Editorial—Special issue of the 7th European workshop on lipid mediators

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The Seventh European Workshop on Lipid Mediators (7EWLM) was held at Université catholique de Louvain in Brussels, Belgium September 12-14, 2018. The aim of the workshop was to bring together those researchers and students interested in the field of bioactive lipid mediators. The seventh edition of this biennial workshop was organized by Giulio Muccioli, Mireille Al Houayek, Gerard Bannenberg, Joan Clària, Per-Johan Jakobsson, Xavier Norel, Nils Helge Schebb and Chengcan Yao. The three-day event provided a good opportunity for participants to present their work, and enjoy a variety of presentations by experts, a session for young scientists, an educational session on analytical chemistry of lipid mediators, and poster sessions (see full program and download the abstract book at https://workshop-lipid.eu//7EWLM/index.php?cat=Program). More than 200 scientists from across and outside Europe attended the workshop on the impressive campus of Université catholique de Louvain located in -Brussels. The workshop placed special focus on the following themes: i) lipid mediator receptors and signalling, ii) lipid mediators in immune and inflammatory responses, iii) lipid mediators in vascular and metabolic diseases, iv) endocannabinoids, v) lipidomics and advances in fatty acids and their derivatives.

Here, we present to you this Special Issue of Prostaglandins and Other Lipid Mediators with a total of fourteen publications equally comprised of reviews and original publications by speakers who presented at the 7EWLM. This Special Issue is neither a systematic nor comprehensive review

of all the topics and presentations delivered at the 7EWLM, but rather highlights the voluntary contributions of the participating scientists and their research colleagues.

In the first of the six reviews in this special issue, the organiser of the former EWLM in Frankfurt, **Steinhilber** and colleagues provide an overview of the cellular functions of 5-lipoxygenase (5-LOX). This paper summarizes the factors that regulate 5-LOX expression and addresses the biological functions of 5-LOX beyond its largely recognized role in leukotriene and SPM formation, especially its interaction with p53 and the regulation of developmental pathways. **Balvers, Albada** and colleagues reviewed recent progress on the roles of omega-3 long-chain polyunsaturated fatty acid (n-3 LCPUFA)-derived fatty acid derivatives and their oxygenated metabolites in the modulation of inflammation. It is suggested that n-3 LCPUFA intake changes circulating LCPUFA, oxylipin and endocannabinoid profiles and that n-3 LCPUFA-derived metabolites, such as the endocannabinoid-like compounds eicosapentaenoyl ethanolamide (EPEA) and docosahexaenoyl ethanolamide (DHEA), have higher anti-inflammatory and anti-proliferative potential than their precursors. The authors also discuss the emergent need for development of chemical probes to study n-3 LCPUFA metabolism. The next comprehensive review focusses on oxysterols. Oxysterols are located in the pathway from cholesterol to bile acids and are now considered as lipid mediators of great interest. **Griffith and Wang** summarize the mechanisms for the formation of the main oxysterols. Disruption of these metabolic pathways is responsible for several diseases such as Lysosomal Storage Disorders that are also discussed by the authors in the context of oxysterol metabolism. **Weigert** and colleagues, discuss in their review that cancer associated fibroblast (CAF) are promoting tumour progression, an effect partly due to their ability to produce PGE_2. However, these authors show an opposition with the protective effect of PGE_2 in most fibrosis models. PGE_2 is a pro-tumour lipid mediator whilst at the same time PGE_2 can attenuate the CAF phenotype in a homeostatic manner. A potential pharmacological intervention in cancer, but also cardiovascular and other diseases, are inhibitors of microsomal prostaglandin E synthetase 1. **Jakobsson** and colleagues assessed recent results on development of mPGES-1 inhibitors in preclinical models and their future clinical applications. The integration of fatty acids and lipid mediators in the membrane requires their activation by coenzyme A. In the next review, **Kuwata and Hara** summarize and discuss the current knowledge on acyl synthetase long-chain isoform (ACSL) 4 in the context of PUFA, and especially arachidonic acid, metabolism.

The first original research publications focus also on the multiple roles of PGE_2 in the regulation of pathological states. In cancer, inhibition of tyrosine kinase receptors (like epidermal growth factor receptor (EGFR)) is an efficient treatment, but resistance is a challenge. **Morbidelli,**

Donnini and Coworkers found an increased mPGES-1/PGE_2 pathway in gefitinib (EGFR inhibitor) -resistant non-small cell lung cancer (NSCLC). PGE_2 amplifies the pro-tumorigenic properties in these human NSCLC cells resistant to gefinitib. This effect is associated with acquisition of mesenchymal and stem-like properties and nuclear EGFR translocation. One mPGES-1 inhibitor (MF63) is able to overcome acquired resistance to gefitinib in NSCLC cell lines. Therefore, mPGES-1 inhibitors as well as cyclooxygenase-2 inhibitors are increasingly suggested to be therapeutic approaches for treating aggressive and resistant lung cancers.

