International Conference on the Bioscience of Lipids

MONTRÉAL 2022
62nd edition
4th-7th of September

icbl

Lipids in Metabolic Health and Disease

Cœur des sciences, UQAM
175 Av. du Président-Kennedy
Montréal, Québec

icbl.info

UQÀM | Université du Québec à Montréal

Welcome To ICBL

62nd ICBL Montréal

Dear Colleagues,

It is a great pleasure to welcome you to the 62nd edition of the International Conference on the Bioscience of Lipids (ICBL). The thematic of this year's conference will be ***Lipids in Metabolic Health and Disease***.

This is the first time that the ICBL will be held in Montreal, Canada and this year's program will provide an exceptional showcase for research in the field of lipid metabolism and related diseases. After the last two pandemic years where most meetings have been held virtually, we are happy to invite you to Montreal for a face-to-face meeting.

This year the ICBL symposium will focus on the role of various lipids in different metabolic pathways and their impact on disease development. This will be a great opportunity for researchers and students to interact and create new bridges that link fundamental and applied research for disease treatment. We have the privilege of attending the Van Deenen lecture given by Dr. Christine Desrosiers of the University of Montreal, entitled: "***Enhancing disease mechanism and biomarker discovery in humans using untargeted comprehensive plasma lipidomics".***

This annual conference will also look to support the next generation of researchers by offering 3 oral presentation and 6 poster awards. In addition, special sessions will be organized by the student ICBL committee and provide trainees with opportunities to develop important professional skills.

The conference will take place at the *Coeur des sciences* in downtown Montreal between September 4 and 7. This central conference venue will allow you to enjoy our vibrant city and provide you with easy access to many tourist attractions.
We hope that you will join us in September in Montreal, the heart of our beautiful Québec.

Your local organizing committee,

Catherine Mounier (Chair)
Thierry Alquier
David Mutch
David Rhainds
Marc Surette

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Scientific Program

Sunday 4th

14h00-16h00 Registration
14h30-15h30 Workshop : Professional development
16h00 Welcome from UQÀM & ICBL President
16h15 Van Deenen Lecturer – Dre Christine Desrosiers (ICM, Canada)
17h15 Welcome Cocktail

Monday 5th

8h30-10h40 Session 1: Lipids desaturation in metabolism
10h40-11h00 Break & Posters session A
11h00-13h15 Session 2: Lipid mediators of inflammation
13h15-15h00 Lunch & Posters session A
15h00-17h15 Session 3: Fluxolipidomics

Tuesday 6th

8h30-10h40 Session 4: Triacylglycerol metabolism
10h40-11h00 Break & Posters session A
11h00-13h15 Session 5: Ceramides and endocannabinoids
13h15-15h00 Lunch & Posters session B
13h30 Workshop: Satellite Conference
From 15h00 Social events & Conference dinner

Wednesday 7th

8h30-10h40 Session 6: Lipids in neural systems
10h40-11h00 Break & Posters session B
11h00-13h15 Session 7: Reverse cholesterol transport – A paradigm in revision
13h15-14h45 Lunch & Posters session B
15h45-16h30 Presentation ICBL2023, Awards & Closing remarks

Sunday, September 4th

Van Deenen Lecturer Session

14h00	Registration
14h30 – 15h30	**Workshop: Professional development** For trainees, organized by ICBL student committee with support of s2bn group
16h00	Welcome from Jean-Christian Pleau, VP academic affairs, UQAM Welcome from Christian Wolfrum, ICBL President
16h15	Van Deenen Lecturer **Dre Christine Desrosiers** (Montreal Heart Institute, CA)

Enhancing disease mechanism and biomarker discovery in humans using untargeted comprehensive plasma lipidomics

17h15	Welcome Cocktail, Hilton Hotel

Monday, September 5th

Session 1 : Lipids desaturation in metabolism

Moderator : *Dr. David Mutch – University of Guelph, Canada*

8h35 **James M. Ntambi** (University of Wisconsin, USA)

The Role of Hepatic Stearoyl-CoA Desaturase in Systemic Metabolism

9h05 **Richard Bazinet** (University of Toronto, CA)

New methods lead to new findings in the omega-3 synthesis pathway

9h35 **Marie-Claude Vohl** (Laval University, CA)

Gene-diet interactions with omega-3 fatty acids: Impact on plasma triglyceride levels

10h05 Short talk: **Chenxuan Wang** (University of Guelph, CA)

Δ-6 desaturase (Fads2) deficiency promotes lipolysis and reduces lipid storage in murine white adipose tissue

10h20 Short talk: **Natalie Burchat** (Rutgers University, USA)

Intestinal Stearoyl-CoA Desaturase 1 modulates intestinal and systemic lipid metabolism and energy homeostasis

10h35-11h00 BREAK & POSTER SESSION A

Monday, September 5th

Session 2 : Lipids mediators of inflammation

Moderator : *Dr. Marc Surette – University of Moncton, Canada*

11h05 **Eric Boilard** (Laval University, CA)

The interaction of secreted phospholipase A2-IIA with the microbiota promotes inflammation

11h35 **Valerie O'Donnell** (Cardiff University, UK)

Phospholipid and fatty acid metabolism in innate immunity and coagulation.

12h05 **Oliver Werz** (University Jena, Germany)

Targeting of pro-inflammatory and pro-resolving lipid mediator networks

12h35 Short talk: **Takehiko Yokomizo** (Juntendo University, Japan)

The leukotriene B4/BLT1-dependent neutrophil accumulation exacerbates immune complex-mediated glomerulonephritis

12h50 Short talk: **Grzegorz Sumara** (University of Würzburg, Germany)

Platelet-derived 20-HETE promotes pancreatic β cell function

13h05-15h00 LUNCH & POSTER SESSION A

Monday, September 5th

Session 3 : FluxoLipidomics

Moderator : *Dr. Michel Lagarde– Lyon University, France*

15h05 **Markus Wenk** (National University of Singapore, SG)

Intergenerational landscape of the human circulatory lipidome during pregnancy and early life

15h35 **Pierre Chaurand** (University of Montreal, CA)

Fluxolipidomics by imaging mass spectrometry: examples in cancer research and neurobiology

16h05 **Makoto Arita** (Keio University, JP)

Advanced non-targeted lipidomics to explore lipidome changes associated with aging and commensal bacteria

16h35 Short talk: **Gwendolyn Barcelo Coblijn** (University of the Basque Country, Spain)

In-depth characterization of the tumor microenvironment MALDI-IMS focusing on immuneinfiltrates

16h50 Short talk: **Johannes Plagge** (University of Munich, Germany)

The gut microbiota reduces intestinal lipid absorption by induction of host phospholipase A1 activity in bile

18h00-19h30 Steering committee meeting (*room SB-1115*)

Tuesday, September 6th

Session 4 : Triacylglycerol metabolism

Moderator : *Dre. Catherine Mounier– UQÀM, Canada*

8h35 **Denis Blondin** (University of Sherbrooke, CA)

The Glycerolipid-free fatty acid cycle: A thermogenic perspective

9h05 **Guenter Haemmerle** (University of Graz, Austria)

Mammalian Carboxylesterase 2 proteins: Novel players in lipid metabolism and metabolic disease

9h35 **Czech Michael** (University of Massachusetts, USA)

CRISPR-enhanced adipocyte fatty acid oxidation to reduce liver triglyceride

10h05 Short talk: **Elite Possik** (University of Montreal, CA)

G3PP/PGPH-2: a novel dietary restriction mimetic enzyme that protects from glucolipotoxicity and promotes healthy aging via the AMPK-TFEB-Autophagy axis in C.elegans

10 : 20 Short talk: **Sabri Ahmed Rial** (University of Montreal, CA)

14-3-3zeta enables the early steps of adipogenesis by modulating cellular functions indispensable for proliferation, differentiation, and lipid anabolism in preadipocytes

10h40-11h00 BREAK & POSTER SESSION A

Tuesday, September 6th

Session 5 : Ceramides and endocannabinoids

Moderator : *Dr. Maurizio Crestani– University of Milano, Italy*

11h05 **Mauro Maccarrone** (University of L'Aquila, Italy)

The Endocannabinoid System and its Complexity in the Brain

11h35 **Yusuf Hannun** (Sony Brook, USA)

Compartment specific functions of neutral sphingomyelinase and ceramide

12h05 **Antonio Gomez-Munoz** (University of the Basque Country, Spain)

New insights into ceramide-1-phosphate biology

12h35 Short talk: **Pegah Poursharifi** (CrCHUM, CA)

ABHD6 Suppression Prevents Lipopolysaccharide and High-fat Diet Induced Pro-inflammatory Macrophage Phenotypic Response

12h50 Short talk: **Mads Foged** (DCRC, Denmark)

Increased dependence on ethanolamine in a cancer cell line leads to accumulation of choline-based plasmanyl ether lipids

13h10-15h00 LUNCH & POSTER SESSION B

13h30 Worshop: Satellite Conference From Novartis

Dr. Benoit Arsenault (Laval University)

Inclisiran and RNA interference therapeutics in preventive cardiology

From 15h00 Social events & Conference dinner

Wednesday, September 7th

Session 6 : Lipids in neuronal systems

Moderator: *Dr. Thierry Alquier Université de Montréal, Canada*

8h35 **Karl Fernandes** (University of Sherbrooke, CA)

Lipids and the pathogenesis of Alzheimer's disease.

9h05 **Maria S. Ioannou** (University of Alberta, CA)

Mechanisms and function of neuronal lipid release.

9h35 **Sophie Layé** (University of Bordeaux, France)

Dietary polyunsaturated fatty acids, mood and cognitive disorders, role of brain oxylipins.

10h05 Short talk: **Shingo Nakajima** (CrCHUM, CA)

GPR120 activation increases the activity of primary midbrain dopamine neurons

10h20 Short talk: **Josephine Robb** (CrCHUM, CA)

Microglial Adipose Triglyceride Lipase (ATGL) regulates neuroinflammation and diet-induced obesity

10h40-11h00 BREAK & POSTER SESSION B

Wednesday, September 7th

Session 7 : Reverse cholesterol transport – A paradigm in revision

Moderator:*Dr. David Rhainds-Montréal Heart Institute, Canada*

11h05 **Cédric Le May** (University of Nantes, France)

From blood to intestinal lumen: a mysterious but promising trans intestinal route for plasma cholesterol elimination

11h35 **Gwendalyn J. Randolph** (Washington University, USA)

HDL trafficking and inflammatory disease

12h05 **Gaétan Mayer** (Montreal Heart Institute, CA)

Loss of hepatic GLG1 reduces apolipoprotein B-100 secretion by promoting autophagy

12h35 Short talk: **Marta Turri** (University of Milan, Italy)

Lipoproteins and Central Nervous System: HDL metabolism in Alzheimer's disease.

12h50 Short talk: **Alexandre Légiot** (UQÀM, CA)

Implication of the Stearoyl-CoA Desaturase-1 in the formation of very-low density lipoproteins

13h15-14h45 LUNCH & POSTER SESSION B

14h45-15h45 Worshop: Dissemination of sciences for the society

Details coming soon

15h45-16h30: Presentation ICBL 2023, Awards, & Closing remarks

ABOUT THE SPEAKER

SUNDAY, September 4th

Van Deenen Lecturer

Christine Desrosiers (Université de Montréal, CA)

Enhancing disease mechanism and biomarker discovery in humans using untargeted comprehensive plasma lipid omics.

Dr. Christine Des Rosiers has over 30 years of research experience in metabolic investigations using mass spectrometry (MS). After joining the MHI in 2004, she moved from predominantly basic research to more clinically oriented research focusing on the use of metabolomics for biomarker discovery in various diseases. For this, she led the validation and implementation of workflows for a panel of liquid-chromatography MS-based methods to profile metabolites in clinical samples that are relevant to the pathophysiological mechanisms (dysregulated energy metabolism; inflammation and microbiome), which included an untargeted discovery-based lipidomic workflow (>1,000 lipid signals or >500 unique lipids from all classes).The application of untargeted lipidomics to plasma samples in various human cohorts, which was part of multidisciplinary projects for which she led the metabolomic arm, opened novel perspectives on the molecular mechanisms underlying these diseases, on patient classification and response to therapy.

These projects focused on mitochondrial disorders such as the Leigh Syndrome French Canadian Type (LSFC) and Friedreich Ataxia, inflammatory bowel diseases and heart failure with preserved ejection fraction. For all her research activities, she received continuous funding from several peer-reviewed granting agencies, such as the Canadian Institute for Health Research (CIHR) and Genome Canada. She has published over 150 original and review articles and book chapters and has supervised >100 trainees at all levels. Illustrating her dedication to heart research and training, she has been a founding member (2002-) & President (2015-2018) of the Society for Heart and Vascular Metabolism (SHVM), a non-profit international organization promoting collaboration and training in cardiac metabolic research through annual meeting organizations.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 1 : Lipids desaturation in metabolism

James M. Ntambi (University of Wisconsin, USA)

The Role of Hepatic Stearoyl-CoA Desaturase in Systemic Metabolism

Professor of biochemistry and Steenbock professor of nutritional sciences at the University of Wisconsin Madison, USA. Ntambi received his BSc. and MSc. degrees in Biochemistry and Chemistry from Makerere University Kampala, Uganda and his PhD. in Biochemistry and Molecular Biology from the Johns Hopkins University School of Medicine in Baltimore, MD USA, where he started his work on the molecular biology of parasites and the regulation of genes of lipid metabolism.

Ntambi has made distinguished contributions to the field of nutritional biochemistry and his pioneering work on the genetic regulation of the stearoyl-CoA desaturase has recently led to many new insights into the importance of this enzyme in metabolism and in disease states such as obesity, diabetes, fatty liver disease, atherosclerosis, inflammation and cancer.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 1 : Lipids desaturation in metabolism

Richard Bazinet (University of Toronto, CA)
New methods lead to new findings in the omega-3 synthesis pathway.

Dr. Bazinet received his BSc. from the University of Western Ontario and completed his PhD under the supervision of Dr. Stephen Cunnane at the University of Toronto in 2003. Dr. Bazinet then completed a postdoctoral fellowship in Dr. Stanley Rapoport's Brain Physiology and Metabolism Section at the National Institute on Aging, National Institutes of Health. Dr. Bazinet joined the University of Toronto in 2006, where he is currently a Professor and Canada Research Chair in Brain Lipid Metabolism. Dr. Bazinet is the recipient of several awards, including the Early Career Award from the International Society for the Study of Fatty Acids and Lipids; the Jordi-Folch-Pi Memorial Award from the American Society for Neurochemistry; the Future Leaders Award from the International Life Sciences Institute, the Young Scientist Award for the American Oil Chemists' Society, the Early Researcher Award from the Canadian Society for Nutrition and the Ralph Holman life time achievement award from the Oil Chemists' Society.

Dr. Bazinet sits on several editorial boards and is currently Editor-in-Chief of Prostaglandins, Leukotrienes and Essential Fatty Acids as well as a Senior Associate Editor of Lipids. The overall goal of Dr. Bazinet's research program is to identify the mechanisms that regulate brain lipid metabolism (signaling) and to identify the role of brain lipid metabolism in the pathogenesis of neurodegenerative diseases and neuropsychiatric disorders. Dr. Bazinet has published over 180 papers, largely in the field of brain fatty acid metabolism and is co-author of the joint WHO/FAO joint expert consultation on dietary fats and the central nervous system during aging and disease. Dr. Bazinet is currently the past-president of the International Society for the Study of Fatty Acids and Lipids (ISSFAL).

ABOUT THE SPEAKER

MONDAY, September 5th

Session 1 : Lipids desaturation in metabolism

Marie-Claude Vohl (Université Laval, CA)

Gene-diet interactions with omega-3 fatty acids: Impact on plasma triglyceride levels.

Canada Research Chair in Genomics Applied to Nutrition and Metabolic Health, Professor at the School of Nutrition (Université Laval), and responsible of the Precision Nutrition Research Axis of the FRQS-funded Centre Nutrition, santé et société (NUTRISS), is conducting research with three objectives in mind. First, Dr. Vohl and her team are seeking to identify the genetic and epigenetic factors that modulate cardiometabolic disease risk factors in obese individuals. Second, they are identifying how these genes interact with diet to modulate cardiometabolic disease risk factors. Finally, they are studying the factors that hinder and facilitate the use of nutrigenomics results by healthcare professionals.

Since the beginning of her career, Professor Marie-Claude Vohl has published more than 300 peer-reviewed papers and 420 research communications. She has been invited to give several presentations in national and international conferences. Her research programs are funded among others by the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada and Natural Sciences and Engineering Research Council of Canada.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 2 : Lipid mediator of inflammation

Éric Boilard (University Laval, CA)

The interaction of secreted phospholipase A2-IIA with the microbiota promotes inflammation

Eric Boilard was trained in the laboratory of Dr. Marc Surette in immunology at Université Laval, and then underwent a first postdoctoral fellowship in the laboratory of Dr. Gerard Lambeau at Université de Nice-Sophia Antipolis in France. With the knowledge acquired on PLA2 and lipid mediators of inflammation during these trainings, he then joined the laboratory of Dr. David Lee at Havard Medical School, where he highlighted the contribution of sPLA2 in rheumatoid arthritis using mouse model of disease.

Eric Boilard is a senior awardee from the Fonds de Recherche en Santé du Quebec and Full Professor of Medicine in the department of infectious diseases and immunity at Université Laval. In 2017, he was awarded the prestigious prize André Dupont, given to the most meriting young investigator in clinical research in the province of Quebec. In 2019, his group was awarded the prestigious Cozzarelli Prize from the National Academy of Sciences (USA) for the originality and high quality of their research on inflammation. His studies aim to define how sPLA2 can contribute to inflammation by the identification of endogenous sPLA2 substrates in sterile inflammation such as autoimmune diseases.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 2 : Lipid mediator of inflammation

Valerie O'Donnell (Cardiff University, UK)

Phospholipid and fatty acid metabolism in innate immunity and coagulation

I am a lipid biochemist and Professor of Biochemistry at Cardiff University. Prior to this, I was Wellcome Trust Fellow (Cardiff), Parker B Francis Fellow (University of Alabama at Birmingham) and EU Marie Curie Fellow (University of Berne). My research is focused on using mass spectrometry for discovery and characterization of lipids in inflammation, wound healing and thrombosis. We mainly focus on around 150 molecular species of lipids termed enzymatically oxidized phospholipids (eoxPL) made by platelets, neutrophils, monocytes and eosinophils.

We showed that they are essential for normal blood clotting, and conversely are elevated in thrombotic disease. The detailed biochemical and biophysical mechanisms of action were elucidated. We also showed they regulate neutrophil antibacterial actions and transcriptional activation in monocytes. We found that they are part of the healthy innate immune system, however when inappropriately generated in the blood stream or in excess, they contribute to vascular inflammation. Recently, we demonstrated a role for mitochondria in oxylipin metabolism during inflammation.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 2 : Lipid mediator of inflammation

Oliver Werz (University Jena, Germany)

Targeting of pro-inflammatory and pro-resolving lipid mediator networks

Oliver Werz studied pharmacy and received his PhD in 1996 in pharmaceutical chemistry at the Univ. Tübingen. After postdoctoral stays at the Univ. Frankfurt (1996-1997) and the Karolinska Institute in Stockholm with Nobel Laureate Bengt Samuelsson (1998-2000), he became lecturer in 2002 for pharmaceutical chemistry at the Univ. Frankfurt. In 2005 he was appointed full professor for pharmaceutical analytics at the Univ. Tubingen. In 2010 he switched to a full professorship at the Friedrich Schiller University Jena, where he is the chair for pharmaceutical/medicinal chemistry since. In 2015/2016 he was a visiting professor at Harvard Medical School in Boston/USA with Prof. Charles N. Serhan. His research interests include the biosynthesis and pharmacology of inflammation-related lipid mediators with focus on lipoxygenases producing leukotrienes and specialized pro-resolving mediators in innate immune cells; he published >350 peer-reviewed papers.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 3 : FluxoLipidomics

Markus Wenk (National University of Singapore, SG)

Intergenerational landscape of the human circulatory lipidome during pregnancy and early life

Markus Wenk has been interested in membrane lipids, their structure and function since his undergraduate years at the Biozentrum of the University of Basel. At Yale he introduced and established techniques for analysis of phospholipid metabolism at the neurological nerve terminal. Since then, he has been spearheading novel approaches in systems scale analysis of lipids and their interactors (lipidomics) and is recognized as a thought leader in this field. His main scientific focus is determination and understanding of natural biological variation of circulating metabolites and lipids beyond the well-known examples of cholesterol. He is Provost's Chair Professor, Department of Biochemistry, Yong Loo Lin School of Medicine, founder and Director of the Singapore Lipidomics Incubator (SLING) at the National University of Singapore (NUS) as well as Director of the newly formed Precision Medicine Translational Research Program NUS.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 3 : FluxoLipidomics

Pierre Chaurand (University of Montreal, CA)

Fluxolipidomics by imaging mass spectrometry: examples in cancer research and neurobiology

Dr. Pierre Chaurand (Ph.D. 1994, Université Paris Sud, Orsay, France) is Professor of Chemistry at the Université de Montréal (2009 - present). His background is in fundamental and analytical mass spectrometry (MS). With over 30 years of research expertise, he is one of the pioneers of the mass spectrometry imaging (MSI) technology. His research interests are focused on the development of new strategies and methods to improve the specificity and sensitivity of MSI with applications in clinical biology and forensic science. Dr. Chaurand has over 100 peer reviewed publications and book chapters in the field of MS, with over 70 in the specific field of MSI.

