrity of the brain contribute to Alzheimer's disease pathogenesis. However, it remains to be determined if there are changes in PUFA containing phospholipids (PL) and the expression of lipid transporters within the brain vasculature in relation to the E4 allele and AD diagnosis.

Methods: We performed liquid chromatography/mass spectrometry based lipidomic analysis of the cerebrovascular and parenchymal fractions from autopsied human brain tissue of pathologically confirmed AD cases and controls stratified by APOE genotype. To determine if there were changes in the expression of lipid transporters in relation to the APOE E4 allele, we performed antibody based examination of the major facilitator superfamily domain containing 2A (mfsd2a) protein in the cerebrovasculature from these subjects.

Results: In general, docosahexaenoic acid (DHA) and arachidonic acid (AA) containing PL species were lower in homozygous E4 AD patients than E4 controls in both the cerebrovascular and parenchymal fractions. However, certain ether PL species containing AA was elevated within the cerebrovasculature of E4 carriers relative to non-carriers and was highest among homozygous E4 AD specimens compared to E4 controls. We observed an APOE E4 dependent difference in mfsd2a expression. Among AD patients, E4 homozygotes had lower expression of mfsd2a than E4 heterozygotes and non-carriers.

Conclusion: These findings demonstrate PUFA deficiencies within the brains of APOE E4 carriers may, in part, be due to lower expression of mfsd2a. Thus, targeting this transport mechanism may improve the bioavailability of DHA to the brain of APOE E4 individuals providing a novel approach to the treatment of AD.

POSTER #3

Adipose prostaglandin D_2 enhances body weight gain and suppresses lipolysis through DP2 receptors

Ko Fujimori[1,3], Eri Wakai[1], Kosuke Aritake[2,3], Yo Oishi[2,3], Nanae Nagata[2,3], Fumio Amano[1], Michael Lazarus[2,3], and Yoshihiro Urade[2,3]

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Lipocalin-type prostaglandin (PG) D synthase (L-PGDS) is expressed in adipocytes, and its expression level is elevated in adipose tissue in obese. However, the role of L-PGDS and PGD_2 in adipose tissue is still unclear. To explore the functions of L-PGDS and PGD_2, and their regulatory mechanisms in adipose tissue, we employed a Cre/loxP system to generate adipose-specific LPGDS gene knockout mice using an aP2-*Cre* transgene (*aP2-Cre/L-PGDS*$^{flox/flox}$). *aP2-Cre/L-PGDS*$^{flox/flox}$ mice and their control littermates (*L-PGDS*$^{flox/flox}$ mice) were fed either a low-fat or a high-fat diet (HFD). The expression level of the L-PGDS gene and production of PGD_2 were decreased in white adipose tissue, but not in other L-PGDS-expressing tissues in HFD-fed *aP2Cre/L-PGDS*$^{flox/flox}$ mice. When fed a HFD, *aP2-Cre/L-PGDS*$^{flox/flox}$ mice reduced body weight gain with smaller adipose size, as compared with control *L-PGDS*$^{flox/flox}$ mice. Expression levels of the adipogenic and lipogenic genes were lowered in HFD-fed *aP2-Cre/L-PGDS*$^{flox/flox}$ mice. In contrast, the transcription levels of the lipolytic genes were enhanced in HFD-fed *aP2-Cre/L-PGDS*$^{flox/flox}$ mice. Moreover, serum glucose level was decreased and insulin sensitivity was improved in HFDfed *aP2-Cre/L-PGDS*$^{flox/flox}$ mice. In addition, L-PGDS-produced PGD_2 in adipocytes suppressed the lipolysis by inhibition of cAMP-dependent protein kinase A-mediated phosphorylation of hormone-sensitive lipase through the DP2 receptors. These results indicate that adipose LPGDS-produced PGD_2 increased body weight gain and enhanced insulin resistance with repression of lipolysis via the DP2 receptors under nutrient dense condition like HFD.

POSTER #4
MGST2-generated LTC_4 is the major mediator of stress-triggered DNA damage

Efrat Dvash, Adi Katov and Menachem Rubinstein

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The ubiquitously-expressed enzyme microsomal glutathione-S-transferase 2 (MGST2) was shown to catalyze biosynthesis of leukotriene C_4 (LTC_4) by conjugating LTA_4 with glutathione *in vitro*, however, its physiological role has not been established. We have recently elucidated its physiological function by showing that endoplasmic reticulum (ER) stress and major chemotherapeutic agents (doxorubicin, 5-FU, vincristine, bortezomib) induce MGST2-based biosynthesis of LTC_4 in cells of non-hematopoietic lineage. Biosynthesis took place at the nuclear envelope by stress-triggered co-localization of MGST2, 5-lipoxygenase, 5-lipoxygenaseactivating protein and cytoplasmic phospholipase A2. ER stress and chemotherapy triggered nuclear translocation of the two LTC_4 receptors as well. Acting in an intracrine manner, LTC_4 then elicited nuclear translocation of NADPH oxidase 4 (NOX4), ROS accumulation, oxidative DNA damage and dsDNA breaks. *Mgst2* deficiency, RNAi and LTC_4 receptor antagonists abolished ER stress- and chemotherapy-instigated ROS accumulation and DNA damage in cell cultures and in mouse kidneys. Cell death and mouse morbidity were also significantly attenuated. Our finding that doxorubicin-triggered dsDNA breaks were prevented by LTC_4 receptor antagonists revealed a missing component in the mechanism of doxorubicin anti neoplastic action. Tumor cells of hematopoietic lineage do not express MGST2, and indeed, LTC_4 inhibitors did not affect their susceptibility to chemotherapy. We therefore propose that LTC_4 inhibitors, commonly used for the treatment of asthma, may alleviate chemotherapy associated morbidities when used in hematopoietic malignancies. We also found that LTC_4 inhibitors attenuated statin-triggered DNA damage and cytotoxicity in muscle cells, as well as glucotoxicity in pancreatic β cells. Other studies reported that such inhibitors attenuated disease progression in models of neurodegeneration and myocardial infract. Therefore, approved LTC_4 receptor antagonists may find use in a broad range of human morbidities.

POSTER #5

APOE ε4 increases the ratio of serum phospholipid arachidonic acid to docosahexaenoic acid and aids in the identification of individuals with preclinical Alzheimer 's disease

James E. Evans[1], Laila Abdullah[1], Tanja Emmerich[1], Thinh Nguyen[1], Gogce Crynen[1], Ben Shackleton[1], Jon Reed[1], Andrew P. Keegan[1], Cheryl Luis[1], Leon Tai[2], Mary J. LaDu[2], Michael Mullan[1], Fiona Crawford[1], and Corbin Bachmeier[1]

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Introduction: The apolipoprotein E (APOE) ε4 allele is a major genetic risk factor for Alzheimer's disease (AD) and increases the risk of developing AD by 2-3 fold. The apoE protein plays a key role in the transport and metabolism of lipids. In this study, we investigated the association of the ε4 allele with changes in the blood phospholipid (PL) profile and subsequent development of AD.

Methods: We performed lipidomics on serum from a cohort of 195 cognitively normal individuals of whom a subset developed mild cognitive impairment (MCI)/AD. Lipids were extracted from human serum and mouse plasma (plus internal standards) using the Folch method. Phospholipids were separated using normal phase liquid chromatography and detected by mass spectrometry using a Thermo LTQ-XL MS. Mass spectra were processed using LipidomeDB online to identify and quantify PL molecular species. A ratio of arachidonic acid (AA)/docosahexaenoic acid (DHA) containing species was calculated. *In vitro* blood-brain barrier (BBB) studies were performed to examine the transit of labeled AA and DHA from the "blood" to the "brain" compartment.

Results: APOE ε4-carriers converting to MCI/AD within 2-3 years had higher AA/DHA ratios in PL compared to cognitively-normal ε4 and non-ε4 carriers. A combination of AA/DHA ratios, ε4status and Aβ42/40 ratios provided 91% accuracy for detecting presymptomatic MCI/AD. Fish oil/omega-3 fatty acid consumption was associated with lower AA/DHA ratios. We also observed higher plasma AA/DHA ratios in transgenic AD mice expressing human APOE4 compared to mice with other isoforms. *In vitro* BBB studies showed that AA/DHA transit to brain is diminished using human ε4/ε4 serum compared to ε3/ε3.

Conclusion: These studies suggest further examination into the transport of AA and DHA into the brain with respect to the ε4 status and that blood levels of AA and DHA containing PL may be useful as biomarkers for detecting early AD.

POSTER #6

Pigment Epithelium- Derived Factor (PEDF) regulation of docosanoid-mediated signaling enhances corneal nerve regeneration by targeting neurotrophins, semaphorins, and regeneration associated genes (RAGs)

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[1] Neuroscience Center and [2] Department of Ophthalmology, LSU Health Sciences Center, New Orleans, LA 70112

Introduction: The cornea is one of the most innervated tissues of the body. Sensory neurons from the trigeminal ganglia (TG) project their axons into the cornea and end as free nerve terminals on the corneal surface. The nerves maintain homeostasis and integrity of the tissue that is necessary for vision. Using the mouse cornea as a model of peripheral nervous system regeneration , we assessed (1) the effect of DHA+PEDF on axons regeneration after injury; (2) ensuing bioactivity on specific neurotrophins, semaphorins, and RAGs and (3) the significance of calcium-independent Phospholipase A_2 ($iPLA_2$) and 15-lipoxygenase-1 (15-LOX-1) in nerve regeneration.

Methods: Mouse corneal nerves were injured and treated with docosahexaenoic acid (DHA) +PEDF for one or two weeks (3 times/day). Dissected corneas were stained with anti-Protein gene product 9.5 (PGP 9.5) antibody to determine nerve density. Gene activation of dissected corneas and TG were quantified by q-PCR and the levels of targeted protein secretions were analyzed by Western blot after DHA+PEDF or neuroprotection D1 (NPD1) treatment for 3h, 24h, and 48h. In some experiments, the mice were also pre-treated with the inhibitors of $iPLA_2$ Bromoenol lactone (BEL) and atglistatin or the 15-LOX-1 inhibitor PD146176.

Results: Topical treatment with DHA+PEDF for 1 and 2 weeks showed increased corneal nerve regeneration after injury in the mouse. Five neurotrophins, one neurotrophin receptor, and one semaphorin were up-regulated in the cornea and three RAGs were elevated in TG neuron after DHA+PEDF or NPD1 treatment. BEL (50μM), atglistatin (10μM) and PD146176 (10μM) inhibited the expression of these genes.

Conclusion: DHA+PEDF stimulates axonal re-growth in mouse corneal nerves. The mechanism involves the activation of $iPLA_2$ and 15-LOX-1 which stimulates the synthesis of NPD1 that in turn induces gene and protein expression of specific neurotrophins, Semaphorin 7A, and the RAGs *npy*, *vip* and *sprr1A*.

Funded by NIH-NEI grant R01-EY019465.

POSTER #7

Subcellular localization of a 2-arachidonoyl glycerol signaling cassette in developing retinal ganglion cell axons is consistent with formation of hotspots

David T. Stark[1] and Joseph Caprioli[1]

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Objective: Endocannabinoids (eCBs) modulate axon growth in glutamatergic projection neurons, but their role in retinal ganglion cells (RGCs) is poorly understood. We investigated whether RGCs exhibit an eCB system topology consistent with formation of 2-arachidonoyl glycerol (2-AG)-enriched hotspots in an embryonic retinal explant model.

Methods: Explants were stained for monoacylglycerol lipase (MGL), diacylglycerol lipase α (DGLα), and cannabinoid receptor type 1 (CB1R) and imaged by confocal microscopy. Images were segmented into regions of interest (ROIs) including growth cone (GC) central and peripheral domains (CDs and PDs) and 5 µm segments of axon. Gray value for each ROI was recorded and normalized to the CD.

Results: CDs showed maximal expression for MGL and DGLα, while PDs stained lightly. Moving proximally from CDs along MGL-stained processes, expression was stable in the distal 35 µm of axon then tapered down slowly, while DGLα tapered down rapidly from the CD through the first segments of distal axon. CB1R signal complemented DGLα, rapidly tapering up >2-fold in the same region. CB1R antagonist O-2050 enhanced MGL expression in an MGL inhibitor JZL184-sensitive manner, while JZL184 alone reduced MGL expression.

Discussion: Previous studies of non-RGC glutamatergic neurons demonstrated exclusion of MGL from the GC, where DGLα was enriched. Putative 2-AG "hotspots" may spatially restrict 2-AG signaling competence. Our model of RGC axon growth shows differential expression of MGL, DGLα, and CB1R in the distal axon and GC that is distinct from the previously reported pattern but consistent with the hotspot hypothesis. This arrangement should favor enhanced 2AG tone in the distal axon and GC that leads CB1R expression. We also find that axonal MGL expression is suppressed by 2-AG tone at CB1R. Forebrain projection target-derived 2-AG might coordinate synaptogenesis with acquisition of mature eCB system topology through related mechanisms.

This work is supported by Glaucoma Research Foundation.

POSTER #8

Normalizing Membrane Phospholipid Derangement from Epigenetic Insults in Neurological Disease with Lipids and Resolvins

Patricia C. Kane, Ph.D.[1], Shideh Pouria, MD[2,3],Annette L. Cartaxo, MD[2,4],Kristine Gedroic, MD[2,5] Damien Downing, MD[2,6], Thomas Wnorowski PhD[2], Edward Kane[2], and Mark O'Neal Speight, MD[2,7]

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We have found that neurological disorders are hallmarked by characteristic accumulation of very long chain fatty acids revealing cell membrane derangement per disturbance in peroxisomal respiration following which interrupts cell membrane integrity and neurometabolic function. We have observed that our subjects with neurological disorders have DNA adducts that further compromise gene expression due to epigenetic factors that result in not only an increase in PLA_2 expression, but in abnormal formation of membrane phospholipids. In capturing visual images of distorted cell and mitochondrion membranes we have linked the impact of the DNA adducts (toxins) altering gene expression to aberrations in lipid metabolism, cellular dysfunction and alteration of the structure of phospholipids in the cell membranes characteristic to the presenting diagnosis and symptoms. To optimize organelle and cellular membrane architecture we address appropriate balance, fluidity and content of phospholipids which are crucial towards normal cellular processes to optimize neurometabolic function. Therapeutic intervention includes a PLA_2-suppressing membrane stabilizing diet with targeted bioactive lipid therapy including phenylbutyrate to stimulate the formation of resolvins and protectins. Addressing epigenetic aspects by clearing DNA adducts with intravenous phospholipids further enhances treatment outcomes. Our membrane stabilizing protocol yields marked clinical neurological improvement in our subjects following 6 months of a targeted phospholipid regime corresponding with significant normalization in red cell lipid analysis, cardiolipin, epigenetic status, cellular structure viewed in images of the subject's membrane phospholipid leaflets. We have documented significant clinical neurological improvement in our subjects, including cessation of seizures, along with marked normalization of cellular architecture and myelination status with a targeted phospholipid regime. The membranes of the organelles, cell leaflets, cardiolipin, the nuclear envelope, suppression of PLA_2 and DNA adducts are new therapeutic goals to consider in neurological disorders. Stabilization of phospholipid membranes, including cardiolipin, phospholipids are new targets to consider in addressing neurological disease.

POSTER #9

Maresin 1 modulates hypoxia-induced and lipotoxic ER stress in primary hepatocytes

Rius, Bibiana[1]; Titos, Esther[1,2]; López-Vicario, Cristina[1]; Lopategi A[1]; Casulleras, Mireia[1]; Alcaraz-Quiles, José[1]; and Clària, Joan[1,2,3]

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Perturbation of the endoplasmic reticulum (ER) results in an evolutionarily conserved adaptive mechanism stress response called the unfolded protein response (UPR) leading to increased transcription of genes coding for inflammatory factors, chaperones and autophagy. In cases where ER stress cannot be resolved, cellular functions deteriorate, often leading to cell death. ER stress and activation of UPR are common findings in non-alcoholic fatty liver disease (NAFLD). In this disease, stimuli such as hypoxia and free fatty acid accumulation (lipotoxicity) are known to disturb protein folding and activate UPR. Recently, a novel genus of specialized pro-resolving mediators (SPM) including resolvin and maresin families, have been described to ameliorate the inflammatory process by expediting its resolution. In the current study we explored whether SPM can modulate hepatic ER stress. Obese mice with NAFLD showed a remarkable hepatic up-regulation of CA-9 and HIF-1α and increased phosphorylation of eif2α and JNK, which are well established markers of hypoxia and ER stress, respectively. Primary hepatocytes cultured under hypoxic conditions showed an induction of ER stress sensors (i.e. pIRE1α, peif2α, CHOP and ATF3) and autophagy markers. Among the different SPM, maresin 1 (MaR1) was the most effective in reducing ER stress and autophagy markers Moreover, increasing concentrations of MaR1 prevented hepatocyte cell death. In addition, primary hepatocytes cultured under lipotoxic conditions showed an induction of markers of ER stress and autophagy, effects that were reverted by pre-treatment of these cells with MaR1. On the other hand, in experiments in precision-cut liver slices (ex vivo model), MaR1 prevented the hypoxia-induced up-regulation of TNFα and IL-1β. Interestingly, MaR1-treated Kupffer cells growing in a lipotoxic environment showed a remarkable improvement in their phagocytic capacity. Taken together, these results demonstrate that MaR1 is able to reduce ER stress and re-establish the autophagic flux in hepatocytes preventing liver cell death and the progression of NAFLD.

POSTER #10
Identification of Cyclooxygenase-related Enzymes in Bacteria

Zahra Mashhadi, William E. Boeglin, and Alan R. Brash

Department of Pharmacology and the Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, TN, USA

About 2% of sequenced prokaryotic genomes harbor cyclooxygenase (COX)-related genes, so far completely uncharacterized. These genes, which may have been picked up from eukaryotes, have been retained as functionally intact, strongly implying they confer an evolutionary advantage. COX-related enzymes in animals, plants and fungi have critical functions but the importance of these genes in bacteria is unknown. Bacterial COX-related enzymes fall into two distinct groups: α-dioxygenases (α-DOX), forming 2-hydroperoxy fatty acids, and potential "midchain" fatty acid DOX. We have partially characterized four selected enzymes:

- From the cyanobacterium *Nostoc punctiforme* we identified a linoleate and oleate 10*S*-DOX ("mid-chain", previously annotated as "COX-2"). It occurs in a small group of genes including a potential lipase and a catalase-related gene that cleaves the product to aldehydes and alcohols.

- From the cyanobacterium *Acaryochloris marina* we identified an α-DOX by HPLC and NMR analysis of products. This α-DOX seems to be part of an operon including an upstream "hydrolase" which may release the fatty acid substrate, and several downstream genes and altogether may have a biosynthetic function.

- From *Mycobacterium smegmatis* we identify another α-DOX. *M. smegmatis* utilizes oleic acid for growth and it is prominent in the mycobacterial broth OADC–Oleic Acid/Dextrose/Catalase. We propose this α-DOX has a catabolic function.

- From *Streptomyces avermitilis* and 16 other *Streptomyces* we identify an α-DOX fused to catalase, which may protect against DOX-generated oxidants although a potential relation to the secondary metabolite synthesis by this industrial organism prompts our attention.

In the near future we plan to investigate the role and importance of the COX-related genes in bacteria utilizing gene-knockouts and by identifying the functioning of close gene neighbors.

FRIDAY, MAY 20

7:00 to 7:50am - Breakfast

8:00-9:55 am - Session 6: Phospholipases and Lipid Signaling

Chairpersons: Nicolas G. Bazan and Alan Brash

Welcome Chancellor UC San Diego; Dr. Pradeep K. Khosla

- Edward A. Dennis - Phospholipase A_2 and Lipid Mediators
- Shuh Narumiya - Prostaglandins and immune inflammation
- John Burke - Structural and dynamic studies of phosphoinositide signaling enzymes in health and Disease
- Larry Marnett - Modulation of endocannabinoid metabolism by COX-2

9:55-10:15 am - Coffee break

Alan R. Brash

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Bio: Alan Brash, a native of Scotland, received his Bachelor's degree in Medical Sciences from Cambridge University and his Ph.D., focused on LC and GC-MS methods for the analysis of prostaglandins, from the University of Edinburgh. After completing a Research Fellowship at the Department of Clinical Pharmacology, Royal Postgraduate Medical School in London, he moved to Vanderbilt University in Nashville, Tennessee, where he is now Professor of Pharmacology. In the course of his career at Vanderbilt his research interests evolved towards analysis of the mechanisms of formation and transformation of lipoxygenase products with an interest in their physiological role. A co-author on over 250 research articles, his work includes studies on stereochemical aspects of lipoxygenase catalysis and on the role of epithelial lipoxygenases. His findings also initiated work on the biochemistry of the CYP74 family of cytochrome P450s, and on the catalase-related hemoproteins that also metabolize fatty acid hydroperoxides. Dr. Brash is an Associate Editor of *Lipids*, on the editorial board of the *Journal of Lipid Research* and a three-time member of the editorial board of the *Journal of Biological Chemistry*. In 2013 Dr. Brash was elected as an AAAS Fellow and in 2015 he delivered the 11th William E. Lands Lecture at the University of Michigan.

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Phospholipase A_2 and lipid mediators

Abstract: The LIPID MAPS Consortium developed novel liquid chromatographic-mass spectrometric based lipidomics techniques termed "CLASS" [*Ann Rev Biochem* 80, 301-25 (2011)] to solve lipidomics problems, often in the context of an overall omics analysis of immunologically-activated macrophages integrating transcriptomics, proteomics, and metabolomics of lipid metabolites. As part of the LIPID MAPS Consortium [www.lipidmaps.org], our laboratory developed a robust and comprehensive approach to the lipidomics analysis of hundreds of fatty acids, acylethanolamines and inflammatory eicosanoids. We have built on our previous application of lipidomic analysis to characterize "synergistic" cellular lipid signaling of Toll-like (TLR) and purinergic receptors in stimulated macrophages as models of bacterial infection and inflammation *[Nature Immunol Rev* 15, 511-523 (2015] including fluxomics analysis. This has recently led to the elucidation of the dual role of aspirin in enhancing lipoxin formation during inflammasome formation [*Proc Natl Acad Sci USA* 111, 12746-51 (2014)] and the dual role cytosolic PLA_2 [*Chem Rev* 111, 6130-85 (2011)] plays in lipoxin synthesis. We have also elucidated the details of how cytosolic and calcium-independent PLA_2s associate allosterically with membranes and extract the phospholipid substrate so as to release arachidonic acid for eicosanoid formation [*Proc Natl Acad Sci USA* 112, E516-25 (2015)]. We have now employed lipidomic approaches to determine PLA_2 specificities and molecular dynamics and simulations to relate the specificities to substrate and potent selective inhibitor binding in the catalytic site of these enzymes. [Supported by LIPID MAPS Glue Grant U54 GM069338 and R01 GM020501-40].

Bio: Edward A. Dennis is Distinguished Professor of Chemistry and Biochemistry and of Pharmacology in the School of Medicine at the University of California at San Diego (UCSD). He received his BA from Yale in 1963 and a Ph.D. from Harvard in 1967 and was a postdoctoral fellow at Harvard Medical School 196769. At UCSD he has served as Chair of the Department of Chemistry and Biochemistry, as Chair of the Faculty Academic Senate, and on the Board of Overseers. He has served as Visiting Professor at Harvard Medical School, Visiting Scientist at Brandeis University, Adjunct Professor at The Scripps Research Institute, Visiting Professor at the Collège de France, and Visiting Research Professor at Université Pierre et Marie Curie. Dr. Dennis' career research focus has been on the mechanism of the enzyme phospholipase A_2, signal transduction, inflammation, lipid metabolism, eicosanoid action, and lipidomics. He has authored over 375 research publications and patented numerous inventions. He is currently Editor-in-Chief of the *Journal of Lipid Research* and Director of the LIPID MAPS Consortium. Dr. Dennis was named a Fellow of the AAAS in 1984 and was the recipient of the American Society of Biochemistry and Molecular Biology's Avanti Award in Lipid Enzymology, the European Federation for Lipid Science and Technology's European Lipid Science Award, and the Yale Medal. Dr. Dennis served as Chair and President of the Keystone Symposia Board of Directors from 1996-2004 where he is now an Emeritus Trustee, as Chair of the Board of Directors of the Gordon Research Conferences, and on the Yale University Council. He currently serves on the Council of the American Society for Biochemistry and Molecular Biology, and the Board of Directors of the ResMed Foundation, the Eicosanoid Research Foundation, and the La Jolla Playhouse.

Shuh Narumiya

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Prostaglandins and immune inflammation

Abstract: Inflammation is in principle a body defense mechanism that is evoked by noxious stimuli and terminates on exclusion of the initial stimuli by local vascular and cellular responses. However, inflammation often becomes chronic by repeated exposure to stimuli and enhanced immune responses. Prostaglandins (PGs) have been traditionally regarded as mediators of acute inflammation. However, our recent studies revealed that, in addition to these roles, PGs cooperate with cytokines, amplify their actions by making a positive feedback loop, and are critically involved in the above processes. As such, PGs can facilitate acquired immunity and induce long-lasting immune inflammation. For example, PGE_2 facilitates IL-12mediated Th1 differentiation and IL-23-mediated Th17 expansion. Here, PGE_2 mobilizes cAMP-PKA pathway via its receptor EP2/EP4, which up-regulates expression of receptors for critical cytokines, IL-12 receptor β2 chain and IFN-γ receptor α chain in Th1 differentiation and IL-23 receptor in Th17 expansion. In parallel with elucidating the molecular mechanisms of such induction, we used KO mice deficient in EP2/EP4 and antagonists to these receptors and verified that these PGE_2 actions critically regulates disease outcome in experimental allergic encephalomyelitis, transfer colitis and IL-23-induced skin lesions, mouse models for multiple sclerosis, Crohn's disease and psoriasis, respectively. These findings are consistent with GWAS studies identifying PTGER4, the human EP4 gene, as one of genetic risk factors of these diseases.

Bio: Dr. Shuh Narumiya received his M.D. degree in 1973 and his Ph.D. degree in biochemistry in 1979 from Kyoto University Graduate School of Medicine. He received his postdoctoral training in pharmacology at the Wellcome Research Laboratories in England from 1979 to1981. He has two research interests, PG receptors and the small GTPase Rho. His team cloned all the members of PG receptor family, and utilizing KO mice and selective agonists/antagonists they developed, have clarified various physiological and pathophysiological roles PGs play in the body. In his second interest, his team discovered botulinum C3 exoenzyme, a molecular probe for Rho, cloned Rho effectors such as ROCK, mDia and citron, and discovered a specific ROCK inhibitor, Y-27632. Utilizing these tools, his team identified how actin monomers are polymerized and form actomyosin bundles, and how this mechanism is used in cell movement and tissue architecture. He has authored more than 400 refereed publications on these topics. He served as the Dean, Kyoto University School of Medicine, from 2004-2007, as the President of the Japanese Biochemical Society and as the President of the Japanese Pharmacological Society. He was the chair of the Gordon Research Conference on Cell Signaling and of the Keystone Symposium on Lipid Mediators. He received many awards including the Imperial Prize and the Japan Academy Prize and the Lifetime Achievement Award from the Eicosanoid Foundation. Currently, he is directing alliance projects with industry for drug discovery in Kyoto University.

John Burke

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Structural and dynamic studies of physphoinositide signaling enzymes in health and disease

Abstract: Lipid phosphoinositides are essential regulators of many cellular processes, including growth, proliferation, membrane trafficking, and cytokinesis. The enzymes that modify these species are frequently misregulated in numerous human diseases. This is emphasised by the fact that one of the most frequently mutated genes in human cancer is the gene for phosphoinositide 3 kinase alpha (PIK3CA). I will discuss our work examining the regulation of phosphoinositide 3 kinases and phosphatidylinositol 4 kinases, and the molecular basis of how disease linked mutations modify their regulation. A specific focus will be on our synergy of X-ray crystallography, Hydrogen deuterium exchange mass spectrometry (HDX-MS), and functional biochemical assays to probe enzyme structure, dynamics, and function. These enzymes all act on membrane surfaces, and I will also focus on our development of novel biophysical tools to examine membrane signaling complexes in their native lipid environment.

