## Abstract: 13S

**Lipidomic profiling identifies hepatic phosphatidylserine synthesis as a novel signature of resistance to non-alcoholic steatohepatitis – Targeting of phosphatidylserine synthase 1 for therapeutic intervention**

Marziyeh Anari[1#], Hamzeh Karimkhanloo[1,2#] , Gio Fidelito[1], Shuai Nie[3], Jacqueline Bayliss[1], Stacey N. Keenan[1], Paula M. Miotto[1], William De Nardo[1], Camille Devereux[1], Nicholas A. Williamson[3], Matthew J. Watt[1], **Magdalene K. Montgomery**[1]

[1] *Department of Anatomy and Physiology, School of Biomedical Sciences, Faculty of Medicine Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC 3010, Australia*

[2] *Metabolism, Diabetes and Obesity Program, Monash Biomedicine Discovery Institute, and Department of Physiology, Monash University, Clayton, Victoria, Australia*

[3] *Melbourne Mass Spectrometry and Proteomics Facility, Bio21 Molecular Science & Biotechnology Institute, The University of Melbourne, Melbourne, Victoria, Australia.*
# Equal first author

Non-alcoholic steatohepatitis (NASH) is characterised by presence of hepatic steatosis, lobular inflammation, and hepatocyte injury, in the absence or presence of hepatic fibrosis, which can further progress to end-stage liver diseases, including liver cancer and cirrhosis, contributing to liver-related and all-cause mortality. Despite this increasing clinical epidemic, there are currently no approved pharmacotherapies for NASH and liver fibrosis. This is related to our limited understanding of the metabolic adaptations that occur within the liver during the development of NASH. While it is known that the early stages of disease progression are characterized by defective lipid metabolism, previous lipidomics studies in both rodents and humans have been inconsistent in identifying NASH-regulated lipids and lipid metabolism pathways.

To increase our understanding of changes in hepatic lipid metabolism in NASH, our group recently compared NASH pathology across eight common mouse strains fed a western-style diet, which was accompanied by detailed lipidomics profiling in the liver, and generation of bioinformatic prediction models of lipid metabolism pathways associated with susceptibility and resistance to NASH. Using this comprehensive lipidomics analysis, we identified phosphatidylserine (PS) accumulation and preservation of PS synthase 1 (PSS1) expression as a novel lipid signature associated with resistance to NASH. Indeed, adeno-associated virus (AAV)-mediated overexpression of PSS1(Q353R), a gain of function mutant, in the livers of mice with NASH reduced lipid accumulation, lipid droplet area and markers of hepatic fibrosis. Despite improvements in hepatic lipid metabolism and NASH pathogenesis, PSS1-AAV mice showed increased adiposity, hyperglycaemia and glucose intolerance, pointing to metabolic adaptations beyond the liver.

Together, this study indicates that increasing hepatic PS content could be a therapeutic strategy for prevention or reversal of NASH and liver fibrosis.