ABOUT THE SPEAKER

MONDAY, September 5th

Session 3 : FluxoLipidomics

Makoto Arita (Keio University, JP)

Advanced non-targeted lipidomics to explore lipidome changes associated with aging and commensal bacteria

Dr. Makoto Arita received his Ph.D. from the Graduate School of Pharmaceutical Sciences, University of Tokyo in 1997. Currently he is a Professor of Pharmaceutical Sciences at Keio University, and a Team Leader of RIKEN Center for Integrative Medical Sciences. Dr. Arita has experience leading multidisciplinary research teams as a principal investigator for “Biology of LipoQuality” a program project supported by JSPS Grant-in-aid for Scientific Research on Innovative Areas (FY2015-2020). He successfully organized the 60th International Conference on the Bioscience of Lipids (ICBL2019, Tokyo) as a chair, and serves as an Executive Editor for the Progress in Lipid Research. Now he is leading JST-ERATO Lipidome Atlas Project (FY2021-2026) to pioneer the spatiotemporal biology of lipid diversity through a creation of the Lipidome Atlas, and to discover unknown molecules associated with important biological processes.

ABOUT THE SPEAKER

TUESDAY, September 6th

Session 4: Triacylglycerol metabolism

Denis Blondin (University of Sherbrooke, CA)

The Glycerolipid-free fatty acid cycle: A thermogenic perspective

Pr Denis P. Blondin is an Assistant Professor and holder of a GSK Research Chair in Diabetes in the Faculty of Medicine and Health Sciences at the Université de Sherbrooke and researcher at the CHUS research centre. His research mainly focuses on tissue-specific energy metabolism in response to environmental or pharmacological stimuli and their impacts in obesity, type 2 diabetes and non-alcoholic fatty liver disease using a unique integration of medical imaging (PET and MRI), high-resolution respirometry, stable isotopic tracers and indirect calorimetry. His research is currently funded through NSERC, FRQS and FRQNT and is the recipient of a Fonds de recherche en santé du Québec Junior 1 Scholarship.

ABOUT THE SPEAKER

TUESDAY, September 6th

Session 4: Triacylglycerol metabolism

Guenter Haemmerle (University of Graz, Austria)

***Mammalian** Carboxylesterase 2 proteins: Novel players in lipid metabolism and metabolic disease*

Guenter Haemmerle studied microbiology in Graz and received his PhD in biochemistry in 2001 at the University of Graz, Austria. Since 2010, Guenter Haemmerle is an Associate Professor at the Institute of Molecular Biosciences, Graz. His research interests are understanding the role of lipid hydrolases in energy catabolism and the development of metabolic disease. His most important scientific contributions encompass the generation and characterization of mutant mouse models lacking or overexpressing neutral lipases (Atgl/PNPLA2, Hsl/LIPE) and co-regulators (Cgi-58/ABHD5, Perilipin 5), which significantly contributed to the understanding of the in vivo role of lipases and co-regulators in energy catabolism and the onset of metabolic disease (h-index: 43). Over the last years, his group aims to understand the metabolic role of mouse and human Carboxylesterase 2 (Ces2/CES2) proteins in liver and intestinal lipid metabolism.

ABOUT THE SPEAKER

TUESDAY, September 6th

Session 4: Triacylglycerol metabolism

Michael Czech (University of Massachusetts, USA)

CRISPR-enhanced adipocyte fatty acid oxidation to reduce liver triglyceride

Michael P. Czech is currently the Isadore and Fannie Foxman Professor at the University of Massachusetts Medical School, where he was also Chairman of Biochemistry (1981-1989) and founding Chair of the Program in Molecular Medicine (1989-2018). Czech's laboratory applies RNAi- and CRISPR-based technologies to address mechanisms of insulin signal transduction, metabolic regulation and insulin resistance in obesity and type 2 diabetes. His group's work revealed insights into signaling by receptors for insulin and the IGFs and identified several new regulators of adipose tissue and systemic metabolism. Czech has received the Elliot P. Joslin Medal (1998), the Banting Medal (2000), and the 2009 Jacobaeus Prize presented in Umea Sweden.

ABOUT THE SPEAKER

TUESDAY, September 6th

Session 5: Ceramides and endocannabinoids

Mauro Maccarrone (University of L'Aquila, Italy)

The Endocannabinoid System and its Complexity in the Brain

Mauro Maccarrone, Dr. Enzymology and Bio-Organic Chemistry is Professor and Chair of Biochemistry at the Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila (Italy). He is also Head of the Lipid Neurochemistry Unit at the European Center for Brain Research – IRCCS Santa Lucia Foundation, Rome. For his research activity he has received the "4th Royan International Research Award for Reproductive Biomedicine" (2003), the "2007 IACM (International Association for Cannabinoid Medicines) Award for Basic Research", the "2016 Mechoulam Award", the "2020 Tu Youyou Award", and the "2020 International Space Station Research and Development Award" by the American Astronautical Society with NASA and CASIS. Chair of the 2015 Gordon Research Conference on "Cannabinoid Function in the CNS". Visiting Professor at Leiden University (Leiden Institute of Chemistry, The Netherlands) in 2017, and at University of Cambridge (Department of Psychology, U.K.) in 2019. Faculty member of The Lambert Center for the Study of Medicinal Cannabis and Hemp at Thomas Jefferson University in Philadelphia, since 2019. Visiting Professor of the National University of Rosario (Argentina) in 2021. Holder of 9 granted patents. Published more than 520 full papers, of which 65 with I.F. ≥ 9 (total I.F. > 2700; citations = 20795, h-index = 76 according to Scopus). Due to his scientific activity and impact, is included by Stanford University in the "2021 World Top 2% Scientists' List", where he holds the 179th position among 4955 Italian researchers. He is also listed among the "Top Italian Scientists".

ABOUT THE SPEAKER

TUESDAY, September 6th

Session 5: Ceramides and endocannabinoids

Yusuf Hannun (Sony Brook, USA)

Compartment specific functions of neutral sphingomyelinase and ceramide

Yusuf A. Hannun, M.D. is the Director of the Stony Brook Cancer Center and the Joel Kenney Professor in Cancer Research. Over the past 4 decades, Dr. Hannun's work has been in the areas of lipids, protein kinases, and signal transduction. His work led to the launching of the field of bioactive sphingolipids and their roles in biology. Dr. Hannun has published over 600 scientific manuscripts. His H index is currently 147 (83,000 citations). Dr. Hannun is an elected fellow of the AAAS, AAP, and ASCI. He is a recipient of the Mallinckrodt Scholarship, the Pew Scholarship, the South Carolina Governor's Award for Excellence in Research, and the Feodor Lynen Lectureship of the German Society of Biochemistry and Molecular Biology. In 2010, he received the Avanti Award for excellence in Lipid Research from the ASBMB and in 2012 he received the Kuwait Prize. He was awarded an honorary doctorate from the American University of Beirut in May 2014, and in 2015, he received The European Lipid Science Award.

ABOUT THE SPEAKER

TUESDAY, September 6th

Session 5: Ceramides and endocannabinoids

Antonio Gomez-Munoz (University of the Basque Country, Spain)

New insights into ceramide-1-phosphate biology

Antonio Gomez-Muñoz received his PhD in Biochemistry and Molecular Biology from the University of the Basque Country (Bilbao, Spain) in 1988. He achieved predoctoral training at the Medical School of the University of Nottingham, UK in 1987 and obtained a postdoctoral position at the University of Alberta (Edmonton, Canada) from 1988 to 1994. He then accepted a Research position at the Spanish Research Council in Madrid from 1995 to 1996. From 1997 to 1998 he was a Research Associate in the Faculty of Medicine, University of British Columbia (Vancouver, BC, Canada). He then returned to the University of the Basque Country where he is currently Professor of Biochemistry and Head of the Lipid and Cell Signaling Group. He belongs to the Editorial Board of various prestigious scientific journals, including Biomedicines and IJMS. His major research interest is on the targeting of sphingolipid metabolism for prevention of inflammatory diseases and has produced over 100 publications in the field.

ABOUT THE SPEAKER

TUESDAY, September 6th

Satellite conference sponsored by Novartis

Benoit Arsenault (Laval University, CA)

Inclisiran and RNA interference therapeutics in preventive cardiology

Dr. Benoit Arsenault obtained his Ph.D. in Physiology-Endocrinology from Université Laval in Québec City, Canada in 2009. After two postdoctoral fellowships at the Academic Medical Center in Amsterdam and at the Montreal Heart Institute, Dr. Arsenault joined the Department of Medicine of Université Laval in 2013. He is also a research scientist in the cardiology axis at the Québec Heart and Lung Institute. Dr. Arsenault's team use genetic toolssuch as Mendelian randomization and family studies to investigate the causes and consequences of cardiometabolic diseases such as non-alcoholic fatty liver disease, dyslipidemia, type 2 diabetes and cardiovascular diseases. He also leads a research program funded by the Canadian Institute of Health Research on the basis and genetic mechanisms through which Lipoprotein(a) contributes to heart valve disorders such as calcific aortic valve stenosis using multiomic technologies. Dr. Arsenault holds a senior scholar award from the Fonds de recherche du Québec: Santé (FRQS) and his research is also funded by the Foundation of the Québec Heart and Lung Institute. Dr. Arsenault is also the Co-President of the Québec Society of Lipidology, Nutrition and Metabolism (SQLNM). He has authored or co-authored more than 150 peer-reviewed manuscripts.

ABOUT THE SPEAKER

WEDNESDAY, September 7th

Session 6: Lipids in neuronal systems

Karl Fernandes (University of Sherbrooke, CA)

Lipids and the pathogenesis of Alzheimer's disease

Karl Fernandes (PhD) holds a Canada Research Chair in Brain Aging and Repair at the University of Sherbrooke and the Sherbrooke Research Center on Aging (Canada). His laboratory's research program investigates how mechanisms of neural plasticity can be exploited to promote repair of the adult and aging brain. A major focus of his lab is Alzheimer's disease, with current research themes that include cerebral lipid metabolism, adult neurogenesis, and the mechanisms underlying the beneficial effects of exercise- and dietary-based strategies. For more information, visit www.fernandeslab.com.

ABOUT THE SPEAKER

WEDNESDAY, September 7th

Session 6: Lipids in neuronal systems

Maria S. Ioannou (University of Alberta, CA)

Mechanisms and function of neuronal lipid release.

Dr. Maria Ioannou obtained her BSc and MSc with Dr. Margaret Fahnestock at McMaster University in Hamilton ON, where she studied proneurotrophins. She completed her PhD with Dr. Peter McPherson at McGill University in Montreal QC where she studied the regulation of endosomal transport by Rab GTPases. She then moved to Ashburn VA, to complete her post-doctoral training with Drs. Zhe Liu and Jennifer Lippincott-Schwartz at the Howard Hughes Medical Institute Janelia Research Campus. It was here that she began to study neuronal lipid transport. She started her lab at the University of Alberta in May 2019 where she continues to investigate the mechanisms and function of lipid transport in the brain. She is a Sloan Fellow in Neuroscience, a National New Investigator from the Heart & Stroke Foundation of Canada, and a Canada Research Chair in Brain Lipid Cell Biology.

ABOUT THE SPEAKER

WEDNESDAY, September 7th

Session 6: Lipids in neuronal systems

Sophie Layé (University of Bordeaux, France)

Dietary polyunsaturated fatty acids, mood and cognitive disorders, role of brain oxylipins

S. Layé is Research Director at Inrae. She created the NutriNeuro Institute (Bordeaux Univ), the international lab OptiNutriBrain (Bordeaux U-Laval U, Canada) and the International Research Network Food4Brainhealth (13 partners in France and Canada). Her scientific career is devoted to understand how nutrition contributes to mood and cognitive disorders, focusing on the effect of food and nutrients on brain functions using integrative and translational approaches. This research aims at defining a healthy nutrition for the brain, finding reliable predictive biomarkers of cognitive and mood disorders and new food-derived bioactive molecules in the brain to develop innovative nutritional and pharmacological strategies to prevent and treat brain diseases. She has been awarded several times for her academic achievements and received the prestigious “Lauriers de l’Inrae” in 2015.

ABOUT THE SPEAKER

WEDNESDAY, September 7th

Session 7: Reverse cholesterol transport – A paradigm in revision

Cédric Le May (University of Nante, France)

From blood to intestinal lumen: a mysterious but promising trans intestinal route for plasma cholesterol elimination

Cédric Le May is Research Director at CNRS and a member of the "institute du thorax" at Nantes. His scientific career is dedicated to better understand lipoprotein metabolism and to identify new targets to reduce cardiovascular (CV) diseases. He is currently leading the axis « New pathways in lipoprotein metabolism » in the team 4 of the "institute du thorax". His scientific program is divided in two interconnected major parts: the first is a genetic strategy to identify novel drug targets in CVD beyond LDL-C lowering (i.e., by focusing on atheroprotective factors in FH) while the second is focusing on the functional characterization of identified targets. Among them, the TransIntestinal Cholesterol Excretion (TICE) pathway is a promising, efficient but poorly characterized route that favor plasma cholesterol elimination. His studies contributed to a better understanding of the functioning of TICE. For this, he notably received the prestigious "ATVB, Daniel Steinberg, Early Career investigator award in atherosclerosis/lipoproteins" in 2014.

ABOUT THE SPEAKER

WEDNESDAY, September 7th

Session 7: Reverse cholesterol transport – A paradigm in revision

Gwendalyn J. Randolph (Washington University, USA)

HDL trafficking and inflammatory disease

Gwendalyn J. Randolph, PhD is the Emil R. Unanue Professor of Immunobiology in the Department of Pathology at Washington University in St. Louis. She received her PhD at Stony Brook University with Martha Furie as her thesis advisor, went on to postdoctoral training at Rockefeller and Cornell in New York City with Bill Muller and Ralph Steinman. She started her independent laboratory at Mount Sinai in New York and later moved to Washington University in St Louis. She is now the Director of the Immunology Graduate Program at Washington University. Her awards include the NIH Director's Pioneer Award, NIAID MERIT Award, and NIDDK Catalyst Award. She has expertise in monocyte/macrophage biology and in the lymphatic vasculature. Her laboratory considers how the transit of cells (monocytes and dendritic cells) and molecules (lipoproteins) out of tissue influences the inflammatory microenvironment and inflammation-associated disease.

ABOUT THE SPEAKER

WEDNESDAY, September 7th

Session 7: Reverse cholesterol transport – A paradigm in revision

Gaétan Mayer (Montréal Heart Institute)

Loss of hepatic GLGI reduces apolipoprotein B-100 secretion by promoting autophagy

Dr. Gaétan Mayer is Director of the Cellular and Molecular Biology Laboratory at the Montreal Heart Institute Research Center and Professor at the Faculty of Pharmacy of the Université de Montréal since 2010. His work focuses on the mechanisms that control the levels of blood cholesterol and triglycerides, which are major causes of atherosclerosis and cardiovascular disease. More specifically, his laboratory studies the proteins capable of strongly increasing or decreasing LDL-cholesterol and ApoB-lipoproteins and their role in the etiology of the metabolic syndrome. His team is also working on the development of new orally available drugs that are complementary to statins and that reduce the level of blood cholesterol and atherosclerosis. These studies aim to develop innovative therapeutic approaches and apply them in human health to treat hypercholesterolemia and reduce deaths from cardiovascular disease.

SELECTED PRESENTATIONS

Session 1 : Lipids desaturation in metabolism

1- Δ-6 desaturase (*Fads2*) deficiency promotes lipolysis and reduces lipid storage in murine white adipose tissue

C. Wang[a], B. Hucik-Worndl[a], O. Sarr[a], L. Brown[a], K. Wells[b], M. T. Nakamura[c], E. Harasim-Symbor[d], A. Chabowski[d], D. M. Mutch[a]*

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[b] Department of Pharmacology, Dalhousie University, Saint John, NB, Canada

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[d] Department of Physiology, Medical University of Bialystok, Bialystok, Poland

Background: The Δ-6 desaturase (D6D) enzyme is not only critical for the synthesis of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from α-linolenic acid (ALA), but recent evidence suggests that it also plays a role in adipocyte lipid metabolism and obesity resistance. However, the mechanisms remain largely unexplored. We hypothesized that a *Fads2* deficiency would inhibit lipid storage and alter lipid metabolism in white adipose tissue (WAT) depots due to a disruption in EPA and DHA production.

Methods: Male C57BL/6J *Fads2* knockout (KO) and wild-type (WT) mice were fed either a Lard diet (7% w/w lard) or a Flax diet (7% w/w flaxseed oil) for 21 weeks. Energy expenditure data was collected with metabolic caging. Inguinal and epididymal WAT were analyzed for changes in tissue weight, fatty acid composition, adipocyte size, and markers of lipogenesis, lipolysis, and insulin signaling.

Results: KO mice had reduced body weight, smaller WAT depots, and reduced adipocyte size compared to WT mice without altered caloric intake, energy expenditure, or physical activity, regardless of the diet. *Fads2* deficiency-induced changes in total ALA, EPA and DHA levels were reflected in the triglyceride fraction but not in the phospholipid fraction in both depots. Genotype, but not the diet, showed significant main effects for most of the analyzed lipogenic and lipolytic markers in both WAT depots. Specifically, markers of lipogenesis and lipolysis were higher in KO mice compared to WT mice. Moreover, KO mice had a higher serum non-esterified fatty acid (NEFA) and NEFA/glycerol ratio compared to WT mice, regardless of diet. Lastly, increases in markers of lipolysis in KO mice was associated with reduced insulin signaling in WAT depots.

Conclusions: A *Fads2* deficiency promotes lipolysis and reduces lipid storage in WAT depots which is partially attributed to reduced WAT insulin signalling.

2-Intestinal Stearoyl-CoA Desaturase 1 modulates intestinal and systemic lipid metabolism and energy homeostasis

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[b] Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ 08901, USA

Background: Stearoyl-CoA Desaturase 1 (SCD1) is an enzyme in the endoplasmic reticulum membrane that catalyzes the conversion of saturated fatty acids (SFAs) into monounsaturated fatty acids (MUFAs). The MUFA products of SCD1 are the preferred substrates for the synthesis of esterified lipids such as triacylglycerols and cholesterol esters. Given the important role for liid esterification in the enterocyte for efficient lipid assimilation, we hypothesized that intestinal SCD1 may modulate lipid composition in the intestine and systemically. **Methods:** To interrogate the role of intestinal SCD1 in modulating whole body metabolism, intestine specific Scd1 knockout (iKO) mice were generated by crossing mice with floxed Scd1 alleles with mice expressing Cre recombinase under the Villin 1 promoter. Studies included analysis of whole-body lipid content and composition and energy handling upon administration of various nutritional challenges. **Results:** Scd1 expression was enhanced in the distal small intestine and colon and was upregulated by acute sucrose feeding. Deletion of intestinal SCD1 significantly reduced intestinal lipids, particularly in the distal portion of the intestine. Furthermore, iKO mice had decreased plasma triacylglycerols, diacylglycerols, cholesterol esters and free cholesterol as well as reduced hepatic diacylglycerols and cholesterol esters. Plasma and hepatic lipids displayed specific reductions in the myristoleic (14:1) to myristic (14:0) acid ratio, with associated changes in the hepatic SIRT1-PGC1α signaling. Apart from lipidomic changes, plasma and hepatic bile acids were unexpectedly elevated in iKO mice. This resulted in the activation of TGR5 signaling in brown adipose tissue and the ileum and consequent increases in energy expenditure and plasma GLP-1 levels. **Conclusions:** Our results indicate that deletion of intestinal SCD1 has significant impacts on both intestinal and systemic lipid metabolism as well as on whole-body energy balance potentially mediated by changes in bile acid homeostasis and TGR5 signaling.

Session 2 : Lipid mediators of inflammation

3-Platelet-derived 20-HETE promotes pancreatic β cell function

Till Karwen[1,*], Katarzyna Kolczynska[2,*], Carina Gross[3] , Mona C. Löffler[1] , Mike Friedrich[1] , Angel Loza-Valdes[2] , Werner Schmitz[4] , Agnieszka Demczuk[2] , Filip Dziaczkowski[2] , Jonathan Trujillo-Viera[1] , Rabih El-Merahbi[1] , Sameena Nawaz[5] , Benoit Hastoy[5] , Manuela Erk[1] , Mariusz R. Wieckowski[2] , Patrik Rorsman[5,6,7], Katrin G. Heinze[1] , David Stegner[1,3,&,] Bernhard Nieswandt[1,3,&] and **Grzegorz Sumara**[1,2]

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Background: Metabolic homeostasis is ensured by a complex interplay between multiple organs mediated by nutrients and hormones. Pancreatic β cells secrete insulin, a major hormone regulating circulating levels of glucose and other nutrients. Loss of β function results in hyperglycemia, a hallmark of diabetes. In type 1 diabetes, autoimmune destruction of β cells leads to absolute insulin deficiency, whereas in type 2 diabetes obesity and peripheral insulin resistance result in relative insulin deficiency that may culminate in glucolipotoxicity causing β cell death. Both type 1 and type 2 diabetes are associated with an increased prevalence of vascular diseases which, besides other factors, is driven by increased platelet reactivity. This suggests that platelets might become activated in response to high glucose and raises a possibility that these cells might be implicated in the systemic response to elevated glucose levels. **Methods:** We assessed the contribution of platelets to homeostatic function using genetic, pharmacological, cell biology and multiomics approaches in combination with intravital imaging and computational techniques. **Results:** Here we show that factor(s) derived from β cells stimulate platelet activity. Moreover, platelets selectively localize to the vascular endothelium of the pancreatic islets. Both, depletion of platelets and ablation of major platelet adhesion or activation pathways, consistently results in impaired glucose tolerance and decreased circulating insulin levels. Furthermore, we identified platelet-derived 20-Hydroxyeicosatetraenoic acid (20-HETE) to promote insulin secretion. Finally, we demonstrated that the levels of platelet-derived 20-HETE decline with age, and so the platelet impact on β cell function does.**Conclusions:** Our findings identify an unexpected function of platelet-derived lipid-derivative 20-HETE in the regulation of insulin secretion and glucose metabolism, which promotes the metabolic fitness in young individuals.

