58th International Conference on the Bioscience of Lipids (ICBL) Zürich, Switzerland, September 10-14th, 2017

Scientific Report: "Lipid signaling in health and disease"

The 58th ICBL was held in Zürich the biggest city in Switzerland, located close to Lake Zürich at the center of Europe. The ICBL delegates met for four days at the main building of the Eidgenössische Technische Hochschule Zürich (ETH Zürich), in the center of Zürich City. The local Scientific Committee represented all three Zürich academic institutions in life science research and consisted of the co-chairs Christian Wolfrum (ETH Zürich), Arnold von Eckardstein (University Hospital Zürich) and Thorsten Hornemann (University of Zürich). The conference was attended by more than 150 scientists and accompanying persons from more than 20 countries, including scientists from every continent with the exception of Antarctica.

After a welcome address given by Lazlo Vigh the president of ICBL, the Conference opened on the evening of September 10 with the 21st Laurens van Deenen Lecture entitled "Circadian control of lipid metabolism and pathological consequences of clock perturbations", delivered by **Bart Staels from the University de Lille in France**. Bart Staels who has been instrumental in delineating the role of lipid mediated regulation of transcription factors and the implications for cellular function, reported on his new and mostly unpublished research linking food intake to the cellular clock and the regulation of metabolism of lipid metabolism. As it is known that disturbance of the circadian rhythm, as observed in shift workers, can lead to alterations in lipid metabolism and predispose towards the development of type 2 diabetes, his research will in the future help us to link these observations with molecular mechanisms, which might provide novel targets to treat metabolic disorders. The award, sponsored by BBA Molecular and Cell Biology of Lipids, was presented by both Laszlo Vigh, and Christian Wolfrum. Based on the presented information that alcohol dehydrogenase expression is under circadian control, the audience put their newfound knowledge to practice at a welcome reception in the Dozentenfoyer of the ETH Zürich, overlooking Lake Zürich with a beautiful view of the Alps in the sunset.

The scientific program continued for the next four days with six sessions on the topic of lipid sensing and signaling in health and disease. Each session included two to three invited presentations of leaders in their respective fields, followed four to six short presentations from young researchers, who had been selected by the organization committee, based on the submitted abstracts (15 invited lectures and 28 short presentations, in total). Over 70 posters were continuously displayed to facilitate exchanges between presenters and attendees, young and old, established and new researchers, offering many hours for in depth discussion and exchange of ideas accompanied by cheese and wine. The poster committee, which

consisted of the invited speakers as well as the local organizers, was chaired by Christian Wolfrum in his role as the ICBL vice-president. The committee had multiple excellent submissions to consider. It awarded the poster prize to **Cynthia Weigel** from the **University of Jena** on the topic of "Genotoxic stress-induced sphingosine 1-phosphate lyase suppression as a protective mechanism against systemic inflammation" and **Wenfei Sun** from the **ETH Zürich** on the topic of "Paternal cold exposure induces brown adipose tissue hypersensitivity in offspring and ameliorates diet induced obesity". The prices were given out at the gala dinner held in the Zunfthaus zur Zimmerleuten in Zürich. In addition, a second price was awarded to the best oral presentation from a young researcher, evaluated by the oral communication committee, which consisted of several invited speakers and was chaired by Lazlo Vigh in his role as the ICBL president. The price was awarded for the excellent presentation of **Anna Worthmann** from the **University Hospital Hamburg** on the topic of "Cold-induced conversion of cholesterol to bile acids in mice shapes the gut microbiome and promotes adaptive thermogenesis".