Using prostanoids as biomarkers, **Pawelzik** and coworker**s** studied the effect of obesity on urinary prostanoid levels. In their paper, they report that tetranor-PGDM and tetranor-PGEM are the two major urinary prostanoid metabolites in the obese subjects studied. They also found that these two mediators' urinary levels associate with metabolic parameters. **Norel** and coworkers investigate the interaction between PGI_2 and ET-1 pathways in vascular smooth muscle from pulmonary hypertension patients: Prostacyclin analogues and endothelin-1 receptor antagonists are used for treating pulmonary hypertension. In this study, the researchers investigate whether the combination of a PGI_2 analogue and an endothelin-1 receptor antagonists may be more effective than each treatment alone to treat pulmonary hypertension Group-III patients. They found that antagonizing ex vivo the endothelin receptor type B increases endothelin-1 production in pulmonary arteries and parenchyma. Moreover, the combination of an antagonist of the ETA receptor with iloprost results in a larger inhibition of human pulmonary artery smooth muscle cell proliferation than each drug alone.

Fowler and coworkers focuses on the endocannabinoid system in the context of neuroblastoma. They used a human neuroblastoma cell line, i.e. SH-SY5Y cells, to investigate the expression of the genes coding for the enzymes involved in the synthesis and catabolism of endocannabinoids. When considering the important role of 2-arachidonoylgleycerol in the CNS, an interesting finding was the relatively low expression and enzymatic activity of monoacylglycerol lipase (MAGL) compared to α/β hydrolase domain 6 (ABHD6) in these cells.

Two papers in this Special Issue focus on the analytical chemical methods necessary to quantify lipid mediators in biological samples. **Garscha** and coworkers developed a new analytical approach for the identification and quantification of glutathione (GSH) conjugates of oxygenated polyunsaturated fatty acids. These lipid mediators comprise pro-inflammatory conjugates such as the cysteinyl leukotrienes, eoxins and five-oxo-GSH conjugate (FOG7) derived from arachidonic acid, as well as conjugates involved in tissue regeneration (CTRs) that include maresin CTRs (MCTRs), protectin CTRs (PCTRs) and resolvin CTRs (RCTRs), which are biosynthesized from docosahexaenoic acid (DHA). The analytical approach consists of a gradient UPLC-MS/MS method for the analysis of pro-inflammatory and pro-resolving GSH conjugates using positive electrospray ionization and collision-

induced fragmentation for identification and structural information, and a negative ionization mode for quantification. Several applications are highlighted in the publication. Targeting esterified eicosanoids and other oxylipins, **Schebb** and Coworkers made a systematic evaluation of the influence of the method used for the extraction of lipids and the removal of proteins, the base hydrolysis conditions and the solid phase extraction approach on the precise and reproducible quantification of esterified oxylipins in plasma. The optimized methodology is of fundamental and practical use to all researchers interested in enhancing the sensitivity for quantification of oxygenated lipid mediators in biological systems. The optimized approach was demonstrated by measuring the changes in oxylipin pattern following omega-3 LCPUFA feeding in rats. The biological effect of these long chain polyunsaturated fatty acids (PUFA) being precursors of various lipid mediators are investigated in the last two papers of the special issue. LCPUFAs have been indicated to be protective in asthma, but it is unclear whether modulation of lung miRNA expression by LCPUFAs is involved. **Fussbroich** and colleagues found that for 62 miRNAs that were dysregulated significantly in mouse allergic asthma, LCPUFA supplementation restored 21 of them, relating to TGF-b signalling, extracellular matrix receptor interaction and fatty acid biosynthesis. This might be associated with LCPUFA reduction of COX2 and 5-LO activity. **Güler, Schebb** and colleagues describe the effects of dietary supplementation with both EPA and DHA on kidney tubular function in a murine model of acute kidney injury. Omega-3 LCPUFA -rich feeding for two weeks increased systemic and renal levels of omega-3 LCPUFA, as well as eicosanoids and other lipid mediators derived from omega-3 LCPUFA, while omega-6 LCPUFA-derived mediators were decreased. Renal function impairment, renal damage and inflammation were not influenced, but tubular function was found to be protected, as shown by a higher expression of the tubular transport marker alpha-1 microglobulin (A1M) in proximal tubular epithelial cells and upregulation of heme oxygenase-1 (HO-1). The results suggest that discrete functional adaptations take place that may protect kidney function in the face of acute kidney injury.

The 7EWLM organizers would like to acknowledge the contributions of both the young as well as senior researchers that presented their work in Brussels. We also thank the local staff at UCL Brussels led by Giulio Muccioli and Mireille Al Houayek who helped to organize the workshop logistics and made the event a wonderful experience for all participants. We would also like to sincerely acknowledge the generous sponsors of the 7th EWLM: Ambiotis, Antibodies-online, Avanti Polar Lipids, Bertin Pharma, Cayman, Genomics Online, Marine Ingredient KD Pharma, Lipidomix, Metagenics, ONO Pharmaceutical, Sanofi Aventis, VWR and Waters. Without their generous support this workshop would not have been possible.

We are **pleased to announce** that the next edition of this workshop, 8EWLM, will be held at the Karolinska Institute in Stockholm June 24-26, 2020. The preliminary scientific program is attractive including a plenary lecture of Nobel laurate Bengt Samuelsson. For more information on our next event and to view the list of invited speakers, see our website: https://workshop-lipid.eu/index.php?cat=Program. A special session for young researchers, and a session of educational presentations, will also be organized.

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