4-The leukotriene B4/BLT1-dependent neutrophil accumulation exacerbates immune complex-mediated glomerulonephritis

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Backgrounds: Although neutrophils are known to play an important role in the progression of anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis, the detailed mechanism how neutrophils are involved in its pathogenesis has not been clarified. **Methods:** We tried to demonstrate that a lipid chemoattractant, leukotriene B4 (LTB4), and its receptor BLT1 are primarily involved in disease pathogenesis in a mouse model of immune complex-mediated glomerulonephritis, which mimics human ANCA-associated glomerulonephritis, using mice deficient in BLT1 and LTA4 hydrolase, an enzyme required for LTB4 biosynthesis. **Results:** Circulating neutrophils accumulated into glomeruli within 1 hour after disease onset, which was accompanied by LTB4 accumulation in the kidney cortex, leading to kidney injury. LTB4 was produced by cross-linking of Fc gamma receptors on neutrophils. Mice deficient in BLT1 or LTB4 biosynthesis exhibited suppressed initial

neutrophil infiltration and subsequent thrombotic glomerulonephritis and renal fibrosis. Administration of a BLT1 antagonist before and after disease onset almost completely suppressed induction of glomerulonephritis. Finally, we found that the glomeruli from patients with ANCA-associated glomerulonephritis contained more BLT1-positive cells than glomeruli from patients with other etiologies. **Conclusions:** The LTB4-BLT1 axis is the key driver of neutrophilic glomerular inflammation, and will be a novel therapeutic target for human ANCA-associated glomerulonephritis. Reference Yokomizo, T., Nakamura, M., Shimizu, T. Leukotriene receptors as potential therapeutic targets. (Review) J Clin Invest 128, 2691-2701 (2018)

Session 3: FluxoLipidomics

5- In-depth characterization of the tumor microenvironment MALDI-IMS focusing on immune infiltrates

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Background: Overall survival of patients with advanced stages of colon cancer (CC) has not improved despite the progress made in the field. The tumor microenvironment (TME) plays a crucial role in tumorigenesis, tumor expansion, and metastasis. Thus, a better understanding of the intricate network orchestrating TME heterogeneity may hold the key to identifying immunotherapy biomarkers and the development of new tools for patient stratification. Herein, we aim to characterize the membrane lipidome of tumor-infiltrating immune cells directly on CC tissue sections, which may convey critical information regarding tumor fate and its response to therapy. **Methods:** Peripheral blood was withdrawn from CC patients (n=12) and control subjects (n=8), while CC specimens were obtained during surgery. Circulating and infiltrated immune cells were isolated by *FACS* and plated on poly-L-lysine-coated glass slides. Sections of ~10 µm thickness from surgical biopsies were prepared in a cryostat. A consecutive section was stained for structure identification. Sections were scanned in negative- and positive-ion mode at 10 µm of spatial resolution using the orbitrap analyzer of an LTQ-Orbitrap XL (ThermoFisher). The spectra were analyzed using the software MSIAnalyst. **Results:** The lipidomic analysis revealed a distinctive lipid species pattern for each of the seven cell types analyzed. Furthermore, the comparison between control subjects and CC patients revealed a significant impact on arachidonic acid-containing PE and PE-plasmalogen species. Finally, IMS allowed the identification of infiltrated immune cells within tissue sections due to their differential content in PI38:4. **Conclusions**: The high sensitivity and reproducibility of the developed methodology provide a unique tool to analyze the lipidome of minor subsets of immune cells. In circulating immune cells, the impact of CC their lipidome turned out to be highly cell type-dependent. Further, these profiles can be identified within the MALDI-IMS generated images, enabling an in-depth approach for the TME characterization.

6-The gut microbiota reduces intestinal lipid absorption by induction of host phospholipase A1 activity in bile

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Background: Uptake of dietary lipids is a three-step process taking place in the small intestine. It comprises emulsification and hydrolysis of the lipids in the intestinal lumen, trafficking of the released fatty acids and monoacylglycerols from the apical to the basolateral site of enterocytes, and their re-esterification and secretion into the circulation. The gut microbiota promotes hepatic lipid synthesis, but its role in lipid uptake from the nutrition is unclear. **Methods:** Here, we apply stable isotope labeled lipid tracers in gnotobiotic mouse models in combination with mass spectrometric analyses to show that systemic uptake of dietary lipids depends on microbial colonization. Physiology-based kinetic multi-compartment modelling was used to investigate *in vivo* lipid flux and metabolism from the gut lumen to peripheral tissues. **Results:** We found that the gut microbiota inhibits intestinal lipid absorption from the gut lumen. Using lipidomics and proteomics, we discovered a microbiome-influenced phospholipase A1 (PLA_1) activity in bile. Gut microbes stimulate biliary PLA_1 via taurocholic acid, causing phosphatidylcholine degradation and in turn, suppressed intestinal lipid absorption. **Conclusions:** Our study unveils a new mechanism of metabolic interplay between gut microbiota and the host mediated by an enzyme activity in bile relevant in understanding physiological homeostasis. Microbiome

manipulation or pharmacological intervention of biliary glycerophospholipid metabolism present new targets to modulate dietary lipid absorption.

Session 4: Triacylglycerol metabolism

7-G3PP/PGPH-2: a novel dietary restriction mimetic enzyme that protects from glucolipotoxicity and promotes healthy aging via the AMPK-TFEB-Autophagy axis in *C.elegans*

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Background: Metabolic stress due to nutrient excess and lipid accumulation is at the root of many age-associated disorders and the identification of therapeutic targets that mimic the beneficial effects of calorie restriction has clinical importance. We recently discovered a key evolutionarily conserved enzyme at the heart of metabolism named glycerol-3-phosphate phosphatase (G3PP) (gene name *Pgp*), that operates a glycerol shunt by hydrolyzing glucose-derived glycerol-3-phosphate (Gro3P) to glycerol. Gro3P regulates flux of various metabolic pathways and particularly, the glycerolipid/fatty acid cycle associated with obesity and cardiometabolic disorders. In a recent work published in *Nature Communications*, we have characterized the roles of G3PP *in vivo* using the nematode *C.elegans* and demonstrated that its activation reduces fat accumulation, promotes healthy aging and acts as a calorie restriction mimetic at normal food intake without altering fertility via an unknown mechanism. **Methods:** We generated stable transgenic lines overexpressing PGPH-2, the major G3PP worm homolog and tested various possibilities for its mode of action via transcriptomics analysis and genetics. **Results:** We demonstrate that PGPH-2 activation mimics calorie restriction and protects from ectopic lipid accumulation with age and excess glucose. RNA seq analysis reveals a longevity and catabolic signature mediated by PGPH-2 overexpression (o/e) and largely dependent on TFEB/HLH-30, a regulator of lysosomal biogenesis and autophagy. Mechanistically, we demonstrate that PGPH-2 o/e constitutively activates the AMPK-HLH-30-autophagy axis, a key evolutionarily conserved pathway involved in organismal longevity. We show that PGPH-2 o/e induces HLH-30 nuclear translocation in a TOR-independent and AMPK-dependent manner. We further show that the increased autophagic activity in PGPH-2 o/e animals requires AMPK and HLH-30. Importantly, loss of AMPK, HLH-30, and autophagy in animals overexpressing PGPH-2 abrogates the enhanced healthspan and protection from glucotoxicity. **Conclusion:** A 'glycerol shunt' involving G3PP detoxifies excess glucose, protects against metabolic stress and promotes healthy aging via the AMPK-TFEB-autophagy axis.

8-14-3-3zeta enables the early steps of adipogenesis by modulating cellular functions indispensable for proliferation, differentiation, and lipid anabolism in preadipocytes

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Introduction: Initiation of adipogenic programme is triggered by-well defined transcription factors (TF) such as C/EBP-β and C/EBP-δ that in turn induce the expression of essential adipogenic TF, like C/EBP-α and PPARγ. Although these TF require nuclear translocation to fulfill their adipogenic functions, the molecular adaptor(s) that coordinate their nuclear entry remain unknown.We previously found that 14-3-3ζ, a ubiquitous scaffold protein that undergoes nuclear translocation during adipogenesis, was indispensable for adipocyte differentiation. Thus, we hypothesize that 14-3-3ζ anchors, nucleates and/or regulates essential transcriptional complexes required for the adipogenic programme. **Methodology**: TAP-3T3-L1 cells were generated from CRISPR-Cas9 editing of 3T3-L1 to express a TAP-tagged 14-3-3ζ. At 0, 24, and 48 hours of adipogenesis, nuclear TAP-14-3-3ζ complexes were purified to elucidate the 14-3-3ζ interactome by mass spectrometry, followed by Gene Ontology (GO) annotation. The most significantly enriched biological functions were assessed for their roles in adipogenesis using pharmacological inhibitors or siRNA screening. In parallel, whole chromatin accessibility was profiled by ATAC-Seq from control or 14-3-3ζ-depleted 3T3-L1. **Results**: At 24h and 48h post-differentiation, the 14-3-3ζ nuclear interactome was enriched with 62 and 113 peptides, respectively (FC ≥ 1.5, $p \leq 0.05$), including CEBP-β. According to GO annotations, proteins in the TAP-14-3-3z interactome were primarily associated (FDR ≤ 0.001, Fold Enrichment ≥ 1.0) with histone H2B ubiquitination, DNA unwinding for replication, DNA hypermethylation and ribosome assembly. Pharmacological inhibition or depletion by siRNA of key effectors of these biological functions significantly restricted 3T3-L1 cells differentiation. ATAC-seq analysis revealed that 14-3-3ζ depletion, at 24h and 48 post-differentiation, significantly downregulates the accessibility of 2,187 genomic regions primarily associated with genes involved with fat cell differentiation and lipid anabolism. **Conclusion**: 14-3-3ζ governs early steps of adipogenesis via critical nuclear protein-protein interactions and epigenetic modifications in differentiating mice preadipocytes.

Session 5: Ceramides and endocannabinoids

9-ABHD6 Suppression Prevents Lipopolysaccharide and High-fat Diet Induced Pro-inflammatory Macrophage Phenotypic Response

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Background: Obesity is considered as a low-grade inflammatory disease, characterized by proinflammatory macrophage infiltration into adipose tissue (AT). Depending on the microenvironment, AT macrophages (ATMs) alter their polarization between pro-inflammatory (M1-like) and anti-inflammatory (M2-like) phenotypes. Besides, certain populations of ATMs can also adopt a metabolic activation state. However, the immunometabolic pathways regulating their polarization are not well understood. Deletion of the monoacylglycerol lipase α/β-hydrolase domain-6 (ABHD6)

demonstrated the therapeutic potential of ABHD6 inhibition against metabolic and inflammatory disorders. However, the role of ABHD6 in macrophage activation/polarization under inflammatory conditions remains to be ascertained. **Methods:** We investigated the role of ABHD6 in macrophage polarization and if ABHD6 suppression is protective against lipopolysaccharide (LPS) and diet-induced inflammation using whole-body ABHD6-KO mice, macrophage cell lines (J774 and RAW 264.7) and a specific ABHD6 inhibitor. **Results**: Pharmacological inhibition of ABHD6 in LPS-challenged macrophage cell-lines attenuated the expression and release of pro-inflammatory cytokines. In addition, ABHD6 KO mice showed lower susceptibility to systemic LPS-induced inflammation, as indicated by lower plasma TNFα and MCP-1 levels and reduced expression of pro-inflammatory markers in peripheral blood mononuclear cells and lungs. Pharmacological inhibition of ABHD6 in palmitate/glucose/insulin treated macrophage cell-lines attenuated the metabolically-induced expression of proinflammatory cytokines. Consistently, AT depots from high-fat diet (HFD)-fed ABHD6-KO mice contained lower number of proinflammatory macrophages, with decreased expression of M1-like macrophage markers, compared to HFD-fed wild type mice. Liver, heart and spleen from HFD-fed ABHD6-KO mice, showed reduced weight, downregulation of proinflammatory cytokines, and lower fat content. **Conclusions:** Collectively, our data support the view that ABHD6 has a pro-inflammatory role under LPS- and diet-induced inflammatory conditions. The results suggest the therapeutic potential of ABHD6 inhibition in the treatment of inflammation.

10-Increased dependence on ethanolamine in a cancer cell line leads to accumulation of choline-based plasmanyl ether lipids

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Background: Ether lipids are a group of glycerophospholipids differing from their acyl-counterparts by carrying an ether-linked fatty alcohol side chain at their *sn*-1 position. Aberrant cellular levels of ether lipids have been observed under pathological conditions including cancer, suggesting that they play important roles in health and disease. However, in spite of this, the roles of ether lipids, in particular 1-O-alkyl (plasmanyl) ether lipids, are largely unknown. Under certain conditions, hexadecenal, a product of sphingosine-1-phosphate (S1P) degradation, is known to be reduced and incorporated into ether lipids as the alcohol side chain. Based on this, we hypothesized that the elevated levels of plasmanyl ether lipids observed in certain cancer cell lines are an indirect effect of accelerated turnover of sphingolipids. **Methods:** To investigate this, we performed mass spectrometry-based shotgun lipidomics on cultured cell lines. We utilized an isogenic colon cancer cell line pair: HCT 116 and HKh-2, of which HCT 116 show markedly higher levels of 1-O-alkyl,2-acylglycerophosphocholine (PC O-) under normal growth conditions. **Results:** Our results showed that HCT 116 experienced a deficiency of ethanolamine, and suggested that this deficiency was compensated for by increased catabolism of S1P, thus producing phosphoethanolamine as well as hexadecenal, of which the latter was likely incorporated into plasmanyl ether lipids. Knockdown of phosphatidylserine decarboxylase, which represents a mitochondrial pathway of phosphatidylethanolamine synthesis, appeared to aggravate the deficiency, increasing the PC O- levels further. In contrast, antioxidant supplementation and ferroptosis inhibitors seemed to partially relieve the requirement for ethanolamine.

Conclusions: We propose that the observed accumulation of PC O- is a consequence of a mechanism for protection against ethanolamine deficiency, whereby excess fatty aldehydes arising from increased S1P catabolism are reduced and stored as non-toxic ether glycerophospholipids.

Session 6: Lipids in neuronal systems

11- GPR120 activation increases the activity of primary midbrain dopamine neurons

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Background: Metabolic impairments increase the risk of mood disorders. We previously found that omega-3 polyunsaturated fatty acids (n-3 PUFA) supplementation or central GPR120 (G-protein coupled receptor 120; FFA4) agonism can mitigate anxiety-like behavior in diet-induced obese mice. However, the role of GPR120 in central nervous system function remains unclear. In view of the role of mesolimbic dopamine (DA) tone in the control of emotions and mood states and observed GPR120 expression in the ventral tegmental area (VTA) of the midbrain, we sought to determine its contribution to dopamine neuronal function. **Methods:** We evaluated GPR120 mRNA expression in developing primary cultured DA neurons at 7-13 days in vitro (DIV). Intracellular calcium (Ca^{2+}) mobilization and DA release in GFP+ neurons were monitored before and after treatment with a selective GPR120 agonist (AZ13581837; 0.5-10 µM) at 7-8 DIV using a Ca^{2+} indicator (Biotracker 609) or a fluorescent dopamine transporter (DAT) substrate (FFN102), respectively. Downstream signaling of GPR120 was assessed by measuring phosphorylated cAMP-response element binding protein (pCREB) by immunoblotting. **Results:** GPR120 mRNA expression unchanged between 7 and 13 DIV. Bath perfusion of the GPR120 agonist increased intracellular Ca^{2+} levels in GFP+ neurons in bell-shaped, dose-response manner, but it did not affect the frequency of Ca^{2+} spikes. GPR120 agonist and n-3 PUFA enhanced the releasing of FFN102 from cultured DA neurons. In addition, GPR120 agonism also transiently increased pCREB levels in cultured DA neurons. **Conclusions:** These results uncover GPR120 activation as an enhancer of DA tone and suggest that this as one possible mechanism underlying the anxiolytic effects of central GPR120 agonism. NSERC RGPIN-2018-06565

12-Microglial Adipose Triglyceride Lipase (ATGL) regulates neuroinflammation and diet-induced obesity

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Background: Pro-inflammatory microglia contribute to dysregulation of energy and glucose homeostasis in rodents. Lipid droplets (LDs) act as intracellular triglyceride stores and are a source of various inflammatory mediators. LDs accumulate within microglia during pro-inflammatory activation, in a similar manner to that observed in macrophages. Adipose triglyceride lipase (ATGL) catalyzes the first step of triglyceride

hydrolysis in LDs. Loss or inhibition of ATGL reduces inflammation in macrophages, suggesting an active role for LDs lipolysis in inflammatory signaling pathways. Our data show that ATGL is enriched in microglia compared to other neural cells. Taking these data together, we hypothesize that microglial ATGL regulates neuroinflammation in response to inflammatory conditions, and behavioral and metabolic responses to a high fat diet (HFD). **Methods:** Mouse primary microglial cultures were treated with ATGL inhibitor Atglistatin (50 µM) and/or lipopolysaccharide (LPS; 0.1 µg/mL) to assess the role of ATGL on LD accumulation and inflammatory gene expression. We generated and validated a novel mouse model with inducible knock-out (KO) of ATGL in microglia (Cx3CR1-CreER/ATGL$^{lox/lox}$) to study the role of microglial ATGL on 1: neuroinflammation induced by LPS and 2: energy homeostasis and diet-induced obesity (HFD during 12 weeks). **Results:** Both LPS-induced inflammation and inhibition of ATGL led to accumulation of LDs *in vitro*. Inhibition of ATGL activity *in vitro* and microglia specific ATGL KO *in vivo* reduced expression of pro-inflammatory cytokines in response to LPS. Loss of microglial ATGL did not affect energy balance parameters or anxio-depressive behaviors in chow-fed male or female mice but increased the susceptibility to diet-induced obesity, without affecting food intake. Interestingly, glucose tolerance was improved in ATGL KO mice without changes in insulin secretion. **Conclusions:** Together these data suggest that microglial ATGL inhibition or deficiency reduces neuroinflammation and may have a beneficial impact on glucoregulatory responses.

Session 7: Reverse cholesterol transport – A paradigm in revision

13-Lipoproteins and Central Nervous System: HDL metabolism in Alzheimer's disease.

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Background: A growing number of evidence indicates a strong inverse association between the risk of developing Alzheimer's disease (AD) and plasma HDL-C levels, suggesting an involvement of cholesterol metabolism in the etiology and progression of AD. In addition apoE4 isoform is the strongest known genetic risk factor for the disease, however the mechanism is still unclear. Within this study the HDL metabolism in plasma and CSF of AD patients was investigated. **Methods:** 50 AD (19M/31F, 73±7 y.o.), 20 non-AD dementia (11M/9F, 69±8) and 5 cognitively-intact control subjects (3M/2F, 75±10) were recruited at the San Gerardo hospital with a complete neurological examination. Plasma lipid-lipoprotein profile was determined using a Roche Cobas c311 analyzer. The esterification process in CSF has been evaluated as total cholesterol (TC) and unesterified cholesterol (UC) content measured by HPLC, apolipoproteins content by Western blot. HDL subclasses have been characterized in plasma and CSF by non-denaturing two-dimensional (2D)-electrophoresis. The apoE genotype was obtained. **Results:** The isoform apoE4 has a frequency of 44% in AD cohort. In AD and non-AD

dementia plasma HDL-C levels are normal and interestingly HDL-C levels are lower in patients with major cognitive decline (measured with Mini-Mental State Exam). Plasma HDL subclass distribution is analogous to that of healthy controls. CSF apoE-containing lipoproteins showed only α-migrating particles. Curiously CSF apoA-I and apoA-II-containing lipoproteins are very similar to plasma HDL in AD, even if these apolipoproteins are not synthetized in the CNS. UC/TC ratio in AD CSF (0.47±0.12) is higher than controls (0.40±0.12) and tends to be directly associated to cognitive decline. **Conclusions:** This study supports the hypothesis of a direct role of plasma HDL in brain cholesterol homeostasis and a defect of cholesterol esterification in AD related to cognitive decline.

14-Implication of the Stearoyl-CoA Desaturase-1 in the formation of very-low density lipoproteins

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Background: Apolipoprotein B100 (**ApoB100**) is the core element of the very low-density lipoprotein (**VLDL**). Previous studies predict the acylation of ApoB100 with palmitate in the reticulum (**ER**). This palmitoylation prevent ApoB100 degradation by the proteasome and promote VLDL formation. Yet saturated fatty acid like palmitate or stearate can be mono-desaturated into palmitoleate and oleate by the Stearoyl CoA-desaturase-1 (**SCD1**) also in the ER. The activity of SCD1 could make available oleate and palmitoleate for the acylation of ApoB100 thus promoting VLDL formation. **Methods:** We used hepatocarcinoma cell HepG2 and Huh7.5 for our experiences. We identified by mass spectrometry proteins that co-precipitated with SCD1. By immunofluorescent, we determined the subcellular localisation of SCD1 and ApoB100. We quantified ApoB100 within the cells and the culture medium by western blot or ELISA in diverse conditions. **Results:** The mass spectrometry analysis suggest an interaction between SCD1 and ApoB100. This interaction is also supported by the partial subcellular co-localization of SCD1 and ApoB100. When the cells are exposed to a specific SCD1 inhibitor, the concentration intra and extra cellular of ApoB100 strongly decrease. When oleate is added to the medium it reverses the effect of the SCD1 inhibitor. Pulse chase experiment performed in Huh7.5 cells shows that oleate treatment can partially prevent the degradation of ApoB100. **Conclusion:** Our study suggests that SCD1, mostly through its product oleate, would stabilize intracellular ApoB100 allowing its excretion and greater synthesis of VLDL by the hepatocytes. This stabilization could be due to the acylation of ApoB100 by oleate.