Bio: Dr John Burke carried out his undergraduate research at the University of California at Berkeley in both Chemistry and Molecular and Cellular Biology. He then moved to the University of California at San Diego where he carried out doctoral work in Biochemistry with Dr Edward Dennis. After this he was awarded an EMBO postdoctoral fellowship to study with Dr Roger Williams at the MRC Laboratory of Molecular Biology from 2009-2014. Dr Burke initiated his own research group at the University of Victoria in 2014. His work focuses on studying the molecular basis for how phosphoinositide modifying enzymes are regulated, and their involvement in disease. His research particularly focuses on understanding the complex dynamics of how membrane resident proteins are regulated using a synergy of biophysical tools including X-ray crystallography, and mass spectrometry. He is the recipient of the Biochemical Society Early Career Award (2014), as well as a CIHR new investigator (2015).

Lawrence J. Marnett

Mary Geddes Stahlman Professor of Cancer Research
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Modulation of Endocannabinoid Metabolism by COX-2

Abstract: The endocannabinoids, 2-arachidonoylglyerol (2-AG) and arachidonylethanolamide (AEA), bind to the CB1 and CB2 receptors and exert analgesic, anxiolytic and anti-inflammatory effects *inter alia*. 2-AG and AEA are metabolically inactivated by hydrolysis to arachidonic acid (AA) and are also oxygenated by cyclooxygenase-2 (COX-2) to prostaglandin glycerol esters and prostaglandin ethanolamides, respectively. A major determinant of the extent of oxygenation of 2-AG and AEA is binding of substrates or inhibitors to the allosteric site of COX-2. For example, AA is a potent allosteric inhibitor of 2-AG oxygenation whereas 13-methyl-AA is an allosteric activator. Certain non-steroidal anti-inflammatory drugs selectively block 2AG oxygenation without inhibiting AA oxygenation by binding in the allosteric site. Substrate-selective modulation of COX-2 oxygenation of endocannabinoids provides a method to assess the importance of COX-2 in the control of endocannabinoid levels and biology in vivo as well as a potential target for drug discovery. Supported by NIH grant CA89450.

Bio: Lawrence J. Marnett received his B.S. in Chemistry from Rockhurst College and his Ph.D. in Chemistry from Duke University. He did postdoctoral work at the Karolinska Institute and Wayne State University. He began his academic career at Wayne State University then moved to Vanderbilt in 1989. Marnett's research program focuses on the mechanism of action of non-steroidal anti-inflammatory drugs and the role of chronic inflammation in cancer. He is the author of over 500 research publications and 14 patents. Marnett has received awards including the American Cancer Society Faculty Research Award, the Sigma Xi Research Award, an Outstanding Investigator Award and a MERIT Award from the National Cancer Institute, the Founders Award from the American Chemical Society Division of Chemical Toxicology, and the George and Christine Sosnovsky Award for Cancer Research from the American Chemical Society. He is a Fellow of the American Association for the Advancement of Science and a Fellow of the American Chemical Society. He was founding editor of the American Chemical Society journal, *Chemical Research in* Toxicology, a position he held for 25 years. Marnett served as Associate Director of Basic Research of the Vanderbilt Ingram Cancer Center from 1993-2002 and Director of the Vanderbilt Institute of Chemical Biology from 2002. He is currently Associate Vice-Chancellor of Research and Senior Associate Dean for Biomedical Sciences at Vanderbilt School of Medicine.

FRIDAY, MAY 20

10:20-11:35 am - Session 7: Inflammation and Obesity

Chairpersons: Jesper Z. Haeggström and Andreas Plückthun

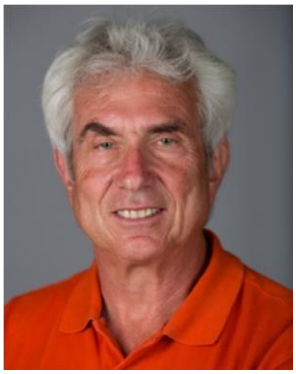
- Michael Karin - From inflammation to immunity: Understanding cancer and improving its treatment
- Yasuhito Shrai - Function of diacylglycerol kinase
- Dennis Vance - The unexpected role of phospholipid methylation in diabetes and obesity

Andreas Plückthun

Professor of Biochemistry, Department of Biochemistry University of Zurich

http://www.bioc.uzh.ch/plueckthun

Bio: Dr. Andreas Plückthun received his BS degree (Vordiplom) from the University of Heidelberg (Germany) and his PhD degree from the University of California at San Diego with Ed Dennis. His postdoctoral training was at Harvard University with Jeremy Knowles. He became group leader at the Gene Center at the Max-Planck-Institute for Biochemistry (Martinsried near Munich, Germany). In 1993, he became Full Professor in the Dept. of Biochemistry, University of Zurich (Switzerland), and he is currently the Head of the Department. His research is focused on protein engineering, with an emphasis on antibody engineering, new scaffolds as binding proteins, and stabilization of membrane proteins to enable them as drug targets. His laboratory combines biophysical methods, directed evolution and cell biology. He was elected member of the German Academy of Science and the European Molecular Biology Organization. He received the Young Investigator's Award of the German Chemical Industry Trust, the Karl-HeinzBeckurts Award (Munich, Germany), the J. P. Morgan Chase Health Award (San Jose, CA, USA), the Wilhelm-Exner Medal (Vienna, Austria) and The Jury's Grand Prix (European Grand Prix for Innovation, Monaco) and the 2016 Christian B. Anfinsen award of the Protein Society. He has authored over 390 publications with have been cited >22,000 times. He is cofounder of three companies, Morphosys (TecDAX MOR), Molecular Partners (SIX MOLN) and G7 Therapeutics (privately held).



Michael Karin

Distinguished Professor of Pharmacology
Ben and Wanda Hildyard Chair for Mitochondrial and Metabolic Diseases
American Cancer Society Research Professor University
of California, San Diego

http://pharmacology.ucsd.edu/faculty/karin.html

From Inflammation to Immunity: Understanding Cancer and Improving its Treatment.

Abstract: p62/SQSTM1 is an ubiquitin-binding autophagy receptor and signaling protein that accumulates in premalignant liver diseases and most hepatocellular carcinomas (HCC). Although p62 was proposed to participate in formation of benign adenomas in autophagy-deficient livers, its role in HCC initiation was not explored. Here we show that p62 is necessary and sufficient for HCC induction in mice and that its high expression level in non-tumor human liver predicts rapid HCC recurrence after curative ablation. High p62 expression is needed for activation of NRF2 and mTORC1, induction of c-Myc and protection of HCCinitiating cells from oxidative stress-induced death.

Bio: Dr. Karin received his BSc in Biology in 1975 at Tel Aviv University, Tel Aviv, Israel and his PhD in Molecular Biology in 1979, at the University of California, Los Angeles. Dr. Karin is currently a Distinguished Professor of Pharmacology and Pathology at the School of Medicine, University of California, San Diego, where has been on the faculty since 1986. He was a cofounder of Signal Pharmaceutical (currently Celgene) and served as a member of the National Advisory Council for Environmental Health Sciences. He has been an American Cancer Society Research Professor since 1999. Dr. Karin was elected as a member of the US National Academy of Sciences in 2005, the Institute of Medicine in 2011 and as an associate member of the European Molecular Biology Association in 2007. Much of Dr. Karin's current activity is focused on understanding the link between inflammation, cancer and metabolic disease as well as on understanding the signaling mechanisms used by receptors involved in inflammation and innate immunity. In addition to establishing molecular links between obesity, inflammation and cancer, this work has revealed new targets for cancer prevention and therapy.

Yasuhito Shirai

Professor of Department of Laboratory of Chemistry and
Utilization of Animal Production Resources
Department of Agrobioscience
Graduate School of Agricultural Science, Kobe University, Kobe, Japan

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Function of diacylglycerol kinase

Abstract: Obesity is major risk of a number of chronic diseases including cardiovascular disease, high blood pressure and diabetes. Above all, diabetes becomes a serious social problem because a number of diabetic patients all over the world reached over four billions. For diabetic patients, control of diabetic vascular complications (DVC) such as diabetic nephropathy (DN), neuropathy and retinopathy, is very important. One of causes for DVC is abnormal protein kinase C (PKC) activation that caused by diacylglycerol (DG) synthesized through *de novo* pathway. However, several trials to develop medicines inhibiting PKC for DVC have failed. Diacylglycerol kinase (DGK) can attenuate PKC activity by converting DG to phosphatidic acid (PA), suggesting that activation of DGK may improve DVC. Indeed, we found that vitamin E (VtE) and galloylated-catechins including EGCg improved DN via activation of DGK✔ in diabetic mice. In addition, DGK is also involved in insulin secretion and DGK❤ KO mice show type II diabetes. These facts indicate a balance between two lipid messengers, DG and PA is important for controlling DVC, and DGK is a good candidate for a pharmaceutical target of diabetes and DVC. In this talk, functions of DGK related to diabetes and DVC and mechanism underlying the VtE- and EGCg-mediated improvement of DN are presented and discussed.

Bio: Dr. Yasuhito Shirai received B.A and M.S. degrees from Kobe University. He obtained his first Ph.D. in 2004 from Graduate school of Agricultural Science and then got the position as Assistant Professor at Graduate School of Science and Technology of Kobe University. During an assistant professor, he also worked as a visiting scholar at Zoology, University of Cambridge in 1995. He moved to Biosignal Research Center (BSRC) of Kobe University in 1997. After the experience as a visiting scholar in University California, San Diego from 2000-2001, he was promoted to an Associate Professor in the BSRC. He got a second Ph.D from School of Medicine of Kobe University and was finally promoted to a Professor in Laboratory of Chemistry and Utilization of Animal Production Resources, department of Agrobioscience, Graduate school of Agricultural Science. His major is a signal transduction research to develop medicine and functional (medical) food He was awarded the prize of “Young Scientist Award of the Japanese Pharmacological Society (2004).

Dennis E. Vance

Distinguished University Professor
University of Alberta Medicine, Edmonton, Canada

http://biochem.med.ualberta.ca/Research/faculty/Professors/Pages/Vance.aspx

The unexpected role of phospholipid methylation in diabetes and obesity

Abstract: Phosphatidylethanolamine (PE) is converted in the liver to phosphatidylcholine (PC) by phosphatidylethanolamine *N*-methyltransferase (PEMT). When Bremer and Greenberg first characterized PEMT in 1961, they would not have considered that PEMT would be linked to obesity and insulin resistance (IR). Such a link was discovered only after we constructed mice lacking PEMT. Wild-type mice became obese and developed IR when fed a high-fat diet whereas *Pemt*$^{-/-}$ mice did not. The mechanism for protection of *Pemt*$^{-/-}$ mice from obesity and IR is under investigation. When *Pemt*$^{-/-}$ mice were fed the highfat diet supplemented with surplus choline, these mice were no longer protected from obesity and IR. Moreover, mice with a liver-specific deletion of the CDP-choline pathway for PC biosynthesis are not protected from obesity and IR even though hepatic PC levels are decreased by 30%, the same as in *Pemt*$^{-/-}$ mice. An intact hepatic branch of the vagus nerve is required for the *Pemt* mice to exhibit the beneficial phenotype. *Pemt*$^{-/-}$ mice have attenuated biosynthesis of glucose in the liver which we ascribe to decreased ratio of PC to PE in mitochondria resulting, in increased oxidation of fatty acids. However, *Pemt*$^{-/-}$ mice develop fatty liver and liver disease when fed the high-fat diet, a complication that is alleviated by oral fenofibrate, an activator of PPARα that promotes β-oxidation in the liver. A possible treatment for humans with IR and obesity will be discussed.

Bio: Dennis E. Vance is a Distinguished University Professor at the University of Alberta. He has an international reputation for his seminal contributions to understanding the regulation of phosphatidylcholine biosynthesis and its function. His research has evolved into understanding the mechanism by which the lack of an enzyme that synthesizes phosphatidylcholine protects against diabetes and obesity. He has supervised 25 PhD theses and 37 postdoctoral fellows. He was Professor and Chair of the Department of Biochemistry at the University of British Columbia (1982-86). He moved to the University of Alberta in 1986 to establish a Lipid Research Group. He was Director of the SCOLAR (Stroke, Cardiovascular, Obesity, Lipid, Atherosclerosis Research) Training Program from the Canadian Institutes of Health Research (CIHR). He is Principal Investigator on a grant from CIHR that he has held continuously since 1973. His research on mammalian phosphatidylcholine metabolism has been recognized by the Boehringer Mannheim Canada Prize of the Canadian Biochemical Society in 1989, the Heinrich Wieland Prize awarded in 1995 in Munich, Germany, election as Fellow of the Royal Society of Canada (1996), a Canada Research Chair (2002), the Avanti Award from the American Society of Biochemistry and Molecular Biology (2006), the Kaplan Award from the University of Alberta (2009) the Chancellor's Award Lecture at Louisiana State University (2015). He co-authored with Geoff Zubay Principles of Biochemistry, an introductory biochemistry textbook and co-edited with Jean Vance five editions of an advanced textbook, Biochemistry of Lipids, Lipoproteins and Membranes. Prof. Vance was Editor in Chief of BBA, 2007 - 2012.

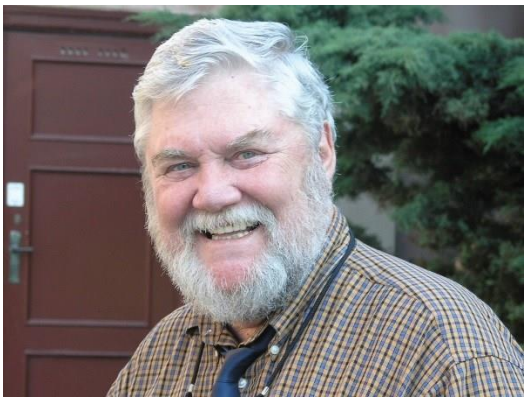
FRIDAY, MAY 20

11:35 am–12:50 pm - Session 8: Phospholipid Signaling

Chairpersons: Robert E. Anderson and Jean Vance

- Richard Phipps - Resolvins in airway inflammation: An effective therapy for chronic obstructive pulmonary disease?
- Jack Dixon - A novel family of secretory kinases
- Makoto Murakami - Novel roles of the phospholipase A_2 family in metabolic regulation

12:50-1:50 pm - Lunch and Posters



Robert Eugene Anderson

Professor, Department of Cell Biology
George Lynn Cross Research Professor
Dean McGee Professor of Ophthalmology
Adjunct Professor of Geriatric Medicine
University of Oklahoma, College of Medicine
Oklahoma City, OK

Robert-Anderson@ouhsc.edu

Bio: Robert Eugene Anderson, MD, PhD holds faculty appointments in the Departments of Ophthalmology, Cell Biology, and Geriatric Medicine at the University of Oklahoma Health Sciences Center. He is the Dean McGee Professor of Ophthalmology, George Lynn Cross Research Professor, and Director of Research in the Department of Ophthalmology and the Dean McGee Eye Institute. Dr. Anderson received his PhD in Biochemistry (1968) from Texas A&M University and his MD from Baylor College of Medicine (1975). In 1968, he was a postdoctoral fellow at Oak Ridge Associated Universities. At Baylor, he was appointed Assistant Professor in 1969, Associate Professor in 1976, and Professor in 1981. He joined the faculty of the University of Oklahoma Health Sciences Center in 1995. He served as director of the Oklahoma Center for Neuroscience from 1995-1999 and chairman of the Department of Cell Biology from 1998-2007.

Dr. Anderson has published extensively in the areas of lipid metabolism in the retina and biochemistry of retinal degenerations. He has edited 16 books, 15 on retinal degenerations and one on the biochemistry of the eye. Notable discoveries from Dr. Anderson's laboratory include: 1) First demonstration of the essential role of omega-3 fatty acids in retinal function, 2) The role of the phosphoinositide cascade in phototransduction in the invertebrate retina, 3) The role of the insulin receptor/PI 3-kinase/Akt pathway in stress-induced retinal degenerations, 4) The role of oxidant stress in light-induced apoptosis of photoreceptor cells, 5) The identification of the biosynthetic step catalyzed by ELOVL4, which is mutated in AD Stargardt-like macular dystrophy (STGD3), (6) The neuroprotective properties of phenyl-N-tert-butyl nitrones (PBN) and related derivatives in animal models of retinal degeneration, and 7) The discovery that very long chain saturated fatty acids (≥ 28 carbons) are essential for normal brain development and function.

Jean E. Vance, PhD, FRSC

Professor of Medicine
Molecular and Cell Biology of Lipids Group
University of Alberta, Edmonton, Canada

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Research Interests: Dr. Vance's research focuses on understanding the mechanisms of intracellular lipid trafficking in mammalian cells. She identified a region of the endoplasmic reticulum, designated mitochondria-associated membranes (MAM), which forms contact sites with mitochondrial outer membranes; these contact zones are required for the import of phosphatidylserine (PS) into mitochondria for decarboxylation to phosphate-dylethanolamine (PE). Her lab has generated and characterized mice lacking PS synthases as well as mice lacking PS decarboxylase in which mitochondrial PE was reduced and mitochondrial function was severely impaired. Dr. Vance's other major research interest is in cholesterol trafficking in the brain. Her lab has studied cholesterol transport defects in the neurodegenerative disease, Niemann-Pick type C (NPC) disease, using primary neurons and glial cells isolated from brains of NPC1-deficient mice. Her lab recently elucidated mechanisms in the brain that underlie the beneficial effects of cyclodextrin, currently used as a treatment for NPC disease.

Bio: Dr. Jean Vance received a BSc degree in Chemistry from London University (UK) and a PhD in Biochemistry from the University of Pittsburgh. Following a postdoctoral fellowship with Dr. Daniel Steinberg at the University of California San Diego she became an Instructor in Biochemistry at the University of British Columbia (Canada). Dr. Vance is currently a Professor of Medicine at the University of Alberta (Canada) and is a founding member of the Group on the Molecular and Cell Biology of Lipids at that university. She has served on editorial boards of the *Journal of Biological Chemistry* and the *Biochemical Journal,* and is currently an editorial board member of the *Journal of Lipid Research* and *Biochimica Biophysica Acta* (Lipids). Dr. Vance was Chair of a Gordon Conference on the Molecular and Cellular Biology of Lipids, as well as Chair of the Deuel Conference on Lipids and the Kern Aspen Lipid Conference. In addition, she served as co-chair of two ASBMB conferences on lipids. Her research contributions were recognized by her election as a Fellow of the Royal Society of Canada. She co-edited with Dr. Dennis Vance five editions of an advanced textbook: "Biochemistry of Lipids, Lipoproteins and Membranes".

Richard P. Phipps

Wright Family Research Professor of Environmental Medicine
Director of the Lung Biology and Disease Program
University of Rochester School of Medicine
Rochester, NY

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Resolvins in airway inflammation – An effective therapy for chronic obstructive pulmonary disease?

Abstract: Rationale: Chronic obstructive pulmonary disease (COPD) is a major global health problem predominantly caused by smoking tobacco, but also by inhalation of biomass smoke. COPD is the third leading cause of death in the United States. Cigarette smoke is a profound inflammatory stimulus and curiously the effects of smoking persist long after smoking cessation. This supports the idea that cigarette smoke interferes with the normal processes that resolve inflammation.

Hypothesis: Specialized pro-resolving lipid mediators (SPM) have profound pro-resolving effects on acute and chronic lung injury. Treatment with SPM promote resolution: a novel and important therapeutic goal for inflammatory diseases caused by cigarette smoking.

Results: Using primary human lung cells we show that certain SPMs work well to dampen inflammatory mediator production stimulated by tobacco smoke extract. And, using exhaled breath condensate that the profile of SPMs is dysregulated in human smokers. Our pre-clinical mouse models of acute and chronic cigarette smoke-incited inflammation demonstrate that SPM such as resolvin D1 (RvD1) dampen neutrophilic inflammation and promote its resolution through M2 pro-resolving macrophages. SPM also prevent smoke-induced emphysema with reductions in apoptosis and oxidative stress. Mechanistic studies revealed that RvD1 inhibits pro-inflammatory signaling by blocking both the MAPK and NF-kappaB pathways through a common regulatory kinase.

Conclusions: These studies show for the first time that pro-resolving mediators can be used to prevent inflammation and accelerate resolution/repair of lung injury due to both acute and chronic cigarette smoke exposure. Our results will pave the way for translational development of these exciting new compounds that have the potential to be effective therapies against human diseases of chronic inflammation and smoking. Supported by NIH grants R01 HL120908 and TL1 TR000096.

Bio: Dr. Phipps has authored or co-authorized over 250 articles, and numerous book chapters and reviews concerning control of normal and malignant B lymphocyte activation, cellular and molecular characterization of fibroblasts as mediators of inflammation, wound healing and fibrosis, Graves' ophthalmopathy, and platelet biology. He is on the editorial board of Clinical Immunology, PPAR Research, Frontiers in Immunology and Laboratory Investigation and is an ad hoc reviewer for many journals including the Journal of Clinical Investigation, Trends in Immunology, and the Journal of Immunology. He has served on numerous review committees for the NIH and other government agencies.

Dr. Phipps was awarded four patents related to bacterial autoinducer molecules and one patent on new methods to enhance platelet production.

Dr. Phipps has dedicated his career to advancing biomedical research and training pre and postdoctoral students. His research studying prostaglandins, cytokines, and fibroblasts have contributed to a better understanding of B cell lymphoma, Graves ' disease, COPD and inflammatory processes.

Jack E. Dixon

Distinguished Professor in Pharmacology, Cellular and Molecular Medicine, Chemistry and Biochemistry and Associate Vice Chancellor for Scientific Affairs, Office of the Vice Chancellor for Health Sciences, University of California San Diego
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A Novel Family of Secretory Kinases

Abstract: Protein phosphorylation is a fundamental mechanism regulating nearly every aspect of cellular life. Several secreted proteins are phosphorylated, but the kinases responsible are unknown. We identified a family of atypical protein kinases that localize within the Golgi apparatus and are secreted. Fam20C appears to be the Golgi casein kinase that phosphorylates secretory pathway proteins within S-x-E motifs. Fam20C phosphorylates the caseins and several secreted proteins implicated in biomineralization, including the small integrin-binding ligand, N-linked glycoproteins (SIBLINGs). Consequently, mutations in Fam20C cause an osteosclerotic bone dysplasia in humans known as Raine syndrome. Fam20C is thus a protein kinase dedicated to the phosphorylation of extracellular proteins.

Bio: Dr. Dixon earned a Ph.D. at the University of California Santa Barbara and did postdoctoral research at the University of California San Diego (UC San Diego.) In 1973, he joined the faculty at Purdue University and subsequently became the Wiley Distinguished Professor of Biochemistry. In 1991, Dr. Dixon moved to the University of Michigan where he was the Minor J. Coon Professor of Biological Chemistry and the Chair of the Department of Biological Chemistry. In 2003, he returned to the UC San Diego School of Medicine as Professor and Dean of Scientific Affairs. In 2007, Dr. Dixon was appointed Vice President and Chief Scientific Officer of the Howard Hughes Medical Institute (HHMI), a position he held until June of 2013. Following his retirement from HHMI in 2013, Dr. Dixon returned to UC San Diego where he is currently a Distinguished Professor of Pharmacology, Cellular and Molecular Medicine, and Chemistry and Biochemistry. He is also serving as Associate Vice Chancellor for Scientific Affairs, in the Office of the Vice Chancellor for Health Sciences.

Makoto Murakami

Lipid Metabolism Project, Tokyo Metropolitan Institute of Medical Science
Graduate School of Medicine and Faculty of Medicine
The University of Tokyo Setagaya-ku,
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http://www.igakuken.or.jp/lipid/

Novel roles of the phospholipase A_2 family in metabolic regulation

Abstract: Phospholipase A_2s (PLA_2s) are a group of enzymes that hydrolyze the *sn*-2 position of phospholipids to generate fatty acids and lysophospholipids, which serve as lipid mediators or their precursors. Mammalian genomes encode genes for more than 30 PLA_2s or related enzymes, which are subdivided into several groups on the basis of their structures, enzymatic properties, and evolutional relationships. Among them, the Ca^{2+}-dependent cytosolic PLA_2 ($cPLA_2$), Ca^{2+}-independent PLA_2 ($iPLA_2$), and secreted PLA_2 ($sPLA_2$) families are regarded as the "big three". Recent studies using transgenic and knockout mice for various PLA_2s, in combination with lipidomic analyses, have revealed their distinct contributions to various pathophysiological events through mobilizing unique lipid pathways. From a general viewpoint, $cPLA_2$ ✔ plays a central role in the initiation of arachidonic acid metabolism, the $iPLA_2$ family regulates membrane homeostasis or energy metabolism, and the $sPLA_2$ family affects various biological events by modulating extracellular phospholipid milieus in response to given micro environmental cues (*J Biol Chem* 2016, *J Exp Med* 2015, *Cell Metab* 2014, *Nat Immunol* 2013, *J Exp Med* 2013, *J Clin Invest* 2010, etc). In this symposium, novel aspects of the $sPLA_2$ and $iPLA_2$ families in metabolic regulation, as revealed by studies using their gene-manipulated mice in combination with comprehensive metabolomics, will be discussed.

Supported by AMED-CREST and MEXT KAKENHI.

Bio: Dr. Makoto Murakami received his B.A. (1986), M.S. (1988) and Ph.D. (1991) degrees from the University of Tokyo. His postdoctoral training was at the University of Tokyo (1991-1993) and Harvard University (1993-1995). He worked as an associate professor at Showa University (1995-2005) and as a project leader at Tokyo Metropolitan Institute of Medical Science (2005-2016), and is now a professor at the University of Tokyo (2016-). He has authored 170 peer reviewed original articles and 50 review articles on phospholipase A_2s and lipid mediators. He is a fellow of the Japanese Lipid Biochemistry Society and is the recipient of the Young Investigator Awards for the Pharmaceutical Society of Japan and the Japanese Society of Inflammation and Regeneration, Investigator Awards for the Tokyo Metropolitan Institute of Medical Science and the Bureau of Social Welfare and Public Health at Tokyo Metropolitan Government, and Award for the Terumo Science Foundation. He is a former chair of the 6th International Conference on Phospholipase A_2 and Lipid Mediators (PLM2015) held in Tokyo.

FRIDAY, MAY 20

1:55-2:45 pm - Session 9: Lysolipids as Mediators of Disease

Chairpersons: Suzanne E. Barbour and Joan Clària

- Sarah Spiegel - Sphingosine-1-phosphate rheostat
- Junken Aoki - ATX-LPA1 axis contributes to proliferation of chondrocytes by regulating fibronectin assembly leading to proper cartilage formation

Suzanne E. Barbour

Professor
Dept. of Biochemistry & Molecular Biology Virginia Commonwealth University

sbarbour@vcu.edu

Bio: Suzanne E. Barbour is a native of New Jersey where she completed a BS in Chemistry at Rutgers University in 1983. She earned a doctorate in molecular biology and genetics from The Johns Hopkins University in 1990 and went on the postdoctoral studies with Dr. Edward Dennis at the University of California San Diego. Suzanne's postdoctoral work sparked her interest in lipid metabolism and phospholipase A_2 and she focused on these areas when she started he faculty position at Virginia Commonwealth University in 1993. Suzanne was on faculty at VCU for more than 20 years. During that time, she developed a research program focused on the group VIA phospholipase A_2, ran a graduate program in biochemistry, served on numerous training grant study sections (including BRT-B, for which she was committee chair), and started her service on the ASBMB EPD committee which continues today. In 2013, Suzanne left VCU to take a position as a Program Director in the Division of Molecular and Cellular Biosciences at the National Science Foundation. She ran a program in Cellular Dynamics and Function until she left NSF in July 2015 to become dean of the Graduate School at the University of Georgia.