The first session on Monday morning opened with a welcome address from Detlef Günther the vice president of ETH Zürich for research and industrial affairs who welcomed the delegates to ETH Zürich. The following scientific session on sphingolipids started with the presentation of **Thorsten Hornemann (University Zürich)** on the physiology and metabolism of 1-deoxySphinglipids. **Thorsten Hornemann** reported a non-canonical catabolic pathway for the degradation of 1-deoxy-Sphingolipids, which could be a new therapeutic target in T2DM. **Timothy Hla (Harvard Medical School)**, the second invited speaker in the sphingolipid session presented data on ApoM as a specific chaperone for Sphingosine-1P. He showed that endothelial dysfunction, a hallmark of vascular disease, is restored by HDL bound S1P. The following presentation was a short talk of **Regula Steiner (University Zürich)** on the metabolism of 1-deoxymethylsphingolipds. These lipids belong to the class of 1-deoxysphingolipids, however **Regula Steiner** demonstrated that 1-doxmethSA is structurally and metabolically different to 1-deoxySA. Whereas 1-deoxySA has a 14-15 cis double bond, 1-deoxymethSA bears a 4-5 trans double bond similar to canonical sphingolipids. Following was a second short presentation by **Tetsuya Hirabayashi (University of Tokyo),** who spoke about the role of the phospholipase PNLP1 in the formation of omega-O-acyl-ceramides. These metabolites play an important role in skin physiology and mutations in the PNPLA1 gene cause autosomal recessive congenital ichthyosis in humans due to epidermal permeability barrier defects and severe trans-epidermal water loss. The session on sphingolipids was continued by **Giovanni D'Angelo (National Research Council)**, who

presented data on the metabolic crosstalk between sphingolipids and phosphoinositides at the Golgi complex. He showed that sphingolipid flux to the Golgi triggers a signaling pathway leading to PtdIns(4)P dephosphorylation as part of the homeostatic circuit that maintains a constant lipid composition of Golgi and post-Golgi membranes. The next two presentations were short talks from **Anthony Don (University of Sidney)** and **Srividya Velagapudi (University Hospital Zürich)**. **Anthony Don** spoke about C18 ceramides as a central mediator of insulin resistance in muscle. He introduced a potent and selective CerS1 inhibitor and investigated the effect of CerS1 inhibition on fat metabolism and insulin sensitivity in vivo. Subsequently, **Srividya Velagapudi** spoke about the role of S1P receptors as regulators of the trans-endothelial transport of lipoproteins (LDL, HDL). She showed that the pretreatment of aortic endothelial cells with inhibitors for S1P1 and S1P3 decreased the specific association and transport of HDL but increased the association and transport of LDL. After the lunch break, the session on sphingolipids was concluded by three short presentations. First, **Nozomu Okino (Kyushu University)** reported that the induction of neutral ceramidase in Pseudomonas aeruginosa is triggered by the presence of sphingosine from the host lipid pool. This induction is mediated by a newly identified sphingosine-responsive regulator (SphR), which encodes a transcriptional regulator. The next short talk was held by **Maija Ruuth (Helsinki University)** who showed that the susceptibility of LDL particles for aggregation is a predictor for future cardiovascular deaths. A causative role of LDL lipid composition in LDL aggregation was established by lowering the proportion of sphingomyelins in LDL. Finally, **Songhwa Choi (Stony Brook University)** reported that myristate induced the expression of ER stress markers while palmitate did not. She investigated the role of Ceramide synthases 5 and 6 in this response and showed that a pan inhibition of all CerS isoforms with FB1 but also the knockdown of CerS5 and CerS6 suppressed the myristate-induced ER stress.

The second session started on Monday afternoon on Microorganisms and Immunity and addressed the novel interest in microorganism's regulation lipid metabolism and function, which has generated a tremendous amount of interest in recent years as a novel important contributor to systemic metabolism. Invited lectures were presented by **Thierry Soldati (University of Geneva)** on the *Mycobacteria marinum* and its access to host lipids. He demonstrated that these microorganisms not only are transferred by hijacking host lipid droplets, but also through usage of the host phospholipids via diacylglycerol acyltransferases. **Patrice Cani (University Louvain)**, the second invited speaker presented his new work on the role of gut immunity and the implications for alterations in metabolism leading to the development of obesity and type 2 diabetes. He demonstrated that *Akkermansia muciniphila* plays a major role in the protection from obesity and might thus constitute the first therapeutic bacterium. Short presentations were given by **Josef Ecker (Technical University Munich)** on the role of gut microbiota in the regulation of hepatic fatty acid desaturation and elongation. Using an