POSTERS

Session A

A1- INSIGHTS INTO THE STRUCTURE OF THE DESATURASE CRUCIAL FOR PLASMALOGEN BIOSYNTHESIS

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Background: Plasmalogens are an abundant class of glycerophospholipids, occurring in high concentrations in brain and immune cell membranes. Their biosynthesis starts in peroxisomes and is completed in the endoplasmic reticulum. In a crucial final step, the 1-*O*-alk-1'-enyl double bond is introduced by plasmanylethanolamine desaturase (PEDS1). Using comparison of enzymatic activity and public mRNA-seq data from human cell lines and mouse tissues, we got as best correlating gene *Tmem189*, which we confirmed to encode PEDS1 using elimination and overexpression in cells. Mutagenesis of a conserved histidine motif revealed that each of the eight histidines was essential for PEDS1 activity. **Methods:** Using site-directed mutagenesis we mutated additional 28 residues to alanine – 20 of which were conserved amongst animal PEDS1 – and analyzed their ability to form fluorescently labeled plasmalogens after transient transfection in a PEDS1-deficient HAP1 cell line. A homology model for PEDS1 was obtained by MOE using available structures of stearoyl-CoA reductase (SCD1) as starting point. Additionally, the PEDS1 structure was predicted using the machine learning approach AlphaFold2. **Results:** Only a single mutation, aspartate 100, led to a total loss of PEDS1 activity. The second strongest impact had mutation of phenylalanine 118, leaving only 6% residual activity. The two structural models both predicted this D100 residue to interact with H96, and F118 to interact with H187, both being essential histidines assumed to be involved in the coordination of the di-metal center of the enzyme. Also in the structures of SCD1 a conserved asparagine residue is located in close proximity to the essential histidines. **Conclusions:** We found a pattern showing that the conserved histidines not only in the models for PEDS1 but also in the structures of SCD1 have an essential aspartate or asparagine residue in close proximity, which can contribute to stabilize the di-iron-binding site.

A2- Deficiency of stearoyl-CoA desaturase 1 promotes formation and survival of α-cells over β-cells in pancreatic islets

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Background: Stearoyl-CoA desaturase 1 (SCD1) is a lipogenic enzyme involved in saturated fatty acids metabolism, that exhibits protective role against lipotoxicity in pancreatic β-cells. It was shown that SCD1 deficiency contributes to β-cell failure and development of type 2 diabetes (T2D). However, the molecular mechanisms underlying this process are poorly understood. The aim of present study was to determine whether SCD1 influences both mature α-and β-cell identity, and α- and β-cell differentiation during pancreas morphogenesis. **Methods:** The experiments were carried out on pancreatic explants/islets isolated from wild type and *Scd1* knock-out mice (day 15.5 and 18.5 embryos, newborn, and adult animals). Morphological and functional characteristics of islets was evaluated by ELISA assays, immunofluorescence labeling, morphometric analyses and transmission electron microscopy techniques. Protein and gene expression levels were assessed by WB and qRT-PCR, respectively. **Results:**. Our data showed that loss of SCD1 at day 15.5 was manifested by higher expression of *Arx*, decreased expression of *Pax4*, expanded formation of α-cells and delayed formation of β-cells in embryonic pancreas. Furthermore, whereas expression of α-cell key genes remains unaltered, inhibition of SCD1 decreased expression of β-cell signature genes (e.g.: *Pdx1*, *Nkx6.1* and *MafA*) and led to β-cell dedifferentiation in adult pancreatic islets. Such molecular changes caused by SCD1 downregulation were followed by increased pancreatic α-cell mass and islets dysfunction – impairment of insulin maturation and glucose stimulated insulin release, simultaneous with elevation of basal glucagon secretion. **Conclusions:** Altogether, our data showed that SCD1 activity is essential for proper α-cell and β-cell lineage determination during the morphogenesis of the pancreas, as well maintenance of mature β-cell identity. These findings provide additional mechanistic insights toward understanding the role of SCD1 in the pathogenesis of T2D.
This work was supported by grants from the National Science Center, Poland, grants no UMO-2017/27/N/NZ3/01987 and UMO-2015/19/D/NZ4/03705.

A3- Selective impact of polyunsaturated fatty acids on lipid composition and metabolism in breast cancer cells

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Background: Fatty acids are closely involved in lipid synthesis and metabolism in tumor, especially in breast cancer. Their amount and composition are dependent on dietary supply and tumor microenvironment. Polyunsaturated fatty acids (PUFA), in particular docosahexaenoic acid (DHA), play beneficial roles in breast cancer prevention and therapy. The most prominent mechanism for antitumor action of n-3 PUFA is their suppressive effect on the production of arachidonic acid-derived prostanoids, which has been implicated in the immune response to inflammation, cell proliferation, differentiation, apoptosis, angiogenesis, metastasis, but they are also able to perturb lipid phenotype and metabolism. **Methods:** The present study investigated the impact of DHA incorporation in triple-negative breast cancer (TNBC) and Luminal A human breast adenocarcinoma cells on lipid metabolism, lipid peroxidation and energy pathways. **Results:** Different types of breast cancer cells exhibited specific sensitivity to lipid modulation. After DHA exposure, the TNBC cell line showed a selective sensitivity compared to the Luminal A cells correlating with a distinct lipid phenotype. This specific cell response is strictly closed to the peculiar lipid profile and metabolism that

characterizes each cell subset. In addition, long exposure to exogenous FA affects the lipid composition of the microsomal membrane. In particular, DHA treatment determines a significant alteration of the MUFA and PUFA contents of the endoplasmic reticulum (ER) compartment in TNBC cells, with consequent changes in resident enzyme activity. Indeed, the ER membrane is the site where FA can be further modified through elongation and desaturation processes. **Conclusions:** This study sustains the crucial role of lipid metabolism as an innovative hallmark to discriminate breast cancer subclasses and to develop personalized nutritional and pharmacological strategies.

A4- Molecular compositions of mitochondrial cardiolipins are closely controlled by the saturation state of their lipid environment

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Background: The mitochondrial phospholipid cardiolipin encompasses four fatty acyl side chains that are iteratively remodeled with the help of the transacylase tafazzin. Impairment of tafazzin function causes Barth Syndrome and results in abnormal cardiolipin states in patients. The exact molecular architecture of cardiolipin side chains follows a strong organism-, tissue-, and cell type-specificity, is enriched for polyunsaturated fatty acyls, and thus appears to originate from a tightly regulated process.**Methods** However, the individual elements that drive cardiolipin metabolism – including tafazzin – are often reported to be non-specific or promiscuous. Nevertheless, in concert they generate highly specific and reproducible lipid compositional endpoints. Here, we investigated the still largely ambiguous regulatory origin of tissue-specific cardiolipin states by conducting integrative analyses of lipidomics and transcriptomics datasets in mouse tissues and additionally employed data-driven machine learning strategies. **Results：** We could demonstrate that instead of transcriptional regulation, cardiolipin specificity is largely controlled through the phospholipid side chain environment, particularly their linoleoyl content and the presence of other polyunsaturated fatty acyls. Furthermore, in a tafazzin-deficient cell culture model, we could reveal an equally strong impact of the nutritional lipid composition on cardiolipin states. Interestingly, a considerable proportion of this effect was independent of the presence or absence of functional tafazzin. **Conclusions：** The strong influence of the lipid environment on cardiolipins provides a deeper understanding of the regulatory origin of their tissue-specificity and the interplay with the availability of essential polyunsaturated fatty acids. It is important to take these effects into account in further research, especially in translational studies, as well as when designing novel treatment options for lipid related diseases.

A5- Diet regulation of D5D and D6D activity: Investigating the role of soy and dairy protein on hepatic EPA and DHA synthesis.

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Background: The delta-5 and delta-6 desaturase enzymes (D5D, D6D) are highly regulated by various dietary factors, such as protein. We recently demonstrated that D5D and D6D indices were reduced in young adults who consumed soy containing foods,

but not in those who consumed dairy containing foods. However, the underlying mechanism of action is poorly defined. The aim of this study was to investigate the effects of dairy and soy protein on hepatic synthesis of omega-3 (n-3) long-chain polyunsaturated fatty acids (LC-PUFA) and advance understanding of the potential underlying mechanism-of-action. **Methods:** C57BL/6 male mice (n=12 per diet) were fed a Western diet (35%/50%/15% kcal from fat/carbohydrate/protein) containing either 1% kcal or 3.5% kcal of alpha-linolenic acid (ALA). Protein content corresponded to either dairy (skim milk powder) or soy protein isolate. After 8 weeks of feeding, liver tissues were collected, and gas chromatography was used to examine hepatic fatty acid content. Desaturase and elongase gene and protein expression were quantified by qPCR and Western Blot, respectively. To assess enzymatic activity, we plan to isolate microsomes from perfused livers and incubate them with a labelled ALA tracer. **Results:** Relative hepatic n-3 PUFA (ALA, stearidonic acid, eicosapentaenoic acid, and docosapentaenoic acid) content was significantly lower in soy-fed mice compared to dairy-fed mice, regardless of ALA content. Desaturase and elongase protein expression did not differ between groups, while gene expression is currently being analyzed. **Conclusions:** While mice fed soy protein have lower hepatic levels of n-3 PUFA compared to those fed dairy, this does not appear to be due to a reduction in desaturase or elongase protein content. Gene expression and microsomal analyses will help to clarify the underlying basis for these differences.

A6- Molecular mechanisms underlying the impact of monounsaturated fatty acids on cancer cell migration

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Background: Monounsaturated fatty acids, specifically oleate (OA), which are synthesized by stearoyl-coenzyme A desaturase-1 (SCD1), play a fundamental role in health and disease as an energy source and as bioactive signaling molecules. Studies have shown a positive correlation of high levels of SCD1 and MUFA with cancer emergence and metastasis. We recently showed that inhibition of SCD1 or treatment with OA are both associated with changes in cellular migration properties of MDA-MB-231 cells, including altered speed and direction of movement, as well as cell morphology. This effect occurred via the modulation of a specific intracellular signaling pathway involving phospholipase D2 (PLD2) and mTOR. However, the underlying molecular mechanisms remain poorly understood. **Methods**: To investigate the impact of OA on the formation of cell membrane ruffling and cell protrusions, we used Phalloidin-TRITC to visualize actin-rich cell protrusions and localization in fixed MDA-MB-231 cells by confocal microscopy. Anti-caveolin-1 and anti-PLD2 antibody were also used to analyze the colocalization of caveolin-1 and PLD2 with cell actin-rich structures by immunofluorescence. Then we quantified the dorsal ruffling and filipodia by Fiji Macro and Filoquant program. **Results**: Comparted with non-treated cells, OA treatment caused rapid and intense changes of MDA-MB-231 cell actin-rich leading edges. Quantification results show that there are significantly increasing cell membrane ruffling and filopodia in OA treatment cells. In addition, we showed that OA treatment caused recruitment of caveolin-1 around ruffling area and changed the localization of PLD2. **Conclusions**: OA is thought to have an effect on cell shape, inducing the formation

of cell membrane ruffling and cell protrusions. This morphology change will contribute to cancer cell migration and metastasis. We think that OA can reorganize lipid rafts in the membrane triggering recruitment of specific signaling complexes such as PLD2 and the mTOR downstream effectors.

A7- SCD1 deficiency modulates obesity-induced metabolic changes in perivascular adipose tissue

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Background: Excess lipid accumulation in perivascular adipose tissue (PVAT) in obesity induces PVAT dysfunction which is detrimental to the adjacent vasculature. Periaortic PVAT exhibits differential phenotype and function in regard to either thoracic (TPVAT) or abdominal (APVAT) localization. Stearoyl-CoA desaturase 1 (SCD1) is an enzyme that synthesizes monounsaturated fatty acids from their respective saturated precursors. Furthermore, SCD1 has been shown to regulate many physiological processes, such as lipolysis, β-oxidation, and inflammation, in various tissues. **Methods:** Wildtype (WT) and SCD1 knockout mice (SCD1-/-) were fed high-fat diet (HFD) for 8 or 16 weeks. Fatty acids composition of triglycerides was determined using GC-MS. Mitochondrial architecture was evaluated using TEM electron micrographs. Mitochondrial proteins were analyzed by Western blotting. Expression of macrophage-related genes was determined by RT-qPCR. **Results:** The level of 16:0 and 16:1 was decreased, whereas 18:0 was increased in TPVAT and APVAT in HFD fed SCD1-/- mice when compared to WT HFD fed controls. 18:1 content in both tissues was unaffected by SCD1 deficiency. Loss of SCD1 combined with HFD led to an increase in mitochondrial cristae density in TPVAT and to a decrease in APVAT compared with WT mice. In both PVAT depots in SCD1 deficient mice HFD feeding led to upregulation of all OXPHOS complexes. These alterations correlated with UCP1 and PGC1α protein levels. In TPVAT and APVAT loss of SCD1 reduced HFD-induced expression of M1 macrophage marker CD11c when compared to WT mice. **Conclusions:** Regional heterogeneity of PVAT reflects its differential response to obesity. Despite similar fatty acid composition pattern in TPVAT and APVAT, SCD1 deficiency drives opposing effects on mitochondrial morhphology and function as well as macrophage polarization.

A8- 12-HHT/BLT2 axis promotes cell membrane repair and protects epithelial cells from pore-forming toxin-induced cell death

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The plasma membrane is composed of lipids and proteins, and serves as a natural barrier to prevent external invasion. Bacterial pore-forming toxins (PFTs) such as pneumolysin (PLY), streptolysin O (SLO), and α-hemolysin (α-HL) bind to the outer leaflet of the plasma membrane and form pores leading to cell lysis. For self-healing, cells possess some self-repair systems that senses and fixes cell membrane impairment. Leukotriene B_4 (LTB_4) receptor type 2 (BLT2), a member of the GPCR, is a low-affinity receptor for LTB_4 and high-affinity receptor for 12(*S*)-hydroxyheptadeca-5*Z*,8*E*,10*E*-trienoic acid (12-HHT). We previously showed that BLT2 is expressed in intestinal epithelial cells and skin keratinocytes, and that 12-HHT/BLT2 signaling maintains skin and intestinal barrier function and accelerates skin wound healing. Recently, we found

that BLT2 is expressed in pulmonary epithelial cells and vascular endothelial cells in mouse lung, and plays protective roles in PLY-dependent acute lung injury through inhibition of cysteinyl leukotrienes receptor 1-induced vascular leakage. Here, we report that overexpressed BLT2 protects epithelia from cell death caused by PFTs. In contrast, primary cultured keratinocytes form BLT2-deficient mice or BLT2 overexpressing cells treated with BLT2 antagonist were more sensitive to PFTs than their controls cells. Moreover, the resistance of BLT2 to PFTs-induced cell injury was irrelevant to the cell surface binding ability to PFTs, but dependent on a rapid cell membrane repair which was triggered by an uncontrolled-influx of extracellular Ca^{2+} through PFTs-forming pores. Surprisingly, we found that BLT2 promotes the elimination of PFTs-punched membrane by release of extracellular vesicles (EVs) containing damaged membrane. 12-HHT/BLT2 axis stimulate the activation of Rac1 and reorganization of cytoskeleton, both of which leads to maintain membrane integrity and cell survival. Taken together, 12-HHT/BLT2 signaling plays a critical role in the self-repair systems against cell membrane damage induced by PFTs.

A9- Greywick is a mouse model for GATA4-associated metabolic subtype of polycystic ovary syndrome

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Background: Polycystic ovary syndrome (PCOS), a complex heterogenous disorder, is the leading cause of female infertility. It is characterized by reproductive, endocrine, and metabolic abnormalities. PCOS etiology remains poorly understood, although a central role is suspected for neural crest-derived gonadotropin-releasing hormone (GNRH) neurons located in the hypothalamus. **Results:** We generated a new transgenic mouse model for PCOS, named *Greywick* (*Gw*). *Gw* females recapitulate the PCOS phenotype (including subfertility and obesity). These mice bear a neural crest-specific *Gata4* promoter-driven *RFP* reporter, which we found to be inserted in the pseudogene *Gm10800*. Independent CRISPR-based knockout showed that *Gm1800* disruption is not responsible of the PCOS phenotype. Other data suggest that it is instead due to knockdown of endogenous *Gata4* through promoter competition. Accordingly, *Gata4* is downregulated in the hypothalamus of *Gw* females but not in ovaries. *Gw* mice might thus help to explain the reported association of a *GATA4* single nucleotide polymorphism with human PCOS. In the present study, we aimed to further characterize the reproductive, endocrine, and metabolic phenotypes of *Gw* female mice. **Methods/Results:** RT-qPCR analyses show that the reduced *Gata4* expression in the hypothalamus is associated with misexpression of genes linked to fertility and obesity. Using ELISA, we found that adult *Gw* females have increased serum levels of testosterone, LH and estrogen. Serum levels of leptin are also increased, explaining why

Gw females eat more. Moreover, these mice have impaired glucose and insulin tolerance, and immunofluorescence data show increased endoplasmic reticulum (ER) stress in ovarian follicles. Targeting these anomalies using metformin and TUDCA allows to rescue the otherwise decreased number and viability of *Gw* oocytes. **Conclusions:** These data suggest that the *Gw* mouse model of the metabolic PCOS subtype represents an original tool for the identification of the mechanisms involved in its pathogenesis and for the development of new therapeutic options.

A10- Air pollution induces inflammation, lipid reshaping and changes in lipid mediators in mice tissues.

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BACKGROUND: Adverse health effects of airborne particulate have been well documented in the last couple of decades. Airborne particulate, PM10 and Diesel exhaust particles (DEPs) exposure is a great concern and have been correlated to increased cardiovascular mortality, neurodegenerative diseases and morbidity in occupational and environmental settings. **AIM:** Air pollution increases pro- and antioxidant protein and activates inflammatory response in respiratory and cardiovascular systems, inducing ROS that damages membrane lipids. The membrane provides lipid mediators (LMs) modulating communication, inflammation, and resolution processes, suggesting the importance of understanding lipid modifications induced by environmental particulate of different origin. To this aim we analyzed the effects PM10 and DEP on lipid plasma membrane composition, lipid peroxidation, and LMs in different mice tissues. **METHODS:** Male BALB/c mice were instilled with acute and sub-acute protocols with 100 mg of PM, or 50 mg of DEP, or saline solution. Animal tissues were evaluated for markers of cytotoxicity, inflammation, oxidative stress, phospholipid, cholesterol, fatty acid composition and LC-MS quantification of LMs. A bioinformatic pipeline was settled to evaluate the functional enrichment of lipid sets belonging to the specific biological processes (Lipid Set Enrichment Analysis-LSEA). **RESULTS AND CONCLUSIONS**: In PM10 experiments, results demonstrated a direct involvement of PM10 in affecting lipid metabolism and oxidative stress in peripheral tissues that might be related to systemic air-pollution effects on human health. In DEP experiments, the lipidomic approach confirmed the role of LMs in DEP induced inflammation; DEP acute exposure significantly upregulates cortex eicosanoid metabolism sustaining the generation of systemic inflammation. LMs also correlate with inflammation and oxidative stress proteins, upregulated by acute and subacute DEP treatment in cortex tissues (HO-1, COX2 and iNOS). The lipidomic data, analyzed with a new bioinformatic approach, the LSEA, allows deep omic data analysis to obtain insight into the functional metabolic pathways related to their variations.

A11- Protectin DX analogues as a potential new class of antidiabetic drugs

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Background: Obesity is characterised by a chronic low-grade inflammation that either initiates or worsens metabolic complications such as type 2 diabetes (T2D). Protectin DX (PDX) is a docosahexaenoic acid metabolite member of the lipid mediator class known as specialized pro-resolving mediators (SPM). PDX has recently sparked interest for its ability to reduce metabolic inflammation and insulin resistance, and to mitigate end-stage-renal-disease in mouse models of T2D. Unfortunately, production of PDX at large scale for human treatment is an unresolved challenge that limit its pharmaceutical development. Consequently, our multidisciplinary team set out to design, produce and characterize more synthetically accessible and cost-effective PDX analogues with the aim of obtaining molecules that could be used to mimic PDX effects in humans. **Methods:** The development of an efficient chemical synthetic route leading to PDX analogues in 10-12 steps has been achieved allowing the preparation of various substituted PDX derivatives in a convergent fashion. On a molecular structural basis, the key E,Z,E configuration trienic system of PDX has been conserved in the synthesized analogues but the carboxylic chain moiety was changed with a variety of substituents. Analogues were screened for anti-inflammatory activity in LPS-induced J744 macrophages (iNOS inhibition) and glucose metabolism using 2-[^{3}H]DeoxyGlucose uptake in L6 and C2C12 myocytes. **Results:** More than 30 PDX analogues were successfully synthesized. Of those, 15 analogues significantly inhibited iNOS activity while 6 molecules increased basal and/or insulin-stimulated glucose uptake. Two analogues showed remarkable potency against iNOS as well as for their glucoregulative capacity as compared to PDX. **Conclusions:** The successful production of PDX analogues with potent biological effects is a promising advance towards the development of new SPM-based therapeutics to alleviate obesity-linked inflammation and T2D.

A12- Fish oil and a stearidonic acid-rich dietary oil alleviate joint inflammation in a mouse model of inflammatory arthritis

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Background: Marine n-3 polyunsaturated fatty acids (PUFA) are linked to beneficial health effects, including in rheumatoid arthritis (RA) patients. However, the precarious sustainability of fish oils (FO) suggests that renewable sources of dietary n-3 PUFA such as the stearidonic acid-rich *Buglossoides arvensis* (BA) seed oil should be investigated in RA. **Methods**: C57BL/6 mice consumed control diets based on human western diets (4.4kcal/g) providing 34% of energy from lipids, 50% from carbohydrates and 16% from protein. Treatment groups consumed control diets in which 3.3% or 10% of energy was from BA oil, or 3.3% was from FO for 3 weeks. RA was then induced (day 0 and 2) by

injections of K/BxN mouse serum. Clinical index, ankle thickness and mouse activity using Smart cages were then measured over 14 days. Liver phospholipids and triglycerides were separated by TLC and fatty acid methyl esters were prepared and measured by GC-FID. **Results**: No differences in weight gain were measured between groups. Animals consuming BA or FO diets showed significant increases ($p<0.05$, 1-way ANOVA) in liver n-3 PUFA compared to controls. All groups had elevated liver triglycerides at days 8 and 14 compared to day 4 ($p<0.05$). Changes in ankle thickness were smaller in the low dose BA and FO groups compared to the control group ($p<0.05$). No significant differences in clinical index were measured between groups. Travel (cm/hour) was greater in the low dose BA ($p=0.01$) and FO ($p=0.57$) groups compared to the control group. **Conclusions**: On a western diet background, low dose BA and FO alleviated joint inflammation and positively impacted on mobility in this RA model. This study suggests that a clinical trial investigating the impact of *Buglossoides arvensis* oil on RA severity may be warranted. Planned lipid mediator and cytokine analyses may reveal mechanisms of action of this intervention.