Joan Clària

Senior Consultant at the Biochemistry and Molecular Genetics Service of the Hospital Clínic and Associate Professor at the Department of Biomedicine of the University of Barcelona Medical School.

CLARIA@clinic.ub.es

Bio: Joan Clària is currently a Senior Consultant at the *Clinical Laboratory Service: Biochemistry and Molecular Genetics* of the *Hospital Clínic of Barcelona*. He is also an Associate Professor at the *Department of Biomedicine* at the *School of Medicine* of the *University of Barcelona*. He was trained as a specialist in Clinical Biochemistry and initiated his scientific career as a research fellow from 1987 to 1992 at the *Liver Unit* of the *Hospital Clínic of Barcelona*. From 1993 to 1996 he performed his post-doctoral studies as a Fulbright scholar at the *Brigham and Women's Hospital and Harvard Medical School* (Boston, MA) with Professor Charles N. Serhan, working with novel aspirin-triggered lipid mediators that promote the resolution of inflammation. He has also been a Visiting Scientist at the *University of North Carolina* (Chapel Hill, NC) (2001) and *The Jackson Laboratory* (Bar Harbor, ME) (2007) and a Visiting Professor at the *Harvard Institutes of Medicine* (*Brigham and Women's Hospital/Harvard Medical School*) (Boston, MA) (2010-2011). His laboratory is mainly interested in the study of lipid mediators implicated in the resolution of inflammation, with a special emphasis on the role of specialized pro-resolving mediators (SPM) derived from omega-3PUFA in obesity-associated liver complications. He is a member of the Editorial Board of *Journal of Immunology*, *Molecular Innate Immunity, World Journal of Immunology*, *Gut, Lipids Insight and Frontiers in Lipidology and Metabolism*. He is the current President of the *European Society for Lipid Mediators*.

Sarah Spiegel

Professor and Chair
Mann T. and Sara D. Lowry Chair in Cancer Research
Dept. of Biochemistry & Molecular Biology
Virginia Commonwealth University, VCU Massey Cancer Center

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Sphingosine-1-phosphate: A Bridge From Bench To Clinic

Abstract: The sphingolipid metabolite sphingosine-1-phosphate (S1P), a ligand for five specific GPCRs, designated S1PR1-5, and the kinases that produce it, SphK1 and SphK2, have emerged as critical regulators of numerous fundamental biological processes important for inflammation and cancer. Although most of the actions of S1P are mediated via S1PRs, we have shown that nuclear S1P formed by SphK2 is an endogenous inhibitor of histone deacetylases (HDACs). Obesity, which is now endemic, increases breast cancer risk and is associated with worse prognosis, perhaps due in part to chronic inflammation induced by obesity, the high frequency of triple negative breast cancer (TNBC), and ineffective hormonal therapy. This lecture will highlight the role of the SphK/S1P/S1PR axis in obesity promoted breast cancer progression, and discuss its involvement in a feed-forward amplification loop leading to activation of the master transcription factors NF-kB and STAT3. Focus will also be on a new mechanism of action in cancer of the pro-drug FTY720/fingolimod that is used for treatment of multiple sclerosis. The sphingosine analogue FYY720 is phosphorylated in the nucleus by SphK2 to the active form FTY720-P that like S1P binds and inhibits class I HDACs to regulate gene transcription. Treatment of ERα negative human and murine breast cancer cells with FTY720 reactivated expression of silenced ERα and sensitized them to tamoxifen. Oral administration of FTY720 suppressed development, progression, and aggressiveness of breast tumors in high fat diet fed MMTV-PyMT mice and strikingly reversed the loss of ER ✔ and PR in advanced carcinoma. In addition, treatment of mice bearing ERα negative syngeneic breast tumors with FTY720 also re-expressed ERα in the tumors and increased therapeutic sensitivity to tamoxifen *in vivo*. These results suggest that FTY720 deserves consideration as a multi-pronged attack for effective treatment of conventional hormonal therapy-resistant breast cancer and TNBC. Supported by NIH grants RO1CA061774 and RO1GM043880 and the DoD award W81XWH-14-1-0086.

Bio: Dr. Sarah Spiegel received her BS in Chemistry and Biology in 1974 from The Hebrew University in Jerusalem, her PhD in Biochemistry in 1983 from the Weizmann Institute in Rehovot. She did postdoctoral work at NIH. Her early research focused on the role of ganglioside GM1 in cell signaling. After joining the faculty in the Department of Biochemistry at Georgetown University Medical School, her focus shifted to the roles of the bioactive sphingolipid metabolite, sphingosine-1-phosphate (S1P), whose functions as a pleiotropic signaling lipid were discovered in her lab. In 2002, she became Chair of the Department of Biochemistry & Molecular Biology at the Virginia Commonwealth School of Medicine. In 2007, she assumed the Mann T. and Sara D. Lowry Chair in Oncology at the Massey Cancer Center, where she co-directs the MCC Cancer Cell Signaling Program. She has received many awards for her work, including the Virginia Outstanding Scientist of the Year (2008), the Ernst and Berta Scharrer Medal from Goethe University (2008), the ASBMB Avanti Award in Lipids (2009), NIH Merit Award (2003), election as a Fellow of the American Association for the Advancement of Science (2009), was a keynote speaker at numerous international meetings, received Sackler Lectureship, Tel Aviv University, Israel (2014), and Journal of Lipid Research Special Lectureship (2015).

Junken Aoki

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ATX-LPA1 axis contributes to proliferation of chondrocytes by regulating fibronectin assembly leading to proper cartilage formation

ABSTRACT: The lipid mediator lysophosphatidic acid (LPA) signals via six distinct G protein-coupled receptors to mediate both unique and overlapping biological effects, including cell migration, proliferation and survival. LPA is produced extracellularly by autotaxin (ATX), a secreted lysoPLD. ATX-LPA receptor signaling is essential for normal development and implicated in various (patho) physiological processes, but underlying mechanisms remain incompletely understood. Through gene targeting approaches in zebrafish and mice, we show here that loss of ATX-LPA1 signaling leads to disorganization of chondrocytes, causing severe defects in cartilage formation. Mechanistically, ATX-LPA1 signaling acts by promoting S-phase entry (DNA synthesis) and cell proliferation of chondrocytes both in vitro and in vivo, at least in part through β1-integrin translocation leading to fibronectin assembly and further extracellular matrix deposition; this in turn promotes chondrocyte-matrix adhesion and cell proliferation. Thus, the ATX-LPA1 axis is key regulator of cartilage formation.

BIO: Dr. Junken Aoki received his B.A. degree from University of Tokyo in 1987, M.S, degree from University of Tokyo in 1989, and Ph. D. degree from University of Tokyo in 1992. His postdoctoral training was at Tokyo Metropolitan Institute of Medical Science in Dr. Akio Nomoto's laboratory. In 1996, he started his work on lipid mediator at Tokyo University in Keizo Inoue's laboratory as an assistant professor. In 2000, he continued his worn on lysophospholipids (lysophosphatidic acid and lysophosphatidylserine) at University of Tokyo in Hiroyuki Arai's laboratory. In 2007, he became independent at Tohoku University at Tohoku University and continued his work on lysophospholipids and phospholipase A_1. From 2016, he is now a director of the Japanese Biochemical Society and the biology part of the Japanese pharmaceutical Society.

FRIDAY, MAY 20

2:45-3:35 pm - Session 10: Phospholipids and Lysolipids in Disease

Chairpersons: Tim Hla and Sophie Layé

- Jerold Chun - Diseases involving lysophosphatidic acid (LPA) or sphingosine 1-phosphate (S1P) receptor signaling
- Joan Heller Brown - Sphingosine 1-phosphate signaling in inflammation and disease

3:35-4:00 pm - Coffee break

Sophie Layé

Research Director
Head of NutriNeuro Department, INRA , University of Bordeaux
Head of the international Lab OptiNutriBrain, Laval University (Québec, Canada), Bordeaux University, INRA (France)

http://www.optinutribrain.ulaval.ca/
https://www6.bordeaux-aquitaine.inra.fr/nutrineuro

Bio: Dr Sophie Layé received her BS degree in genetic from Paul Sabatier University (Toulouse, France), MS degree and PhD in Neuroscience from Bordeaux University (France). Her post-doctoral training was at Stockholm University in Stockholm (Sweden). Dr Layé's laboratory is recognized for its work on the influence of nutrition on brain functions, in particular n-3 and n-6 polyunsaturated fatty acids in neuroinflammation, neuronal plasticity, depression and cognition and obesity/diabetes on neuro-inflammatory processes. She also studies the protective effect of micronutrients (such as polyphenols) on cognitive decline and neurodegenerative diseases. She has authored more than 120 publications, review articles and book chapters on the mechanisms underlying the effect of nutrition on brain functions and behavior and has been invited to more of 90 conferences and congresses. Dr Layé is a research fellow at Institut National de la Recherche Agronomique, and is the recipient of the prestigious Laurier INRA Scientific Breakthrough Award, the INRA Award for Excellence in Research, the faculty mentor Award from Bordeaux University, the fondation pour la Recherche Medicale Award, the IPSEN Investigator Award (Neuroimmunoendocrinology), the post-doctoral INSERM Award and the scholarship Award from the French Ministry of Research. She is the former chair and organizer of the French Society of Nutrition Congress and served as chair for the French Diabetes Society committee, the European Meeting on Glial Cells in Health and Disease and the GERLI meeting lipidomic congress. She is the organizer of the International summer school "Nutrition and Brain functions" (Cajal advanced courses in Neuroscience). She serves the editorial board of "Brain Behavior and Immunity" and "Frontiers in Neuroendocrine Science, as specialty of Frontiers in Endocrinology". She is a member of the International Life Science Institute (ILSI) Europe Expert Group and the knowledge Hub on Malnutrition in the elderly (JPI healthy diet for a healthy life).

Joan Heller Brown

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Sphingosine 1-phosphate signaling in inflammation and disease

Abstract: Sphingosine 1-phosphate (S1P) is generated in and delivered to tissues subject to inflammatory insults. Our work demonstrates that stimulation of S1P2 and S1P3 receptors by S1P activates the low molecular weight GTPase RhoA leading to inflammation and aberrant growth. One pathway by which RhoA signals is through the novel phospholipase C isoform PLC epsilon (PLCε), which has domains for regulation by RhoA and another small G-protein, Rap1. In astrocytes S1P acts on PLCε to elicit prolonged activation of phosphoinositide (PI) hydrolysis, protein kinase C and D (PKD). As a consequence, NFkB is translocated to the nucleus and inflammatory genes including interleukins and cyclooxygenase -2 (COX-2) are induced. Prolonged signaling by PLCε is conferred by its perinuclear localization, and the ability of its unique CDC25 Rap exchange domain to activate Rap1 and feedback regulate PI hydrolysis. *In vivo* studies using PLCε KO mice demonstrate that inflammatory changes and astrogliosis following brain injury are diminished, and that clinical signs and inflammation in the EAE model of multiples sclerosis are attenuated. S1P also signals through RhoA to stimulate proliferation of glioblastoma cells through induction of transcriptional pathways. The matricellular protein CCN1 is markedly upregulated and signals through binding to integrins, providing a mechanism for GPCR/integrin crosstalk. Rap1 also contributes to inside out integrin signaling. Blocking CCN1, integrins or Rap1 function prevents agonist induced cell proliferation *in vitro*. In addition, *in vivo* growth of tumor xenografts is prevented by Rap1 knockdown. Further studies demonstrate that S1P stimulates nuclear translocation of two transcriptional co-activators, MRTF-A and YAP. Both are required for CCN1 induction and cell proliferation. RNA seq analysis of CRISPR/Cas9 MRTF-A and YAP KO cells reveals, however, that a subsets of genes are selectively induced through only one or the other transcriptional co-activator and are involved in distinct cellular responses. Experiments using intracranial xenografts are in progress with the aim of demonstrating that these pathways contribute to *in vivo* glioblastoma growth and invasion.

Bio: Dr. Joan Heller Brown earned her B.A. degree at Cornell University and her Ph.D. in Pharmacology at the Albert Einstein College of Medicine. Following postdoctoral studies she moved to UCSD and has risen to the rank of Distinguished Professor and Chair of the Department of Pharmacology. Dr. Heller Brown was the recipient of a Faculty Development Award from the Pharmaceutical Manufacturer's Association and of an Established Investigator Award from the American Heart Association (AHA). She is an elected Fellow of the AHA, of the International Society for Heart Research, and of the APS Cardiovascular Section. Her awards include the Janice Pfeffer Distinguished Lecture, Louis S. Goodman Lecturer, Lucchesi Distinguished Lectureship in Cardiac Pharmacology, the PhRMA Foundation Award in Excellence, the Albert Einstein College of Medicine Distinguished Ph.D. Alumna Award and the Distinguished Achievement Award from the Basic Cardiovascular Sciences Division of the AHA. She has served on multiple Scientific Advisory Boards and on the Editorial boards of numerous journals including the Journal of Biological Chemistry, Circulation, Circulation Research, and Nature Reviews Drug Discovery. An active member of the American Society for Experimental Therapeutics, she served as editor of their flagship journal, Molecular Pharmacology. Her scientific interest is on how neurohormones regulate cellular responses i.e. "signal transduction" by G-protein coupled receptors (GPCRs). Recent studies have demonstrated roles of GPCRs in cell proliferation, survival and inflammation in models of cardiac and CNS disease. She has maintained continuous extramural grant support, published more than 230 papers and review articles, mentored 50 predoctoral and postdoctoral trainees and directs the departments NIH training grant in Pharmacological Sciences.

FRIDAY, MAY 20

Friday, May 20

4:00-5:15 pm - Session 11: New Frontiers

Chairpersons: Marianne Schultzberg and Nicos A. Petasis

- Takap Shimizu - Mechanism of glycerophospholipid diversity and its biological consequence
- Hiroyuki Arai - Cellular responses to loading with excess SFAs or PUFAs
- Jean-Pierre Changeux - Lipids as allosteric modulates of ligand-gated ion channels

5:15-5:45 pm - Concluding Session

Nicolas G. Bazan, Jerold Chun, Jesper Z. Haeggström, Tim Hla, Charles N. Serhan, and Takao Shimizu

Marianne Schultzberg

Professor in Clinical Neuroscience
Karolinska Institutet
Huddinge, Sweden

http://ki.se/en/people/marisc

Bio: Dr. Marianne Schultzberg received her B.Sc. degree from Stockholm University and her Ph.D. from Karolinska Institutet (KI). Her postdoctoral training was in the Department of Physiology, University of Liverpool, and she was a visiting scientist at NIMH, USA. She currently serves her second term as ProDean for doctoral education at KI. She has 206 publications, and an h-index of 44. Major contributions from Dr. Schultzberg's earlier work include ground-breaking studies on coexistence of neuropeptides and classical neurotransmitters. Since the 1990's her research concerns the role of neuroinflammation in neurodegenerative disorders such as Alzheimer's disease (AD), and combines cellular and animal experimental models in a translational approach based on *in vivo* and *in vitro* models in close association with the geriatric clinic at Karolinska University Hospital, with the goal to find new treatments strategies. The resolution of inflammation in the brain is her current research focus, with important original findings of alterations in the synthetic pathways and signaling of the resolution of inflammation in AD.

Nicos A. Petasis

Harold & Lillian Moulton Chair in Chemistry
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Bio: Nicos Petasis, a native of Cyprus, received his B.Sc. degree from the Aristotle University of Thessaloniki in Greece, and his Ph.D. from the University of Pennsylvania in Philadelphia, USA. Following a postdoctoral appointment at the same university he joined the faculty at the Department of Chemistry at the University of Southern California (USC), where he is also a member of the USC Loker Hydrocarbon Research Institute, the USC Norris Comprehensive Cancer Center, and the USC Institute of Biomedical Therapeutics. His research interests span from synthetic organic chemistry, medicinal chemistry and chemical biology, to the development of new therapeutics for inflammation, cancer, and neurodegenerative diseases. In addition to the discovery of novel and widely used reactions, his research has focused on the chemistry, biology, and medicinal applications of novel specialized pro-resolving lipid mediators, which are derived from polyunsaturated fatty acids. His chemical studies and collaborative efforts on the lipoxins, resolvins, protectins/neuroprotectins, and maresins led to the elucidation of their beneficial roles in the resolution of inflammation, neuroprotection, and tissue regeneration. Dr. Petasis is the recipient of the Arthur C. Cope Scholar Award by the American Chemical Society, and was elected Fellow of the American Association for the Advancement of Science.

Hiroyuki Arai

Professor of Department of Health Chemistry
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Cellular responses to loading with excess SFAs or PUFAs

Abstract: The degree of fatty acid unsaturation in membrane phospholipids affects many membrane associated functions and can be influenced by dietary consumption of fatty acids such as saturated fatty acids and polyunsaturated fatty acids (PUFAs). Cells must adapt to changes in composition of membrane fatty acids by regulating lipid-metabolizing enzymes. Loading cells with excess SFAs causes an increase of SFA-containing phospholipids and triggers various cellular responses such as cell death, insulin resistance, inflammatory response, and unfolded protein response (UPR), which are associated with lipotoxicity in metabolic syndrome. To deal with the SFA-induced toxicity, cells reduce the accumulation of SFAs in membrane phospholipids by converting some of them to monounsaturated fatty acids via stearoylcoenzyme A desaturase (SCD). Because unsaturated fatty acids (UFAs) cannot be converted into fatty acids with fewer double bonds in mammalian cells, cells must respond to excess PUFAs by a mechanism other than saturating them. Although a portion of excess PUFAs can be degraded by β-oxidation or esterified to form triglycerides that function to sequester PUFAs into lipid droplets, how cells deal with excess PUFAs in membrane phospholipids is not fully understood. In this talk, I will summarize our recent study on how cells deal with excess SFAs or PUFAs.

Bio: University of Tokyo, Japan, B.S. (Biochemistry; Department of Health Chemistry, Graduate School of Pharmaceutical Sciences) 1979
University of Tokyo, Japan, Ph.D. (Biochemistry; Department of Health Chemistry, Graduate School of Pharmaceutical Sciences) 1984
University of Illinois, U.S.A, Post-doctoral Fellow (Department of Food Science) 1984-1994
Tufts University, Medical School, U.S.A, Post-doctoral Fellow (Department of Physiology) 1986-1988
University of Tokyo, Japan, Assistant Professor, 1988-1994
(Department of Health Chemistry, Graduate School of Pharmaceutical Sciences)
University of Tokyo, Japan, Associate Professor, 1994-2000
(Department of Health Chemistry, Graduate School of Pharmaceutical Sciences)
University of Tokyo, Japan, Professor, 2000-present
(Department of Health Chemistry, Graduate School of Pharmaceutical Sciences)

Jean-Pierre Changeux

Kavli Institute for Brain & Mind UCSD & Institut Pasteur, Paris France

Lipids as allosteric modulators of ligand-gated ion channels

Abstract: The concept of allosteric interaction (1) contrasts with the classical mechanism of competitive, steric, interaction between ligands for a common site since allosteric interactions take place between topographically distinct sites and are mediated by a discrete and reversible conformational change of the protein. The concept was soon extended to membrane receptors for neurotransmitters (2) and shown to apply to the signal tranduction process which, in the case of the acetylcholine nicotinic receptor (nAChR), links the ACh binding site to the ion channel (3). Pharmacological effectors, such as Ca++ ions and ivermectin, referred to as allosteric modulators, were discovered and shown to enhance the transduction process by binding to sites distinct from the orthosteric ACh site and the ion channel (4). The recent X-ray structures, at atomic resolution, have revealed the resting and active conformations of prokaryotic and eukaryotic homologs of the nAChR, in combination with atomistic molecular dynamics simulations (5). AChRs are transmembrane proteins embedded in the lipid bilayer which interact with lipid monolayers with a high specificity more readily with cholesterol than with ergosterol, phosphatidylcholine, or other phospholipids (6). Its affinity is also higher for long-chain phosphatidylcholines than for short-chain ones. Lipids are necessary for the reconstitution of nAChR function and influence conformational selection by stabilizing varying proportions of activatable versus nonactivatable conformations (7). The structure of apo GLIC a prokaryotic homolog of nAChR at 2.9A shows electron density at the protein/lipid bilayer interface consistent with the presence of three lipid molecules per subunit. Among the three lipid molécules observed, the upper lipid is located just behind the GLIC binding site for general anesthetics and is significantly displaced in the propofol GLIC structure (8). Lipids, free fatty acids, and steroids are known to allosterically modulate pLGICs, notably nAChRs. These binding sites constitute likely candidates for allosteric modulation by lipids as endogenous ligands.

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2. Changeux (1964) PhD Thesis; (1965) [On the allosteric properties of biosynthesized lthreonine deaminase. VI. General discussion]. *Bull Soc Chim Biol* (Paris) 47:281-300.

3. Taly A, Corringer PJ, Guedin D, Lestage P, Changeux JP. (2009) Nicotinic receptors: allosteric transitions and therapeutic targets in the nervous system *Nat Rev Drug Discov.* 8:733-50.

3. Corringer, P.J., Poitevin, F., Prevost, M.S., Sauguet, L., Delarue, M., Changeux, J.P.(2012) Structure and pharmacology of pentameric receptor-channels: from bacteria to brain. *Structure* 20, 941–956 5.

4. Changeux JP (2015) Protein dynamics and the allosteric transitions of pentameric receptor channels. *Biophys Rev*. 6:311-321.

5. Cecchini M, Changeux JP (2014) The nicotinic acetylcholine receptor and its prokaryotic homologues: Structure, conformational transitions & allosteric modulation. *Neuropharmacology*. 96 137-49.

6. Popot JL, Demel RA, Sobel A, Van Deenen LL, Changeux JP.(1978) Interaction of the acetylcholine (nicotinic) receptor protein from Torpedo marmorata electric organ with monolayers of pure lipids. *Eur J Biochem*.85 27-42.

7. Baenziger JE, Hénault CM, Therien JP, Sun J.(2015) Nicotinic acetylcholine receptor-lipid interactions: Mechanistic insight and biological function. *Biochim Biophys Acta*. 1848 1806-17.

8. Nury H, Van Renterghem C, Weng Y, Tran A, Baaden M, Dufresne V, Changeux JP, Sonner JM, Delarue M, Corringer PJ.(2011) X-ray structures of general anaesthetics bound to a pentameric ligand-gated ion channel. *Nature.* 469:428-31.

Bio:

Jean-Pierre Changeux PhD is International Faculty at the Kavli Institute for Brain & Mind University of California San Diego and Honorary Professor at the Collège de France & Institut Pasteur, Paris.

Changeux PhD studies led to the discovery that chemical signals regulate the biological activity of proteins by acting at "allosteric" sites distinct from the biologically active sites via a conformational change (19611965). He then proposed (1964,1966) that this type of regulation applies to receptor mechanisms engaged in the transmission of chemical signals in the nervous system and through his life-time work, validated this insight. His studies were initiated by the first identification of a neurotransmitter receptor: the nicotinic acetylcholine receptor together with Lee & Kasai (1970) and culminated by a contribution, with Corringer and Delarue to establishing the 3-D structure and conformational transition of prokaryotic orthologs of nicotinic receptors by X-ray crystallography and molecular dynamics (2005-15). Changeux and his colleagues also deciphered the topology of allosteric modulatory sites for pharmacological ligands (19962011), thereby substantiating a novel strategy of drug design based on allosteric modulation.

Moving to neuronal networks, Changeux, together with Courrège & Danchin (1973, 1976) formulated and experimentally tested the theory that long-term epigenesis of neuronal networks occurs by the activity-dependant selective stabilization and elimination of developing synapses.

Last, in particular with Dehaene, he proposed and tested models for defined cognitive tasks and their pharmacological modulation (1991-2015) in particular, a neuronal hypothesis for conscious processing, implicating a "global neuronal workspace" composed of a brain-scale horizontal network of long axon neurons (1998-2015).

Changeux has published several books including Neuronal Man (1985), What Makes Us Think? (with Paul Ricoeur, 2002), Physiology of truth (2002).

His academic accolades include the Gairdner award (1978), the Wolf prize (1983), Médaille d'Or, Centre National de la Recherche Scientifique, Paris, (1992), the Goodman and Gilman Award in drug receptor pharmacology (1994), the Balzan Prize (2001), the US National Academy of Sciences Award in Neurosciences (2007), the Japanese Society for the Promotion of Science Award for Eminent Scientists, Tokyo (2012) and the Olav Thon prize Oslo (2016).