integrated analysis of lipidomics, proteomics and transcriptomics he was able to demonstrate that gut microbiota contribute to the hepatic fatty acid synthesis through regulation of Scd1 and Elovl5, which was causative in modulating the saturation profile in different lipid classes. The next speaker, **Jonathan Muri (ETH Zürich)** presented new work on the characterization of oxidized phospholipids in the context of immune cell regulation. He showed that specific epoxycyclopentenones derived from PAPC are potent anti-inflammatory signaling molecules that regulate cellular function via Nrf2. Further short talks were given by **Peiying Yang** from the **Anderson Cancer Centre** in Texas on the link between dietary sugar intake and the effect on mammary gland tumorigenesis through 12-lipoxygenase. **Takao Sanaki (Shionogi University)**, who concluded the session, presented his new work on the inhibition of dengue virus infection through phosphatidylinositol from bovine liver contrary to phosphatidylinositol from soybeans.

The third session on protein lipid-interactions and lipid sorting was started on Tuesday morning by **Jay Horton (Southwestern University)** with a presentation on the regulation of acetyl-CoA carboxylase. Apart from transcriptional regulation by SREBP-1c and (de)phosphorylation, this lipogenic enzyme is also regulated by protein polymerization through the cytosolic protein MIG12 by lowering the threshold for citrate-induced ACC activation. His group has now identified a lipogenic complex that channels products/substrates to enhance fatty acid synthesis. **Bart van de Sluis (Groningen University)** identified a prominent role of the CCC (COMMD1-CCDC22-CCDC93) and WASH complexes in systemic cholesterol homeostasis by facilitating the endosomal trafficking of the LDL receptor. Perturbations in CCC complex lead to impaired recycling of hepatocyte LDLR causing hypercholesterolemia in mice, dogs and humans. Hepatic depletion of *Commd1*, *Commd6* or *Commd9* resulted in massive reduction in the expression of all COMMD proteins, increased plasma LDL cholesterol levels, and promoted the development of atherosclerosis. **Alexander Bartelt (Harvard Medical School)** identified the cold-induced, ER-localized transcription factor nuclear factor erythroid factor-2, like-1 as a master regulator of proteasomal activity and BAT metabolic adaptation. Mice lacking Nfe2l1 specifically in brown adipocytes displayed global accumulation of ubiquitinated proteins, particularly in the ER, mitochondria and lipid droplets and displayed abolished lipoprotein uptake into BAT and insulin resistance in response to high-fat diet. **Thomas Grewal (Sidney University)** identified Annexin A6 as a novel limiting factor for cholesterol efflux from late endosomes (LE)/lysosomes in addition to Niemann Pick Type C1/C2 proteins, oxysterol-binding proteins ORP1L and ORP5, STARD proteins, ABC transporters and several Rab proteins. AnxA6 is recruited to LDL-cholesterol enriched LE and recruits a Rab7-GTPase activating protein to cholesterol-rich LE as well as ORP1L, which enables the formation of membrane contact sites and thereby cholesterol transfer between LE and the endoplasmic reticulum. **Bob Farese (Harvard Medical School)** investigates the molecular processes that govern the synthesis of energy storage lipids as well as their storage in and mobilization from lipid droplets. He presented a model of LD formation from the ER in distinct steps and highlight the biology of proteins that govern this biophysical process. The first step is triacylglycerol Synthesis within the ER by diacylglycerol acyltransferase. The second step is the formation of an oil lens in the ER

membrane, which involves several proteins. The third step, budding and nascent lipid droplet formation, is initiated by seipin. The forth step is lipid droplet growth and expansion via acquisition of specific proteins that requires the COP-I/coatamer protein machinery. **Vesa Olkonen (Helsinki University)** reported on his recent findings on the role of the oxysterol-binding protein ORP2 in lipid transport and signalling at membrane contact sites. His findings suggests that the function of endogenous ORP2 in hepatocytes involves the control of cellular energy metabolism but also regulation of F-actin, cell adhesion, migration and proliferation. **Dr. Suguru Komenoi (Chiba University)** reported on the characterization of mice with a knock out of the one isofom of diacylglycerol kinase, which phosphorylates diacylglycerol to produce phosphatidic acid. DGKη-KO mice displayed an overall behavioral profile that is similar to human mania. Moreover, these phenotypes were significantly attenuated by the administration of lithium.