A13- Potential anti-inflammatory and neuroprotective effect of docosahexaenoic acid and bioactive lipid mediators in SARS-CoV-2 neuroinvasion

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Background: Coronavirus Disease 2019 or COVID-19 have infected until day more than 500 million confirmed cases including more than 6 million deaths, reported by World Health Organization WHO. COVID-19, originated by Severe Acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), cause respiratory problems in addition to neurological symptoms in some patients. **Results**: In the present paper, we discussed SARS-CoV-2 journey to the brain from neurological symptoms and Blood-Brain-Barrier disruption to potential anti-inflammatory and neuroprotective effect of omega-3 polyunsaturated fatty acid Docosahexaenoic Acid DHA and its active lipid mediators. In SARS-CoV-2 neuroinvasion, the disruption of Blood-Brain-Barrier BBB might occur. Brain Microvascular Endothelial Cells BMEC can be infected by SARS-CoV-2 due to the expression of Angiotensin-Converting Enzyme ACE2, receptor of SARS-CoV-2. This infection could lead to an inflammatory response known as Cytokine Storm with expression of high levels of cytokines and chemokines. In addition, a lipid remodeling in host cells was linked to SARS-CoV-2 infection hence proposing the potential of lipid metabolism regulation as a druggable target for coronaviruses infections. Indeed, DHA as well as its bioactive lipid mediators such as protectins (PD1/NPD1/PDX), maresins and resolvins have anti-inflammatory and neuroprotective effect. Several clinical trials are on their way in COVID-19 patients and in older people to estimate whether diet enhancement with DHA could defend patients against COVID-19. Further studies of the biosynthesis, lipid metabolism and target molecules would allow a better understanding of the physiological importance of DHA and bioactive lipid mediators in maintaining tissue homeostasis, and also as potential therapeutic targets for inflammation in case of viral infection.

A14- In-depth characterization of the tumor microenvironment MALDI-IMS focusing on immune infiltrates

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Background: Overall survival of patients with advanced stages of colon cancer (CC) has not improved despite the progress made in the field. The tumor microenvironment (TME) plays a crucial role in tumorigenesis, tumor expansion, and metastasis. Thus, a better understanding of the intricate network orchestrating TME heterogeneity may hold the key to identifying immunotherapy biomarkers and the development of new tools for patient stratification. Herein, we aim to characterize the membrane lipidome of tumor-infiltrating immune cells directly on CC tissue sections, which may convey critical information regarding tumor fate and its response to therapy. **Methods:** Peripheral blood was withdrawn from CC patients (n=12) and control subjects (n=8), while CC specimens were obtained during surgery. Circulating and infiltrated immune cells were isolated by *FACS* and plated on poly-L-lysine-coated glass slides. Sections of ~10 µm thickness from surgical biopsies were prepared in a cryostat. A consecutive section was stained for structure identification. Sections were scanned in negative- and positive-ion mode at 10 µm of spatial resolution using the orbitrap analyzer of an LTQ-Orbitrap XL (ThermoFisher). The spectra were analyzed using the software MSIAnalyst. **Results:** The lipidomic analysis revealed a distinctive lipid species pattern for each of the seven cell types analyzed. Furthermore, the comparison between control subjects and CC patients revealed a significant impact on arachidonic acid-containing PE and PE-plasmalogen species. Finally, IMS allowed the identification of infiltrated immune cells within tissue sections due to their differential content in PI38:4. **Conclusions**: The high sensitivity and reproducibility of the developed methodology provide a unique tool to analyze the lipidome of minor subsets of immune cells. In circulating immune cells, the impact of CC their lipidome turned out to be highly cell type-dependent. Further, these profiles can be identified within the MALDI-IMS generated images, enabling an in-depth approach for the TME characterization.

A15- Close friends from far away – role of platelet-derived lipid mediators in beta cell function

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Background: Systemic glucose homeostasis is tightly regulated in order to ensure normal body function and is maintained by specific hormones, like insulin and glucagon. In response to elevated blood glucose pancreatic beta cells release insulin, which in turn stimulates glucose uptake in peripheral tissues. Besides stimulation through glucose, insulin secretion can be also regulated by other nutrients and signalling molecules. Recently, we showed that functional platelets are indispensable for maintenance of glucose homeostasis. Genetic or pharmacological interference with major platelet adhesion or activation mechanisms consistently resulted in a reduction of insulin secretion and glucose intolerance. However, the mechanism mediating this phenomenon remained unclear. Thus, the aim of the study was to unravel the role of platelets action in regulation of insulin secretion. **Methods:** To test directly if platelets

stimulate insulin secretion, a co-culture experiment of platelets and the rat pancreatic beta cell line, INS1 was performed. To check if the effect of platelets on insulin secretion from beta cells is mediated by a secreted factor, supernatants from activated human and mouse platelets were generated. Both platelet supernatants and platelet supernatant-treated beta cells were then further analysed using molecular biology and biochemical techniques. **Results:** The presence of the platelets in the culture markedly increased insulin secretion from INS1 cells. Moreover, stimulation of INS1 cells with human platelet supernatant resulted in a dose-dependent increase in insulin secretion. Stimulation of INS1 cells with platelets supernatant promoted insulin secretion in the presence of low and high glucose. Lipidomic analysis of platelet supernatant revealed presence of various lipid molecules, including 20-hydroxyeicosatetraenoic acid (20-HETE) known for insulin release promotion. At the same time, treatment with lipid-depleted platelet supernatant did not affect insulin release from INS1 cells. **Conclusions:** Taken together, obtained data indicates that platelet-derived 20-HETE directly stimulates insulin secretion from pancreatic beta cells.

A16- Apolipoprotein D overexpression modulates inflammation in mice fed a high fat high sugar diet.

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Background: The lipocalin Apolipoprotein D (ApoD) is a multi-functional protein mainly express in the central nervous system (CNS), where it has been associated with a reduction of inflammation and oxidative stress. We recently demonstrated that ApoD can exit the central nervous system and accumulate in peripheral organs. Transgenic mice overexpressing the human ApoD in the CNS (Thy1/HApoD) develop a hepatic steatosis without inflammation. In humans, ApoD's level in the round ligament of obese women has been associated with a lower inflammation level and a better metabolic profile. Using Thy1/HApoD mice, we evaluate the effect of a high fat high sugar (HFHS) diet on the development of systemic inflammation **Methods:** Male and female Thy1/HApoD and Wild-Type (WT) mice were fed with a (HFHS) diet for 12 weeks. Mouse weight was measured weekly. Insulin and glucose tolerance were assessed at week 1/2, 5/6, and 11/12. Mouse were also subjected to Open field test (OFT) and Forced swim test (FST) at week 11 and were put in metabolic cages for 48h at week 12. Inflammation markers (IL-6, TNF-a, IL-1b, NF-kB, IL-10) were quantified by RT-qPCR and Western Blot in liver, kidneys, brain, heart, muscles, plasma, and omental and subcutaneous adipose tissues. **Results**: Preliminary results shows no statistical difference between Thy1/HApoD and WT mice in terms of insulin tolerance and glucose intolerance. Although no statistically significant, female Thy1/HApoD tend to swim more during the FST, suggesting an effect of ApoD on depression, which is associated with inflammation in obesity. Thy1/HApoD mice also tend to eat less, but do not weight more than WT mice. RT-qPCR revealed a lower level of multiple inflammation markers, including TNF-a, IL-1b and IL-6 in the liver and brain of the Thy1/HApoD mice. **Conclusions:** Our preliminary results suggest that ApoD may have an impact in modulation of chronic inflammation observed in obesity.

A17- Plasma lipidomic profiling reveals metabolic adaptations to pregnancy and signatures of cardiometabolic risk: a preconception and longitudinal cohort study

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Background: Metabolic adaptations are essential to meet the physiological demands of pregnancy and any aberration may result in adverse outcomes for both mother and offspring. Lipids in circulation are critical for maternal-fetal metabolism and potential markers of cardiometabolic health. However, there is a lack of population-level studies to define the longitudinal changes to the baseline lipidome starting at preconception through pregnancy to postpartum. Similarly, there is a need for in-depth understanding of the association of circulating lipids with body weight changes and other cardiometabolic risk factors in a longitudinal manner in childbearing women. **Methods:** High coverage plasma lipidomics was performed on plasma samples collected at preconception, 26-28 weeks' pregnancy and three months postpartum (N=1595). Longitudinal changes in plasma lipids were studied from preconception into pregnancy and postpartum in relation to the body weight changes. Associations of pre-pregnancy body mass index (BMI), measures of glucose homeostasis and insulin resistance with lipidomic profiles across three physiological states were investigated in order to identify their influences on circulating lipid levels. **Results:** Around 56% of the lipids increased and 24% decreased in pregnancy before returning to the preconception levels at postpartum. We observed significant association of body weight changes with lipid changes across different physiological states, and low circulating levels of phospholipids and sphingomyelins in pregnant mothers with pre-pregnancy obesity. Analysis of

longitudinal measures of glucose homeostasis and insulin resistance identified early lipid signatures of gestational diabetes mellitus. **Conclusions:** This study describes the longitudinal landscape of the circulating lipidome from preconception to postpartum in childbearing women and provides novel insights into the retention and reversion of pregnancy-induced metabolic phenotype. We identified lipid signatures linked with cardiometabolic risk factors such as body weight change, pre-pregnancy obesity, and glucose homeostasis and insulin resistance with potential implications both in pregnancy and postpartum life.

A18- Elucidation of a bacteria-lipid metabolic network linking the microbiota and tissue homeostasis

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Background: The abnormal gut microbiota observed with ulcerative colitis (UC) is considered to be a contributing factor to the disruption of intestinal homeostasis. The gut microbiota is known to produce unique lipids and interact with host tissues and bacteria, suggesting that it is involved in tissue homeostasis. However, the contribution of bacterial lipids to the intestinal repair process is unclear. In this study, we aimed to identify the bacterial lipids that contribute to intestinal homeostasis by using advanced untargeted lipidomics technology. **Methods and Results:** Comprehensive fecal lipidomics of colitis resolution phase model mice was performed in liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS). The results showed that 258 lipids were identified which increased during the early stages of tissue repair. Among these, specific fatty acyls were especially present in high concentrations. These are dramatically reduced with antibiotics cocktail administration, suggesting that it is produced by microbiota. Producing bacteria and enzymes were identified using human representative gut bacteria. Indeed, Specific fatty acyls and their producers were significantly decreased in fecal samples of UC patients compared to healthy individuals (Ethics application: H30-33(3)). Based on the disrupted microbiota in UC patients, we considered that these lipids may be shaping the gut microbiota. Accordingly, specific fatty acyls showed bacteriostatic activity against pathogens that increase in UC patients. **Conclusions:** Our findings demonstrate that a specific lipid metabolic pathway in gut microbiota inhibits the growth of pathogenic bacteria and could contribute to host homeostasis.

A19- Odd-chain fatty acid accumulation in white adipose tissue of propionic acidemia: protective or toxic?

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Background. Propionic acidemia (PA) is a severe infantile-onset autosomal recessive inborn error caused by propionyl-CoA carboxylase (PCC) deficiency. We studied PA transgenic (Pat) mice, that lack endogenous PCCA but express a hypoactive human PCCA cDNA, permitting survival. Like PA patients, Pat mice have often-fatal metabolic decompensations and characteristic plasma and urine metabolites. We hypothesize that odd-chain number long-chain fatty acids (OLCFAs) will be synthesized in Pat mice from propionyl-CoA, and may affect pathophysiology in PA. **Methods.** Liver acyl-CoA analysis (Zhao, *Mol Genet Metab*, 2022, 135:47) and lipidomics (Herzog, *J Lipid Res*, 2016. 57:1447) of perigonadal white adipose tissue (WAT) were as described. In six 10-week-old Pat males and six controls, not acutely ill, sacrificed at 4-hour fasting, blood and tissues were collected for lipidomics. **Results.** Liver propionyl-CoA levels were 47.9±8.4 versus 3.3±0.2 nmol/g in Pat and control mice ($p<0.001$), respectively. WAT lipidomics showed higher OLCFAs in Pat mice versus controls: C15 (7.6±0.7µmol/g vs 0.9±0.1µmol/g, $p<0.001$), C17 (4.0±0.5µmol/g vs 0.9±0.1µmol/g, $p<0.001$) and C17:1 (7.7±0.8µmol/g vs 1.0±0.1µmol/g, $p<0.001$). Together, C15, C17 and C17:1 accounted for 4.7% of Pat WAT FAs versus 0.6% in controls ($p<0.001$). **Conclusions/Discussion.** In WAT, triglycerides containing OLCFAs presumably derive from FA synthesis, principally in liver, starting from propionyl-CoA rather than acetyl-CoA. In Pat liver, propionyl-CoA exceeds acetyl-CoA level, but OLCFAs comprise only 4.7% of Pat WAT FAs, suggesting inefficient FA synthesis from propionyl-CoA. Physiologically, in the well-nourished state, WAT OLCFAs provide a detoxification mechanism for hepatocyte propionyl-CoA, resulting in OLCFA synthesis, export and storage in WAT. In contrast, during adipocyte lipolysis and FA oxidation in extra-adipose tissues, OLCFAs will produce propionyl-CoA in FA-oxidizing tissues. This could cause toxicity in these tissues during fasting and infectious illnesses, as seen during metabolic decompensations of PA patients. WAT OLCFA accumulation may therefore influence the course of PA.

A20- Mitochondria associated membranes – lipid biosynthesis and transferring hub as a platform for redox related proteins.

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Background: Cellular membranes interacting with the outer mitochondrial membrane, namely mitochondria associated membranes (MAM), play a special role in the network of subcellular communication. Contact sites between the ER and mitochondria have been discovered as a platform for phospholipids biosynthesis and transfer, enriched with enzymes essential for this activity such as: phosphatidylethanolamine-N-methyltransferase, phosphatidylserine synthase-1 and -2. Currently, MAM role in the regulation of metabolism, calcium homeostasis, redox balance, autophagy and

apoptosis is studied. MAM creates a niche endowed with a set of proteins present permanently, or temporarily under certain conditions, e.g. oxidative stress. We are focused on the oxidative stress related protein - p66Shc and its interactions with other proteins in the MAM fraction. It has been demonstrated that these interactions are important for the cell's response to oxidative stress and apoptosis initiation. **Methods:** p66Shc localization in MAM fraction, obtained by differential centrifugation from HepG2 cell line was examined with immunochemical methods. Oxidative stress and metabolic functions were evaluated by the multiplate reader measurements with the use of fluorescent probes. p66Shc interacting proteins were investigated by co-immunoprecipitation followed by mass spectrometry analysis. **Results:** We confirmed that p66Shc translocates to the crude mitochondrial fraction under oxidative stress condition in human hepatocarcinoma cells. p66Shc localization in crude mitochondrial fractions, which contains ER-mitochondria contact sites, is associated with an increased activation of pro-oxidant p66Shc pathway. We observe differences in the profile of p66Shc potentially interacting proteins between the conditions studied. **Conclusions:** p66Shc may interact with other proteins in MAM, supporting that MAM are crucial also for other processes than lipid biosynthesis and transfer. The potentially p66Shc-interacting proteins have various functions and are involved in multiple pathways including control of cell fate and redox homeostasis. The knowledge of p66Shc interacting proteins could help to indicate the targets in the future therapeutic strategies.

A21- A synthetic diet supplemented with vitamins B9, 12 and nicotinamide riboside reverses the circulating lipidomics' disturbances and improves cardiac function in mouse female exhibiting heart failure.

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Background: Heart failure (HF) remains a major global health problem for which there is a need to find complementary or alternative therapeutic strategies. HF pathogenesis involves disturbances in cardiac lipid metabolism. The **overall objective** of our study is to evaluate the curative benefit of a synthetic diet enriched with a combination of nicotinamide riboside (B3), B9 and B12 - or BVit - in a mouse model of HF based on the **hypothesis** that this enriched diet is beneficial for cardiac function through an improvement of lipid metabolism. **Methods:** Pressure overload was induced by transverse aortic constriction (TAC) in 8-week-old male (M) and female (F) C57Bl6/N mice. Four weeks post-TAC mice were randomized to a diet ± BVit. Mice survival was evaluated and cardiac function was assessed by echocardiography every 4 weeks. **Results:** We show no functional or survival benefit in males. In contrast, mortality in females was reduced from 12 weeks of treatment and we observed improved cardiac ejection fraction (+20%, $p<0.05$) and a reduction in cardiac hypertrophy (-13%, $p<0.05$). Using a mass spectrometry-based untargeted lipidomics approach, in F-TAC, we revealed a decrease in several triglycerides (TGs; ~45%; $p<0.05$) while 29 choline-type glycerophospholipids (from ~30 to 250%; $p<0.05$) were increased. Conversely, in M-TAC,

we mostly identified increased TGs (from ~35 to 210%; p<0.05). Finally, in response to BVit, the lipid profile in females was normalized while we observed an exacerbation in males. **Conclusions:** Our study suggests a sexual dimorphism in the response to BVit treatment in HF. Indeed, the benefit of BVit treatment is only shown in females with a delay in the mortality rate associated with improved cardiac function and normalisation of lipid disturbances. To explore and understand the mechanisms underlying this sexual dimorphism, the lipid profile hypothesis appears as a relevant avenue to explore in further work.

A22- The functional benefit of pharmacological inhibition of the epigenetic enzyme EZH2 is associated with the prevention of lipid metabolism disturbances in a myocardial infarction mouse model

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Background: EZH2 is an epigenetic enzyme repressing a wide variety of gene expression including genes related to metabolism. This study aims evaluating the benefit of EZH2 inhibition in heart failure with reduced ejection fraction (HFrEF) induced by myocardial infarction (MI). We hypothesize that EZH2 modulates fatty acid (FA) cardiac metabolism and its inhibition minimizes lipid metabolism disruptions and improves cardiac function. **Methods:** MI was induced by ligation of the left anterior descending coronary artery in female mice and treated for 7 days with vehicle or GSK-343 (EZH2 inhibitor) and compared to sham mice. MI induced a reduction of EF from 46% (sham) to 18% (MI) while GSK-343 prevents this dysfunction (EF~38%). Cardiac metabolic gene expressions were quantified using qPCR. The circulating lipidome was assessed using a mass spectrometry-based untargeted lipidomics. **Results:** The measured transcripts markers of FA metabolism, comprising markers of FA transporters (Cd36, Cpt2), FA oxidation (Vlcad) and their regulators (Pgc1-α, Ppar-α) were significantly decreased in MI. In contrast, the GSK-343 treatment partially and significantly restore their expression suggesting that GSK-343 limits the perturbations of FA metabolism. Because disruption in FA utilization affect the lipidome, we used an untargeted lipidomics approach to evaluate the global impact of MI ±GSK-343. In MI, we showed, among the most discriminant dysregulated lipids, an accumulation of 18 individual triglycerides (1.24 to 2.43-fold; p<0.05) and a decrease of 32 individual choline glycerophospholipids (PC; 0.55 to 0.81-fold, p<0.05). In addition, we found that these perturbations were normalized by GSK-343. Finally, while some of these lipids positively correlated with EF, such as PC40:6 (R=0.84, p=0.004), the treatment with GSK-343 abolish most of these correlations, here illustrated with the PC40:6 (R=-0.13, p=0.71). **Conclusion:** Our study suggests that the EZH2 inhibition in HFrEF induced by MI improves cardiac function, a process associated with the normalization of lipid metabolism.

A23- A simple analytical approach to distinguish plasmanyl from plasmenyl glycerophospholipids using Liquid Chromatography-Mass Spectrometry.

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Background: With the great complexity of lipid biology comprising >43 000 lipids until now, untargeted lipidomic offers a wide potential for biomarkers discovery in various disease. One major bottleneck, however, is the precise identification of lipid structures, a challenge particularly true for specific subclasses of glycerophospholipids (GPL): the ether lipids. From now, it has been challenging to distinguish plasmanyl *vs* plasmenyl GPL due to their similar structure, the main difference being the linkage in sn1 position: ether *vs* vinyl-ether, respectively. Our main goal is to differentiate both forms given the increasing identification of ether lipids as markers for various diseases. **Methods:** Lipids were extracted from human plasma sample (n=3, in duplicate) according to *Forest et al, 2018.* For half of the duplicates, an additional acid-catalyzed hydrolysis step was applied before being analyzed using liquid chromatography-quadrupole time-of-flight (LC-QTOF) with a long-gradient chromatography which promoting the separation of GPL isomers. The plasmanyl/plasmenyl distinction relies on their differences in acid sensitivity. **Results**: We first analyzed plasmanyl and plasmenyl synthetic standards following the addition, or not, of the acid-catalyzed hydrolysis step. While no difference of signal intensity was observed for plasmanyl, the acidification step induced a ~300-fold decrease in the plasmenyl signal intensity. We replicated this experiment in 3 human plasma and over the ~4000 endogenous MS signals, 47 plasmanyl and 26 plasmenyl were identified according to the following signal intensities ratio: acid/non acid-treated samples. From this list, and using an in-house bioinformatic tool, we were able to align and annotate both ether lipid forms in three other biological matrices: plasma and hearts from mice as well as ether lipids deficient-cells. **Conclusions**: This method is a simple way to easily distinguish plasmanyl (O-alkyl) from plasmenyl (P-alkyl) GPL in an untargeted lipidomic dataset that may help to enhance our comprehension of the lipid biology.