POSTERS

1. **2016 Journal of Lipid Research Junior Investigator Award - Lipoxin A4 and lipoxin B4 attenuate adipose tissue inflammation in obese patients** – Emma Börgeson, Ville Wallenius, Per Björklund, Marianne Quiding-Järbrink, Kumar Sharma, Catherine Godson (Institute of Clinical Sciences, Department of Gastrosurgical Research and Education and Diabetes Complications Research Centre, School of Medicine and Medical Sciences, Conway Institute, University College Dublin, England)
2. **APOE4 genotype dependent deficits in DHA containing phospholipids and DHA transporters in the cerebrovasculature of Alzheimer's disease patients -** Laila Abdullah**,** James E. Evans, Ben Shackleton, Joseph O. Ojo, Thinh Nguyen, Jon Reed, Michael Mullan, Fiona Crawford and Corbin Bachmeier (Roskamp Institute, Sarasota, FL, USA)
3. **Adipose prostaglandin D2 enhances body weight gain and suppresses lipolysis through DP2 receptors** - Ko Fujimori, Eri Wakai, Kosuke Aritake, Yo Oishi, Nanae Nagata, Fumio Amano, Michael Lazarus, and Yoshihiro Urade (Osaka University of Pharmaceutical Sciences and Osaka Bioscience Institute, Osaka, Japan)
4. **MGST2-generated LTC4 is the major mediator of stress-triggered DNA damage** - Efrat Dvash, Adi Katov and Menachem Rubinstein (Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel)
5. **APOE ε4 increases the ratio of serum phospholipid arachidonic acid to docosahexaenoic acid and aids in the identification of individuals with preclinical Alzheimer's disease** - James E. Evans, Laila Abdullah, Tanja Emmerich, Thinh Nguyen, Gogce Crynen, Ben Shackleton, Jon Reed, Andrew P. Keegan, Cheryl Luis, Leon Tai, Mary J. LaDu, Michael Mullan, Fiona Crawford and Corbin Bachmeier (Roskamp Institute, Sarasota, FL, USA)
6. **Pigment epithelium-derived factor (PEDF) regulation of docosanoid-mediated signaling enhances corneal nerve regeneration by targeting neurotrophins, semaphorins, and regeneration associated genes (RAGs)** - Thang Luong Pham, Azucena Kakazu, Jiucheng He, Haydee H.P. Bazan (Louisiana State University Health New Orleans, School of Medicine, Neuroscience Center of Excellence, New Orleans, LA, USA)
7. **Subcellular localization of a 2-arachidonoyl glycerol signaling cassette in developing retinal ganglion cell axons is consistent with formation of hotspots** - David T. Stark, Joseph Caprioli (Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA)
8. **Normalizing membrane phospholipid derangement from epigenetic insults in neurological disease with lipids and resolvins** – Patricia C. Kane, Shideh Pouria, Annette L. Cartaxo, Kristine Gedroic, Damien Downing, Thomas Wnorowski, Edward Kane, Mark O'Neal Speight (Director, NeuroLipid Research Foundation, Millville, New Jersey, USA)
9. **Maresin 1 modulates hypoxia-induced and lipotoxic ER stress in primary hepatocytes** – Bibiana Rius, Esther Titos, Cristina López-Vicario, A. Lopategi, Mireia Casulleras, José AlcarazQuiles, Joan Clària (Department of Biochemistry and Molecular Genetics, Hospital ClínicIDIBAPS, Barcelona, Spain)
10. **Identification of cyclooxygenase-related enzymes in bacteria** - Zahra Mashhadi, William E. Boeglin, and Alan R. Brash (Department of Pharmacology and the Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, TN, USA)
11. **Prostaglandin D_2 DP1 receptor ameliorates, stroke outcomes through cerebral blood flow and homeostasis** – Abdullah Shafique Ahmad, Thomas M. Dougherty, Shah Narumiya, and Sylvian Dore (Department of Anesthesiology, Center for Translational Research and Neurodegenerative Disease, University of Florida, Gainesville, FL, USA)
12. **Alterations in lysophoshatidylcholine-related metabolic parameters in the plasma of mice with bacterial peritonitis** – Won-Gyun Ahn, Jun-Sub Jung, Hyeok-Yil Kwon, and Dong-Keun Song (Departments of Pharmacology, Chunchon, S. Korea)

13. **The role of diplamitoylphosphatylcholine produced by lysophosphatidycholine acyltransferase 1 in polyunsaturated fatty acid-induced cytotoxity** – Sosuke Akagi, Nozomu Kono, Hiroyuki Ariyama, Hideo Shindou, Takao Shimizu, and Hiroyuki Arai (Department of Health Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan)
14. **Lipocalin-type prostaglandin D synthase: a transporter of prostaglandin D_2 and scavenger of prostaglandin D_2-degraded products** – Kosuke Aritake, Shigeru Shimamoto, and Yoshihiro Urade (Molecular Sleep Biology, International Institute for Integrative Sleep Medicine (IIIS), University of Tsukuba, Ibaraki, Japan; Osaka Bioscience Institute, Osaka, Japan)
15. **Neuroprotectin D1 (NPD1) stereoselectively modulates inflammasome transcription and activation in human retinal pigment epithelial cells** – Aram Asatryan and Nicolas G. Bazan (Neuroscience Center of Excellence, SOM, LSUHSC, New Orleans, LA, USA)
16. **PUFA-mediated proinflammatory to ionizing radiation** – Evagelia C. Laiakis, Katrin Strassburg, Steven Lai, Rob J. Vreeken, Thomas Hankemeier, Rob Plumb, Albert J. Fornance Jr., and Giuseppe Astarita (Department of Biochemistry and Molecular & Cellular Biology, Georgetown University, Washington DC and Waters Corporation, Health Sciences, Milford, Massachusetts USA)
17. **PLA_2G5-expressing M2 macrophages in mouse and human type 2 inflammation** – Munehiro Yamaguchi, Jennifer Zacharia, Tanya M. Laidlaw, and Barbara Balestrieri (Department of Medicine, Harvard Medical School; Jeff and Penny Vinik Center for Allergic Disease Research, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA)
18. **Very long-chain fatty acid-containing phosphotidylcholine molecular species are altered in age-related macular degeneration (AMD)** – Surjyadipta Bhattacharjee, Bokkyoon Jun, William C. Gordon, Nicolas G. Bazan (Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA)
19. **Sphingosine 1-phosphate bound to ApoM+HDL modulates generation of the adaptive immune response at different stages of lymphocyte ontogeny** – Victoria A. Blaho, Sylvian Galvani, Eric Engelbrecht, Catherine Liu, Steven L. Swendeman, Mari Kono, Richard L. Proia, Lawrence Steinma, May H. Han, and Timothy Hla (Center for Vascular Biology, Department of Pathology and Laboratory Medicine, and Brain and Mind Research Institute, Weill Medical College of Cornell University, New York, NY, USA)
20. **Rapid normal-phase separation of lysophosphatidic acid and other lysophospholipids by ultra-high performance supercritical fluid chromatography** – Joost Brandsma, Thomas Sutton, Julie Herniman, Clair Brooke, Anthony Postle, Timothy Jenkins, and John Langely (University of Southampton, Faculty of Medicine, Southampton, UK)
21. **Novel regulatory mechanism of the inflammatory response mediated by Neuroprotectin D1 (NPD1) targeting transcription of Wnt5a** – Jorgelina Calandria and Nicolas G. Bazan (Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA)
22. **Novel omega-3 endocannabinoid epoxides emnating from the cross-talk between the endocannabinoid and cytochrome P450 metabolic pathways** – Daniel R. McDougle and Aditi Das (Department of Comparative Biosciences, Department of Biochemistry, Department of Nutrional Sciences, University of Illinois Urbana-Champaign, Urbana, IL, USA)
23. **A defect in Δ^6 and Δ^5 desaturases may be a factor predisposing to insulin resistance, obesity and metabolic syndrome** – Undurti N. Das (UND Life Sciences, Federal Way, WA, USA)
24. **Soluble-amyloid precursor protein α (sAPPα) and neuroprotectin D1 (NPD1) engage in a beneficial cycle to sustain human retinal pigment epithelial cell integrity when confronted with the onset of dysfunction** – Khanh Do and Nicolas G. Bazan (Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA)
25. **Cysteinyl leukotriene 2 receptor enhances angiogenesis, vascular permeability and tumor metastasis** – Ernest Duah, Vinay Kondeti, Nosayba Al-Azzam, Ravi Adapala, Prachi Patil, Charles Thodeti, and Sailaja Paruchuri (Department of Chemistry, University of Akron, Akron,

OH, Department of Integrative Medical Sciences, NEOMED, Rootstown, OH, USA)

26. **Lung edema and mortality induced by scorpion venom are mediated by inflammasome activation and regulated by eicosanoids** – Karina F. Zoccal, Carlos A. Sorgi, Juliana I. Hori, Francisco W.G., Paula-Silva, Eliane C. Arantes, Carlos H. Serezani, Dario S. Zamboni, and Lúcia Helena Faccioli (Departamento de Análises Clínicas, Toxicológicas e Bromatológicas, Universidade de São Paulo, Ribeirão Preto, São Paulo, Brazil)
27. ***Pseudomonas aeruginosa* promotes persistent inflammation in the cystic fibrosis airway by preventing the generation of 15-epi liposin A_4** – Becca A. Flitter, Kelli L. Hvorecny, Emiko Ono, Taylor Eddens, Jun Yang, Daniel H. Kwak, Christopher D. Bahl, Christophe Morisseau, Bruce D. Hammock, Xinyu Liu, Janet S. Lee, Jay K. Kolls, Bruce D. Levy, Dean R. Madden, and Jennifer M. Bomberger (Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA)
28. **A heart-liver metabolic circuit mediated by a cardiac-specific secreted PLA_2** –S. Hernandez-Anzaldo, E. Berry. V. Brglez, D. Leung, TJ Yun, JG Filep, Z. Kassiri, C. Cheong, M. Murakami, MH Gelb, G. Lambeau, R. Lehner, and Carlos Fernandez-Patron (Department of Biochemistry, Cardiovascular Research Group and Mazankowski Alberta Heart Institute, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada)
29. **A therapeutic approach for experimental ischemic stroke combining a PAF-receptor antagonist plus docosanoids** – Raul Sousa Freitas, Shawn J., Marcell, Hemant Menghani, Sung-Ha Hong, Larissa Khoutorova, Andre Obenaus, Nicos A. Petasis, Ludmila Belayev, and Nicolas G. Bazan (Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA)
30. **Cardioprotection following injury heart failure afforded by a non-enzymatic oxygenated metabolite of omega 3 fatty acid involves Ryanodine receptor mechanism and mitochondrial function** – J. Roy, C. Oger, J. Fauconnier, J. C. Y. Lee, C. Farah, P. Bideaux, V. Scheurmann, V. Bultel-Ponce, C. Vigor, A. Lacampagne, Jean-Marie Galano, T. Durand, and J-Y. Le Guennec (Institut des Biomolécules Max Mousseron, CNRS UMR 5247, Université de Montpellier, ENSCM, Montpellier, France)
31. **GIIA-Phospholipases A2 Isolated from snake venoms induce vascular smooth muscle foam cell formation** – Karina C. Giannotti, Elbio Leiguez, Mariana N. Viana, Neide Galvão do Nascimento, Thais L. Araújo, Renata H. A. Hernandez, Suely Sampaio, Bruno Lomonte, and Catarina Teixeira (Laboratório de Farmacologia, Instituto Butantan, São Paulo/SP)
32. **The 5-LOX/COX-2 cross-over eicosanoid HKE_2 modulates platelet aggregation** – Juan Antonio Gimenez Bastida and Claus Schneider (Division of Clinical Pharmacology, Department of Pharmacology, Vanderbilt University, Nashville, TN, USA)
33. **Very long-chain polyunsaturated fatty acid/DHA-containing phosphatidylcholine molecular species show gender-specific changes in age-related macular degeneration (AMD)** – William C Gordon, Bokkyoo Jun, Uday Patel, Nicolas G. Bazan (Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA)
34. **Prostaglandin $F_{2\alpha}$ FP receptor antagonist improves outcomes after experimental traumatic brain injury** – Alexander V. Glushakov, Sean W. Robbins, Connor L. Bracy, Shuh Narumiya, and Sylvian Doré (Department of Anesthesiology, University of Florida College of Medicine, Gainesville FL, USA)
35. **Role of group VIB calcium-independent phospholipase A_2 ($iPLA_{2\gamma}$) in carcinogenesis** – Shuntaro Hara, Yuka Sasaki, Yuhki Morikaku, Ryosuke Yamada, Reiko Hirai, and Emiko Yoda (Division of Health Chemistry, Department of Healthcare and Regulatory Sciences, School of Pharmacy, Showa University, Tokyo, Japan)
36. **Molecular organization of specific phosphotidycholine (PC) lipid mediators containing novel very long chain polyunsaturated fatty acids (VLC-PUFAs) in the human retina** – Jarrod C. Harman, Bokkyoo Jun, Uday Patel, William C. Gordon, and Nicolas G. Bazan (Neuroscience Center of Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA)
37. **Docosahexaenoic acid-derived lipids in human rod and cone photoreceptor cells** – H. Elizabeth Hill, William C. Gordon, Bok Kyoo Jun, and Nicolas G. Bazan (Neuroscience Center of

Excellence, School of Medicine, Louisiana State University Health New Orleans, New Orleans, LA, USA)

38. **PNPLA 7-mediated catabolic pathway for phosphatidycholine has a crucial role in hepatic choline metabolism and systemic energy homeostasis** – Tetsuya Hirabayashi, Misa Mouri, Suzumi M. Tokuoka, Yoshihiro Kita, Rieko Nakata, Kazutaka Ikeda, and Makoto Murakami (Lipid Metabolism Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan; AMEDCREST, AMED Tokyo, Japan)
39. **Quantification of sphingosine 1-phosphate in plasma of colorectal carcinoma patients by LC-MS/MS** – Wei Hu, Bo Yang, Gaofeng Hu, Lei Yin, Xu Zhao, Zhengwu Guo, Linzhange Li, Pengfei Song, Jingkai Gu, and Wei Xu (Department of Clinical Laboratory, The First Hospital of Jilin University, Changchun, PR China)
40. **UPLC-MS/MS identifies lipids associated with perceptual speed performance in healthy adults. Kevin Huynh**, Virginie Lam, Matthew Albrecht, Corey Giles, Ryusuke Takechi, John Mamo, Peter J Meikle, (Baker IDI Heart and Diabetes Institute and Monash University, Melbourne Australia, Melbourne, Australia).
41. **Biallelic deletions in MBOAT7 link phosphatidylinositol lipid remodeling to autism spectrum disorders** – Anide Johansen, Rasim Rosti, Damir Musaev, Evan Sticca, Berit Johansen, Maha Zaki, Matloob Azam, Tipu Sultan, Rami A. Jamra, and Joseph G. Gleeson (Laboratory of Pediatrics Brain Disease, Department of Neurosciences, University of California, San Diego, CA 92093, USA)
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POSTER #11

Prostaglandin D_2 DP1 Receptor Ameliorates Stroke Outcomes Through Cerebral Blood Flow and Hemostasis

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Background and Purpose: The association of PGD2 with vasculature and blood makes it a prime candidate to be investigated in stroke. Here, we tested whether selective DP1 receptor agonist BW245C treatment after stroke improves the outcomes by regulating cerebral blood flow (CBF) and hemostasis.

Methods: First, the effect of BW245C on basal CBF was determined by giving a single i.p. injection of vehicle or 0.02, 0.2, 2.0mg/kg BW245C in WT and $DP1^{-/-}$ mice. Mice were given an i.p. injection of the vehicle or 0.2mg/kg BW245C and excised tail tip was placed in PBS to record bleeding time. To test the effect of BW245C on *ex-vivo* coagulation, mouse blood was mixed with vehicle or BW245C and the un-coagulated content was quantified. Next, WT and $DP1^{-/-}$ mice were subjected to MCAO. Immediately at reperfusion mice were given a single i.p. injection of vehicle or 0.02, 0.2, 2.0mg/kg BW245C, and the functional and anatomical outcomes were tested at 96h. Further, to determine if BW245C can improve CBF during or after stroke, BW245C was given during occlusion and changes in CBF in peri-infarct and core were continuously recorded.

Results: BW245C treatment significantly increased the basal CBF only in WT. Interestingly, the tail bleeding time was significantly higher in BW245C group (29.0±14.7%; $p<0.01$) as compared with the vehicle group, and similarly the un-coagulated content was also higher in BW245C group (14.9±5.9%; $p<0.005$). The infarction volume was significantly reduced to 38.7±8.1% in 0.2mg/kg BW245C group as compared with the control (51.2±7.1%) and vehicle (52.7±8.6%) groups. Moreover, a strong correlation was observed between the decrease in infarction and CBF improvement. The infarction in $DP1^{-/-}$ was significantly higher (66.3±11.4%) than the WT control mice and it was unaffected by BW245C treatment.

Conclusions: Overall the data suggests that activation of the DP1 receptor after stroke improves CBF, and minimizes brain damage and functional deficits partially through CBF and hemostasis regulation.

This work was supported by AHA SDG (ASA), NIH R01 (SD), and the Department of Anesthesiology.

POSTER #12

Alterations in lysophosphatidylcholine-related metabolic parameters in the plasma of mice with bacterial peritonitis

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Lysophosphatidylcholine (LPC) concentration is decreased in the plasma of septic patients compared with healthy group. Further, administration of LPC to septic mice has protective effects against sepsis. So the alteration of LPC metabolism may be important for understanding pathophysiology of sepsis. However, the mechanisms of sepsis–induced decrease in plasma LPC levels are not currently well known. In this study, we examined alterations of LPC-related metabolic parameters in mice with cecal ligation and puncture (CLP), a model of sepsis regarded as clinically reliable. We investigated alterations of phosphatidylcholine (PC), lysophosphatidic acid (LPA), secretory phospholipase A2 ($sPLA_2$), lecithin: cholesterol acyltransferase (LCAT), autotaxin (ATX) and albumin in the plasma of CLP-treated mice. LPC, PC and albumin levels were decreased in the plasma of CLP-treated mice compared with control group, and enzyme activities of LCAT, ATX and $sPLA_2$ were also decreased. On the other hand, LPA measured with ELISA was increased in the plasma of CLP-treated mice. As LPA is a well-known key molecule in inflammation, the alteration of plasma LPA in CLP-treated mice could affect the immune system in sepsis. We could not find causal association between ATX, LPCAT and plasma LPC level, as ATX inhibitor (PF-8380) did not affect plasma LPA or LPC in CLP-treated mice. Further study is needed to elucidate the exact mechanisms about alterations of LPC metabolism in CLP-treated mice.

POSTER #13

The role of diplamitoylphosphatidylcholine produced by lysophosphatidylcholine acyltransferase 1 in polyunsaturated fatty acid-induced cytotoxicity

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The degree of fatty acid unsaturation in membrane phospholipids affects many membrane-associated functions and can be influenced by dietary fatty acids and by altered activities of lipid-metabolizing enzymes. Therefore, the fatty acid composition in membrane phospholipids must be tightly regulated. When loaded with excess saturated fatty acids (SFAs), cells convert SFAs to unsaturated fatty acids (UFAs) to prevent the incorporation of excess SFAs into membrane phospholipids. However, it is unclear how cells deal with the incorporation of excess UFAs because UFAs cannot be converted into fatty acids with fewer double bonds. Here, we show that loading mammalian cells with polyunsaturated fatty acids (PUFAs) stimulates the production of dipalmitoylphosphatidylcholine (DPPC) to protect against PUFA-induced cytotoxicity. DPPC was produced time- and dose- dependently by PUFA treatment and its production was correlated with the production of PUFA-containing phospholipids. An RNAi screen of lipid-metabolizing enzymes revealed that lysophosphatidylcholine acyltransferase 1 (LPCAT1) was involved in the DPPC production. Moreover, prevention of DPPC production by LPCAT1 knockdown markedly enhanced the cytotoxicity and unfolded protein response (UPR) induced by loading with excess PUFAs. PUFA-induced cytotoxicity was dependent on caspase and UPR sensor proteins inositol requiring 1 (IRE1) and protein kinase R-like endoplasmic reticulum kinase (PERK), indicating that excess PUFAs trigger UPR-mediated apoptosis. In murine retina, in which PUFAs are highly enriched, DPPC was produced along with increases of PUFA-containing phospholipids. In LPCAT1 knockout mice, DPPC level was reduced and UPR was activated in the retina. Our results provide insight to understanding of the retinal degeneration seen in *rd11* mice that lack LPCAT1.

POSTER #14

Lipocalin-type prostaglandin D synthase: a transporter of prostaglandin D_2 and scavenger of prostaglandin D_2-degraded products

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Lipocalin-type prostaglandin (PG) D synthase (L-PGDS) is responsible for the production of PGD_2, a potent endogenous sleep substance, and is secreted into the cerebrospinal fluid (CSF) as beta-trace, a major protein of human CSF. L-PGDS belong to the lipocalin superfamily, which consists of small secretory transporter proteins of various lipophilic ligands such as retinoids, biliverdin, bilirubin with high affinities. PGD_2 is chemically unstable lipid in aqueous solution and non-enzymatically dehydrated to produce the J series of PGs, such as PGJ_2, Δ12-PGJ_2, and 15deoxy-$\Delta^{12,14}$-PGJ_2 *in vitro*. However, the stability and metabolism of PGD_2 *in vivo* remain to be clarified. In this study, we characterized the binding affinity of L-PGDS to PGD_2 and its degraded products, and analyzed the complex of L-PGDS and PGJs in CSF.

Surface plasmon resonance analysis and isothermal titration calorimetry measurements revealed that PGD_2 bound to L-PGDS in two binding-site with high affinities of Kd=$3x10^{-8}$-$8x10^{-7}$ M and with low affinities of $3x10^{-5}$-$4x10^{-5}$ M , and its binding was reversibly in the short duration.

On the other hand, the degraded products, PGJs-binding to L-PGDS was irreversible. Using MALDI-TOF mass spectroscopy, we showed that the binding of PGD_2 to L-PGDS was covalent and irreversible. 15-deoxy-$\Delta^{12,14}$-PGJ_2 dose-dependently inactivated L-PGDS enzyme activities. We identified that Cys65 is the residues for the PGD_2 degraded products-binding, proven by NMR titration analysis and in-source decay analysis using a MALDI-TOF mass spectrometer. We also detected the complex form of L-PGDS covalently bound PGJs from human CSF.

We propose that PGD_2 is stabilized via binding to L-PGDS providing a stable transport towards its receptors. Moreover, L-PGDS consecutively acts as scavenger for J-type PGs through covalent binding providing a balance in the biological PGD_2 system.

POSTER #15

Neuroprotectin D1 (NPD1) stereoselectively modulates inflammasome transcription and activation in human retinal pigment epithelial cells

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Drusen isolated from retinas from age-related macular degeneration patients (AMD) activate the NLRP3 inflammasome[1]. Uncompensated oxidative stress and inflammation are prominent features of AMD. The stress-response mediator NPD1 down-regulates inflammasome-related genes AIM2, NLRC4, NOD-2, and IL-1β (unpublished studies from our lab). NOD-2 is of particular interest since mutations of it are associated with Blau syndrome, which results in uveitis and retinal damage in childhood. We hypothesized that NPD1 stereo-specifically regulates the expression of inflammasome components at the transcriptional level.

Human retinal pigment epithelial (hRPE) cells were used as an *in vitro* model. Incubating cells with 600μM of H_2O_2/TNFα (10ng/ml) mimics oxidative stress (OS) and induces the expression of NOD-2 gene. To understand whether NPD1 stereoselectively regulates NOD-2 expression, we induced oxidative stress in hRPE cells and co-treated with NPD1, its stereoisomers, resolvin D1, resolvin E1 and lipoxin A4 at 200nM concentration each. Extracted RNA was analyzed using RT-PCR. To understand the scope of NPD1 action, NOD-2 promoter was subcloned into PGL4 luciferase vector and, along with GFP vector, co-transfected into hRPE cells to analyze NOD-2 promoter activity in response to oxidative stress.

Oxidative stress, as observed previously, induced NOD-2 expression. All lipid mediators suppressed the activation of NOD-2 to some extent, but NPD1 had the greatest effect and down-regulated NOD-2 expression more than 2.5 fold. NPD1 suppressed the transcriptional activation of NOD-2 gene two fold 2h after introduction of oxidative stress in our luciferase assay experiment.

In summary, our results show that NPD1 repressed the expression of NOD-2 stereospecifically at the transcriptional level. NOD-2 is an intracellular pattern-recognition receptor and has a synergistic effect on NLRP3 inflammasome activation. NOD-2 is also involved in activation of caspase 1 and IL-1β, however this requires the presence of NLRP3. NOD-2 forms so-called “nodosomes” that result in the activation of pro-inflammatory NF-κB. NOD-2 defects have been correlated with failed activation of IL-1β.

This research was funded by National Institutes of Health grants EY005121 and GM103340 (NGB), and by the Eye, Ear, Nose & Throat Foundation (NGB).

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POSTER #16
PUFA-mediated Proinflammatory Response to Ionizing Radiation

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The identification of cancer patients who might develop severe adverse reactions in response to radiotherapy has been hindered by the complexity of individual variation in sensitivity to radiation. The molecular response to ionizing radiation, however, is still not completely understood. Here we screened mouse serum for metabolic alterations following an acute exposure to gamma radiation using a multi-platform, mass-spectrometry-based strategy. A global, molecular profiling allowed to monitor the effects of radiation exposure on key biochemical pathways. . Exposure to gamma radiation induced a significant increase in the serum levels of ether phosphatidylcholines (PCs) while decreasing the levels of diacyl PCs carrying PUFAs. In exposed mice, levels of pro-inflammatory, oxygenated metabolites of arachidonic acid increased, whereas levels of anti-inflammatory metabolites of omega-3 PUFAs decreased. The obtained molecular biosignature might be used as an indicator of radiation exposure and, potentially, as a predictor of radiosensitivity. Verification studies are currently undergoing in human samples. If validated, baseline levels of eicosanoids (e.g., omega6/omega-3 ratio) might serve as a companion diagnostic tool for radiation therapy, to help differentiate cancer patients who would respond best to radiotherapy treatment from radiosensitive patients, who may be unable to tolerate the additional inflammatory response induced by radiotherapy. Most importantly, the ability to control eicosanoids pathways with pharmacological or dietary interventions (i.e., omega-3 supplementation) might alleviate and eventually offset many of the side effects linked to radiation therapy.

POSTER #17

PLA_2G5-expressing M2 macrophages in mouse and human type 2 inflammation

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Phospholipases A_2 (PLA_2) are enzymes that liberate membrane bound lipids in a tissue and cell-specific fashion. We have previously shown that group V secretory PLA_2 (Pla2g5) is induced by IL-4 in mouse and human M2 macrophages. We also showed that Pla_2g5 is required for the development of M2 macrophages and their effector functions in a mouse model of type 2 allergic airway inflammation. However, the function of PLA_2G5 in human M2 activation and type 2 inflammation was ill-defined. Transglutaminase 2 (TGM2), a protein crosslinking enzyme, is a newly identified marker of both human and mouse IL-4-activated M2 macrophages, and is also found in the lungs of patients with asthma. Here we report that PLA_2G5 and TGM2 colocalized in macrophages of human nasal polyp tissue obtained from patients with type 2 eosinophilic inflammation, and their co-expression positively correlated with the number of eosinophils in each tissue specimen. We demonstrate that in human monocyte-derived macrophages activated by IL-4, PLA_2G5 translocated and colocalized with TGM2 in the cytoplasm and on the membrane of macrophages. Moreover, knocking down PLA_2G5 with siRNA reduced macrophage trans-glutaminase activity, while mass spectrometry analysis of lipids also showed reduced prostaglandin E_2 (PGE_2) production. Finally, exogenous PGE_2 restored transglutaminase activity of PLA_2G5-siRNA-treated macrophages. Thus, our study shows a novel function of PLA_2G5 in regulating the transglutaminase activity of human IL-4activated M2 macrophages through PGE_2 generation and suggests that PLA_2G5 is a functionally relevant enzyme that may have therapeutic value for the treatment of human Th2 inflammatory disorders.

POSTER #18

Very long-chain fatty acid-containing phosphatidylcholine molecular species are altered in Age-related Macular Degeneration (AMD)

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Docosahexaenoic acid (DHA), an essential ω-3 fatty acid (22 carbons (Cs), 6 double bonds; 22:6), is dietarily acquired, packaged by hepatocytes, and selectively transported to retinal photoreceptors, where it is principally incorporated into phosphatidylcholine (PC) phospholipids at the sn-2 carbon position. Importantly, up to 50% of retinal phospholipids are PCs, indicating a major role in photoreceptor structure and function. Moreover, elongated fatty acids (with 24 to 38Cs; very long-chain polyunsaturated fatty acids, VLC-PUFAs) become incorporated at the sn-1 position. Furthermore, VLC-PUFAs play a role in maintaining photoreceptor integrity[1]. In AdipoR1 KO mice, which possess characteristics of retinal degeneration, lack of functional AdipoR1 results in inability to take up and incorporate DHA[2]. Thus, photoreceptors attempt to compensate for this lack by substituting other fatty acids; VLC-PUFAs are not incorporated at the sn-1 position of these PCs. This change leads to photoreceptor loss resembling that observed in human retinal degeneration. Therefore, we asked if PCs from human donor retinas are compromised under conditions of retinal degeneration.

AMD and normal donor eyes were analyzed by LC-MS/MS tandem mass spectrometry, and PC containing VLC-PUFAs (24-38Cs in length) were characterized and quantitated.

In normal and AMD retinas, the prevalence of PC44:12 (22:6/22:6 n3) is about 25% more than PC40:8 (20:4/20:4 n6); these are the precursors of long chain omega-3 and omega-6 fatty acid PCs, respectively. VLC-PUFA-containing PCs with 56Cs, PC(56:12), PC(56:11) and PC(56:10), are most abundant, suggesting a general end point in elongation. Also, there is a 20% reduction in the ratio of VLC-PUFA-containing PCs/total PCs between normal and AMD retinas. Moreover, central retinal VLC-PUFA-containing PCs, PC(34:5/22:6) and PC(34:6/22:6), are lost as AMD progresses.
VLC-PUFA occurrence differs between normal and AMD retinas with AMD retinas, overall, having less VLC-PUFA-containing PCs, implying that this reduction may reflect impaired synthesis in AMD. Since VLC-PUFAs are important for rod function[3], initial compromised rods may foreshadow onset of AMD.

Supported by grants NEI EY005121 and NIGMS GM103340 (NGB), and the EENT Foundation

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POSTER #19

Sphingosine 1-phosphate bound to ApoM+HDL modulates generation of the adaptive immune response at different stages of lymphocyte ontogeny

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Activation and mobilization of lymphocytes is a tightly controlled process, the dysregulation of which can have severe pathophysiological consequences. The lipid mediator sphingosine 1phosphate (S1P) has well-characterized roles in numerous facets of endothelial cell biology; however, lymphocyte-intrinsic effects of S1P signaling, beyond modulation of trafficking, have only recently gained attention. Although the majority (~65%) of plasma S1P is bound to apolipoprotein M (ApoM) in the high-density lipoprotein (HDL) particle, how the ApoM-S1P complex regulates immunity is unknown. Here we show that, while dispensable for trafficking, ApoM-S1P restrains lymphopoiesis by activating the receptor $S1P_1$ on bone marrow lymphocyte progenitors. *Apom*$^{-/-}$ mice have increased $Lin^-Sca1^+cKit^+$ hematopoietic stem and progenitor cells (LSK) and common lymphoid progenitors (CLP) in BM. Upon immunization with immunogenic peptide, *Apom*$^{-/-}$ mice develop more severe experimental autoimmune encephalomyelitis (EAE), characterized by increased lymphocytes, particularly T_h1 T cells, in the central nervous system and breakdown of the blood-brain barrier. However, *in vitro* studies indicate that $ApoM^+$HDL does not regulate proliferation of naïve mature lymphocytes, but rather modulates T_h1 versus T_h17 phenotype decisions. Lipidomic analyses of plasma revealed loss of ApoM affects concentrations of multiple sphingolipid species, which may also impact development of adaptive immune responses. These data demonstrate that the ApoM-S1P-$S1P_1$ signaling axis regulates the lymphocyte compartment at various stages of ontogeny, from progenitor to mature cell, by differentially affecting proliferation or phenotype. Thus, S1P chaperones maybe provide developmental stage-specific novel targets for the modulation of adaptive immunity.