The fourth session, which was dedicated to novel enabling technologies to understand lipid signaling started on Tuesday afternoon. The session opened with an invited talk from **Jörg Heeren (University Hospital Hamburg)** who presented novel technologies to image the molecular mechanism of lipoprotein processing. He demonstrated the use of novel tracer techniques in combination with in vivo imaging to understand the lipoprotein import into brown adipose tissue. His talk was followed by Howard **Riezmann (University of Geneva)** who presented his work on the role of sphingolipid metabolism and function in anoxia. Using several untargeted analyses of lipidomics, he identified deoxyceramieds as mediators of toxicity related to anoxia-induced death in worms, which seems to be mediated through mitochondria and actin as possible mediators. These presentations were followed by two short talks, the first being from **Silvia Munoz (Instituto de Investigaciones Marinas)** on targeting adipose tissue as a key of lipid mediator modulation in pre-diabetic state. She showed that that adipose tissue is a valuable target to study the presence of chemical mediators and demonstrated significant differences in the formation of fatty acid derived epoxides, together with fatty acid hydroxides, which are known precursors of lipoxins resolvins and protectins in obesity and type 2 diabetes. The next short talk was by **Anirikh Chakrabarti (Nestle Institute of Health Science)** on the computational biochemical network characterization of ketometabolism. In his study, he used a combination of genome scale metabolic models to computationally enumerate all the biochemical routes of MCFA metabolism in a ketogenic diet to different ketone bodies and other key intermediates. Using a combination of computational and 13C labeling studies, he furthermore demonstrated the interdependencies within the metabolic routes, relationships between key ketogenic/glucogenic amino acids and energy metabolism. The last talk of the session was presented by **Gerhard Liebisch (University Hospital of Regensburg)**, who talked about the dangers and pitfalls of lipidomics analyses. Based on his studies he suggests that it is an absolute prerequisite for lipidomics data quality to implement minimum reporting standards for both shotgun and LC-MS lipidomics. Additionally, based on his work it is clear that certified lipid standards and sample material with certified target values, and cross-platform and inter-laboratory will be required to identify error sources and to establish solid concentrations for lipid species.

The fifth session of Fatty acids and their Derivatives started on Tuesday afternoon and commenced on Thursday morning. On Tuesday, the session was opened by **Ingrid Fleming (Goethe University Frankfurt)** with a talk on signaling by PUFA-derived epoxides and diols. It is well established that endogenously stored polyunsaturated fatty acids can be metabolized by several enzymes, however the information on the role of cytochrome P450, which can metabolize PUFAs to bioactive epoxides, which are in turn metabolized to diols by the soluble epoxide hydrolase. In this context, she demonstrated the presence of two separate

signaling mechanisms, which regulate cholesterol metabolism and physiology. The last talk on Tuesday was given by **Gaston Prez (Institute of Molecular and Cell Biology of Rosario)**, who talked about arachidonic acid derived endocannabinoids as mediators of cholesterol trafficking in Caenorhabditis elegans. He described a novel role for endocannabinoid signaling molecules in cholesterol trafficking mechanisms and he showed that endocannabinoids can rescue the arrest from PUFAs deficiency, but also abolish the larval arrest caused by impaired cholesterol trafficking.