A24- Chemical Composition and Antimicrobial Activity of the Essential Oils of Two Aromatic Plants Cultivated in Morocco (*Cinnamomum cassia* and *Origanum compactum*)

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Background: The present study aims to evaluate the antibacterial properties of natural products according to a pharmacodynamic approach in order to propose them as alternatives to synthetic products. **Methods:** Two essential oils (*Cinnamomum cassia* and *Origanum compactum*) were the subject of the chemical and biological study. First, we evaluated the sensitivity of the strains of avian *Salmonella* to the main antibiotics used and then to the chromatographic analysis of the composition of the two essential oils (EO); finally, we proceeded to the in vitro evaluation of the antibacterial activities of these EO (alone and in combination with antibiotics). **Results:** The results obtained showed that carvacrol (35.2%), followed by c-terpinene (20.1%), was the main constituent of the essential oil of *O. compactum* while cinnamaldehyde (69.1%) represents the major component of the essential oil of *C. cassia*. The antibioresistance profile of the *Salmonella* tested showed resistance to ampicillin (35%) and

oxytetracycline (41.3%). Active products extracted from the essential oils studied showed antibacterial activity against Salmonella strains. *C. cassia* products were shown to be more active for *Salmonella enteritidis* (average inhibition diameter: 16.3mm) and for *Salmonella gallinarum* (average inhibition diameter: 27.7mm). The best synergistic activity with antibiotics has been obtained with the essential oil of *C. cassia* and its active product cinnamaldehyde. The minimum inhibitory concentration (MIC) of cinnamaldehyde is the lowest (0.05%). **Conclusions:** The results prove the presence of an antibacterial activity and a synergistic effect of two essential oils studied with the main antibiotics.

A25- DEUTERIUM LABELING OF ERYTHROCYTE MEMBRANES TO STUDY THE ACTION MECHANISM OF ANTIMICROBIAL PEPTIDES

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Cationic antimicrobial peptides (AMPs) act by perforating the bacterial cell membrane through specific interactions with their negatively-charged phospholipids. They are thus considered as promising alternatives to broad-spectrum antibiotics to address the worldwide problem of bacterial resistance. To reach the market, AMPs should not act against human cells. It is thus of great importance to verify and understand their action on mammalian cells. In this context, the objective of our work was to study the interaction of two cationic AMPs, aurein 1.2 and caerin 1.1, with red blood cells (RBCs) membranes *in situ* by solid-state nuclear magnetic resonance (SS-NMR). We have developed a protocol to label RBC ghosts (hemoglobin free) membranes using deuterated (^{2}H) fatty acids (FAs). The incorporation of FAs and the integrity of the phospholipid bilayer were confirmed by SS-NMR spectroscopy and fluorescence confocal microscopy. The phospholipids and FA chains profile of the labeled ghost membranes were characterized using by ^{31}P solution NMR and GCMS.
The perturbation of the ghost membranes by the AMPs was assessed from the ^{2}H SS-NMR spectra combined to a complementary analysis of ^{31}P SS-NMR spectra as a function of peptide concentration. Our results for aurein 1.2 are compatible with a membrane perturbation through a carpet mechanism, while caerin 1.1 would form pores in the membrane. Those mechanisms are similar to those taking place with bacterial membranes, although both membranes have a different surface composition. This work highlights the importance of hydrophobic effects in determining the mode of membrane perturbation, and the need for *in situ* molecular-level membrane-interaction analysis to guide peptide engineering en route to clinical applications.

A26-Secreted phospholipase A2-IIA expression alters the fecal lipidome and promotes arthritis

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BACKGROUND: Secreted phospholipase A2-IIA (sPLA2-IIA) is a small (14kDa) protein that hydrolyzes membrane phospholipids in the extracellular space, thereby releasing free fatty acids and lysophospholipids. Elevated levels of sPLA2-IIA are found in the blood and synovial fluid of rheumatoid arthritis (RA) patients. A role for sPLA2-IIA during arthritis was suggested, which is supported by the enhanced arthritis measured in transgenic mice overexpressing human sPLA2-IIA (sPLA2-IIATGN). The mechanisms by which sPLA2-IIA promotes arthritis are poorly understood. Despite the poor affinity of sPLA2-IIA toward mammalian cells, prior studies mainly focused on endogenous substrates for the enzyme. On the other hand, sPLA2-IIA has a high affinity toward bacterial membranes and is highly expressed in the intestine, where it was suggested to impact the intestinal microbiota. HYPOTHESIS: We hypothesize that sPLA2-IIA promotes arthritis severity through its activity on the intestinal microbiota and the release of lipid mediators. METHODS AND RESULTS: The contribution of the intestinal flora to the enhanced arthritis severity found in sPLA2-IIATGN mice was investigated. Broad spectrum antibiotics were administered to mice via oral gavage to deplete their intestinal microbiota before arthritogenic K/B×N serum was injected to induce arthritis. Interestingly, the enhanced susceptibility of sPLA2-IIATGN mice to inflammatory arthritis was abolished upon depletion of their microbiota. This suggests that the enzyme promotes arthritis through its activity on the microbiota. To determine whether an alteration of the intestinal flora by sPLA2-IIA could be promoting this enhanced inflammatory process, a fecal microbiota transplantation was performed. The microbiota of mice was depleted using antibiotics, then reconstituted by gavage of resuspended feces from mice expressing or not the enzyme. The transplantation of the sPLA2-IIATGN flora failed to promote arthritis in WT mice, suggesting that sPLA2-IIA does not promote arthritis through alteration of the microbiota composition. sPLA2-IIA activity on bacterial membranes may release bioactive lipid metabolites. We thus used mass spectrometry to perform lipidomic analysis of stool samples from sPLA2-IIATGN and WT mice. We observed profound alterations in the fecal lipidome of sPLA2-IIATGN mice compared to control mice, suggesting that sPLA2-IIA could promote arthritis through the release of lipid metabolites via its activity on bacterial membranes. CONCLUSION: Our findings reveal that sPLA2-IIA may contribute to inflammatory arthritis through functional interactions with the microbiota and associated lipidome.

Interfering with those interactions could lead to the discovery of new original targets for the treatment of RA.

Session B

B1- Regulation of SREBP1c transcriptional activity by oleate

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BACKGROUND: The transcription factor sterol regulatory element-binding protein 1c (SREBP1c) is the main regulator of lipid homeostasis. It is regulated by various nutritional and hormonal stimuli. However, the molecular mechanisms underlying these adaptive responses remain to be elucidated. Preliminary results have shown that a decrease in intracellular oleate concentration leads to a decrease in SREBP1c transcriptional activity and that SREBP1c is labeled when cells are incubated with radiolabeled oleate. These results suggest that SREBP1c may be acylated by oleate, or by one of its metabolites. Acylation, a post-translational modification of a protein by a lipid, increases the hydrophobic character of a protein allowing to regulate its cellular localization, its stability, and its interactions with other proteins. OBJECTIVES: To characterize the molecular mechanisms involved in the regulation of SREBP1c transcriptional activity by oleate. **METHODS AND RESULTS:** Using bioinformatics analysis, we identified a cysteine on SREBP1c that could be acylated. Mutation of this cysteine by an alanine completely prevents SREBP1c proteolytic cleavage and reduce the mRNA level of his target gene Stearoyl-CoA desaturase-1 (SCD1) and Fatty acid synthase (FAS) in cultured hepatocarcinoma cells. Furthermore, using a mass shift technique that exploits the cysteine-specific chemical property, it was shown that mature SREBP1c was present in three different acylation states at the cysteine residues in mouse liver, namely: no acylation, 1 or 2 acylations. Acylated forms of SREBP1c are more present in the livers of mice fed an obesogenic, high oleate diet as opposed to a non-obesogenic, low-fat diet. **CONCLUSION:** The characterization of a new mechanism of regulation of SREBP1c transcriptional activity would constitute a major advance in the field of lipid metabolism and in the understanding of several diseases associated with metabolic disorders.

B2- Suppression of Adipocyte ABHD6 Promotes Healthy Expansion of Adipose Tissue in Obesity

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Background: The expansion of white adipose tissue (WAT) in response to positive energy balance greatly impacts obesity-related metabolic abnormalities. Pathologic WAT remodeling is characterized by reduced adipocyte differentiation capacity, chronic inflammation, ectopic fat accumulation and insulin resistance. Pan-deletion of the

monoacylglycerol lipase alpha/beta hydrolase domain-6 (ABHD6) demonstrated the therapeutic potential of ABHD6 inhibitors against obesity and type-2-diabetes. However, the specific role of adipocyte ABHD6 in diet-induced adipogenesis remains unexplored. **Methods & Results:** We now present evidence employing pharmacological and genetic approaches that adipocyte ABHD6 suppression maintains AT metabolic health during high fat diet (HFD)-induced obesity. ABHD6 expression increases in mouse adipocytes during differentiation, and its expression in the visceral fat of patients with obesity correlates with the adiposity. We generated adipocyte-specific ABHD6-knockout (AT-ABHD6-KO) mice and studied them in the context of diet-induced obesity. Interestingly, HFD fed AT-ABHD6-KO mice displayed metabolically healthy-obese characteristics, including better insulin sensitivity, lowered hepatic and plasma triglyceride levels, and curtailed inflammation. In addition, WAT from ABHD6-deficient mice consisted of smaller lipid droplets, decreased number of crown-like structures, and enhanced stimulated lipolysis and fat oxidation. Finally, using loss and gain of function experiments, we have identified ABHD6 as a negative modulator of *in vitro* adipocyte differentiation. Notably, suppression of ABHD6 in pre-adipocytes led to declined pre-adipocyte proliferation, enhanced adipocyte differentiation capacity, and formation of metabolically active fat cells with small lipid droplets. **Conclusions:** The results suggest that ABHD6 promotes pathologic remodeling of WAT in obesity. Thus, ABHD6 deletion or inhibition enhances AT capacity to recruit new fat cells through differentiation of pre-adipocytes, and reduces lipid spill-over in other organs and ameliorates inflammation. These findings provide an insight into the pathways that underlie healthy WAT expansion, and suggest ABHD6 as a therapeutic target for inflammation and obesity-related complications.

B3- Angptl8 mediated regulation of adipogenic differentiation and thermogenic programming

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Background: ANGPTL8, expressed mainly in the liver and adipocytes, is known to regulate lipoprotein lipase (LPL) and lipid metabolism. Hepatic ANGPTL8 and ANGPTL3 form a complex that is inhibitory to LPL. However, if ANGPTL8 has any specific intracellular role in hepatocytes or adipocytes is not known. **Methods:** We suppressed ANGPTL8 expression with siRNA in mouse primary subcutaneous (SC) pre-adipocytes and differentiated them for 7 days. Oil-Red-O staining and glycerol and fatty-acid (NEFA) release were measured. To understand the intracellular role of ANGPTL8 during adipocyte differentiation, we conducted RNAseq analysis on Angptl8 siRNA or control siRNA transfected SC pre-adipocytes at 0, 2, 4 and 7 days post-differentiation. We also examined the role of adipose ANGPTL8 in cold-induced-thermogenesis, employing chow-fed adipocyte specific ANGPTL8 Knockout (AT-A8-KO) mice. Body-weight, fat-mass and food-intake were measured. Cold exposure of AT-A8-KO and control mice were kept at 6°C in metabolic cages for 24h, to study energy expenditure and various metabolic parameters. **Results:** ANGPTL8 knockdown in SC pre-adipocytes reduced

adipocyte differentiation, glycerol and NEFA release at day 7 post-differentiation. RNAseq-Gene set enrichment analysis indicated ANGPTL8 silencing impeded adipogenic, oxidative phosphorylation pathways and also some major genes of insulin signaling pathway including IRS1, IRS2, PPARG, MTOR, early during differentiation, indicating ANGPTL8 may play a role in the regulation of insulin sensitivity. AT-A8-KO mice showed lower body-weight gain and fat-mass compared to controls. Cold-exposed AT-A8-KO mice displayed elevated body-temperature and energy-expenditure compared to control mice, indicating that ANGPTL8 in adipose tissue negatively modulates cold induced thermogenesis. **Conclusions:** ANGPTL8 plays an important role during adipocyte differentiation, probably by modulating insulin signaling and mitochondrial respiration. Moreover, adipocyte specific deletion of ANGPTL8 in mice led to enhanced cold induced thermogenesis. Results suggest that therapeutic targeting of adipose ANGPTL8 is likely beneficial in preventing obesity and promoting energy expenditure.

B4- Phosphorylation regulates the Nem1-Spo7/Pah1 phosphatase cascade in yeast lipid synthesis

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The conserved Pah1 phosphatidate (PA) phosphatase in *Saccharomyces cerevisiae* catalyzes the dephosphorylation of PA to produce diacylglycerol. Through this reaction, the enzyme regulates the relative synthesis of triacylglycerol and membrane phospholipids. Pah1 is subject to multiple phosphorylations by diverse protein kinases and dephosphorylated by the membrane-associated Nem1-Spo7 protein phosphatase. Collectively, phosphorylation attenuates function by sequestering Pah1 in the cytosol and by inhibiting the PA phosphatase activity. Increase in Pah1 function occurs through its recruitment and dephosphorylation by Nem1-Spo7, which permits PA association and stimulation of PA phosphatase activity at the membrane. There are still many phosphorylation sites in Pah1 for which the relevant protein kinases have yet to be identified. In this talk, recent progress will be discussed on advancing the understanding of Pah1 phosphorylation by identifying Rim11, the yeast homolog of mammalian glycogen synthase kinase-3b, as a protein kinase that phosphorylates and regulates the enzyme. Through defined biochemical studies, we have shown that Pah1 is a *bona fide* substrate for Rim11; the protein kinase catalyzed the incorporation of the g-phosphate of ATP into Pah1, followed zero order kinetics, and was dependent on the concentrations of Pah1 and ATP. A major consequence of phosphorylation, which primarily occurred at Thr-163, Thr-164, and Ser-602, was the inhibition of PA phosphatase activity. Prephosphorylation of Pah1 by the Pho85-Pho80 protein kinase stimulated subsequent phosphorylation by Rim11, and the Rim11-phosphorylated form of Pah1 was dephosphorylated by Nem1-Spo7. A mutagenic *in vivo* analysis of the major sites of phosphorylation revealed that Rim11 contributes to the Nem1-Spo7-mediated regulation of Pah1 for TAG synthesis. Supported by NIH grant GM136128.

B5- The impact of intestinal monoglyceride lipase on whole body energy homeostasis

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Background: Lipases are essential in the uptake of dietary lipids, their distribution within the body, their mobilization, and remodeling for further metabolization. Monoglyceride lipase (MGL) is a ubiquitously expressed enzyme that catalyzes the hydrolysis of monoglycerides (MGs) derived from different intra- and extracellular sources. These MGs are not only intermediate products of lipid degradation but are also signaling molecules (e.g the endocannabinoid 2-AG) or serve as precursors for the synthesis thereof. We and others showed previously that global MGL-deficiency in mice protects from high-fat diet (HFD) induced obesity and insulin resistance. However, the exact mechanisms by which MGL affects whole body lipid and glucose homeostasis remain elusive. Therefore, we aimed to characterize the role of MGL in intestinal MG metabolism. **Methods:** We generated and characterized mice lacking MGL specifically in the intestinal epithelium by crossing MGL-floxed mice with mice expressing Cre-recombinase under the control of a Villin-promotor (iMko). We determined MGL expression, quantified MG levels, and evaluated MG hydrolase activities in the intestine. Moreover, we compared the phenotypes of mice fed normal chow diet or HFD. **Results:** MGL expression and consequently MG hydrolase activities are reduced in iMko mice throughout the intestine leading to the accumulation of MGs including the endocannabinoid 2-AG. iMko mice have a similar phenotype as control mice when fed a normal chow diet, and we observed minor differences when animals were fed a HFD. **Conclusions:** Together our data show that MGL is expressed in the intestinal epithelium affecting intestinal MG metabolism. However, its deletion has only minor impact on whole body energy homeostasis, in contrast to the phenotype observed in whole body MGL-deficient mice.

B6- New insights into the role of mitochondria and peroxisomes in the development of Non-Alcoholic Fatty Liver Disease

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Background: The development of Non-Alcoholic Fatty Liver (NAFL), followed by a possible progression into a more severe NAFLD stage depends on the capacity of hepatocytes and mitochondria to adapt to nutrients overload. NAFL is characterized by the development of steatosis, which can ultimately compromise liver function. Disease progression has implicated multiple mechanisms, chief of which is oxidative stress and mitochondrial dysfunction. However, the sequence of events underlying mitochondrial impairment is still poorly clarified. **Method:** In this work, male C57BL/6J mice were fed with a high-fat plus high-sucrose (HFHS) diet for 16, 20, 22, and 24 weeks. **Results:** HFHS diet caused simple steatosis with phospholipid membrane remodelling along the time of feeding however with no signs of inflammation up to 24th week of feeding. A progressive loss of mitochondrial respiration along HFHS feeding was identified, accompanied by higher susceptibility to mitochondrial permeability transition pore opening. Importantly, our findings prove that mitochondrial alterations and subsequent

impairment are independent of an excessive mitochondrial reactive oxygen species (ROS) generation, which was found to be progressively diminished along with disease progression. Instead, increased peroxisomal abundance and peroxisomal fatty acid oxidation-related pathway suggest that peroxisomes may contribute to hepatic ROS generation and oxidative damage. Accordingly, a de-regulation of antioxidant defense system was observed in cytosolic fraction of hepatocytes. Additionally, this early non-alcoholic fatty liver stage is also associated with autophagic flux impairment. **Conclusion:** We show for the first time the sequential events of mitochondrial alterations involved in NAFL progression and demonstrate that mitochondrial ROS are not one of the first hits that could cause NAFLD progression. Then, the accumulation of damaged/dysfunctional organelles could instigate hepatocyte injuries and NAFLD progression. Funding sources: National Science Centre, Poland (UMO-2018/29/B/NZ1/00589); FOIE GRAS project (Marie Sklodowska -Curie Grant Agreement No. 722619).

B7- Ces2a deficiency provokes hepatic steatosis in mice

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Background: Carboxylesterases (Ces) are well-known and studied for their role in (pro)drug metabolism, but their participation in lipid metabolism has been underappreciated for a long time. Only recently, low Ces2c expression has been linked to the development of fatty liver disease in mice. In humans, low hepatic CES2 expression and activity has been demonstrated in non-alcoholic steatohepatitis patients and obese individuals respectively, implicating a role for CES2 in metabolic disease development. The mouse genome encodes seven Ces2 genes (and a pseudogene) opposed by a single CES2 gene in humans. Ces2a is highly expressed in the liver, which prompted us to study the role of Ces2 in the development of fatty liver disease. **Methods:** Ces2a-knockout (Ces2a-ko) mice were generated and characterized using standard procedures such as monitoring of body weight and composition, calorimetry, diet studies, analysis of plasma (lipid) parameters, gene and protein expression studies, enzymatic activity assays, and lipidomic analysis. Additionally, we investigated the impact of ectopic CES2 expression on lipid and energy catabolism in Ces2a-ko mice via injection of a recombinant adenovirus encoding human CES2 cDNA. **Results:** Global Ces2a deficiency increases body and adipose tissue mass on chow diet and HFD and causes severe hepatic steatosis on HFD. The lack of Ces2a increased liver weight and levels of neutral lipids together with increased expression of genes involved in lipogenesis, fibrosis and inflammation. Ces2a-ko mice showed impaired glucose tolerance on HFD which could be reversed upon ectopic CES2 expression. **Conclusions:**

Our studies show that Ces2a is essential in maintaining whole-body lipid homeostasis in mice, possibly by generating protective signaling lipids, which counteract lipogenesis and insulin resistance during metabolic stress. On the other hand, CES2 is able to control the lipid network that is dysregulated under conditions of obesity and NAFLD, which suggests overlapping functions between mouse Ces2a and human CES2.

B8- Dietary Sugars are the Primary Substrate for Palmitic Acid Synthesis During Mouse Brain Development

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Background: Palmitic acid (PAM) is absorbed from the diet and synthesized via *de novo* lipogenesis (DNL). Previously, it was debated if brain PAM was maintained by diet or DNL. Here, we utilize naturally occurring carbon isotope ratios (CIRs; $^{13}C/^{12}C$; $\delta^{13}C$) to uncover brain PAM origin during development. **Methods:** Dams were equilibrated onto isocaloric diets containing low (<2%), medium (47%) or high (>95%) PAM levels prior to producing one generation of offspring. Importantly, dietary PAM was depleted in ^{13}C (−29.70 ± 0.19 mUr), while dietary sugars were enriched (−11.15 ± 0.65 mUr). Offspring stayed on the respective dam diet and were euthanized at 0, 10, 21, and 35 postnatal days. Isolated brain and phospholipid fraction FAMEs were quantified by gas chromatography (GC)-flame ionization detection, after which, total brain $\delta^{13}C$-PAM was measured by GC-combustion-isotope ratio mass spectrometry. **Results:** PAM levels of total lipids and phospholipid fractions in the brain were maintained across diet groups at all timepoints. Brain $\delta^{13}C$-PAM was enriched overall (-16.31 to -17.97 mUr), revealing that hepatic and *in vivo* brain DNL from dietary sugars contribute to the majority of brain PAM. Interestingly, brain ^{13}C-PAM was dependent on the interaction of diet and time ($p = 0.0006$) where brain ^{13}C-PAM of pups fed low PAM was less enriched at early postnatal days than later, while pups fed high PAM had more enriched brain ^{13}C-PAM at early postnatal days than later. Importantly, brain ^{13}C-PAM was more enriched in pups fed low as compared to high PAM across all timepoints, indicating increased DNL in response to the low PAM diet. **Conclusions:** To the best of our knowledge, our study is the first to utilize CIRs to identify dietary sugars are a major substrate for DNL to maintain brain PAM and are augmented in mice fed low dietary PAM from birth.