POSTER #20

Rapid Normal-phase Separation of Lysophosphatidic Acid and Other Lysophospholipids by Ultra-High Performance Supercritical Fluid Chromatography

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The accurate quantification of physiological levels of bioactive lysophospholipids can be challenging for a variety of reasons. Mass spectrometry-based measurements of lysophosphatidic acid (LPA) species in particular` are susceptible to artifacts created by insource fragmentation of other, much more abundant, glycerophospholipid species. Most reversed-phase liquid chromatography methods lack the resolution to fully separate LPAs from other lysophospholipids classes, whereas normal-phase methods are relatively time-consuming.

We present a new method for lysophospholipid separation using ultra-high performance supercritical fluid chromatography (UHPSFC), also known as convergence chromatography (UPC^2). This novel technology combines a primary supercritical fluid (CO_2) mobile phase with a gradient of organic modifier of choice, and utilizes a range of dedicated sub-2 µm particle columns. Within a single 10 minute run, UHPSFC efficiently separates all major neutral and polar lipid classes, which can then be analyzed by mass spectrometry. Importantly, the method achieves full baseline separation of LPA from other lysophospholipids classes, thereby avoiding false detection of artificially generated LPAs.

Combining speed of analysis with superior chromatographic resolution, UHPSFC-MS can improve the measurement of LPA and other bioactive (lysophospho) lipids in a wide range of disease studies.

POSTER #21

Novel regulatory mechanism of the inflammatory response mediated by Neuroprotectin D1 (NPD1) targeting transcription of Wnt5a

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Neurodegenerative diseases share common pathophysiological mechanisms that include uncompensated oxidative stress, enhanced inflammatory signaling and apoptosis. Docosanoid (NPD1 and other DHA derived mediators) signaling modulates proteotoxic and oxidative stress responses to halt cell death and allow cells to recover from insults (Mukherjee et al, 2004, Calandria et al, 2012). Retinal pigment epithelial (RPE) cells sustain photoreceptors cells integrity and synthesize NPD1 from DHA in response to stress stimuli via 15-lipoxygenase-1 (Calandria et al, 2009). In addition, during ischemia-reperfusion, DHA induces neuronal survival through NPD1 synthesis that, in turn, stereospecifically and in a non-redundant fashion activates the NFκB/cREL pathway (Calandria et al, 2015). In the present work, we tested the hypothesis that DHA/NPD1 promotes survival of neurons in ischemic stroke induced by middle cerebral artery occlusion (MCAo) in rats. DHA treatment after stroke decreased the NFκB/p65driven transcription of Wnt5a as well as other pro-inflammatory genes, including interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNFα). Oxidative stress increased Wnt5a transcription, and secretion was inhibited by NPD1 in primary human RPE cells in culture as well. Frizzled 5 (FZD5), a seven transmembrane receptor for Wnt5a, activates proinflammatory components of NFκB, which in turn enhances the transcription of Wnt5a. NPD1 blocked the oxidative stress-induced transcriptional activation of FZD5, suggesting that, in this manner, this docosanoid interrupts the positive feedback loop that leads to inflammation. Altogether, these results demonstrate a defined anti-inflammatory targeting of DHA/NPD1 signaling.

The grants that support this work are: NEI EY005121, COBRE NIGMS GM103340 and Eye, Ear, Nose & Throat Foundation.

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POSTER #22

Novel Omega-3 Endocannabinoid Epoxides Emanating from the Cross-Talk Between the Endocannabinoid and Cytochome P450 Metabolic Pathways

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The human body contains endocannabinoids that elicit similar effects as Δ9-tetrahydrocanabinol (THC), the principal component of cannabis, which produces similar psychoactive and antinociceptive effects. The two most well studied endocannabinoids include anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are derived from the omega-6 arachidonic acid (AA). Previously, we showed that both of these omega-6 endocannabinoids are substrates for metabolism by epoxygenases to form novel AEA and 2-AG epoxides with distinct biological activity. Recently, it was discovered that the omega-3 fatty acids eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) also form endocannabinoids eicosapentaenoic ethanolamide (EPEA) and docosahexaenoic ethanolamide (DHEA), respectively. Using LC-MS/MS we demonstrate that EPEA and DHEA are metabolized by the epoxygenases to produce novel EPEA and DHEA epoxides with unknown biological functions. We show that we can detect these metabolites endogenously in the brain and other peripheral organs in pigs and rats at the same level as AEA. Furthermore we show that the epoxygenases in the tissues are capable of producing these metabolites. When specific epoxygenases in the brain and vasculature were screened for the metabolism of these substrates, we identified CYP2J2 as the primary metabolizer of EPEA and DHEA. Furthermore we elucidate the nuances of ligand-protein interactions using biophysical methods. We evaluated the biological effects of these newly discovered molecules in the following assays – neuro-inflammatory assays, cannabinoid receptor binding and activity assay, vasodilation using porcine coronary artery, platelet aggregation assay and angiogenesis study using human microvascular endothelial cells (HMVEC). We found that these newly discovered molecules are anti-inflammatory, vasodilatory, anti-platelet aggregatory and anti-angiogeneis. In summary, we have discovered novel omega-3 endocannbinoid epoxides that arise from the cross-talk of the enzymes in the endocannabinoid and epoxygenases pathway that elicit distinct biological activity.

Support acknowledgement: American Heart Association Scientist Development grant [15SDG25760064]

POSTER #23

A defect in Δ^6 and Δ^5 desaturases may be a factor predisposing to insulin resistance, obesity and metabolic syndrome

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Insulin resistance is common in obesity, type 2 diabetes mellitus (type 2 DM), hypertension (HTN), hyperlipidemia and coronary heart disease (CHD). Previously, we noted that arachidonic acid (AA) content of plasma phospholipid fraction is low in type 2 DM, HTN and CHD; eicosapentaenoic acid (EPA) is low in CHD, and docosahexaenoic acid (DHA) is low in type 2 DM and CHD. These results are in contrast to the high circulating levels of prostaglandin E2 (PGE2), thromboxane B2 (TXB2) and leukotriene D4 (LTD4); interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and lipid peroxides and possibly, low levels of resolvins and protectins in type 2 DM and metabolic syndrome. These results suggest that a defect in the activity of Δ^6 and Δ^5 desaturases may have a role in these conditions. AA, EPA and DHA increase cell membrane fluidity and enhance the number of insulin receptors and the affinity of insulin to its receptors; suppress TNF-α, IL-6, macrophage migration inhibitory factor (MIF) and leptin synthesis; increase the number of GLUT-4 receptors, serve as endogenous ligands of PPARs, modify lipolysis, and regulate balance between pro- and anti-oxidants. Calorie restriction enhances activity of Δ^6 and Δ^5 desaturases, decreases free radical generation, and augments anti-oxidant defenses implying that desaturases play a critical role in the expression and regulation of GLUT-4, TNF-α, IL-6, MIF, and leptin by modulating the synthesis and tissue concentrations of AA, EPA and DHA. Defects in the activity of desaturases may alter the formation of prostaglandin E1 (PGE1), prostacyclin (PGI2), PGI3, lipoxins (LXs), resolvins, neuroprotectin D1 (NPD1), NO, and nitrolipids that modulate leukocyte activation, inflammation wound healing and atherosclerosis. In view of this, it is suggested that Δ^6 and Δ^5 desaturases could serve as biological target(s) for the discovery and development of pharmaceuticals to treat insulin resistance and its consequences.

POSTER #24

Soluble-amyloid precursor protein α (sAPPα) and neuroprotectin D1 (NPD1) engage in a beneficial cycle to sustain human retinal pigment epithelial cell integrity when confronted with the onset of dysfunction

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Amyloid beta 42 (Aβ42), one of the end products of the amyloidogenic pathway, is a major component of drusen in age-related macular degeneration (AMD) and in plaques of Alzheimer's disease (AD). In the present study, we wanted to determine if (1) the docosanoid NPD1 is able to shift the toxic amyloidogenic pathway to the non-amyloidogenic pathway in human retinal pigment epithelial (RPE) cells as in human brain cells (Lukiw, *et al*. JCI, 2005); (2) the product of the latter pathway, sAPPα, is engaged in NPD1 synthesis under uncompensated oxidative stress; and (3) sAPPα works in concert with NPD1 to rescue human retinal pigment epithelial (RPE) cells from Aβ42-induced apoptosis and/or uncompensated oxidative stress.

We used plasmid constructs containing Swedish double mutant APP protein (APPsw), which predominantly produces sAPPβ, a precursor of Aβ. This mutation causes one of the forms of familial AD. The synthesized non-amyloidogenic sAPPα and amyloidogenic sAPPβ were analyzed by Western blots after 48h of NPD1 treatment at different concentrations. The dose and time course of sAPPα enhancing NPD1 synthesis was analyzed under oxidative stress by TNF-α and H_2O_2.

Higher sAPPα production was observed as upon increasing NPD1 concentration at 48h, whereas the production of sAPPβ decreased at the same time. Aβ42-stressed human RPE cells were also protected from apoptosis by NPD1. Overall sAPPα exerted similar protective bioactivity as NPD1. Moreover, sAPPα in a concentration dependent manner, induced NPD1 biosynthesis.

The results demonstrate that NPD1 shifts the amyloidogenic to the non-amyloidogenic pathway in human RPE cells and that potently protects human RPE cells from Aβ42 induced apoptosis. NPD1 and sAPPα in concert sustains the functional integrity of RPE cells when confronted with uncompensated oxidative stress. It is of interest that APP is presynaptic in the brain, and that it appears to be in the baso-lateral side of RPE cells (facing away from photoreceptors) and in connection to basal membrane and choriocapilaris vasculature that nurture and removes waste from photoreceptors. Thus this novel lipid mediator, which targets key pro-homeostatic signaling, is relevant to vision in AMD and similar mechanisms might operate in AD onset.

This research was funded by NIH, EY005121 and GM103340 (NGB), the Eye, Ear, Nose & Throat Foundation (NGB), Vietnam Education Foundation (KD) and the Schlumberger Foundation Faculty for the Future (KD).

POSTER #25

Cysteinyl Leukotriene 2 Receptor Enhances Angiogenesis, Vascular Permeability and Tumor Metastasis

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Excessive or insufficient angiogenesis can lead to number of diseases including atherosclerosis, diabetic retinopathy, age-related macular degeneration and cancer. Although long-standing inflammation secondary to chronic infection or irritation mediated by immune cells has been implicated in cancer progression, the contribution of endothelial cells (EC) in the generation of inflammatory mediators and their effects on angiogenesis is relatively unknown. One of the proinflammatory mediators produced by EC are cysteinyl leukotrienes (Cys-LTs: LTC_4, LTD_4 and LTE_4), and they mediate their effects through two main receptors, $CysLT_1R$ and $CysLT_2R$. CysLTs have been shown to be involved in several human cancers including breast cancer and melanoma. Tumor microenvironment comprises numerous signaling molecules and pathways that influence angiogenic response leading to increased and aberrant vascularization. Further, angiogenesis is required for the supply of nutrients and oxygen for tumor growth and also serves as a route of tumor cells metastasis. Therefore, we investigated the role of CysLTR in angiogenesis, tumor progression and metastasis, using mice lacking $CysLT_1R$ ($CysLT_1RKO$) and $CysLT_2R$ ($CysLT_2RKO$).

We observed enhanced $CysLT_2R$ expression, and not $CysLT_1R$ in wild type (WT) tumors and tumor growth as well as angiogenesis were significantly decreased in $CysLT_2RKO$ mice compared to WT and $CysLT_1RKO$ mice in Lewis lung carcinoma (LLC) tumor model. Further, though few in number, tumor vessels in $CysLT_2RKO$ mice showed intact pericyte coverage and reduced permeability with simultaneous reduction in tumor cell metastasis to the lung. Furthermore, we found that activation of $CysLT_2R$, but not $CysLT_1R$ increased EC contraction leading to junctional destabilization and permeability in vitro. Importantly, our results show that $CysLT_2R$ activates Rho kinase and inhibition of Rho kinase significantly attenuated $CysLT_2R$induced EC contraction and permeability. Further, our preliminary results revealed that pericytes express $CysLT_2R$ and display calcium influx in response to LTD_4. Taken together, our results suggest that $CysLT_2R$ promotes leaky blood vessel formation, enhancing tumor growth and metastasis to the lung. Blocking $CysLT_2R$ could offer novel $CysLT_2R$-targeted, therapeutic candidates for the treatment of cancer and other angiogenic disorders.

POSTER #26

Lung edema and mortality induced by scorpion venom are mediated by inflammasome activation and regulated by eicosanoids

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Accidents by *Tityus serrulatus* sting is a serious health problem worldwide, and it's been increased dramatically[1]. The venom of *T. serrulatus* (TsV) induces local and systemic inflammation, lung edema and sometimes death[2]. We have been investigating the mechanisms involved in inflammatory response induced by the TsV and we discovered that the venom is recognized by innate immune receptors resulting in leukocytes recruitment, TNFα, IL-6, PGE_2 and LTB_4 release[3]. More recently, we discovered that TsV induces lung edema, neutrophil recruitment and deaths dependent on NLRP3 inflammasome activation and IL-1β production. Moreover, inflammasome stimulation results in LTB_4 production and additional PGE_2 release, which amplify IL-1β release. Interesting, intranasal administration of LTB_4 to TsV-envenomed mice decreases lung inflammation and abolishes TsV-induced mortality. When TsV-envenomed mice were treated with COX inhibitors, we observed reduction in IL-1β release, lung inflammation and mortality. The molecular mechanism was investigated. Ours results indicate that the balance between LTB_4 and PGE_2 regulates the inflammasome activation and the amount of IL-1β released, and consequently the magnitude of envenomation. We are suggesting COX1/2 inhibition as an applicable additional therapeutic intervention for scorpion envenomation[4].

Financial Support: FAPESP and CNPq.

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POSTER #27

Pseudomonas aeruginosa promotes persistent inflammation in the cystic fibrosis airway by preventing the generation of 15-epi lipoxin A_4

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Chronic *Pseudomonas aeruginosa* infections coupled with persistent, damaging neutrophilic inflammation are characteristic of the chronic lung diseases cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and bronchiectasis. Continuous neutrophil infiltration and robust inflammation cause extensive damage to airway tissue, leading to respiratory failure and death. Lipoxin A_4 (LXA_4) and 15-epi lipoxin A_4 (15-epi LXA_4) are arachidonic acid-derived lipid mediators that play a critical role in resolving inflammation by reducing neutrophil migration and promoting tissue homeostasis. COPD and CF patients have reduced LXA_4 in their airways, potentially contributing to their inability to resolve the inflammatory environment in the lung. Neutrophils can produce 15-epi LXA_4 upon receiving the paracrine stimulus 14,15epoxy-eicosatrienoic acid (14,15-EET), a cytochrome P450-derived eicosanoid produced by inflamed airway epithelial cells (AECS). We hypothesized that the *P. aeruginosa* secreted epoxide hydrolase Cif, catalyzes the hydrolysis of 14,15-EET, thus decreasing neutrophil generation of 15-epi LXA_4, thereby impairing resolution of inflammation in the CF lung. Utilizing purified components and primary CF AECs, we demonstrate that Cif catalyzes the hydrolysis of the 14,15-EET epoxide moiety to produce 14,15-dihydroxyeicosatrienoic acid (14,15-DHET), while a catalytically-inactive mutant of Cif had no hydrolysis activity. Co-culture experiments with CF AECs and human neutrophils demonstrate that through a dramatic reduction in 14,15-EET, Cif decreases the production of 15-epi-LXA_4 by neutrophils and thus, prevent 15-epi LXA_4mediated inhibition of neutrophil transepithelial migration. Furthermore, analysis of broncho alveolar lavage samples from a CF patient cohort revealed that patients with higher Cif protein levels had reduced 15-epi LXA_4 and conversely increased IL-8 in lavage fluid. Moreover, elevated levels of Cif also corresponded with diminished pulmonary function measures in these patients. In conclusion, our data demonstrate that the *P. aeruginosa* virulence factor Cif, reduces the production of 15-epi LXA_4 and thus, promotes a persistent inflammatory environment in the CF lung.

POSTER #28

A heart-liver metabolic circuit mediated by a cardiac-specific secreted PLA_2

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We describe a possibly novel mechanism of systemic metabolic control by the heart. Previous research showed that the heart governs systemic metabolism through cardiac natriuretic peptides and the microRNA-208a/MED-13 pathway. The mechanism identified by the authors is mediated by a cardiac-specific secreted phospholipase A_2 ('cardiac' $sPLA_2$). Cardiac $sPLA_2$ activation and release from myocardium is induced by monocyte-chemoattractant protein-3, which is a pro-inflammatory cytokine normally cleaved and inactivated by matrix metalloproteinase-2 (MMP-2). We suggest that myocardial release of cardiac $sPLA_2$ enables the heart to serve important endocrine functions such as the modulation of lipid metabolism and inflammation in the liver. Further, the pathophysiology of MMP-2 deficiency in either mice or humans is influenced by a heart-centric endocrine mechanism signaled by cardiac $sPLA_2$, whose activity deregulates systemic metabolism and causes inflammation.

POSTER #29

A therapeutic approach for experimental ischemic stroke combining a PAF-receptor antagonist plus docosanoids

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Acute ischemic stroke triggers complex changes that include neurovascular, neuroinflammatory and synaptic alterations. The present study was to test the prediction that blocking proinflammatory platelet-activating factor receptors (PAFR) plus administering selected docosanoids after middle cerebral artery occlusion (MCAo) would lead to sustained neurological recovery. Thus LAU-0901, an antagonist of PAFR that blocks activated pro-inflammatory signaling[1] plus synthetic docosanoids (Aspirin-triggered neuroprotectin D1 methyl-ester; ATNPD1-ME), which activates cell-survival pathways and has potent inflammatory modulatory and neuroprotective bioactivity[2]. Sprague-Dawley rats were anesthetized with isoflurane/nitrous oxide and received 2h MCAo by intraluminal suture. Neurological status was evaluated at 3h and 4h, and on days 1, 2 and 3; a grading scale of 0-12 was employed. Animals were treated with LAU-0901 (i.p. 60mg/kg, 2h after onset of stroke), AT-NPD1-ME (i.v. 333mg/kg, 3h after onset of stroke) and vehicles (cyclodextran and saline). There were four groups: LAU-0901+ATNPD1; LAU-0901+saline; Cyclodextran+AT-NPD1; and cyclodextran+saline. On day 3, *ex vivo* MRI of the brains was conducted using 11.7 T MRI. LAU-0901 and AT-NPD1 treatments alone improved behavioral scores compared to vehicle groups by 22-32%. Using the LAU-0901+ATNPD1 combination, the neuroprotective effect was enhanced, resulting in improved behavioral score up to 50% on day 3. Total lesion volumes, computed using T2WI, were significantly reduced by 80% with LAU-0901+AT-NPD1 treatment compared to vehicle-treated groups. We concluded that combination treatment of the PAFR antagonist LAU-0901 plus AT-NPD1-ME affords synergistic neuroprotection in the post-ischemic brain and might provide the basis for future therapeutics in patients suffering ischemic stroke.

This study was supported by P30GM103340 (NGB, LB) from NIH/NIGMS.

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POSTER #30

Cardioprotection following injury heart failure afforded by a non-enzymatic oxygenated metabolite of omega 3 fatty acid involves Ryanodine receptor mechanism and mitochondrial function

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Cardioprotective effects of long-chain polyunsaturated fatty acids of the n-3 series (PUFAs) have been demonstrated and represent a novel approach to prevent myocardial infarctions or its consequences. Due to the abundance of double bonds, the main n-3 PUFAs; docosahexaenoic acid (C22: 6 n-3, DHA) are very sensitive to free radical oxidation and can undergo non-enzymatic spontaneous peroxidation under oxidative stress conditions as it occurs in ischemia/reperfusion. In this context, a lot of oxygenated metabolites of PUFAs like Neuroprostanes (NeuroPs) are produced and used as oxidative stress biomarkers but their activities were not determined.

We investigated if the pericardial delivery of NeuroPs, protects the myocardium from ischemic damages during and following an ischemia/reperfusion (IR) episode in rats.

Cardiac functions, infarct size and arrhythmias were studied and we observed that NeuroPs afford some cardioprotective effect during or after myocardial infarction. Indeed, compared with controls, NeuroPs-treated animals have significantly decreased infarct size (-28%) determined at the end of reperfusion and reduced ventricular arrhythmia score during reperfusion (-38%). Mechanistically, NeuroPs regulates calcium levels by stabilizing RyR2 activity (Roy et al., 2015), which can explain arrhythmias prevention during IR. Also, our results demonstrated an increase of membrane potential ($\Delta\Psi m$) by the application of NeuroPs. This effect was not due to an augmentation of mitochondrial respiratory chain activity but by the effect leading to the diminution of protons leak. Swelling in response to Ca^{2+} was prevented by NeuroP, indicating a decrease MPTP opening, which can be explain prevention of cell death during IR.

These results suggest a novel pharmacological pathway of n-3 PUFAs and suggest that their well-known cardioprotective effects are mediated by their oxygenated metabolites such as NeuroPs.

POSTER #31
GIIA-PHOSPHOLIPASES A2 ISOLATED FROM SNAKE VENOMS INDUCE VASCULAR SMOOTH MUSCLE FOAM CELL FORMATION

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During atherosclerotic processes, VSMCs differentiate into lipid droplet (LD)-rich foam cells. Increased levels of GIIA-secreted phopholipases A_2 ($sPLA_2$) is frequently seen at the site of atheromatosous lesion and in patient serum. However, the role of these enzymes in LDs formation in VSMCs is unknown. Aims: To investigate the effect of the snake venom GIIA$sPLA_2$s MT-III and BthTx-II on VSMCs evaluating (1) LD formation and (2) activation of distinct factors involved in lipid accumulation. Methods: VSMCs obtained from male Wistar rats (Ethics Committee Protocol 1024/13) were incubated with DMEM (control) or MT-III or BthTx-II for 1-12 h. LD formation was quantified after cell staining with OsO4 and analyzed by phase contrast microscopy. ABCG1, PLIN2, PLIN3, COX-1 and COX-2 distribution and protein expression were analysed by immuno-fluorescence and western blotting assays, respectively. Results: Incubation of VSMCs with MT-III (0.4 to 0.8 µM) or BthTx-II (0.8 µM) significantly increased LDs numbers from 1 up to 12 h. MT-III and BthTx-II did not affect COX-1 expression, but increased COX-2 protein content at 3 and 6h incubation. Moreover, both $sPLA_2$s induced PLIN2 and PLIN3 recruitment without changing protein expression. MT-III increased ABCG1 protein content only at 3h and BthTx-II at 1h. In addition, COX-1, COX-2 and PGE_2 pools were colocalized to LDs in BthTx-II- and MT-III-stimulated cells. Conclusions: These data show for the first time the ability of GIIA $sPLA_2$s to induce LDs biogenesis in VSMCs and to increase expression of the inflammatory COX-2 in these cells. Increased expression of the lipid efflux protein ABCG1 in the early phase of VSMCs response reinforce the excess of lipid accumulation caused by both venom $sPLA_2$s. Furthermore, these results evidence that LDs may constitute intracellular sites for the synthesis of prostanoids in VSMCs stimulated by GIIA $sPLA_2$s.

POSTER #32
The 5-LOX/COX-2 cross-over eicosanoid HKE_2 modulates platelet aggregation

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Inflammation is a normal physiological response of the organism that is regulated by a plethora of molecules (eicosanoids, cytokines or chemokines) and immune cells (monocytes, macrophages, lymphocytes, endothelial cells and platelets among others). Chronic inflammation is associated with the development of diseases, such as atherosclerosis and cardiovascular diseases.

Cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) are essential enzymes in the regulation of the inflammatory response by producing prostaglandins and leukotrienes, respectively. We have recently discovered that COX-2 and 5-LOX enzymes converge resulting in the biosynthesis of novel eicosanoids that we identified as hemiketals (HKs) E_2 and D_2. HK formation involves initial oxygenation of arachidonic acid (AA) by 5-LOX producing 5hydroxyeicosatetraenoic acid (5-HETE), which serves as a substrate of COX-2 for the production of a diendoperoxide. The rearrangement of this unstable diendoperoxide leads to formation of HKs.

Understanding the role of these compounds in the regulation of inflammation may help discover novel therapeutic opportunities in inflammatory diseases. HKs are novel lipid mediators that seem to participate in the regulation of the inflammatory response (i.e., modulating migration and tubulogenesis in endothelial cells). However, whether HKs are able to modulate other mechanism related to inflammation is not known. Thus, in this study, we investigated the effect of HKE_2 on platelets collected from healthy volunteers. Specifically, we determined the ability of HKE_2 to modulate thromboxane receptor (TP) agonist U46,619-induced platelet aggregation in human platelet rich plasma (PRP) as well its effect on ATP release. Our results revealed that HKE_2 was able to inhibit U46,619-induced platelet aggregation at different concentrations. This effect was accompanied by a reduction of ATP release.

These data may contribute to understand this intricate process as well as opening a door to new therapies for the prevention and treatment of chronic inflammatory diseases, including atherosclerosis and thrombotic diseases.

Supported by NIH award GM076592

POSTER #33

Very long-chain polyunsaturated fatty acid/DHA-containing phosphatidylcholine molecular species show gender-specific changes in Age-related Macular Degeneration (AMD)

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Docosahexaenoic acid (22:6) is the precursor of docosanoids, concentrated in photoreceptor cells necessary for vision, and decreased in age-related macular degeneration (AMD). AdipoR1 KO mice display features of retinal degenerative disease and 22:6 uptake/retention is inhibited, resulting in reduced PC-containing VLC-PUFAs and photoreceptors loss[1]. A higher AMD incidence in women than men (65% vs 35%) has been observed[2]. Also, phospholipid fatty acids (FAs) are more abundant in women (2.31g/L) than men (1.97g/L). Therefore, we asked if PC-containing VLC-PUFAs are altered in AMD and if gender-specific differences occur.

AMD and normal male and female donor eyes were analyzed by LC-MS/MS and PC-containing VLC-PUFAs (24-38 carbons in length) characterized and quantified (22:6 occurs at all sn-2 positions).

In normal retinas, sn-1 PC-FAs from 22 carbons (C) to 32C were barely detectable; 32 and 34C VLC-PUFAs were abundant, with low 36 and 38C FAs. Central AMD retinas were similar, but peripheries showed dramatic VLC-PUFA decrease; 32 and 34C FAs were reduced below the 36 and 38C FAs. Ratio analysis revealed no statistical difference between all central-peripheral or all AMD-normal, but female-male comparisons revealed significant decreases in female values ($p \leq 0.007$).

Synthesis of 32 and 34C VLC-PUFAs results in low amounts of 24-32C FAs, indicating shorter chain FAs are steps in long chain synthesis, while 32 and 34C VLC-PUFA abundance, with some 36 and 38C, indicate end points. AMD VLC-PUFAs are reduced up to 90%, with 36 and 38C FAs retained the longest, implying VLC-PUFA reduction in AMD occurs with impaired synthesis. VLC-PUFAs are important in rods[3]; a rod-specific deletion of ELOVL4 in mice results in PC reduction[4]. Female higher ratios indicate increased VLC-PUFAs overall. If 22:6 regulation is decreased in AMD, leading to VLC-PUFA decrease (as in AdipoR1 KOs), and females have higher VLC-PUFA demands, female AMD bias may occur, with peripheral rods first showing changes in the 22:6/VLC-PUFA lipodome.