The sixth session on Sterol and Bile Acid mediated signaling started on Wednesday morning. The session was dedicated to new insights in the signaling capacity of these molecules, which have been recognized as important mediators of systemic metabolism and cellular function through newly identified signaling hubs. The session was started by the invited talk of **Kristina Schoonjans (EPFL Lausanne)** who presented her novel work on the role of the bile acid sensor Tgr5 in regulating brown adipocyte functionality. She could show that brown adipocyte specific TGR5 signaling induces beiging of white adipose tissue and contributes to body temperature maintenance and energy homeostasis. This presentation was followed by a second invited talk from **Stan van de Graaf (AMC Amsterdam)** who presented his new work on the modulation of bile acid transporters to treat metabolic diseases and who underscored the importance of extrahepatic bile acid signaling in the regulation of cellular function. Following the two invited speakers, two young scientists presented their recent research. The first short talk was given by this year's winner of the young scientist oral communication award **Anna Worthmann (University Hospital Hamburg)** who presented her novel research on the influence of liver derived bile acids, which shape the gut microbiome and thereby alter its functionality to regulate systemic thermogenesis. Her work very elegantly demonstrates that hepatic cholesterol and bile acid metabolism are key determinants of cold-induced gut microbiota and are important for brown adipose tissue function, in vivo. The second short talk was given by **Susanne Wolfrum (ETH Zürich)** who presented her research on the novel atypical bile acids THBA and its role in the regulation of adipocyte formation and function. Usage of this bile acid in the future might constitute a nutritional approach to prevent the development of insulin resistance and type 2 diabetes. The third invited talk of this session was given by **Bert Groen** from **AMC Amsterdam** on the subject of bile acid signaling and cholesterol homeostasis. Using various mouse models as well as pharmacological manipulation, he elucidated the regulatory mechanism of trans-intestinal cholesterol excretion, which is achieved through the activation of the sterol exporting heterodimer Abcg5/g8 and regulated via the concerted action of NPC1L1, intestinal FXR and Abcg5/g8 in the intestine. His talk was followed by two short talks the first being given by **Elena Osto** from the **ETH Zürich**, who presented her work on changes in HDL structure and composition in bariatric surgery. She showed that small HDLs, which appear after RYGB, are increased and have enhanced cholesterol efflux capacity. Thus, RYGB seems to achieve a dual benefit by increasing the concentration and function of HDL. The last talk of this session was presented by **Fumika Mi-ichi (Saga University)** who talked about the importance of cholesterol sulfate synthesis in cell differentiation in *Entamoeba mitosomes*.

The session Fatty acids and their Derivatives was continued on Thursday morning with a presentation of **Ivan Tancevski (Innsbruck Medical University)**. He talked about the role of arachidonic-acid derived eicosanoids in cholesterol metabolism. He demonstrated that the arachidonic acid-derived bioactive lipid mediators such as leukotrienes and lipoxins play a central role in cholesterol homeostasis and promote reverse cholesterol transport. Interestingly, genetic polymorphisms of arachidonate 5-lipoxygenase which is involved in the regulation were associated with significant changes in both HDL mass and function in humans. The presentations was followed by three short talks. The first was from **Anggit Sunarwidhi**

(University of Manchester), who talked about the role of endocannabinoids in cutaneous inflammation and who showed that these lipid molecules can affect cutaneous inflammation and keratinocyte differentiation. The second short talk was from **Bing Peng (Leibniz-Institut für Analytische Wissenschaften)**, how presented a novel high-throughput quantitative analysis of lipid mediators for platelet activation. She demonstrated a novel reliable and rapid approach to analyze a wide range of mediators using liquid-liquid extraction, high performance liquid chromatography-tandem mass spectrometry, and high-throughput data analysis. The last short talk was given by **Paola Corsetto (University of Milan)** on the dysregulation of fatty acid metabolism induced by fasting mimicking diet on peripheral blood in cancer patients who could show that nutrient starvation affects systemic lipid metabolism with possible meaningful consequences on cancer cell proliferation and anticancer treatment activity. After a coffee break, the session was continued by an invited talk from **Takehiko Yokomizo (Juntendo University)** on the role of the 12-HHT/BLT2 axis in the protection of acute lung injury. Based on his work he concluded that the increased mortality rate of pneumococcus-infected patients by COX inhibitors is presumably due to the reduced production of 12-HHT, and CysLT1 antagonists. Utilization of these compounds, which are present in anti-asthmatic drugs, might therefore be beneficial to treat patients with pneumococcal pneumonia. The following short talk was given by **Catherine Mounier (Université du Québec à Montréal)** on the role of monounsaturated fatty acids in hepatic fatty liver diseases. Using various animal models, she could show that SCD1 is a key player in the development of hepatic steatosis. Her data therefore suggest that SCD1 inhibition could be a therapeutic option for the treatment of hepatic fatty liver disease. The last talk of the session and the last talk of the conference was presented by **Bernd Helms (Utrecht University)** on the regulation of lipid droplets in hepatic stellate cells. He identified the function of lysosomal acid lipase in the degradation of a specific pre-existing pool of LDs in hepatic stellate cells, which in turn is required for stellate cell activation.