Understanding the mechanism of development of NASH using MS Imaging: Discovery of new disease state biomarkers

Pierre-Maxence VAYSSE², Anita M. VAN DEN HOEK³, Gregory HAMM², Robert KLEEMANN³, ○ Stefan LINEHAN¹, Alain HERON², Jonathan STAUBER², Hans M.G. PRINCEN³

¹Imabiotec, United States, ²Imabiotec, France, ³TNO, Metabolic Health Research, The Netherlands

NASH (Non-Alcoholic Steatohepatitis) is emerging as a real health concern as the progression from simple steatosis to more severe liver pathologies like steatohepatitis and cirrhosis. The characterization of this pivotal step using predictive biomarkers can improve the knowledge on the pathogenesis of the disease in various aspects such as modifications of lipid metabolism, inflammatory processes and development of fibrosis. As the hallmarks required for the diagnosis of NASH still rely on liver biopsy, the identification of biomarkers using a Mass Spectrometry Imaging (MSI) approach associated with histopathological evaluation has a very interesting role to play. Here, we investigated the targeted metabolite profiling in two translational mouse models of metabolism disorders (APOE³Leiden.CETP and LDLR⁻/⁻Leiden) exposed to various diets to assess liver histological specificities. A multimodal approach focused on various molecular classes (small metabolites & lipids) was used to describe alterations in the liver lobules in these NASH models. Potential disease or histology related biomarkers were observed especially at the level of lipids, phospholipids or lysophospholipids classes. Smaller molecules were detected such as bile acids in the portal vein area or the GSH/GSSG couple. Potential association with fibrotic and inflammatory processes has been advanced at a biological point of view. Molecular distribution was correlated with H&E (for classical histology) staining on adjacent tissue section to highlight histological specificities related to metabolites levels. In conclusion, MSI was used to achieve a better understanding of the underlying process in development of NASH by linking changes in metabolite profiles to histopathological alterations.