B9- Measuring the turnover of DHA in the brain, liver, and adipose tissue using compound-specific isotope analysis

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Background: Our laboratory has explored an alternative, cost effective technique, called compound-specific isotope analysis (CSIA) that takes advantage of natural differences in carbon-13 content ($^{13}C/^{12}C$ ratio or $\delta^{13}C$) of the food supply to better understand tissue DHA metabolism. However, previous models have been limited by the selection of timepoints and variations in DHA pool sizes, preventing accurate DHA turnover estimates. In the current study, we take advantage of natural variations in the $\delta^{13}C$-DHA of algal and fish DHA sources while maintaining stable DHA pools to assess tissue DHA turnover. In addition, we used an artificially enriched ^{13}C DHA treatment diet (Spiked-DHA) to test it's use in diet switch studies. **Methods:** 114 twenty-one-day old male BALB/c pups were equilibrated to the fish-DHA diet (control) for 3 months prior to being switched to an algal-DHA treatment diet, or an artificially enriched ^{13}C DHA treatment

diet (Spiked-DHA) for 0 (n=6), 1, 3, 5, 7, 14, 28, 56, 112, and 168 days (n=4) post diet switch. Blood and tissues were collected at each timepoint. **Results:** There were no main effects of diet on tissue DHA levels. The brain DHA half-life was 47 and 46 days in mice fed the algal DHA diet, and spiked DHA diet, respectively. The liver DHA half-life was 5.6 and 7.2 days in mice fed the algal and spiked DHA diets, respectively. **Conclusions:** In this study, we showed that brain half-lives were consistent with previously published studies using various methodologies. Second, by incorporating additional time points and maintaining DHA pool sizes we were able to accurately calculate DHA turnover in tissues other than the brain including the liver. Future work will examine the turnover of DHA in the remaining tissues.

B10- SDR, a new potential regulator of the hepatic response to fasting

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Background: The liver is a critical hub for numerous physiological processes, including lipid and glucose homeostasis. In response to feeding, hepatocytes use dietary lipids to synthesize lipoproteins, which distribute triglycerides and cholesterol to peripheral tissues. During fasting, these cells initiate the production of glucose via the gluconeogenic pathway to maintain glycemia. The hepatocytes also promote fatty acid oxidation to support the production of ketone bodies. Over the years, several proteins and signalling nodes have been identified as playing key roles in regulating the hepatic response to fasting. Despite these advances, new discoveries are constantly emerging and our understanding of the molecular mechanisms controlling this biological process keeps evolving. **Objective:** The main objective of this project is to identify and characterize new proteins regulating liver metabolism in response to fasting. **Methods:** We used hepatocytes isolated by serial dilutions and obtained 36 new clonal lines. Interestingly, we found that some of these lines produced low glucose amounts (Low Lines) whereas others produced high amounts (High Lines). Hepatic glucose production was assessed in these clonal lines since it is a process that occurs during fasting. To identify the factors involved in this variability between these lines, we performed transcriptomic assays and obtained 25 new targets that could be potentially involved in the hepatic response to fasting. **Results:** Our first interesting candidate is a *short dehydrogenase reductase* (*SDR*) gene, whose expression is higher in High Lines versus Low Lines. This *SDR* gene encodes for a protein of unknown function. Our studies indicate that *SDR* is induced by fasting and PPARα, repressed by insulin, and that the SDR enzyme localizes to mitochondria. *SDR* knockdown *in vitro* decreases oxygen consumption and fatty acid oxidation, suggesting an involvement in mitochondrial metabolism. **Conclusion:** we hope to elucidate the role of SDR in regulating the hepatic response to fasting.

B11- The identification of a potential therapeutic agent regulating glucose and metabolic homeostasis

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Background: Obesity is characterized by the excessive accumulation of white adipose tissue (WAT). The expansion of WAT in obesity is linked to a rise in cell size (hypertrophy) and cell number (hyperplasia). Factors controlling the hyperplastic growth of WAT are not well characterized. Recently, ADIPOKINE-Y has been identified as a secreted protein produced by pre-adipocytes that promotes adipogenic commitment. Interestingly, *in vitro* experiments showed that ADIPOKINE-Y depletion impairs adipogenesis, while its overexpression induces it. Yet, the effects of ADIPOKINE-Y overexpression *in vivo* are still elusive. Hence, our objective is to identify the effects of ADIPOKINE-Y overexpression *in vivo*. **Methods:** Mice (adults and pups) were injected with adenovirus to overexpress ADIPOKINE-Y. These mice were then fed a chow or high-fat diet for 3 weeks and body weight measurement was followed. Glucose and insulin tolerance tests were performed. At the end of the study, tissues were collected, and several metabolic genes were measured. Blood metabolites were also analyzed. **Results:** ADIPOKINE-Y overexpressing mice are viable and show normal food intake. ADIPOKINE-Y overexpression significantly reduced body weight and fat pad weight in both adults and pups. Moreover, glucose and lipid metabolic profiles were improved as glucose and triglyceride levels were significantly reduced in response to ADIPOKINE-Y overexpression. This observation was associated with an important improvement in glucose and insulin tolerance. Also, ADIPOKINE-Y overexpression was sufficient to reduce inflammation in adipose tissue and reduce the expression of genes involved in gluconeogenesis in the liver. Interestingly, when ADIPOKINE-Y overexpression faded away, the observed effects were lost. This indicates that these effects are reversible and directly dependent on ADIPOKINE-Y overexpression. **Conclusion:** Collectively, our findings indicate that ADIPOKINE-Y could represent a new therapeutic agent to normalize body weight and improve glycemic and metabolic homeostasis in mice.

B12- Isolation of Adipocyte and Endothelial Cells from Human Visceral Adipose Tissue: To understand lipid dysfunction in distorted Adipose tissue

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Background: White adipose tissue is a key regulator of energy metabolism via lipid storage and secretion of fatty acids and adipokines. Endothelial cells(EC) and adipocytes(APC) communication is crucial to maintain adipose tissue function; It is altered in obesity leading to defective angiogenesis and lipid metabolism. To understand distortions of APC-EC communication, we isolate mature APC and EC from Stromal-Vascular Fraction(SVF) of Human Visceral-Adipose Tissue(VAT) and established APC-EC coculture model. **Methods:** APC and EC were isolated from 1-3gm of VAT from obese (BMI>30) and lean (BMI<25) gall stone surgery. Mature white adipocytes were isolated from VAT using enzymatic digestion and sequential centrifugation. CD31(+)CD144(+) ECs were collected from SVF by FACS sorting. Light/fluorescence microscopy was used to monitor the morphology of EC. Further, adipocyte and EC markers were analyzed using qPCR. Lipidomics, metabolomics and proteomics of these cells were further validating the characteristics of APC and ECs. APC-EC coculture was set up using Membrane-Aggregate Adipocyte Co-Culture(MAACC) to study APC-EC communication. Functional assays were standardized to study the communication. **Results:** White adipocytes and EC were successfully isolated from VAT. The CD31(+)CD144(+) cells accounted for 6-8% of the total SVF and had a viability of >95percent. Fluorescent/phase-contrast microscopic analysis showed a single-population of ECs. This protocol does not require any further differentiation of EC or

APC. Omics analysis revealed that the isolated cells retain the characteristics of humans APC and EC. The MAACC system was set up using white adipocytes and ECs isolated from VAT and was functionally characterized. **Conclusion:** The MAACC system and the novel protocol for EC isolation will help researchers to study communication between APC & EC and lipid distortions in adipose tissue.

B13- Identification of a new E3 ubiquitin ligase involved in the regulation of hepatic metabolism in response to fasting

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Background: The liver plays an important role in carbohydrate metabolism by storing and producing glucose based on the nutritional status. Feeding promotes glucose storage while fasting induces glucose release. However, these processes are impaired in situations of chronic energy surplus such as obesity and type 2 diabetes (DT2). Nutrient excess promotes insulin resistance, leading to increased hepatic glucose production even in the postprandial state. Therefore, identifying new factors involved in the regulation of hepatic metabolism during the fasting/feeding transition could provide new perspectives on the pathophysiological mechanisms contributing to the development of metabolic diseases. **Methods**: We analyzed microarray datasets in which the hepatic response to fasting was characterized. This approach allowed us to identify differentially expressed genes after different periods of fasting. We short-listed 13 genes coding for proteins that have not been studied in this context so far and validated their expression by qPCR. **Results**: We identified "F-box only" (*Fbxo*) as an E3 ubiquitin ligase affected by fasting in the liver. The expression of *Fbxo* increases as soon as 6 hours of fasting, and decreases in obese and diabetic mouse models. To identify potential substrates of FBXO, we performed immunoprecipitation in the liver of fasting mice and samples were analyzed by mass spectrometry. Our results revealed that FBXO could interact with proteins already known to be involved in metabolic processes. **Conclusions**: Our preliminary data indicate that FBXO expression increases during the fasting/feeding transition to rapidly modulate the expression of specific proteins by ubiquitination. This study suggests that FBXO could be deregulated in individuals with obesity and DT2. Therefore, FBXO could be critical for the adaptation of the liver to situations of nutrient excess and contribute to the pathophysiology of metabolic disorders.

B14- KIAA1363-deficiency in hepatic stellate cells impairs retinyl ester turnover at the endoplasmic reticulum

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Background: Large quantities of vitamin A are stored as retinyl esters (REs) in lipid droplets of hepatic stellate cells (HSCs). Under times of nutritional undersupply hepatic RE stores are utilized to meet vitamin A requirements of the body. To date, the enzymes controlling RE degradation in HSCs are poorly understood. Recently we identified

KIAA1363 (also annotated as arylacetamide deacetylase 1 or neutral cholesterol ester hydrolase 1) as an endoplasmic reticulum-associated neutral RE hydrolase affecting RE turnover in cultured and activated HSCs. However, the functional role of KIAA1363 in retinoid homeostasis of HSCs *in vivo* remains elusive. **Methods**: We obtained primary HSCs from KIAA1363-ko and WT mice by liver perfusion, preparation of non-parenchymal cell fractions, and subsequent cultivation and isolation of HSCs by the method of selective detachment. RE hydrolase activity was assessed in *in vitro* activity assays. Cellular retinoids were extracted and analyzed by HPLC fluorescent detection. **Results**: We found that cultured HSCs from KIAA1363-deficient mice exhibited 65% reduced neutral *in vitro* RE hydrolase activity as compared to control cells isolated from wild-type mice. Accordingly, KIAA1363-deficient HSCs showed increased cellular RE content after 12 days of cultivation as compared to control cells. Furthermore, in cell experiments we observed that KIAA1363-deficient HSCs exhibited higher cellular RE levels after a retinol/fatty acid loading phase. Interestingly however, KIAA1363-deficient HSCs were not defective in degrading REs during a serum-starvation period. **Conclusion**: Our data provide evidence that KIAA1363 accounts for the majority of the neutral *in vitro* RE hydrolase activity in HSCs and - if absent - leads to increased cellular RE levels. This suggests that KIAA1363 is essential for functional RE turnover at the endoplasmic reticulum of HSCs.

B15- Human eosinophils and neutrophils biosynthesize novel 15-lipoxygenase metabolites from monoacylglycerols and N-acyl-ethanolamines.

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BACKGROUND: The endocannabinoids 2-arachidonoyl-glycerol (2-AG) and *N*-arachidonoyl-ethanolamine (AEA) are lipid mediators regulating many physiological processes, notably inflammation. 2-AG and AEA are respectively part of the monoacyglycerol (MAG) and *N*-acyl-ethanolamine (NAE) families. Thus, MAGs and NAEs are considered as part of the endocannabinoidome. Endocannabinoid hydrolysis inhibitors are being investigated as potential treatment in numerous conditions. This strategy will not only increase the levels of 2-AG and/or AEA, but also those of other MAGs and/or NAEs. However, increasing MAG and/or NAE levels, it will likely increase the levels of their metabolites. Herein we investigated whether MAGs and NAEs containing polyunsaturated fatty acids were substrates for the 15-lipoxygenase pathway, which is strongly involved in asthma and its severity. We thus assessed if human eosinophils and neutrophils biosynthesized the 15-lipoxygenase metabolites of MAGs and NAEs derived from linoleic acid (LA), eicosapentaenoic acid (EPA),

docosapentaenoic acid n-3 (DPA) and docosahexaenoic acid (DHA). **METHODS:** We synthesized the putative 15-lipoxygenase metabolites of MAGs and NAEs containing LA, EPA, DPA and DHA using Novozym435 and soybean lipoxygenase and optimized their detection by LC-MS/MS. Human eosinophils and neutrophils were isolated from the blood of healthy donors and incubated with MAGs and NAEs at different concentrations and times. **RESULTS:** Eosinophils, which express the 15-lipoxygenase-1, metabolized all the MAGs and NAEs to the expected 15-lipoxygenase metabolites. Human neutrophils, which might express the 15-lipoxygenase-2, also metabolized most of the MAGs and NAEs, but to a much lower extent than eosinophils. Importantly, some of the new 15-lipoxygenase metabolites we disclose were found in tissues from humans and mice. **CONCLUSIONS:** We successfully showed that human eosinophils and neutrophils transform MAGs and NAEs into novel 15-lipoxygenase metabolites. How these new metabolites modulate the inflammatory cascade is now being explored as they could participate in the effects of endocannabinoid hydrolysis inhibitors *in vivo*.

B16- GOLM1 knockdown in Huh-7 hepatocytes modulates intracellular sphingolipid profile, cell growth and mitochondrial function.

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Background: Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer and a global health concern. GOLM1, a Golgi type 2 transmembrane protein is an emerging marker of HCC. However, the causal relationship of GOLM1 with HCC is largely unknown. Therefore, we aimed to study the effects of GOLM1 on hepatocellular carcinoma lipid metabolism and growth. **Methods:** GOLM1 expression was silenced using siRNA against GOLM1 in Huh-7 and non-targeting scramble siRNA was used as control . Quantitative lipid mass spectrometry analysis was employed for profiling lipids in these cells. The mitochondrial function was examined using the Agilent Seahorse XFe96 extracellular flux analyser. Electron microscopy and Immunofluorescence microscopy were used to analyse Golgi structure in GOLM1 silenced cells. Different methods like one step MTT assay, [3H] thymidine labelling and flow cytometry were performed to check cell proliferation. **Results:** An aberrant intracellular accumulation of sphingolipids such as ceramides, hexosylceramides, dihexosylceramides, sphinganine, sphingosine, ceramide-phosphate, and neutral lipids such as cholesterol esters was observed when GOLM1 depleted cells were subjected to mass spectrometric lipidomic analysis. Furthermore, a significant reduction in membrane phospholipids such as phosphatidylethanolamines and lysophosphatidylethanolamines was also detected. GOLM1 knockdown resulted in a decreased basal and maximal mitochondrial oxygen consumption rate (OCR). Additionally, in the absence of GOLM1, EM imaging and immunofluorescence microscopy analyses revealed changes in Golgi structure and distribution. Further, GOLM1 silencing resulted in a decrease in cell proliferation. Cell cycle analysis of the GOLM1 knockdown cells revealed an enrichment of cells in G2 and

S phase. **Conclusion:** GOLM1 depletion altered sphingolipid metabolism, mitochondrial function, Golgi structure, and HCC cell proliferation. GOLM1 could therefore represent a putative new target for HCC therapy.

B17- Effect a simulated 30km time trial under normobaric hypoxia on blood sphingoid base-1-phosphates metabolism in cyclists

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Background: Studies conducted over the last years have shown that exercise significantly affects sphingosine-1-phosphate (S1P) metabolism. It is known that S1P plays an essential role in skeletal muscle function. It was recently found that exposure to hypoxia promotes an increase in the plasma S1P concentration. Thus, this study aimed to assess the effect of hypoxia on post-exercise changes in blood S1P metabolism. **Methods:** Fifteen male cyclists were subjected to a 30km-simulated time trial. The acute exercise was performed under normoxia and normobaric hypoxia (FiO2= 16.5%). Blood samples were taken at three-time points: before exercise (I-point), immediately after exercise (II-point), and following a 30-minute rest (III-point). The concentration of sphingoid base-1-phosphates in plasma and erythrocytes was determined by high-pressure liquid chromatography. **Results:** Our results have demonstrated an increase in plasma sphinganine-1-phosphate (SA1P) concentration in the second and third-time points compared to the basal value as a consequence of the increased release of this compound from erythrocytes. Enhanced synthesis of SA1P in erythrocytes was caused by an elevated availability of sphinganine constituting a substrate for its production. Oxygen availability did not affect these changes. **Conclusions:** The obtained findings revealed that aerobic acute exercise exerts a stronger effect on SA1P metabolism than S1P. The observed alterations highlighted a potential role of SA1P in adaptation to exercise and could contribute to the regeneration of skeletal muscle during the recovery period.

B18- Neuronal Adipose Triglyceride Lipase (ATGL) regulates peripheral metabolism.

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Background: Adipose Triglyceride Lipase (ATGL) catalyzes the first step in triglyceride hydrolysis, and plays a major role in regulating energy homeostasis in peripheral tissues. ATGL is also expressed in different regions and cell types in the brain, including the POMC and AgRP neurons of the arcuate nucleus (ARC) that play key roles in maintaining energy homeostasis. Yet, the physiological significance of brain ATGL expression remains unclear. **Results**: We found that ATGL regulates lipid droplet content in cultured hypothalamic neurons, in line with its effects on lipid droplets in peripheral tissues. When we examined ATGL expression in the ARC, we found ATGL mRNA levels were upregulated by cold exposure and fasting, suggesting ATGL plays a role in adaptive responses to metabolic challenges. Indeed, genetic inhibition of neuronal ATGL in *C.*

elegans and *D. melanogaster* increased peripheral fat accumulation and reduced lipolysis post-fasting, respectively. This suggests a conserved mechanism whereby neuronal ATGL promotes peripheral lipolysis. Supporting this, our data using a viral approach in ATGL *flox* mice show that ATGL knock out specifically in ARC neurons (Synapsin-Cre AAV) affects glucose tolerance, energy expenditure, feeding behaviour (meal pattern) and thermoregulatory responses to cold in chow fed male mice without affecting body weight gain during diet-induced obesity. Similar changes were not observed in female mice, suggesting male-specific regulation of energy homeostasis by neuronal ATGL, a sex difference we reproduced in flies. **Conclusion**: Given that our ongoing studies show changes in fat distribution and glucose homeostasis in mice with a specific ATGL knockout in AgRP neurons, our findings suggest this subpopulation of neurons are involved in the control of energy homeostasis by ATGL in the ARC. Taken together, our findings reveal a previously unrecognized role for neuronal ATGL in regulating whole-body energy homeostasis.

B19- Functional Schwann cells partially rescued after Ketogenic Diet exposure in mouse model of Krabbe's disease.

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Background: Krabbe disease is a lysosomal storage disease mainly affecting children. It is caused by mutations in the gene encoding the galactosylceramidase enzyme (GALC) leading to a loss of function of the protein implicated in myelin recycling. This induced demyelination and neurodegeneration due to accumulation of the cytotoxic psychosine. Interestingly, it has been recently observed that Krabbe children fed with a ketogenic diet (KDiet), (90% Kcal fat, < 0,1% Kcal carbohydrate) show an increase of lifespan and a partial rescue of some physiological functions. More recently, a mouse model of neurodegenerative disorder (Hirschsprung) treated with GDNF (glial cells line-derived neurotrophic factor) show an increase of the Schwann cells neurogenesis.
Methods: Twitcher mice, a model of Krabbe disease (*Twi*), have been exposed to either KDiet or carbohydrate enriched diet from day 15 after birth (P15). Lifespan of pups, neuroinflammation and the presence of functional Schwann cells in the sciatic nerve have been evaluated at P25, P35 and P42 with or without GDNF treatment. **Results:** *Twi* mice fed with the KDiet increased their lifespan compared to the carbohydrate enriched diet (49 vs 45 days, p-value 0,0007) and decreased the expression of pro-inflammatory markers, IL-6 and CD86. Feeding *Twi* mice with the KDiet partially restore, in Schwann cells of the sciatic nerve, the expression of SOX10, one of the key transcription factor implicated in the differentiation of precursor Schwann cells into mature cells (25% of recovery at P35 and 50% of recovery at P42). Moreover, GDNF treatment increased the Schwann cell proliferation in the sciatic nerve in *Twi* mice fed with KDiet. **Conclusions:** The results showed the benefic effect of KDiet increasing lifespan of *Twi* mice and decreasing neuroinflammation. KDiet allows to partially restore functional Schwann cells and this effect could be potentiate with GDNF treatment. Together these data provide promising dietary approach.

B20- Role of Adipose Triglyceride Lipase (ATGL) in neuronal lipolysis and control of energy balance by melanocortin neurons.

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Background: Hypothalamic neurons of the arcuate nucleus (ARC) integrate metabolic signals to regulate energy balance. Evidence suggests the underlying mechanisms involve fatty acids (FA) released from intracellular triglycerides stored in lipid droplets (LD). This model is supported by data from our lab showing that neurons accumulate exogenous FA into triglycerides and that knock-down of Adipose Triglyceride Lipase (ATGL), the first lipase involved in LD hydrolysis, in ARC neurons modulates feeding behavior and energy expenditure in mice. However, the regulation of LD dynamics by ATGL in hypothalamic neurons and the role of ATGL in the central control of energy homeostasis by melanocortin ARC neurons remain unknown. **Methods and Results:** First, our lipidomics data show that palmitate and oleate are the major FA esterified in neuronal LD in GT1-7 and N46 neurons. Esterified FA levels are increased by Atglistatin (ATGL inhibitor) with an enrichment in palmitate. Second, our high-throughput imaging show that neurons accumulate LD in response to oleate and Atglistatin and, Atglistatin reduces LD lipolysis in neurons pre-loaded with oleate and decreases forskolin-induced hydrolysis of LD. FA released upon ATGL activation are in part oxidized in the mitochondria. In primary neuron cultures derived from POMC-GFP mice, oleate stimulates LD formation in POMC neurons. Using Cre-Lox, we generated a POMC specific ATGL KO mouse model that was subjected to metabolic phenotyping. ATGL KO in POMC neurons does not have any major effects on parameters of energy balance in fasted or *ad libitum* fed conditions, metabolic responses to restraint stress, cold exposure, nor susceptibility to diet-induced obesity in males and females. Animals will be exposed cold fasting to assess thermoregulatory responses. **Conclusion:** Together, our data show that ATGL regulates lipolysis and LDs dynamics in hypothalamic neurons and suggest that the lipase is not involved in the control of energy homeostasis by POMC neurons.