Supported by grants NEI 005121 and NIGMS GM103340 (NGB) and the EENT Foundation

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POSTER #34

Prostaglandin $F_{2\alpha}$ FP receptor antagonist improves outcomes after experimental traumatic brain injury

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BACKGROUND: Injuries to the brain promote upregulation of prostaglandins, notably the proinflammatory PGF2α, and over activation of their cognate G-protein-coupled FP receptor, which could exacerbate neuronal damage. Our study is focused on investigation of the FP receptor as a target for novel neuroprotective drugs in a preclinical animal traumatic brain injury (TBI) model.

METHODS: Accordingly, the effects of acute intraperitoneal post-treatment with selective FP antagonist AL-8810 were studied in wild type (WT) and FP receptor knockout (FP-/-) mice after controlled cortical impact (CCI). Neurological impairments were evaluated using neurological deficit scores (NDS) and the grip strength test. Cortical lesions and overall brain pathology were assessed using immunohistochemistry.

RESULTS: Morphological analyses of cerebral vasculature and anastomoses revealed no differences between WT and FP-/- mice. CCI produced cortical lesions characterized by cavitation, neuronal loss, and hematoma with a volume of 20.0±1.0mm3 and significant hippocampal swelling (146.5±7.4% of contralateral) compared with sham ($P<0.05$). Post treatment with AL-8810 (1 to 10 mg/kg) had no significant effect on cortical lesions, which suggests the irreversible effect of primary CCI injury, but significantly reduced hippocampal swelling to a size not significantly different from the sham group. Post-treatment with AL-8810 at a dose of 10mg/kg significantly improved NDS at 24 and 48h after CCI ($P<0.001$ and $P<0.01$, respectively). In the AL-8810 group, CCI-induced decrease in grip strength was three-fold (2.93±1.71) less and significantly different than in the saline-treated group. The FP-/- mice had significantly less hippocampal swelling, but not NDS, compared with WT mice. In addition, immunohistochemistry showed that pharmacologic blockade and genetic deletion of FP receptor led to attenuation of CCI-induced gliosis and microglial activation in selected brain regions.

CONCLUSION: This study provides, for the first time, demonstration of the unique role of the FP receptor as a potential target for disease-modifying CNS drugs for treatment of acute traumatic injury.

POSTER #35

Role of Group VIB Calcium-independent Phospholipase A_2 ($iPLA_2\gamma$) in Carcinogenesis

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Group VIB calcium-independent phospholipase A_2 ($iPLA_2\gamma$) is a membrane-associated $iPLA_2$ enzyme with unique features, such as the utilization of distinct translation initiation sites and the presence of mitochondrial and peroxisomal localization signals. It has been shown that, as well as maintenance of homeostasis of the mitochondrial membrane, $iPLA_2\gamma$ contributes to modulation of lipid mediator biosynthesis. While $iPLA_2\gamma$ is ubiquitously expressed in most tissues, our immunohistochemical analysis revealed that its expression is elevated in cancerous tissues. In the present study, we used $iPLA_2\gamma$-deficient mice to investigate the role of $iPLA_2\gamma$ in carcinogenesis.

We first implanted Lewis lung carcinoma (LLC) cells subcutaneously into wild-type or $iPLA_2\gamma$ deficient mice and evaluated the development of solid tumor around the injected sites. As the results, we found that LLC tumors grafted in $iPLA_2\gamma$-deficient mice grew more slowly than did those grafted into wild-type mice, with concomitant decreases in the density of microvascular networks and the expressions of proangiogenic vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9).

We next examined the effect of $iPLA_2\gamma$ deficiency on azoxymethane (AOM)-induced colon chemical carcinogenesis. $iPLA_2\gamma$ deficiency significantly reduced both total number and size of polyps in colon at 30 weeks after the AOM injection. Among prostanoids, thromboxane (TX) B_2, a stable metabolite of TXA_2, levels in colon tumor tissues of $iPLA_2\gamma$-deficient mice were significantly lower than those in wild-type mice. In $iPLA_2\gamma$-deficent tumor tissues, the expressions of VEGF, CD31 and MMP-9 were also suppressed. These results indicated that $iPLA_2\gamma$ plays a critical role in carcinogenesis, possibly through the modulation of lipid mediator biosynthesis.

POSTER #36

Molecular organization of phosphatidylcholine (PC) molecular species containing very long chain polyunsaturated fatty acids (VLC-PUFAs) in the human retina

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Retinal phospholipids (PLs) containing docosahexaenoic acid (22:6) are enriched in the retina, particularly in photoreceptor cells and are critical to function. VLC-PUFAs derived from 22:6 play important roles in photoreceptor survival[1,2]. Moreover, genetic ablation of the Adiponectin receptor 1 leads to photoreceptor degeneration subsequent to the specific inability to incorporate 22:6 and a concomitant reduction of VLC-PUFAs (up to 90%)[3]. Therefore, we asked if changes in VLC-PUFA-containing PCs accompany age-related macular degeneration (AMD). Here we describe the distribution and molecular organization of these PCs in normal and AMD donor retinas.

20 μm-thick-sections showing all layers of the retina, RPE, and sclera from normal, early, and advanced AMD eye donors were imaged by MALDI mass spectrometry (positive ion analysis). Collision-induced dissociation was performed directly off tissue after imaging in order to determine the identity of the lipid molecular ions.

When macula and periphery were compared in AMD and normal retinas, AMD retinas showed decreased macular PC(34:1/22:6) and peripheral PC(32:0/22:6). Specific phospholipids were localized to the inner retina and photoreceptors. For example, we localized a photoreceptor marker (18:0/22:6) and demonstrated co-localization with the VLC-PUFA PC-(34:5/22:6). We also demonstrated that PC(34:5/22:6) and PC(34:6/22:6) show a decline in abundance in the central retina in advanced AMD. Interestingly, we have also found differences in PL distribution between the rd6 and WT mouse retinas. Overall, AMD retinas contain less VLC-PUFA containing PCs.

We have demonstrated that specific PC species are enriched in photoreceptors and the inner retina, and that these molecules are reduced as degeneration proceeds, suggesting that VLCPUFA distribution is linked to retinal homeostasis.

Supported by grants NEI 005121 and NIGMS GM103340 (NGB) and the EENT Foundation

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POSTER #37

Docosahexaenoic Acid-containing phospholipids In Human Rod and Cone Photoreceptor Cells

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Docosahexaenoic acid (DHA; 22:6(ω -3)) is an essential component of retinal cell membranes[1], a precursor of docosanoids, and necessary for homeostasis and cell survival[2]. The adiponectin receptor 1 has recently been shown to be key in retinal DHA uptake and retention. The genetic ablation of AdipoR1 in mice leads to specific reductions in retinal DHA, as well as phosphatidylcholine (PC)-containing very long-chain polyunsaturated fatty acids (PC-VLCPUFAs), and the onset of photoreceptor cell degeneration which resembles flecked retinal diseases[3]. ELOVL4 mutation affects VLC-PUFA synthesis and is linked to photoreceptor loss[4], and PC-VLC-PUFA loss, occurring in the AdipoR1 KO mouse, is related to DHA derivation and failure to elongate[3]. To ascertain the significance of these molecules in human rod and cone photoreceptor cells, tissue punches were collected from the cone-rich macula and the rod-rich periphery of donated human eyes and analyzed via LC/MS/MS. The VLC-PUFAs, which occur at the sn-1 position (DHA occurs at sn-2), were characterized by mass in these PC phospholipids. Fatty acid (FA) tails with 32 carbons (C) and 34C were abundant, with some apparent 36C and 38C chains. PC-VLC-PUFAs with 56 carbons were the most frequent, suggesting a general end-point in elongation at 34C. The prevalence of VLC-PUFAs differed between the peripheral retina and the macula, with long-chain ω-3 FAs more dominant in the rod-rich periphery. Very long-chain ω-6 FAs were not significantly different between the macula and periphery. Since the peripheral retina contains higher amounts of very long-chain ω-3 FAs, and therefore DHA, it suggests a bias in sensitivity and a decreased ability to generate DHA-derived mediators (docosanoids) under oxidative stress or impaired homeostatic conditions. This may play a role in rod-initiated photoreceptor impairments and retinal degeneration.

Supported by grants NEI EY005121 and NIGMS GM103340 (NGB) and the EENT Foundation

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POSTER #38

PNPLA7-mediated catabolic pathway for phosphatidylcholine has a crucial role in hepatic choline metabolism and systemic energy homeostasis

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Hydrolysis of phospholipids by phospholipases can generate lipid mediators, remodel cellular membranes, and mobilize nutrients. Choline, a biologically essential compound for liver function and fat metabolism, is derived from the diet as well as via the liberation from its largest endogenous pool, phosphatidylcholine (PC), by the sequential action of phospholipase A_1/A_2, lysophospholipase, and glycerophosphodiesterase. Here we show that patatin-like phosphor-lipase domain containing 7 (PNPLA7), a member of the iPLA$_2$/PNPLA family, functions as a lysophospholipase responsible for the hepatic PC degradation machinery that provides glycerophosphocholine (GPC) and thereby choline in the liver. Mice lacking PNPLA7 showed a drastic reduction in hepatic GPC level with a series of signs of choline and methionine deficiency, including decreased hepatic levels of labile methyl groups (choline, betaine and *S*adenosyl methionine), adaptive responses that enhance the metabolic efficiency of the methionine cycle, and impaired secretion of very-low-density lipoprotein triglycerides. The null mutant mice also displayed severe growth retardation, short life span, hypoglycemia with mild ketosis, and a profound reduction in fat mass. This lean phenotype was attributable, at least in part, to increased energy expenditure and "browning" of white adipose tissue, characterized by the presence of multilocular lipid droplets and numerous mitochondria and by the induction of beige fat–related genes such as *Ucp1* and *Cidea*. Moreover, we identified an upstream phospholipase A_2 subtype that supplies the substrate, lysophosphocholine, to PNPLA7. These results indicate that PNPLA7 is a critical molecular component of the PC-catabolic pathway required for hepatic choline metabolism and systemic energy homeostasis.

POSTER #39

Quantification of sphingosine 1-phosphate in plasma of colorectal carcinoma patients by LC-MS/MS

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Sphingosine 1-phosphate(S1P) is a bioactive sphingolipid that regulates cell growth and suppresses apoptosis. It is produced by the enzyme sphingosine kinase(SK) inside cells, and then exported outside by S1P transporters. Previous reports indicated that SK is overexpressed in various human cancer tissues such as brain, breast, lung, stomach, colon, ovary, rectum and small intestine. The gene for SK is regarded oncogenic, and it has been targeted for cancer treatment. Recent studies demonstrated a potential for S1P to become a human disease biomarker for the diagnosis of cancer and various metabolic diseases. It is reported that circulating S1P levels are elevated in murine colon cancer models, and in ovarian cancer patients. However, the plasma S1P decreased in prostate cancer patients, suggesting S1P is potential to serve as a marker for early diagnosis and prediction of prostate cancer. To date, the S1P levels in plasma of patients with colorectal cancer have not yet been fully understood. In the current study, we established a method for analyzing S1P levels in human plasma using LCMS/MS. The results showed that serum S1P levels in patients with colorectal cancer were significantly lower when compared with those of the healthy subjects ($P<0.05$). This decrease might be due to the buffering effect of the circulating blood cells.

This study was supported by the Jilin Science and Technology Foundation (20150101144JC to W.H.) and the Young Scholars Program of Norman Bethune Health Science Center of Jilin University (2014031).

POSTER #40

UPLC-MS/MS identifies lipids associated with perceptual speed performance in healthy adults

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Introduction: Several studies have demonstrated associations between plasma lipids and neurological diseases, including Alzheimer's disease, Parkinson's disease and schizophrenia. However, the relationship between circulating lipids and cognition in healthy individuals has not been well defined. We determined associations between circulating plasma lipids and cognitive measurements in a healthy older population.

Methods: Healthy individuals (age range 43-84, n=286), completed a comprehensive neuro-cognitive test battery including digit symbol coding (DSC), a measure of perceptual speed performance. Lipids were extracted from 10 µL plasma and lipidomic analysis performed using UPLC-MS/MS with a solvent system consisting of water/methanol/tetrahydrofuran containing 10mM ammonium formate. Fatty chain identification of phospholipid peaks were performed on pooled healthy control samples using lithium adducts.

Results: We were able to measure 381 lipid species and assign fatty acid composition for the majority. Linear regression analysis (adjusting for age, gender, BMI, total cholesterol, HDL, triglycerides and statin use) identified lipid species associated with DSC, with 64 of the 381 measured lipids having a significant association ($p<0.05$, uncorrected). 24 lipids remained significant after correction using the Benjamini-Hochberg method ($p<0.05$). Our analysis identified diacyl and ether phospholipids containing omega-3 fatty acids (20:5, 22:5 or 22:6) as positively associated with DSC score.

Discussion and Conclusion: Digit symbol coding is a sensitive measure of perceptual speed and is included in many standard measures of intelligence. Performance deficits of DSC represents one of the largest effect size findings in schizophrenia neuropsychological literature. Several groups have identified plasma lipid changes associated with schizophrenia similar to those observed with DSC in healthy individuals in this study. This suggests that plasma lipid changes seen in schizophrenia may, in part, be reflective of perceptual speed changes and that esterified omega-3 fatty acids could be important in the neurological changes associated with the disease.

POSTER #41

Biallelic deletions in *MBOAT7* link phosphatidylinositol lipid remodeling to autism spectrum disorders

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Background: Autism spectrum disorders (ASD) are characterized by impairment of social interaction and communication skills. ASDs are usually diagnosed before the age of 3, but because of the heterogeneity of these disorders the genetic basis is difficult to establish in most cases. Lysophosphatidylinositol acyltransferase (LPIAT1) is a phospholipid-remodeling enzyme encoded by the membrane-bound O-acyltransferase gene *MBOAT7.* The human MBOAT family has 5 members originating from the yeast gene Ale1p. LPIAT1 facilitates the transfer of fatty acyls to lysophosphatidylinositol (lysoPI). LPIAT1 exhibits a preference for arachidonoyl-containing acyl donors, and contributes to the regulation of free arachidonic acid in the cell.

Objective: To identify the genetic basis and underlying molecular mechanisms involved in the development of ASD and intellectual disability (ID).

Methods: We recruited over 100 consanguineous families from the Middle East with at least one child presenting with presumed autosomal recessive ASD.
Whole exome sequencing was used to identify mutations in DNA from individuals displaying features consistent with the diagnosis. Variants were prioritized following a set of criteria. Fibroblasts were cultured from patient-derived and healthy family member (control) biopsies, and used to study the LPIAT1 activity and cell lipidome.

Results: Affected individuals presented with ASD and ID. Brain MRIs showed mild cortical atrophy and local polymicrogyria. We identified biallelic, inactivating deletions in *MBOAT7* in 4 of the recruited families. Enzyme activity was substantially decreased in patient fibroblasts compared to control, however, levels of phosphatidylinositol phosphates (PIPs) were normal. Calcium ionophore treatment of patient cells induced increased release of arachidonic acid and pro- inflammatory eicosanoid PGE_2, compared to control cells.

Conclusions: Our study establishes a link between human developmental brain disorders and phospholipid remodeling.

POSTER #42

NOVEL INHIBITOR OF CYTOSOLIC GROUP IVA PHOSPHOLIPASE A2 (cPLA2α) HAS SHOWN "Proof of concept" IN TREATMENT OF PSORIASIS

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Introduction: In contrast to the rapid development of new systemic therapies for severe psoriasis there are few options for topical treatment of mild to moderate disease. Group IVA cytosolic Phospholipase A_2 (cPLA$_2$α) is an enzyme regulating inflammation. It has been studied mechanistically in skin keratinocytes and has been suggested to act as a candidate therapeutic target in inflammatory skin diseases. In this study, AVX001, a cPLA$_2$α-inhibitor was investigated in a randomized, double-blind, placebo-controlled, first-in-man study in patients with mild to moderate psoriasis.

Patients and methods: The primary objective was to evaluate cutaneous safety and tolerability of AVX001 in doses 0.002% - 5.0% applied to single psoriasis plaques. The primary endpoint was safety assessed as risk of local skin reaction adverse events (LSRAE) grade 3 or 4, and to define a maximum tolerated dose. The secondary objective was assessment of efficacy of AVX001 on the modified PASI (mPASI) score compared with placebo. In total, 94 Caucasian men with mild to moderate psoriasis on the trunk or extremities were treated with AVX001 and placebo on symmetrically affected psoriasis areas for four weeks with two weeks follow-up.

Results: The drug was safe with no grade 2, 3 or 4 LSRAE. Maximum tolerated dose was not found. The combined doses of 3 and 5% gave a reduction in mPASI score of approx. 32% following 4 weeks treatment (once daily) (p=0.058).

Conclusions: Treatment with AVX001 is safe and well-tolerated in doses up to 5%. Statistically significant reduction in mPASI was seen at the highest dose levels (3%-5%). Longer treatment and higher doses would conceivably result in superior efficacy.

POSTER #43

c-Fos reporter reveals astrocytic activity modulated by S1P – signaling in experimental autoimmune encephalomyelitis

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Fingolimod (FTY720; Gilenya) is the first oral, disease-modifying therapeutic for multiple sclerosis (MS) and has revealed sphingosine 1-phosphate (S1P), as relevant to MS pathology. Fingolimod is an S1P analog when phosphorylated and can interact with four of five S1P receptors (S1PRs), $S1P_{1,3-5}$. When fingolimod binds $S1P_1$ on pathogenic lymphocytes it causes their sequestration in secondary lymphoid organs. Additionally, fingolimod can enter the CNS to access various endogenously expressed S1PRs on several neural cell types. Most markedly, fingolimod produces internalization and functional $S1P_1$ receptor loss on astrocytes, largely responsible for its efficacy in experimental autoimmune encephalomyelitis (EAE). To explore the pertinent role of astrocytic S1P signaling in EAE, and likely MS, a transgenic mouse capable of reporting cellular activity over discrete time periods was utilized. The transgenic mouse line with a tetracycline-suppressible cis element (tTA) and a c-Fos driven nuclear GFP-histone fusion protein was crossed with astrocyte specific $S1P_1$ nulls. Green-fluorescent cells (GFCs) were not observed in the presence of doxycycline food (dox). EAE was induced and dox was removed upon the onset of EAE signs, allowing c-Fos activated cells to express a semi-permanent GFP signal. Histological examination established astrocytes to be the predominantly activated cell type. The extent of astrocyte activation was quantified and compared among untreated, FTY720 treated, and astrocyte specific $S1P_1$ nulls by whole spinal cord imaging and flow cytometry. Fluorescence-activated cell sorting was used to isolate EAE-activated astrocytes and subsequently RNA-seq was performed. Distinct transcriptional changes during EAE and with fingolimod exposure or astrocyte specific $S1P_1$ removal implicate processes that are $S1P_1$ dependent in modifying disease course.

POSTER #44

Oleoylethanolamide improves phospholipid profiles and reduces astroglia activation in a mouse model of Gulf War Illness

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Background: Twenty-five years have elapsed since the 1991 Gulf War (GW) but veterans with Gulf War Illness (GWI) continue to suffer from this chronic illness. As of yet, there are no therapies that can help treat the underlying pathology of GWI. We have developed a mouse model of GWI that exhibits chronic cognitive deficits and anxiety that are similar to the symptoms reported by veterans with GWI. We also observed increased astroglia activation and imbalances of omega-3 and omega-6 containing phospholipid (PL) in the brain at 5-months post-exposure to GW agents.

Objective: The goal of this study is to examine the therapeutic potential of a bioactive lipid oleoylethanolamide (OEA) in targeting omega-6 and omega-3 imbalances and astroglia pathology of GWI in this mouse model.

Methods: C57BL6 mice were co-administered 0.7 mg/kg of PB and 200 mg/kg of PER in a single intraperitoneal injection (i.p.) in dimethyl sulfoxide (DMSO) for 10 days daily to generate the mouse model with the control group receiving DMSO only. At 5-months post-exposure, OEA was administered at 10mg/kg for 10 days daily via i.p. Mice were subsequently euthanized for lipidomics and immunohistochemical analyses. Folch lipid extracts from the brain were examined for the total fatty acid content using gas chromatography/mass spectrometry (GC/MS). Phospholipids were analyzed by hydrophilic interaction liquid chromatography (HILIC) and mass spectrometry (MS) analysis. Individual PL species were identified and quantified with the LipidomeDB software.

Results: We observed accumulation of ether and omega-3 and omega-6 fatty acid containing PL in the brains of GW agent exposed mice. Oleoylethanolamide intervention was able to restore the levels of these PL species in exposed mice to those similar to control mice. Also OEA treatment reduced elevated astroglia activation in GW agent exposed mice. Oleoylethanolamide was also able to uniquely improve the ratio of omega-3 α-linoleic acid (ALA) to its longer chain product, DHA.

Conclusion: Our preliminary preclinical studies indicate that OEA could be useful as a potential treatment for GWI, which warrants further investigation.

POSTER #45
Docosahexaenoyl acyl chains of membrane phospholipids and retina function

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This project aims to understand the significance of docosahexaenoic acid (DHA), docosanoid precursors (NPD1, Maresin and RVD), and of very-long-chain-poly-unsaturated-fatty-acids (VLC-PUFAs) in retinal function. DHA and VLC-PUFAs are abundant in mammalian retinas[1], but may vary in other non-mammalian taxa with different visual ecologies. From a clinical point of view, VLC-PUFAs are important because they are synthesized by the ELOVL4 enzyme, and mutated ELOVL4 results in photoreceptor degeneration and blindness[2]. Evolutionarily, humans are diurnal primates. To understand the evolutionary conservation of this fundamental aspect of retinal biochemistry, we asked whether or not a diurnal frog exhibits similar DHA and VLCPUFA-enriched retinal cellular membranes.

PC spectra for both superior and inferior regions show no significant contribution from VLCPUFAs. For both regions, DHA containing PCs are predominantly paired with fatty acids 16:0 and 18:0. Across the entire retina, a preponderance of PE species contains DHA, whereas relatively fewer PCs contain DHA. We also observe up to PE 48:12 (22:6/26:6) species. With respect to regional differences, the superior has more DHA containing PCs than in the inferior. Additionally, greater diversity of TAG species is observed in the inferior retina as compared to the superior retina. Finally, higher concentrations of total esterified DHA are observed in the inferior retina, as compared to the superior retina.

Differing from human retina and murine retinas, VLC-PUFAs ranging from 32 carbons to 38 carbons, are absent from the frog retina, especially in the PC species. Furthermore, diurnal amphibian retina appears to store DHA primarily in PEs, as opposed to typical mammalian DHA contained within PCs (including PC44:12). In conclusion, our results suggest that DHA and VLC-PUFA incorporation differs between mammals and amphibians, offering an opportunity to unravel function based upon comparatively distinct visual systems.

Supported by grants NEI 005121 and NIGMS GM103340 (NGB) and the EENT Foundation

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POSTER #46

Membrane-type Frizzled Related Protein (MFRP) participates in docosahexaenoic acid (DHA) retention in the retina and as a consequence in photoreceptor cell function

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Photoreceptor cells (PRC) contain the highest concentration of DHA in the human body[1]. DHA is the precursor of docosanoid mediators. The docosanoid neuroprotectin D1 (NPD1), a stress-injury response mediator, promotes survival of PRC, retinal pigment epithelium (RPE) cells, and other neural cells. Mechanisms for DHA uptake from the choriocapillaris to the RPE and retention of the PRC are not fully defined. Recently, the seven transmembrane non-G-protein, Adiponectin receptor 1 (AdipoR1), was shown to be necessary for this function[2]. Both AdipoR1 and MFRP KO mice display flecked retinas followed by a progressive loss of PRC. Here we report the finding that MFRP is also necessary for DHA uptake and photoreceptor function. Our hypothesis is that MFRP works as an alternative/complementary pathway for DHA uptake/retention/distribution to the PRC.

Thickness of photoreceptor layer was determined by OCT for MFRP KO and WT mice. Lipids were extracted from retina of mutant and control animals and phosphatidylcholine (PC) molecular species and other lipid mediators were identified and quantified by LC-MS/MS-based lipidomic analysis.

OCT revealed progressive retinal degeneration in MFRP KO mice between 1 and 9 months-old (MO). The photoreceptor nuclear layer (ONL) thickness significantly declined from 3 MO to 9 MO. DHA-containing PCs (38:6) and (40:6) were reduced by half in MFRP retinas compared to WT. PCs above 40 carbons (C) were greatly reduced in the mutant retina. Comparison of PC molecular species of MFRP and AdipoR1 KO revealed a similar profile, with an increase of 3436C PCs, and reduction of PC(38:6) and (40:6). PC(44:12), corresponding to two DHAs esterified at sn-1 and -2, was greatly reduced in both mutants.

In conclusion, MFRP KO (RD6) retinas displayed drastic reduction in the biosynthesis of PC molecular species, particularly those containing DHA and DHA-elongation products. This may be causative of retinal degeneration. Here we propose that MFRP acts similarly as AdipoR1 in DHA uptake/retention, which, in turn, switches off availability of precursors for pro-homeostatic lipid mediators that sustain RPE and PR cellular integrity.

Supported by grants NEI EY005121 and NIGMS GM103340 (NGB) and the EENT Foundation.

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POSTER #47
Evaluating PLA activity by LPLAT inhibition using ACAT inhibitor

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Phospholipase A (PLA) hydrolyzes an acyl group from phospholipids and generates lysophosholipids (LPLs). LPLs are rapidly reacylated by lysophospholipid acyltransferases (LPLATs). This cooperative reactions of PLAs and LPLATs directly regulates the fatty acid remodeling and might be involved in many biological processes such as vehicle budding and organelle biogenesis. Recently many LPLATs have identified and biochemically characterized. However, PLA, especially PLA_1, involved in fatty acid remodeling remains to be characterized. We focused on two mammalian intracellular PLA_1s ($iPLA_1\alpha$/PA-PLA_1 and $iPLA_1\gamma$/KIAA0725), which was implicated the remodeling of *sn*-1 fatty acid remodeling of PI in *C.elegens*. We overexpressed two $iPLA_1$s in HEK293 and HeLa cells. However, we did not observed any change in LPL profile. It was suggested recently that acyl-coA cholesterol acyltransferase (ACAT) inhibitor, CI-976, inhibited LPLATs and thereby induced the tubulation of Golgi membranes to the endoplasmic reticulum that associated with LPLAT and PLA reactions. We thus tested the effects of various ACAT inhibitors including CI-976 on LPL level in $iPLA_1$overexpressing cells. Accordingly, we found that some ACAT inhibitors dramatically increased the level of 2-acyl-LPLs in $iPLA_1$-overexpressing cells. We also applied the method for evaluation of PLA_2 isozymes and found that ACAT inhibitors acculumated 1-acyl-LPLs in $cPLA_2\gamma$ -overexpressing cells. Our results suggest that some kinds of ACAT inhibitors target LPLATs resulting in the accumulation of LPLs produced by PLAs.

POSTER #48
S1P signaling in an animal model of Multiple Sclerosis

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Multiple sclerosis (MS) is the most prevalent autoimmune disorders of the central nervous system (CNS), with neurological symptoms caused by inflammation and demyelination. Studies of experimental autoimmune encephalomyelitis (EAE), an animal model for MS, have shown that autoreactive T cells secreting IL-17 (Th17 cells) and IFN-γ (Th1 cells) are involved in EAE/MS pathogenesis. The recent breakthrough in the treatment for multiple sclerosis (MS) is that the FDA approved fingolimod (FTY720; GILENYA™, Novartis Pharma AG) as an oral treatment of relapsing forms of MS. The possible mechanism of action of fingolimod is reducing the circulating pathogenic lymphocytes by retaining them in the lymph nodes through S1P receptor, S1P1, resulting in reducing infiltration of pathogenic lymphocytes into CNS. In addition, we previously reported that S1P1 signaling in astrocytes is a nonimmunological CNS mechanism of action for FTY720 in EAE [PNAS, 2011]. However, roles of other S1P receptors and S1P metabolic enzymes have not yet well determined. In this study, we examined the EAE pathogenesis in a variety of S1P receptor and enzyme knockout mice, and found that EAE pathology is orchestrated by S1P signaling.