B21- Stearoyl CoA Desaturase is a central regulator of defects in lipids, inflammation and synapses in Alzheimer's disease

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Background: The defining features of Alzheimer's disease (AD) include alterations in amyloid, tau, immunity, lipid metabolism, and learning and memory. Of these, lipid abnormalities are the least understood. In this study, we examined the role of a crucial regulator of fatty acid desaturation, Stearoyl-CoA desaturase (SCD) in AD pathogenesis.

Methods: We used RNA sequencing to study the transcriptomic effects of SCD inhibition (SCDi) on whole hippocampus and single immune cells specifically, Golgi-cox staining to assess synaptic changes and Morris water maze to measure learning and memory. **Results:** SCDi normalized over 41% of hippocampal DEGs, many of which were lipid, inflammation and synaptic genes. Moreover, SCDi led to widespread cellular benefits, including a decrease in microglia activation, rescue of synaptic number and dendritic complexity and an increase in many immediate early genes. Remarkably, SCDi also led to a functional rescue of learning and memory deficits in symptomatic 3xTg-AD mice. **Conclusions:** Together this data shows that in AD, SCD is a central regulator of key defects in lipids, inflammation and synapses and could be a promising new target for AD treatment.

B22- Glucose metabolism as a function of ApoE genotype

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Background: Alzheimer's disease (AD) is a neurodegenerative disorder and the most common cause of dementia worldwide. Astrocytes are key mediators for maintaining homeostasis and the main producers of the apolipoprotein E (ApoE), its isoform ε4 is the main genetic risk factor for sporadic AD. Our understanding of ApoE's function in the brain is limited. The glucose transporter 1 (GLUT1) is the main glucose transporter in astrocytes and its expression levels have never been assessed as a function of ApoE genotype to our knowledge. Our aim is to understand the differences in the glucose metabolism in astrocytes depending in the ApoE isoform express. **Methods:** Immortalized ApoE3/E4-expressing mouse astrocytes on cell culture were used. Relative protein expression levels were analyzed by western blotting. Cellular glucose uptake was measured using the Glucose-Uptake-Glo assay by Promega and the cell surface presentation of GLUT1 was quantified using flow cytometry. **Results:** Astrocytes mainly relay on GLUT1for glucose uptake, for this reason total protein extraction from cell culture lysates was done to assess for differences in the protein pattern expression of GLUT1 between the different apoE isoforms, finding an increase in relative protein expression of GLUT1 levels by WB in ApoE4 in contrast with the other isoforms. GLUT3 levels were assessed as a control of GLUT1 levels finding an increased in GLUT3 between E4 and E2. GLUT1-expression at the cell surface by flow cytometry was found to be increased in apoE4. However, despite this protein increase, a glucose uptake assay revealed no significant changes in glucose uptake between the difference isoforms. **Conclusion:** ApoE4 expressing mouse astrocytes showed increased expression of GLUT1 in total protein cell lysates and flow cytometry. Despite higher GLUT1 expression, glucose uptake remained unaffected in comparison to the other isoforms. Further analyses will need to be done to characterize this phenotype seen.

B23- The Cholesteryl Ester Transfer Protein in Alzheimer's Disease

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Background: Alzheimer's disease (AD) is the most common form of dementia and affects around 35 million individuals worldwide with currently no cure. Several studies showed an association between high levels of plasma pro-atherogenic low-density lipoproteins (LDL) cholesterol and an increased risk of developing AD. The cholesteryl ester transfer protein (CETP), whose activity leads to more cholesteryl esters in LDL particles, increases levels of LDL cholesterol in the blood. Recent epidemiological studies have shown an association between CETP activity and the risk of developing AD. My project proposes a new perspective on AD research by investigating CETP as main pharmacological target. **Methods:** To examine the effects of CETP inhibition on AD pathology, mice from four different genotypes: wildtype mice, human CETP transgenic mice (hCETP), human APP transgenic mice (hAPP), and hAPP/hCETP double transgenic mice were administered with the CETP inhibitor evacetrapib or vehicle daily at 11 weeks of age for 10 weeks. **Results:** At 21 weeks of age, hAPP mice were cognitively impaired in the evacetrapib and vehicle condition. Interestingly, both hCETP and double transgenic mice were cognitively impaired in females only, which could be rescued by evacetrapib indicating a role of CETP in the early stages of AD. Moreover, using ELISA to quantify Aβ species, we demonstrated that levels of Aβ peptides do not correlate with cognitive impairment, which contrasts with the amyloid hypothesis. Most interestingly, hCETP and hAPP/CETP mice treated with evacetrapib showed a significant increase in brain cholesterol as compared to controls, like hAPP mice in the vehicle and drug condition, suggesting higher cholesterol per se does not affect cognition. **Conclusions:** We propose that the activity of CETP is a contributing factor in worsening the disease, while its pharmacological inhibition may delay the onset of AD.

B24- Effects of the Cholesteryl Ester Transfer Protein on Amyloid-beta generation

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Background: CETP has been linked to Alzheimer's disease through epidemiological studies, but has never been investigated at the molecular level in this disease' context. CETP is a cholesterol transporter transferring cholesteryl esters from high-density lipoprotein particles to low-density lipoprotein particles, whereby effects of CETP on the cellular cholesterol distribution cannot be excluded. A hallmark of Alzheimer's disease is the formation of amyloid-beta peptides, which we here analyzed here in the presence of CETP. **Methods:** We used basic cell culture systems to quantify amyloid-beta formation by ELISA in the presence or absence of CETP and CETP mutants. **Results:** We found that expression of CETP increased amyloid-beta production, while a catalytic inactive mutant of CETP did not affect amyloid-beta formation. The effects are further influenced by extracellular lipoprotein particles and the expression of LDL receptors. **Conclusions:** CETP activity appears to influence amyloid-beta production through modulating the distribution of lipids.

B25- Dietary intake varying in n-6 and n-3 PUFA regulate unique gene signatures in response to ethanol between male and female mouse

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Background: Alcohol use and misuse in women has been in steady rise with drinking gap closing between men and women. This is of concern as studies have demonstrated earlier development of alcohol-related heart disease and brain damage in women. In mouse models for alcohol use, it is established that female mice, with continuous or limited access to ethanol, would voluntarily consume higher levels of alcohol as compared to male mice. Furthermore, dietary fatty acid composition may affect transcriptomic response to ethanol in the brain. However, it is unclear if brain response to alcohol is affected by dietary fatty acid intake between the sexes. **Methods:** Time-pregnant C57BL/6J dams were randomized to one of four dietary interventions. The diets varied in the combination of n-6 PUFA (8 energy% or 1 en% linoleic acid) and n-3 PUFA (0.5 en% or 0 en% EPA+DHA). 15-week-old male and female offspring was subjected to a 9-day 2.5 g/kg and 1-day 5 g/kg ethanol gavage paradigm. Prefrontal cortex, hippocampus, and cerebellum were collected for next generation RNA sequencing. **Results:** Transcriptome t-SNE clusters by brain regions and sex implying that transcriptomic response to ethanol are distinct by brain region and between the sexes. In contrast, t-SNE clusters by diet and ethanol treatment showed random distribution suggesting that interactions of dietary fatty acid and ethanol is complex. However, upon gene-set analysis (fold change ±1.5, FDR $q < 0.05$), unique sets of genes were affected among sexes fed different diets and exposed to ethanol which suggest that dietary fatty acids may contribute to regional brain responses to ethanol by regulating distinct pathway. **Conclusions:** Brain region and sex differentially affect transcriptomic signature in response to ethanol. Moreover, dietary intake varying in n-6 and n-3 PUFA may induce unique gene signatures in response to ethanol between the sexes.

B26- The way to a man's heart is through his stomach- The role of Protein Kinase D2 in the development of atherosclerosis

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Background: Atherosclerotic cardiovascular diseases are one of the the *most common causes* of cardiac *deaths* worldwide. It is estimated that they cause approximately 50% of all deaths in the western world. Atherosclerosis is a chronic, multifactorial disease characterized by the accumulation of lipid and fibrous elements in the walls of arteries. The progress of the disease leads to the formation of atherosclerotic plaques. The enlarging atherosclerotic plaques reduce the lumen of the arteries and lead to thrombogenesis on their surface and ischemia of internal organs. Understanding the exact mechanism of atherosclerotic plaque formation is crucial for the development of a new treatment for atherosclerosis. Our recent study has resulted in a discovery that inactivation, deletion, or inhibition of protein kinase D2 (PKD2) leads to reduced lipid absorption in the intestine as well as an increased level of apolipoprotein A4 (APOA4) in the blood plasma. Importantly, APOA4 mediates reverse transport of cholesterol from foam cells and thus prevents development of atherosclerotic plaque. Thus, we hypothesized that the inactivation of PKD2 may prevent the development of atherosclerosis. **Methods**: To evaluate above mentioned hypothesis we used low-density lipoprotein receptor (LDLr) knockout mice (LDLr KO) treated with CRT0066101, an inhibitor of the PKD family, for 7 weeks during 16 weeks of a cholesterol-enriched diet. Further we used LDLr KO mice with inactivated PKD2. **Results:** We observed that the inactivation of PKD with CRT0066101 inhibitor decreases total cholesterol level in blood and formation of atherosclerotic plaques in aortas in LDLr KO mice fed with a

cholesterol-enriched diet. In line with that LDLr KO mice with inactivated PKD2 showed significantly decreased cholesterol level and atherogenesis upon cholesterol-enriched diet in comparison to control animals. **Conclusions:** Overall, the study showed that inactivation of PKD could be beneficial in the treatment of atherosclerosis.

B27- THE LOW-DENSITY LIPOPROTEIN RECEPTOR FUELS CHOLESTEROL-MTORC1 AXIS DURING CD8 T CELL ACTIVATION

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Background: The activation of T lymphocytes implies a metabolic rewiring of cell machinery, including cellular cholesterol metabolism. Here we evaluated the role of the low density lipoprotein receptor (LDLR) on T cell biology. **Methods**: Immunophenotypic characterization of T cells from WT and LDLR KO mice was performed in vitro (anti-CD3/CD28) and in vivo (ovalbumin vaccination) coupled to proteomics and WB analysis on isolated T cells. T cells from FH (familial hypercholesterolemia) patients, carrying mutations in the LDLR gene, were profiled. **Results**: LDLR mRNA expression increased after in vitro activation of CD8, but not CD4 T cells, suggesting a different regulation of cholesterol homeostasis between T cell subsets. LDLR deficiency mainly affected CD8 T cell activation as demonstrated by reduced in vitro proliferation (-35%, $p<0.01$) and INFγ production (-39.6%,$p<0.01$), and in vivo proliferation and cytokine production (↓IFNγ $p<0.001$,↓IL13 $p<0.01$,↓perforin $p<0.05$) after ovalbumin vaccination of LDL-R KO T cells compared to their wild type counterpart. The addition of LDL to serum free media increased by 15% ($p<0.01$) CD8 proliferation in WT but not in KO CD8 T cells. Proteomic and WB analysis showed that this phenotype is the consequence of reduced mTORC1 activation (pmTOR -40%,$p<0.01$) and impaired lysosomal organization (reduced lysotracker and LAMP-1 expression). The proliferation of CD8 T cells from FH patients was less pronounced compared to sex- and age-matched controls (-36%,$p<0.05$). In addition, CD8 T cells from FH vaccinated for seasonal influenza were tested in vitro with virus-derived peptides, showing a decreased granzyme production (-60.3%,$p<0.01$) compared to CD8 from vaccinated controls. **Conclusions**: LDLR plays a critical role in regulating the immunometabolic reprogramming of activated CD8 T cells by fuelling the cholesterol-lysosome-mTORC1 axis.

B28- Mesenteric lymph derived HDL can act as a donor for TICE and this pathway is impaired with high fat diet and insulin resistance

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Background: Emerging evidence has demonstrated the role of intestine in the reverse cholesterol pathway via trans-intestinal cholesterol excretion (TICE). Some studies show that intestine can produce nascent HDL into mesenteric lymph. The anatomical proximity of lymphatic vessels to the basolateral membrane offers a plausible site as a donor to TICE. The aim of this study was to determine if HDL derived from mesenteric lymph (lymph HDL) can act as cholesterol donor for TICE in JCR:LA-cp rats as a model of insulin resistance (IR) and on a high fat diet. **Methods:** Mesenteric lymph was collected

following intralipid infusion via lymphatic cannulation from control rats. Lymph HDL was isolated using ultra-density centrifugation and labeled with H3 cholesterol. Jejunal explants were obtained from control and IR rats fed chow or a high fat/cholesterol diet. TICE was measured with Ussing Chambers as appearance of H3-cholesterol labeled lymph HDL using micelles as acceptors. **Results:** Lymph HDL-TICE was reduced (6-fold, $p<0.05$) in IR rats compared to control when chow fed. There was no difference in TICE from FC [and mannitol as a marker of paracellular transport]. On the contrary, HDL TICE was increased (5-fold, $p<0.05$) in IR rats compared to control on high fat diet. Under conditions of high fat/cholesterol fed diet, TICE from FC and mannitol was increased in both control and IR rats, suggesting an elevated non-specific permeability of lipids by the basolateral membrane during IR and high fat diet. **Conclusions:** Data from these experiments support the hypothesis that lymph HDL maybe an effective donor for TICE using an ex vivo approach. Specifically, we conclude that while the lymph HDL-TICE pathway may be impaired during insulin resistance, a high fat/cholesterol diet may exacerbate lipid permeability via non-specific efflux pathways.

B29- Trimming the fat from the gut-brain axis": A Role for Intestinal Cholesterol Metabolism in Alzheimer's Disease?

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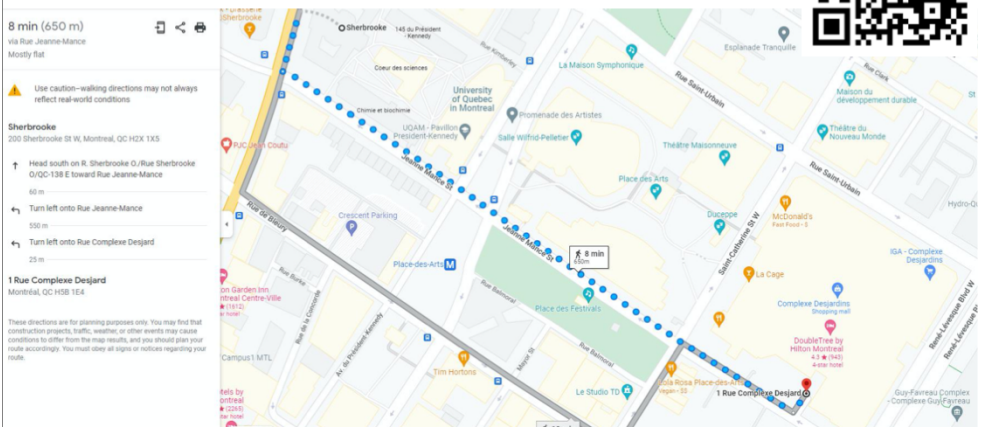
Background: Alzheimer's Disease (AD) is a complex neurodegenerative disorder characterized by progressive memory loss and cognitive decline. Of the many genes studied, the strongest AD risk factors identified converge around one key lipid: cholesterol. Cholesterol dysregulation is linked to the pathogenesis of AD in more ways than one. In the brain, abnormal cholesterol transport by apolipoprotein e-4 is strongly linked to AD. Yet outside the central nervous system, elevated *systemic* cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C), are correlated to AD onset and to a chronic, basal inflammatory state. In this context, we have begun to investigate the elusive connection between systemic and brain cholesterol by focusing on the Cholesterol Ester Transfer Protein (CETP). Once secreted into the plasma, CETP mediates the exchange of triglycerides for cholesteryl esters between HDL-C and LDL-C and is a known modulator of AD risk. **Methods:** We work with mice that transgenically express the human CETP gene (CETPtg) to reliably study peripheral cholesterol transport and AD. We employ bedrock immunological and pharmacological techniques like quantitative PCR, Western Blot, ELISA, and *in-situ* RNA hybridisation assays to study tissue-specific CETP expression and innate immune activity. **Results:** It is known that CETP is predominantly expressed in liver macrophages and stellate cells in response to cholesterol, which we have shown in our CETP transgenic mice (CETPtg). We found that CETP was also expressed in the small intestine of CETPtg mice in a very specific localisation pattern, reflecting a compartmentalisation of nutrient sensing along the intestinal villi. Interestingly, and unlike CETP expression in the liver, this phenomenon appears to be independent of dietary cholesterol. We also examined intestinal pro-inflammatory cytokine expression and levels of fecal lipocalin-2, a marker of intestinal inflammation, over time. **Conclusions:** These results suggest that CETP expression may shape intestinal cholesterol metabolism and immune homeostasis in a murine model of AD pathology.

How to go to the ICBL activities

Welcome Cocktail at Double Tree by Hilton Montreal
1255 Jeanne Mance St, Montreal, Quebec H5B 1B5**Cruise at**

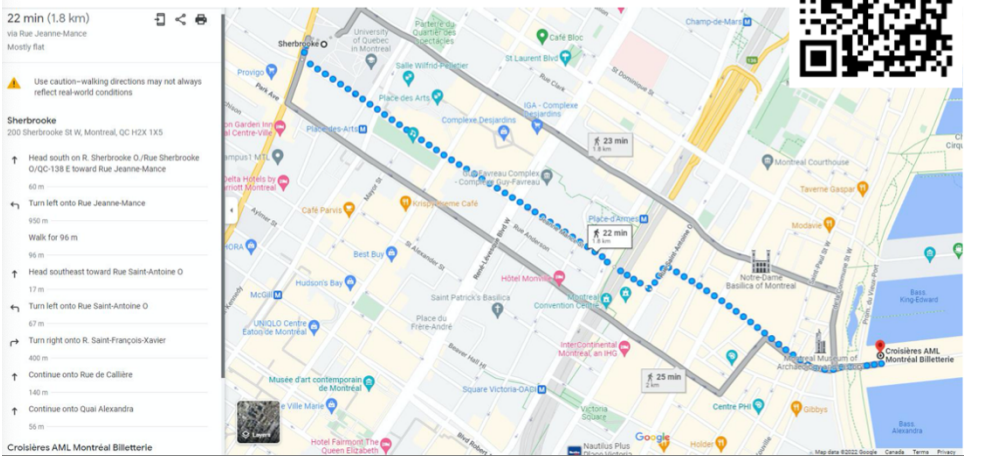
17:15 Sunday 4th: Welcome Cocktail at
DoubleTree by Hilton Montreal, 1255 Jeanne Mance
St, Montreal, Quebec H5B 1E5 (https://goo.gl/maps/uXTn1H9JyBzFvfAL9)



Croisières AML Montréal

200 R. de la commune O, Montréal, Quebec H2Y 4B2

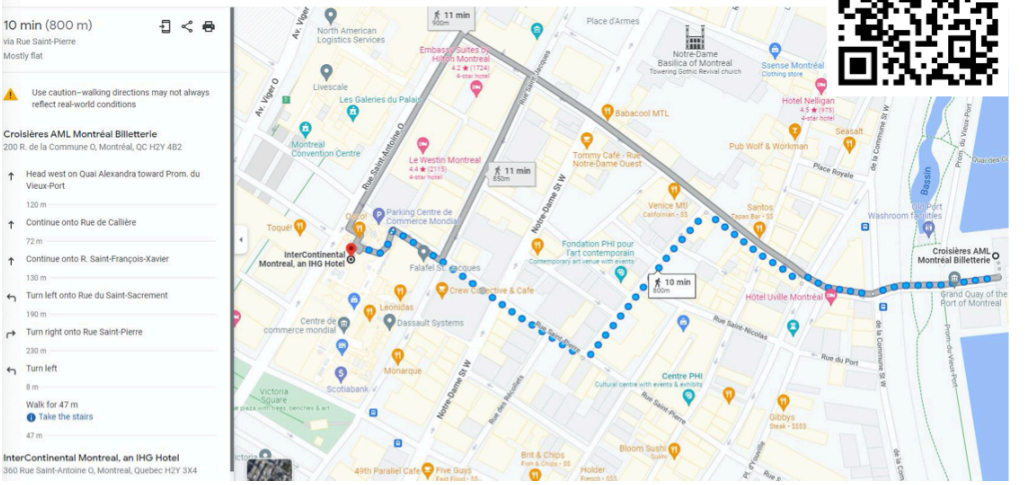
15:45 Tuesday 6th: Cruise at Croisières AML Montréal 200 R. de la Commune O, Montréal, QC H2Y 4B2 (https://goo.gl/maps/ux5JBETWsNhjwyVJ8)



Gala Dinner at InterContinental Montreal

360 Rue Saint-Antoine O, Montréal, Quebec H2Y3X4

17:00 Tuesday 6th: Gala Dinner at InterContinental Montreal, IHG Hotel 360 Rue Saint-Antoine O, Montreal, Quebec H2Y 3X4 (https://goo.gl/maps/i7bc62qy1zsmFBus7)



If you have any trouble

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