POSTER #49

Beta-lactones as a Novel Class of Calcium-independent Phosholipase A_2 Inhibitors

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The recently emerged important pharmaceutical significance of calcium-independent phospholipase A_2 (GVIA iPLA$_2$) prompted us to extend our studies toward the development of potent and selective GVIA iPLA$_2$ inhibitors. In this work, we describe a novel class of GVIA iPLA$_2$ inhibitors based on a beta-lactone ring. Our previous studies on GVIA iPLA$_2$ inhibitors have shown that a potential inhibitor has to be a small non-polar molecule. Thus, we designed beta-lactones carrying a medium length carbon chain with an aromatic ring at varying distances from the lactone ring. The other substituent was designed to be a small aliphatic chain containing from one to six carbon atoms. The substituted beta-lactones were produced via cyclization of the intermediate α,β-substituted β-hydroxy acids, which was derived from pentanoic acids substituted with an aryl group at the 5-position and aliphatic aldehydes with different chain lengths. All synthesized beta-lactones were tested for their in vitro activity on recombinant human GVIA iPLA$_2$ using mixed micelle assays. In addition, their selectivity over human GIVA cPLA$_2$ and GV sPLA$_2$ was also studied using mixed micelle assays. Among the novel beta-lactones, a highly potent inhibitor (GK436) of GVIA iPLA$_2$ with a X_I(50) value of 0.00006 was identified.

Acknowledgments: This research has been co-financed by the European Union (European Regional Development Fund - ERDF) and Greek national funds through the Operational Program ‘‘Competitiveness and Entrepreneurship’’ of the National Strategic Reference Framework (NSRF) - Research Funding Program: “Phospholipases A_2 inhibitors: Developing a drug pipeline for the treatment of inflammatory neurological disorders” and NIH grant RO1 GM20501-40.

POSTER #50

2-Oxoesters: Development of a Novel Class of Potent and Selective Inhibitors of Cytosolic Group IVA Phospholipase A_2

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The development of potent and selective GIVA $cPLA_2$ inhibitors is of great importance, since this enzyme is the rate-limiting provider of arachidonic acid. In the past, we have developed a variety of synthetic inhibitors for the various PLA_2 types. Herein, we present a novel class of GIVA $cPLA_2$ inhibitors based on the 2-oxoester functionality. Several novel compounds were synthesized incorporating the 2-oxoester functionality and a free carboxyl group at a varying distance. 2-Oxoesters with a long aliphatic chain or a chain carrying an appropriate aromatic system, like the biphenyl system, and a free carboxyl group were found to be highly potent and selective GIVA $cPLA_2$ inhibitors exhibiting $X_I(50)$ values of 0.0007-0.0008. In addition, 2oxoester inhibitors incorporating the biphenyl system, for example GK452, present interesting favorable lipophilicity (ClogP values lower than 5). When a methyl 2-oxoester is combined with a short chain carrying a naphthalene ring, selective inhibition of the other major intracellular PLA_2 enzyme, the calcium-independent PLA_2 (GVIA $iPLA_2$), was observed. The novel highly potent and selective GIVA $cPLA_2$ inhibitors are excellent tools for the study of the role of the enzyme in cells and in animals and may contribute to the development of novel medicinal agents for the treatment of inflammatory diseases.

Acknowledgments: This research has been co-financed by the European Union (European Regional Development Fund - ERDF) and Greek national funds through the Operational Program ‘‘Competitiveness and Entrepreneurship’’ of the National Strategic Reference Framework (NSRF) - Research Funding Program: “Phospholipases A_2 inhibitors: Developing a drug pipeline for the treatment of inflammatory neurological disorders” and NIH grant RO1 GM20501-40.

POSTER #51

Leukotriene D_4 and Prostaglandin E_2 Synergism in Inflammation and Asthma

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Rationale: Cysteinyl leukotrienes (LTs-C_4, D_4, E_4) and prostaglandin E_2 (PGE_2) are the metabolites of arachidonic acid, which were shown to be generated at the site of inflammation. However it is not known if there is a cross-talk exists between these two classes of inflammatory mediators.

Methods: We induced vascular (ear) inflammation by injecting agonists into mouse ear and assessed it by measuring ear thickness and histology. Pulmonary inflammation was examined by sensitization and challenge of *Dermatophagoides Farinae* (Der f) (3 ug) intranasally in the presence or absence of LTD_4+PGE_2 and the inflammation was analyzed by histology. The activation of signaling molecules were measured by their expression and phosphorylation by Immuno-blotting and by RT-PCR. PGD_2 and MIP1β generation was measured by ELISA.

Results: LTD_4+PGE_2 potentiated both vascular permeability and edema, gearing the system towards pro-inflammation in WT mice and not in $Kit^{W\text{-}sh}$ mice. Further, LTD_4+PGE_2, via $CysLT_1R$ and EP_3, enhanced Erk and c-fos phosphorylation, inflammatory gene expression, MIP1β secretion, cyclooxygenase-2 (COX-2) up-regulation and PGD_2 generation in MCs. Interestingly, we found that this synergism is mediated through Gi, PKG, and Erk signaling. LTD_4+PGE_2 potentiated effects are partially sensitive to $CysLT_1R$ or EP_3 antagonists, but are completely abolished by simultaneous treatment of both *in vitro* and *in vivo*. Importantly, LTD_4+PGE_2 potentiated Derf-challenged pulmonary inflammation as determined by enhanced cellular infiltration, mucous production and expression of Gob 5, MUC5AC and IL-13 transcripts in lung.

Conclusions: Taken together, our findings unravel a unique LTD_4-PGE_2 interaction impacting MCs via $CysLT_1R$ and EP_3 involving Gi, PKG and Erk, contributing to inflammation *in vivo*. Our results further suggest that targeting both $cysLT_1R$ and EP_3 has an advantage in attenuating inflammation.

POSTER #52
Distinguishing lipid mediators with ion mobility spectrometry and mass spectrometry

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Lipid mediators (LMs) are potent small molecules which are formed from oxidation and subsequent enzymatic and non-enzymatic reactions of precursor fatty acids. LMs are often released upon injury or during diseases, so characterizing their changes is essential for understanding biological systems. One challenge in measuring LMs is that many are isomers, having the same chemical formula but distinct structures. For example, Lipid Maps currently reports 191 prostaglandin (PG) and 159 isoprostane (IsoP) species in their database. Of the 159 IsoP, 118 species either have a molecular formula of $C_{20}H_{32}O_5$ or $C_{20}H_{34}O_5$. These two molecular formulas also comprise 32 of the PG species. Being able to distinguish LMs isomers within any given system is crucial for understanding biological functions and stimulatory responses. Currently, LMs are analyzed in a targeted fashion with GC-MS or triple quadrupole mass spectrometers. While these techniques are sensitive, many LM isomers are still indistinguishable. Ion mobility spectrometry (IMS) offers a rapid gas phase structural separation that can be easily coupled between LC and MS stages for multi-dimensional measurements. LC-IMS-MS measurements provide an opportune technology for rapid, highly sensitive global analyses which distinguish molecular isomers and are extremely sensitive (detection limit of ~100 pM. Using IMS-MS, we analyzed 34 lipid mediator standards comprising 13 unique molecular formulas. Structural separation was achieved for a majority of the isomers with negative polarity including baseline separation between 5S-HETE, 12S-HETE, and 15SHETE; 11(12)-EET and 14(15)-EET; resolvin D1 and D2; and 15R-PGF2a and 8-iso-15RPGF2a. Not all LMs were resolvable using negative ionization including 12S-HETE and 12RHETE; however, upon positive ionization and sodium binding, separation of the R and S isomers was achieved. This presentation will illustrate the use of IMS-MS in LM measurements since currently it is the only technique able to broadly and effectively characterize both low concentration molecules and their isomers.

POSTER #53

Metabolic Pertubations of Postnatal Growth Restriction and Hyperoxia-induced Neonatal Pulmonary Hypertension in a Rat Model of Bronchopulmonary Dysplasia

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Pulmonary hypertension (PH) is a common manifestation of bronchopulmonary dysplasia (BPD) and contributes to increased morbidity and mortality of preterm birth. Postnatal growth restriction has emerged as an independent contributor to the development of PH. Utilizing a rat model combining hyperoxia and post-natal growth restriction, our lab recently investigated the lung histological and protein expression changes caused by BPD-associated vasculature remodeling and consequent PH. The study presented herein utilized a multi-platform approach consisting of complex lipids and lipid mediators, as well as primary metabolism, to characterize the metabolome of lung tissue and plasma from this rodent model. Specifically, Sprague-Dawley neonates underwent three models of PH (growth-restriction, hyperoxia or combined) relative to control. Univariate analyses, multivariate modeling and biochemical networks were utilized to identify and visualize metabolic perturbations. Metabolic changes were characterized by lung-specific 1) decreased total plasmalogen phosphatidylcholines and increased arachidonic acid and docosahexaenoic acid that suggest increased phospholipase A2 activity, linked to surfactant alteration, 2) increased total (non-esterified and esterified) cytochrome P450 (CYP) oxylipins and decreased 12/15-LOX oxylipins were characteristic of pulmonary vascular remodeling, and 3) alterations in primary metabolism indicate a shift to fatty acid oxidation and mitochondrial respiration, as well as pathways indicative of reactive oxygen species production. Although plasma metabolite changes generally showed similar trends as the lung, there were differences. Numerous circulating fatty acids were elevated while total phosphatidylcholines were decreased. Furthermore, plasma non-esterified 5-LOX and soluble epoxide hydrolase (sEH) products involved in the regulation of inflammation, vascular tone, and immune response during development were increased. The present study identifies unique and conserved metabolic perturbations which accompany growth-restriction or hyperoxia-induced PH, providing unique insight into disease pathophysiology.

POSTER #54

Modulation of Blood Accumulation and Angiogenic Responses by PGE_2-EP3 Signaling after ICH in Aged Mice

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With the population aging at an accelerated rate, the prevalence of stroke and financial burden of stroke-related health care costs is expected to continue to increase. Intracerebral hemorrhage (ICH) is a devastating stroke subtype more commonly affecting the elderly population, whom display increased mortality and worse functional outcomes compared to younger patients. This study aimed to investigate the contribution of the prostaglandin E_2 (PGE_2) E prostanoid (EP) receptor subtype 3 in modulating anatomical outcomes and functional recovery following ICH in 24-mo-old mice. PGE_2 levels are dramatically upregulated following brain injury and have been shown to modulate the deleterious excitotoxic and neuroinflammatory processes resulting from activation of glial cells and infiltration of blood cells and proinflammatory molecules through its four EP receptors, EP1-4. EP3 is the most abundant EP receptor in the brain and we have previously shown that signaling through the PGE_2-EP3 axis exacerbates ICH outcomes in young mice. Here, we show that EP3 receptor deletion results in 17.9±6.1% less ICH-induced brain injury ($p=0.0336$) and improves neurological functional recovery, as identified by lower neurological deficit scores at 48h ($p=0.0013$) and 72h ($p=0.0063$), and increased gross ($p=0.0038$) and fine motor ($p=0.0556$) movements and decreased resting time ($p=0.0280$) at 72h. Immunohistological staining was performed to investigate possible mechanisms of EP3-mediated neurotoxicity. Identified mechanisms include reduced blood accumulation ($p=0.0277$) and modulation of angiogenic and astroglial responses, where $EP3^{-/-}$ mice have increased striatal astrogliosis ($p=0.0498$) and VEGF immunoreactivity ($p=0.0115$), and tended to have increased cortical astrogliosis ($p=0.1874$). Using this aged cohort of mice, we have confirmed and extended our previous results in young mice demonstrating the deleterious role of the PGE_2-EP3 signaling axis in modulating brain injury and functional recovery after ICH, further supporting the notion of the EP3 receptor as a putative therapeutic avenue for the treatment of ICH.

POSTER #55

PGE_2 EP1-4 Receptor Expression Levels after Intracerebral Hemorrhage in Young, Aged, and EP1 Deficient Mice

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Intracerebral hemorrhage (ICH) is the most severe form of stroke and is associated with high mortality and morbidity. Neuroinflammation significantly contributes to ICH-induced brain injury and upregulation of prostaglandin E_2 (PGE_2) has been implicated in modulating these deleterious neuroinflammatory pathways. PGE_2 acts on mainly the four G-protein-coupled E prostanoid (EP) receptors, EP1-4, which each have different downstream signaling pathways, tissue distributions, and expression profiles. We have previously demonstrated that EP1 receptor deletion promotes injury following ICH, whereas deletion of EP2 and EP3 is neuroprotective in an equivalent experimental approach. Here, we aimed to investigate the time course, brain sub-region expression profile, and relative level of EP1-4 mRNA expression in young (5-7mo) and aged (12-13mo) wildtype (WT) and EP1 receptor knockout ($EP1^{-/-}$) mice. Following ICH or sham surgery, EP1-4 mRNA levels were assessed by RT-qPCR. Minimal EP14 expression changes are seen at 24h after ICH; although, EP2 (p=0.0.36) and EP4 (p=0.066) are 1.6X increased in the cortex of young WT mice. At 72h post-ICH, EP1 is 3.9x elevated in the cortex (p=0.0003) and 4.6x in the striatum (p=0.012). EP3 is also 1.6x elevated in the cortex (p=0.044). In the contralateral hemisphere, a mean 2.4x increase of EP1-4 ($p<0.01$) expression is seen. In contrast, at 72h after ICH, $EP1^{-/-}$ mice have 0.53x reduced EP3 in the cortex (p=0.030) and 0.68x and 0.71x decreased EP3 (p=0.016) and EP4 (p=0.049), respectively, in the contralateral hemisphere. Aged $EP1^{-/-}$ mice show significantly decreased expression levels of EP2-4 in nearly all areas (cortex, striatum, and contralateral hemisphere). Due to the contralateral differences, basal expression levels of EP2-4 were investigated in the $EP1^{-/-}$ mice, where EP2 is 2.6x, 3.4x, and 3.8x increased in the cortex, hippocampus, and cerebellum; whereas, EP3 trended oppositely. These data indicate a cross-talk interaction between EP1 and the other EP receptors pre- and post-ICH and an association between age and EP receptor expression levels. A better understanding of EP receptor localization and dynamic expression levels after ICH will facilitate the development of effective pharmacological treatments.

POSTER #56

Study of the beta-sulfur effect on the activity of PLA_2 inhibitors based on activated carbonyls

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Synthetic inhibitors of the various phospholipase A_2 (PLA_2) types are excellent tools for the study of their role in cells and in vivo and for the discovery of novel medicinal agents. In our labs, we have developed a variety of synthetic PLA_2 inhibitors. Long chain 2-oxoamides based on γ- or δ-amino acids are selective inhibitors of GIVA $cPLA_2$, while those based on α-amino acids are inhibitors of GIIA $sPLA_2$. Pentafluoroethyl or trifluoromethyl ketones have been developed as selective inhibitors of GVIA $iPLA_2$ exhibiting significant activity in various animal models of autoimmune diseases. The aim of this work was to study the effect of the sulfur atom at the beta-position to the activated carbonyl group. Several fluoroketones containing a betasulfur atom were synthesized applying two different synthetic methods. In addition, a 2oxoamide derivative of AX048, which has been demonstrated to show anti-hyperalgesic activity, was synthesized. Finally, two novel keto-heterocyclic derivatives based on the 1,2,4-oxadiazole ring were designed and synthesized. All the derivatives were tested for their activity against GIVA $cPLA_2$, GVIA $iPLA_2$ and GV $sPLA_2$. The in vitro activity of the trifluoromethyl ketone FKGK11 on GVIA $iPLA_2$ was increased by a factor of ten upon the insertion of sulfur, while the activity of the oxoamide inhibitor AX048 was destroyed. The sulfur derivatives of FKGK18 and GK187 were found to be highly potent inhibitors of GVIA $iPLA_2$. Interestingly, in the case of the novel keto-1,2,4-oxadiazoles derivatives, the sulfur atom caused a remarkable increase of the inhibitory activity toward GVIA $iPLA_2$.

This research was funded in part by the National and Kapodistrian University of Athens and NIH grant RO1 GM20501.

POSTER #57
Docosanoid-mediated neuroprotection in experimental ischemic stroke

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Ischemic stroke triggers a constellation of cellular and molecular disturbances that include lipid peroxidation and neuronal injury. As a protective response, neuroprotectin D1 (NPD1) bio-synthesis is activated that, in turn, reduces polymorphonuclear cell (PMN) infiltration, downregulates apoptosis, and attenuates infarct size after middle cerebral artery occlusion (MCAo). Omega-3 fatty acid-derived mediators, from DHA to EPA, promote inflammation resolution in murine models of acute inflammation. In this study we used behavioral assessment, MRI, and LC-MS/MS-based mediator lipidomic analysis to further unravel the lipidomic basis for our understanding of this potential therapeutic approach. Sprague-Dawley rats received 2h MCAo. DHA (5mg/kg) or vehicle was administered i.v. at 3h after onset of MCAo. In behavioral studies, the neuroscore was conducted during 3 weeks after MCAo. *Ex vivo* MRI and histopathology were carried out on day 21. In lipid mediator studies, rats were treated with NPD1, resolvin D2 (RvD2) or RvE1 (2µg per day during 7 days) or CSF by i.c.v. infusion at 1h after MCAo. Behavioral tests, *ex vivo* MRI, lipidomic analysis and immunohistochemistry were conducted. DHA treatment improved the neuroscore compared to vehicle on day 1 (by 16%), day 2 (by 19%), day 3 (by 22%), week 1 (by 20%), week 2 (by 22%) and week 3 (by 33%), respectively. Treatment with NPD1, RvD2 and RvE1 significantly improved behavioral scores (days 1, 3 and 7) and reduced total lesion volumes computed from T2WI images on day 7. Lipidomic analysis showed that DHA potentiates NPD1 synthesis in the penumbra three days after MCAo. We have shown that administration of docosanoids/pro-resolving mediators provide neurobehavioral recovery, reduce brain infarction and brain edema, activate docosanoid synthesis in the penumbra and promote cell survival. These results provide the basis for assessment in the future to ameliorate ischemic stroke brain damage.

This study was supported by P30GM103340 (NGB, LB) from NIH/NIGMS.

POSTER #58

Efficacy of Laropiprant in Ameliorating Hyperglycemia-Mediated Intracerebral Hemorrhage

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Introduction: The respective importance of PGD_2 and its receptor DP1 in the vasculature, the blood, and the brain warrants further examination of their role in hyperglycemia-mediated intracerebral hemorrhage (ICH).

Hypothesis: In this study, we tested whether deletion of the DP1 receptor or its blockade by the selective antagonist Laropiprant improves functional and anatomical outcomes following ICH in hyperglycemic mice.

Methods: Wildtype (WT) and $DP1^{-/-}$ C57BL/6 mice were given 2g/kg glucose; blood glucose levels and c-peptide levels were monitored over 4h. In the second cohort, WT and $DP1^{-/-}$ mice treated with saline or the DP1 receptor antagonist were given 2g/kg glucose and ICH was induced at 1h by giving a single dose of collagenase in the striatum. Neurologic deficits, brain injury volume, and edema volume were calculated at 72h. Further, the brain sections from these groups were subjected to Perls' staining and Iba1 and GFAP immunoreactivity to determine the effect of Laropiprant on the modulation of iron levels and gliosis.

Results: Acute injection of glucose led to a significant increase in the glucose level in WT and $DP1^{-/-}$ mice. $DP1^{-/-}$ mice exhibited faster clearance of glucose overload compared with the WT mice. Similarly, WT mice treated with Laropiprant also exhibited faster clearance of glucose. Similar patterns were observed in c-peptide levels of these groups. The injury volume in $DP1^{-/-}$ mice compared with WT was significantly lower (8.3 ± 1.8 vs $19.3\pm5.6 mm^3$; $p<0.01$). Furthermore, WT mice treated with Laropiprant also exhibited significantly lower brain lesion volume (9.1 ± 3.2 vs $19.3\pm5.6 mm3$; $p<0.01$). Interestingly, a significant decrease in Iba1 immunoreactivity and Perls'-labelled iron content was observed in hyperglycemic $DP1^{-/-}$ compared with the hyperglycemic WT mice.

Conclusion: Together, the data suggest that inhibition of the DP1 receptor improves glucose tolerance/clearance and attenuates functional and anatomical deficits following hyper-glycemiamediated ICH. Additional studies are underway to investigate further mechanisms.

This work was supported by NIH R01 NS046400 (to S.D.).

POSTER #59
Novel interactions between phosphorylated-endocannabinoids and LPA receptors

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Lysophosphatidic acid (LPA) is a pleiotropic bioactive lipid produced from extracellular lysophospholipids by autotaxin (ATX), as well as derived from membrane glycerophospholipids by phospholipases, to produce a range of LPA chemical species with varied fatty acid chain lengths and saturation. LPA is present in nearly all cells, tissues, and fluids of the body and plays important roles in physiological events including cell proliferation, survival, motility, and cytoskeletal changes. These effects are mediated by cognate cell surface G protein-coupled receptors (GPCRs) consisting of six family members designated LPA_1-LPA_6 that couple to heterotrimeric G protein complexes to activate downstream signaling pathways. Last year we reported the crystal structure of LPA_1 that revealed a binding pocket that might accommodate other ligands beyond LPA. These structural data allowed identification of phosphorylated-anandamide (pAEA) as a signaling molecules acting through LPA_1. Here, we further evaluate pAEA and other phosphorylated-endocannabinoids on additional LPA receptor subtypes. These analyses indicate robust signaling, particularly as assessed by calcium responses in stable cell lines heterologously expressing LPARs. In addition to LPA_1, LPA_5 showed similar activation by phosphorylated-endocannabinoids, compared to the other LPA receptor subtypes. These data support LPA receptors as a shared signaling nexus between LPA and endo-cannabinoid lipid pathways.

Supported by the NIH (NS084398) and a grant from Ono Pharmaceuticals Co., Ltd.

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POSTER #60
Allosteric Regulation of Phospholipase A_2 by Membranes

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Defining the molecular details and consequences of the association of water-soluble proteins with membranes is fundamental to understanding protein–lipid interactions and membrane functioning.[1] Phospholipase A_2 (PLA_2) enzymes, which catalyze the hydrolysis of phospholipid substrates that comprise the membrane bilayer, provide the ideal system for studying protein–lipid interactions.[2] Our current study focuses on understanding the catalytic cycle of two different recombinant human intracellular PLA_2s: the GIVA $cPLA_2$ and GVIA $iPLA_2$, which are responsible for arachidonic acid release for eicosanoid signaling and for membrane phospholipid remodeling, respectively. Molecular dynamics (MD) simulations, guided by hydrogen/deuterium exchange mass spectrometric (DXMS)[3] experimental data, were used to show that the channel to the active sites of these PLA_2s are opened upon allosteric interaction of the enzyme surface with the membrane to facilitate entry of the substrate phospholipid. This constitutes the first detailed study describing the binding and the interaction mechanism of intracellular PLA_2s with the membrane bilayer as well as how they bind a single phospholipid molecule in the catalytic site. These enzymes are implicated in many diseases, and understanding their detailed mechanism of action will aid in the discovery of new therapeutics.

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POSTER #61

Neuroprotectin D1 (NPD 1) targets Sirtuin in retinal pigment epithelial cell survival signaling under- uncompensated oxidative-stress

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Cell survival under uncompensated oxidative stress is important for the understanding of early dysfunctions in retinal degenerations. Sirtuin (SIRT1 & 6) is a protein found in retinal pigment epithelial (RPE) cells that promotes cell survival during cellular stress. NPD1, a DHA-derived mediator, attenuates neuronal cell death under oxidative stress (OS). The subject matter of this research focuses on the involvement of NPD1-mediated upregulation of Sirtuin in cell survival of RPE cells under stress. Human RPE (ARPE-19) and primary human RPE cells were used. A programmed cell death (apoptosis) was used to measure the cell death under OS with or without the presence of NPD1. A Western blot (WB) analysis followed for the expression of SIRT1 and 6 in cells under stressed conditions. SIRT1-si RNA was used to silence SIRT1 in ARPE-19 cells. A transfectable construct of GFP was used as transfection control. Using these cells, experiments were repeated for apoptosis and WB studies as before. NPD1 and its precursor DHA upregulated Sirtuin (1 and 6) abundance in ARPE-19 cells and in primary human RPE cells undergoing OS. NPD1 displayed better effects than DHA. However, OS or NPD1 alone had little or no effect on the SIRT1 and 6 expressions. Moreover, the NPD1-mediated induction of SIRT1 and 6 are time- and concentration-dependent. The upregulation of Sirtuins (1 and 6) by NPD1 peaked 6h after initiation of OS, decreased at 12h, and plateaued at 24h in both RPE cells at 100nm of NPD1. Additionally, upregulation of SIRT1 is specific for NPD1, as other structurally-related lipid mediators were ineffective on SIRT1 under similar conditions in RPE cells. Moreover, SIRT1 silencing in ARPE-19 cells under oxidative stress minimalizes the expression of SIRT1 in the presence of NPD1 and correlates with programed cell death under stress. NPD1 and DHA specifically upregulate SIRT1 and 6 abundance in human RPE cells when confronted with uncompensated OS. As a consequence, remarkable cell survival takes place. The Sirtuin silencing of ARPE-19 cells devoid of NPD1 sensitivity allows us to propose a unique DHA/NPD1 survival signaling that plays an important role in cell survival under uncompensated oxidative stress.

This research was funded by National Institutes of Health grants EY005121 and GM103340 (NGB), the Eye, Ear, Nose & Throat Foundation (NGB)

POSTER #62

Macrophage eicosanoid biosynthesis elicited by oxidized phospholipids and oxidized low density lipoprotein

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Atherosclerosis is a chronic inflammatory condition of large and medium-compliance arteries and is considered the principle underlying cause of cardiovascular disease. Atherosclerotic plaques contain lipid-laden macrophage foam cells, which are a major source of proinflammatory factors that directly contribute to disease progression, plaque instability and ultimately acute coronary events. Macrophage engulfment of oxidized low-density lipoprotein (oxLDL) leads to massive accumulation of cholesterol-esters stored within cytosolic lipid droplets. Lipid droplets produced in response to bacterial lipopolysaccharide have been shown to contain the enzymes required for eicosanoid biosynthesis, suggesting that foam cells may be a source of eicosanoids during atherosclerosis. Eicosanoids are lipid signaling molecules that can have powerful effects on the inflammatory microenvironment of atherosclerotic lesions. Furthermore, macrophage expression of key eicosanoid biosynthetic genes has been demonstrated within human plaques. It is widely accepted that foam cell proinflammatory activity is in part elicited by oxLDL. However, little is known about how oxidized lipids and oxLDL alter macrophage eicosanoid production. Our laboratory has demonstrated that the oxidation of human LDL leads to the formation of 1-palmitoyl, 2-oxovaleryl phosphatidylcholine (POVPC), an oxidized phospholipid. Furthermore, POVPC forms Schiff bases with lysine residues of the LDL apoprotein. Such products are recognized by macrophage receptors including CD36 and are found in plaques from humans with coronary artery disease. We have used lipidomic approaches to quantitate time dependent eicosanoid biosynthesis by macrophages exposed *in vitro* to purified oxidized phospholipids, synthetic POVPC-peptide or oxLDL. Our results suggest POVPC-peptide alone only weakly activates eicosanoid biosynthesis, but does elicit a priming effect whereby secondary exposure to a proinflammatory stimulant (ATP) leads to an enhanced production rate of cyclooxygenase-derived metabolites. Results with oxLDL will also be discussed. These studies will further our understanding of how oxidized lipids influence macrophage activation and eicosanoid metabolism and their potential implication for the pathogenesis of atherosclerosis.

POSTER #63
Resolvin D3 multi-level proresolving actions are host protective during infection

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Resolution of infection and inflammation is governed by innate immune cells. The resolvin family of n-3 mediators produced by resolving exudates stimulates clearance of neutrophils and attenuates pro-inflammatory signals. Using metabololipidomics, endogenous resolvin D3 (RvD3) was identified in self-resolving exudates during active *E. coli* infection. Through a new, independent synthetic route for RvD3, we matched endogenous and synthetic RvD3 and determined that RvD3 (ng doses) potently reduced the resolution interval (R_i) by ~4.5h during *E. coli* peritonitis after administration at peak inflammation (T_{max}=12h) and increased leukocyte phagocytosis of *E. coli* and neutrophils as well as reduced proinflammatory cytokines, chemokines, MMP-2 and MMP-9. At pM-nM concentrations, RvD3 also enhanced human macrophage efferocytosis and bacterial phagocytosis, increased neutrophil bacterial phagocytosis and intracellular ROS generation, and reduced human platelet-PMN aggregation. These results provide additional evidence for potent RvD3 immunoresolvent actions in host defense, host protection and antimicrobial defense.

POSTER #64

Inhibition of TRPV4 mediated signaling decreases TGF-β1 induced fibroblast differentiation and ameliorates house dust mite induced asthma in mice

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Asthma is a chronic progressive lung disease characterized by airway inflammation and lung tissue fibrosis. Key pathological events that occur during tissue fibrosis include fibroblast differentiation to contractile myofibroblasts, fibroblast proliferation, and increased synthesis and accumulation of collagen and other extracellular matrix (ECM) proteins. Fibrosis in the lung tissue results in airway remodeling and increased stiffness, compromising organ function. Transient receptor potential vanilloid 4 (TRPV4), a mechanosensitive ion channel expressed in lung fibroblasts, responds to changes in ECM stiffness and mechanical forces. Previous studies have shown that, TRPV4 plays a role in the differentiation of cardiac fibroblasts to myofibroblasts. In the present study, we show that TRPV4 mediates lung fibroblast differentiation and aim to elucidate the signaling mechanism(s) involved. We found that TRPV4 was functionally expressed in normal human lung fibroblasts (NHLF) and that knocking-down TRPV4 inhibited TGF-β1 induced fibroblast differentiation, as determined by decreased α-SMA expression. Similarly, TRPV4 antagonists AB159908 (AB1) and RN1734 (RN) also significantly inhibited TGF-β1 induced expression of α-SMA and fibronectin protein, as well as pro-fibrotic genes SM22, Collagen1A1, and MRTF-A. We also compared TGF-β1 induced expression levels of these fibrotic markers in NHLF and diseased human lung fibroblasts (DHLF) and found elevated levels in DHLF. To confirm the role of TRPV4 in lung fibroblast differentiation *in vivo*, we employed a house dust mite (HDM) induced asthma model in wild-type (WT) and TRPV4 knock-out (TRPV4 KO) mice. Following exposure to HDM, 3 days a week for 5 weeks, histological analysis of lung tissue and bronchoalveolar lavage fluid (BALF) revealed airway thickening, collagen deposition, goblet cell accumulation, and an increase in the inflammatory response in WT mice. Interestingly, we observed that absence of TRPV4 showed markedly reduced airway remodeling and decreased inflammatory response. Altogether, these findings highlight a major role for TRPV4 in lung fibroblast differentiation and HDM induced asthma in mice.

POSTER #65

Mast cell Activation by Hyperosmolar Mannitol-challenge in Isolated Human Small Airways

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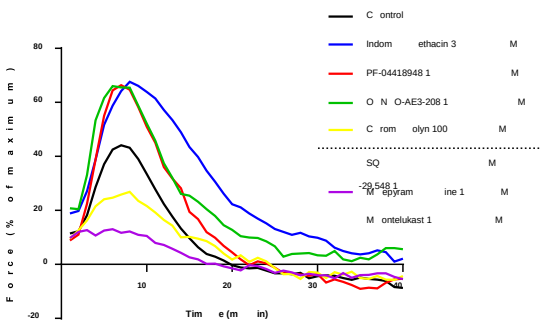
Rationale: Exercise-induced bronchoconstriction (EIB) is believed to occur by loss of water from the airway lining fluid causing a local increase of osmolarity that triggers mast cell activation. This can be mimicked in patients by inhalation of mannitol. The mechanism involved, however, remains unclear. Our aim was to develop a model using isolated human bronchi in order to study the effect of hyperosmolar bronchoconstriction *in vitro*.

Methods: Small bronchi (inner diameter of 0.5-2 mm) were isolated from macroscopically healthy human lung tissue specimens obtained from patients undergoing lobectomies (n=27). The segment were incubated overnight and mounted in a tissue organ bath to measure smooth muscle contractions evoked by challenge with hyperosmolar mannitol in relation to contractions generated by 60 mM of potassium chloride.

Results: In control segments of human small bronchi, hyperosmolar exposure by mannitol during ten minutes first caused a small contraction that reached 12.5 ± 1.4% of maximal contraction. A second further contraction was developed directly after the mannitol was withdrawn from the buffer (E_{max}: 46.1 ± 3.2%, n=23) which lasted for more than 20 minutes. Using a combination of receptor antagonists blocking the thromboxane TP, histamine H_1 and cystenyl-leukotriene $CysLT_1$ receptors (SQ-29,548, mepyramine and montelukast) this second and more substantial contraction was decreased (E_{max}: 13.0 ± 1.6%, n=9; $p<0.05$) whereas the the initial contraction was unaffected, suggesting that it was mediated through direct activation of the smooth muscle. Pretreatment with the mast cell stabilizer cromolyn (100 µM) also reduced the main contraction (E_{max}: 26.8 ± 3.1%, n=5; $p<0.05$). In contrast, global inhibition of the cyclooxygenase enzymes using indomethacin (3 µM) enhanced the bronchoconstriction (E_{max}: 67.6 ± 5.6%, n=13; $p<0.05$). Likewise, treatment with either EP_2 (PF-04418948) or EP_4 (ONO-AE3-208) receptor antagonists also enhanced the mannitol-induced bronchoconstriction
(E_{max}: 67.4 ± 5.2 and 66.0 ± 4.0, n=6, respectively; $p<0.05$) (Figure 1).

Conclusions: When isolated human bronchi are exposed to mannitol a significant bronchoconstriction occurs that is mediated by release of typical mast cell mediators. The increased constriction during cyclooxygenase inhibition suggests a production of prostanoids that counteracts the mannitol-induced bronchoconstriction. These prostanoids acts on both EP_2 and EP_4 receptors possibly inducing both mast cell inhibition and bronchorelaxation, as observed previously for exogenous PGE_2[1]. This first *ex vivo* protocol of hyperosmolar mast cell activation in isolated human bronchi can be used for further mechanistic studies of EIB.



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Human bronchi exposed to mannitol (n:5-23)

Figure 1: Human bronchi exposed to mannitol in presence or absence of enzyme inhibitors, receptor antagonists or mast cell stabilizer.

POSTER #66
Critical Role for Prostacyclin Synthase in a Contact Hypersensitivity Mouse Model

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Prostacyclin synthase (PGIS) is a constitutively expressed enzyme that functions downstream of cyclooxygenase (COX) in the prostacyclin (PGI_2)-biosynthetic pathway. Although PGI_2 receptor IP is known to regulate hapten-induced contact dermatitis, the role of PGIS in contact hypersensitivity (CHS) is still not clear. In this study, we used PGIS-deficient mice to examine the importance of PGIS in CHS *in vivo*.

We used a DNFB (dinitrofluorobenzene)-induced CHS model in WT and PGIS KO mice. The shaved abdominal skin of Balb/c female mice was sensitized with 25 µl of 0.5% DNFB in acetone/olive oil (4:1). 5 days after this sensitization, the ears were challenged with an application of 20 µl of 0.3% DNFB. Ear thickness was measured for each mouse before and 48 h ear elicitation at a predetermined site with a micrometer, and the difference was referred to as ear swelling change.

The severity of ear swelling in PGIS KO mice was much lower than that in WT mice. Histological examination of the ears showed considerable leukocyte infiltration and edema in the dermis of sensitized WT mice, which was less apparent in sensitized PGIS KO mice. These results suggest that PGIS enhanced the DNFB-induced CHS response.

We found that 6-keto$PGF_{1\alpha}$, PGI_2 metabolite level was increased in ears of WT mice by DNFB treatment, whereas no 6-keto$PGF_{1\alpha}$ was detected in those of PGIS KO mice. Quantitative RTPCR of ear skin revealed that the expression levels of inflammatory markers, IFNγ and TNFα were significantly increased in WT mice by DNFB treatment. However these cytokine levels were suppressed in PGIS KO mice.

These results indicate that PGIS-derived PGI_2 promotes DNFB-induced CHS through regulation of inflammatory cytokines such as IFNγ and TNFα.

POSTER #67

Sphingosine kinase 2 deficiency increases proliferation and migration of renal mouse mesangial cells

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Both of the sphingosine kinase (SK) subtypes SK-1 and SK-2 catalyze the production of the bioactive lipid molecule sphingosine-1-phosphate (S1P). However, the subtype-specific cellular functions are largely unknown. In this study, we investigated the cellular function of SK-2 in primary mouse renal mesangial cells (mMC) from wild-type C57BL/6 or SK-2 knockout (SK2ko) mice. We found that SK2ko cells displayed a significantly higher proliferative and migratory activity when compared to wild-type cells, with concomitant increased cellular activities of the classical extracellular signal regulated kinase (ERK) and PI3K/Akt cascades, and of the small G protein RhoA. Furthermore, we detected an upregulation of SK-1 protein and $S1P_3$ receptor mRNA expression in SK-2ko cells. The MEK inhibitor U0126 and the $S1P_{1/3}$ receptor antagonist VPC23019 blocked the increased migration of SK-2ko cells. Additionally, $S1P_3$ko mesangial cells showed a reduced proliferative behavior and reduced migration rate upon S1P stimulation, suggesting a crucial involvement of the $S1P_3$ receptor. In summary, our data demonstrate that SK–2 exerts suppressive effects on cell growth and migration in renal mesangial cells, and that therapeutic targeting of SKs for treating proliferative kidney diseases requires subtype-selective inhibitors.

POSTER #68

Regulation of arachidonic acid metabolism by PLA_2 enzymes in cancer.

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The metabolic networks that mediate and regulate the inflammatory response in cancer are complex and how they promote cancer is still poorly defined. The eicosanoid lipid network, a key mediator of the induction and resolution of inflammation, is inappropriately regulated in the development and progression of cancer. Over the last decade, we and others have established that abberant expression and activation of enzymes that control arachidonic acid flux through these pathways and, in particular, two phospholipase A_2 (PLA_2) enzymes, a secreted PLA_2 (Group IIA PLA_2, hGIIA) and an intracellular PLA_2 (Group IVA PLA_2, cPLA-α) contribute significantly to the promotion of tumour growth in several cancers. Further, pharmacological blockade of these enzymes slows tumour growth in a variety of animal models of cancer[1, 2]. In recent years, we have explored the "upstream" and "downstream" pathways that contribute to PLA_2-mediated promotion of tumour cell growth and the mechanisms by which PLA_2 inhibitors block these effects[3-6]. Taken together our data suggests that evaluation of the benefit of intervention in the eicosanoid network at these enzymes in cancer is warranted.

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POSTER #69

The role of oxidized phaspholipid-derived lipid mediators in IgE-mediated mast cell activation

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Oxidized phospholipids are generated through reactive oxygen species or enzymatic reactions. Although various oxidized phospholipids have been identified in cell membranes, their physiological functions and production control mechanism are not well understood. Intracellular type II platelet-activating factor acetylhydrolase (PAF-AH (II)) is a monomeric 40-kDa enzyme that was originally identified as an enzyme hydrolyzing the *sn*-2 acetyl group of platelet-activating factor. Unlike other intracellular phospholipase A_2, PAF-AH (II) cannot hydrolyze long fatty acyl chains but can hydrolyze oxidized fatty acyl chains attached to phospholipids. However, the physiological role of PAF-AH (II), an oxidized phospholipid-selective phospholipase A_2, remains to be elucidated. Here we show that suppression of PAF-AH (II) impairs IgE-mediated mast cell activation. Immunohistochemistry analysis revealed that PAFAH (II) localized with toluidine blue-positive dermal mast cells. PAF-AH (II) knockout (*Pafah2-/-*) mice show markedly reduced passive cutaneous anaphylaxis (PCA) induced by IgE and antigen. Bone marrow-derived cultured mast cells (BMMCs) obtained from *Pafah2-/-* mice appeared normal but displayed a reduction in antigen-induced degranulation. Lipidomics analysis of mast cells revealed dramatic reduction of some oxidized ω3 fatty acids in *Pafah2-/-* BMMCs. Treatment of *Pafah2-/-* mice with these oxidized ω3 fatty acids restored IgE-dependent-mast cell activation. Taken together, these results suggest that PAF-AH (II) hydrolyze oxidized ω3 fatty acids-esterified phospholipids and PAF-AH (II)-derived oxidized ω3 fatty acids are required for IgE-mediated mast cell activation.

POSTER #70

Modulatory effect of melanoma cells on tumor-associated macrophage eicosanoid metabolism.

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Macrophages (MA) are immune cells, which function in various biological routes, such as on tumor activity response. The immune response is part dependent on stimulation by cytokines of T-lymphocytes response (Th1 or Th2). Classical macrophage activation (M1) is fundamental in the immune response against intracellular microorganisms and anti-tumoral activity. However, alternative macrophage activation (M2) is more varied, but generally plays as promoting tissue repair and remodeling, and also, pro-tumoral activity. Thus, herein we demonstrated the influence of murine melanoma B16F10, on MA lipid metabolism, and correlated the eicosanoid production with the macrophage polarization. Cells isolated from bone marrow of C57Bl/6 mice, were differentiated (*in vitro*) to macrophage (BMDM) by conditioned culture medium with MCSF. BMDM were incubated or not with IFN-γ to polarized to M1, or IL-4/ IL-13 to M2, for 24 hours at 37°C in 5% CO_2. After this period the BMDM were co-cultured with melanoma B16F10. We demonstrated in co-culture of MA and B16F10, that M1 and M0 cells over the time of interaction with tumor cells, presented significantly decreased prostanoids production, such as TXB_2, PGE_2 and PGD_2. In the other hand, the M2 presented in co-culture of tumor cells, increased the 15-HETE and 12-HETE productions, but none effect on prostanoids production. To determine the effect of tumor cell on MA lipid metabolism, qRT- PCR were performed. As compared with control, the co-culture with B16F10 showed up-regulation of COX-2, but downregulation of PGE_2-synthase, 5-LO and FLAP mRNA expression, as well as BLTR1 and CYSLTR1 mRNA expression on macrophages. In bright of these results, we speculated that melanoma cells influenced the MA eicosanoid metabolism, and fashioned a positive microenvironment for tumor growth. The eicosanoids production by tumor-associated macrophage can be important issue for development of anti-tumoral immunotherapies.

Financial support: CAPES, CNPq and grant #2014/07125-6 from São Paulo Research Foundation (FAPESP)

POSTER #71
Fatty acid mediators are critical for male fertility in Drosophila

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Fatty acids can be metabolized into potent lipid mediators that play many important roles in mammalian physiology and disease. Fatty acids are stored in membrane phospholipids by the activity of lysophospholipid acyltransferases (ATs), and they are released by phospholipases A_2 (PLA_2s) in a biochemical pathway known as the Lands Cycle. We are studying the Lands Cycle in Drosophila. By creating knockout mutants, we have shown that the Drosophila Lands Cycle ATs Oys and Nes are required for spermatogenesis. Oys nes mutants are completely male sterile and show defects in the final stage of spermatogenesis, spermatid individualization. This process is mediated by specialized actin structures called individualization complexes (ICs). In oys nes mutants, ICs form normally but do not move properly along the sperm tails. Earlier stages of sperm development are not affected. Manipulation of phosphatidylcholine, phosphatidylethanolamine, or fatty acid levels does not phenocopy the oys nes defect. However, mutants for the Drosophila cyclooxygenase Pxt, which processes fatty acids into prostaglandins, also show similar spermatid individualization defects. Together, our results suggest that specific fatty acid signals, whose abundance is regulated by the Lands Cycle, are critical regulators of spermatogenesis in flies. This is the first demonstration of prostaglandin activity in Drosophila spermatogenesis and is consistent with the importance of these mediators in mammalian male fertility and Drosophila oogenesis. Additionally, of the ten predicted PLA_2 genes in the Drosophila genome, seven are expressed in the male gonad. We are generating PLA_2 knockout mutants and creating transgenes in order to assess loss of function and gain of function phenotypes as well as pursue structure-function analysis in the genetically tractable insect model. Insights from Drosophila will further our understanding of the molecular and cellular functions of the Lands Cycle in all organisms.

POSTER #72
Roles of prostaglandin EP4 receptor in adipose tissue

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Adipose tissue is important not only for energy storage but also as an endocrine organ that regulates energy homeostasis and insulin sensitivity by secreting adipokines such as adiponectin and leptin. Excessive lipid accumulation in adipose tissue results in an imbalance in the secretion of adipokines, leading to diabetes and other metabolic disorders. Therefore, understanding of molecular mechanisms underlying physiological regulation of adipocyte function is an important issue both in biological and clinical aspects. Prostaglandins (PGs) are the arachidonate metabolites synthesized by the action of cycloxygenase (COX) as a rate-limiting enzyme. It has been shown that several PGs regulate adipocyte differentiation or lipolysis in cell culture system. Indeed, we previously identified that PGE_2 suppresses adipocyte differentiation from 3T3-L1 preadipocytes via EP4 receptor. However, the physiological roles of EP4 receptor in adipocyte differentiation or function remain to be determined. To elucidate the roles of endgenous PG on adipocyte differentiation, we first employed an adipocyte differentiation system from mouse embryonic fibroblasts, and found that PGE_2 -EP4 signaling suppresses adipocyte differentiation in an autocrine manner. In this presentation, we would like to show the phenotypes regarding adipocyte development and insulin response of EP4KO mice and discuss on the physiological role of EP4 signaling in the maintenance of adipose homeostasis, also in humans.

POSTER #73

Defining the binding mode of A POTENT INHIBITOR in the Active site of LIPOPROTEIN ASSOCIATED PHOSPHOLIPASE A_2

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Phospholipase A_2 constitutes a superfamily of enzymes that catalyzes the hydrolysis of phospholipid substrates at the *sn*-2 position. Group VIIA lipoprotein associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor acetyl hydrolase (PAF-AH), is known to be associated with LDL and HDL (*Chem. Rev.* 2011, *111*, 6130-6185). Lp-PLA_2 specifically releases oxidized and very short chain fatty acids. Previous DXMS studies and X-ray crystal structures have provided insight into the interaction of Lp-PLA_2 with phospholipid vesicles *(J. Biol. Chem.* 2008, *283,* 31617-31624*)*. Hydrogen Deuterium Exchange Mass Spectrometry (DXMS) studies suggested that Lp-PLA_2 interacts with membrane phospholipids (*Biochemistry.* 2011, *50,* 5314-5321) as well as with apo A1 and at an additional location with intact HDL (*J. Lipid Res.* 2013, *54,* 127-133). The peptide regions of Lp-PLA_2 found to interact with membranes were used to insert the enzyme in a membrane patch. This system was subjected to minimization, equilibration and molecular dynamics (MD) simulations using NAMD (*J. Comput. Chem.* 2005, *26,* 1781-1802). Clustering analysis allowed us to identify different conformations of Lp-PLA_2 suitable for docking calculations. DXMS binding studies were employed to identify the peptide regions of the active site that interact with a potent and specific inhibitor GSK SB-402564. These regions were used to define the binding site during the docking calculation and a 3D enzyme-inhibitor complex was generated revealing a detailed binding mode of the inhibitor. MD simulations of the complex in the presence of the inhibitor allowed us to identify interactions of the inhibitor with the Lp-PLA_2 binding site and conformational changes that occur upon binding. This is the first detailed study on the binding mode of this Lp-PLA_2 inhibitor using HD exchange data and this complex provides insight into the inhibition mechanism of this enzyme. [We are grateful to Dr. Colin Macphee at GSK for inhibitor GSK SB402564 used in these studies and to NIH grant RO1 GM20501-40 for support of these studies.]

POSTER #74

The two secreted phospholipase A_2s PLA_2G2F and PLA_2G2E play distinct roles in skin homeostasis and diseases

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Skin lipids are important for skin homeostasis. However, the entire picture of the roles of lipids, particularly nonceramide lipid species, in skin biology still remains obscure. Here we show that PLA_2G2F is expressed in the suprabasal epidermis, whereas PLA_2G2E is expressed in growing hair follicles. Analyses of *Pla2g2f*$^{-/-}$ and *Pla2g2e*$^{-/-}$ mice revealed distinct roles of these $sPLA_2$s in the skin. *Pla2g2f*$^{-/-}$ mice had a fragile stratum corneum and were strikingly protected from psoriasis, contact dermatitis, and skin cancer. PLA_2G2F was induced by calcium or IL-22 in keratinocytes and preferentially hydrolyzed ethanolamine plasmalogen-bearing docosahexaenoic acid secreted from keratinocytes to give rise to ethanolamine lysoplasmalogen, which promoted epidermal keratinocyte differentiation and activation. In contrast, *Pla*$_2$*g2e*$^{-/-}$ mice exhibited skin abnormalities distinct from *Pla*$_2$*g2f*$^{-/-}$, with perturbed hair ultrastructure, modest changes in steady-state expression of a subset of skin genes, and unaffected psoriasis, contact dermatitis, and skin cancer. PLA_2G2E mobilized various polyunsaturated fatty acids and lysophosphatidylethanolamine species in the skin. Overall, two skin $sPLA_2$s, PLA_2G2F and PLA_2G2E, play non-redundant roles in distinct compartments within mouse skin, underscoring the functional diversity of multiple $sPLA_2$s in the coordinated regulation of skin homeostasis and diseases.

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USEFUL INFORMATION

Meeting Facility Information

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La Jolla, CA 92037 (858)
534-5604
www.sio.ucsd.edu/About/Venue_Rentals/Scripps_Forum

Hotel Information

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(at Avenida de la Playa) (800)
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www.ljshoreshotel.com

Transportation

Walking
It's about a 15 minute walk from the hotel to the Seaside Forum along the beach or street. Please see the maps on the next pages for the walking route.

Driving and Parking
Maps of the San Diego area and the area immediately around the Scripps Seaside Forum are on the next few pages. There is no public parking at the Forum itself (if you park in their lots without a permit or assigned spot you will be ticketed), so we recommend parking at the Kellogg Park parking lot (see map). Parking is free and the park is a 10 minute walk from the Forum (see map for walking route) and we will also have a shuttle pick up attendees at the entrance to the parking lot (and drop them off in the evening). If you arrive early there is also legal street parking on El Paseo Grande.

Shuttles
A shuttle will pick up (AM) and drop off (PM) LIPID MAPS meeting attendees:

1. PLAAt the La Jolla Shores Hotel, 8110 Camino Del Oro (at Avenida de la Playa).
2. At Kellogg Park entrance – corner of Camino del Oro and Calle Frescota (free public parking lot).

- Pickups on both mornings, May 19 and May 20, leave La Jolla Shores Hotel at 6:45 AM, 7:00 AM and 7:15 AM.
- Evening pickup from Scripps Forum for drop-offs at both locations is at 8:30 PM on
- Thursday, May 19 (and if necessary 15 minutes later until all passengers transported) and at 5:30 PM on Friday, May 20 (again with additional pickups until all passengers are transported).

Local Taxi Services

Yellow Cab Company: 619-234-6161
Cloud 9 Shuttle (airport shuttle): 800-974-8885 or 858-278-8877

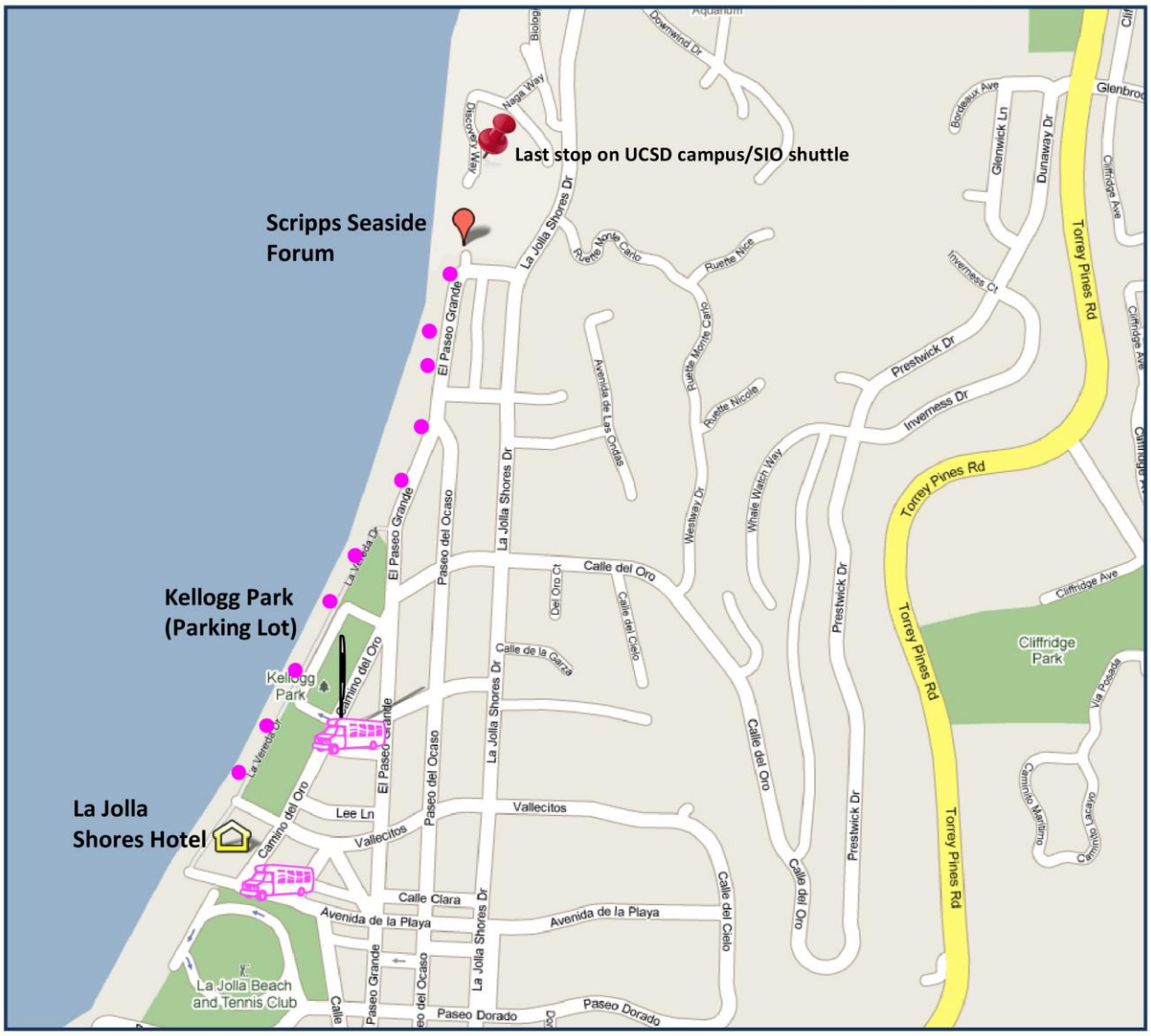
AREA MAPS

For interactive and print maps of the UCSD campus visit http://maps.ucsd.edu

CLOSE-UP MAP OF HOTEL & FORUM

Suggested walking route (about 15 minutes from hotel or 10 from Kellogg Park)

Meeting shuttle pick up points: see shuttle information under transportation, above.



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