Identifying NAFLD/NASH-specific molecular lipid networks with diagnostic, prognostic and therapeutic biomarker value in humans.

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Background
Non-Alcoholic Fatty Liver Disease (NAFLD) represents a spectrum of disease from “benign” hepatic triglyceride accumulation (steatosis, NAFL), through hepatic lipid accumulation with inflammation (non-alcoholic steatohepatitis, NASH) and ultimately progressing to fibrosis/cirrhosis and potentially hepatocellular carcinoma (Anstee et al., 2013). NAFLD is also strongly associated with the Metabolic Syndrome (MetS), representing the clustering in the same individual of obesity, type 2 diabetes mellitus (T2DM), hypertension and dyslipidaemia (Anstee et al., 2013). NAFLD/NASH is an important problem with enormous impact: NAFLD affects 30% of the population in developed countries and is recognized as one of the most common liver disorders and a major public health problem.

Despite its high impact there is still a lack of specific proven treatments specifically for NASH. This is due to a lack of mechanistic understanding of NAFL/NASH and of diagnostic procedures or biomarkers that can identify patients who have/will get progressive hepatic fibrosis, with sequelae of cirrhosis, liver cancer risk and liver-related death.

Methodology
Overview: The successful EBPOD candidate will have access to biological samples from well-characterised (histologically) patients with different stages of NAFLD/NASH as well as appropriate healthy controls. He/She will use systems biology approaches taking advantage of lipidomics, transcriptomics and proteomics data and developing data integration methods to:

1) To identify specific mechanisms of disease (potentially also pathogenically relevant biomarkers), which are amenable to pharmacological intervention and
2) To identify accurate diagnostic, staging and prognostic biomarkers that facilitate patient stratification for therapeutic intervention.

The EBPOD fellow will also compare this data with murine and pig related data and sample sets to identify interspecies relevant biomarkers that could be used in preclinical studies.

Particularly relevant to this fellowship, the candidate will be working in close collaboration with EMBL-EBI and Biochemistry, and MRC MDU promoting the collaboration between the institutes while tackling a question with direct impact on public health. The candidate will have access to a wide network of collaborators with expertise in systems biology of lipids (Petsalaki, Oresic, Dopazo).

Human samples: We have accumulated the most complete collection in UK of clinical data, frozen liver tissue, serum and plasma samples and genomic DNA from over 180 patients with biopsy-proven NAFLD (Allison, CUFT). These patients include the whole spectrum of severity of NAFLD and cover a range of BMIs and degrees of insulin resistance. Also, we have access to data from more than 4000 patients collected in the context of the largest cohort of patients/samples/omics data in Europe (EpooS and LItMUS).

Data types: a) lipidome (Griffin, Vidal-Puig; Oresic et al, 2008), b) transcriptome (Vidal-Puig, MRC MDU, Petsalaki, EMBL-EBI; Curtis et al, 2005) and c) proteome (Vidal-Puig, MRC MDU, Petsalaki, EMBL-EBI)

Data analysis: The EBPOD fellow will employ data integration and pathway modelling approaches to associate changes in the lipidome, transcriptome and proteome with the NASH progression and phenotype, in order to a) uncover the molecular mechanisms underlying NASH development, including defining the associated signalling, metabolic and gene regulatory pathways and their cross-talk, b) define ‘omic’ signatures that are associated with the disease that can be used as biomarkers for stratifying patients, c) perform an interspecies comparison with data from murine or pig samples for common biomarker identification that can be used in pre-clinical trials and discovery of the mechanism of disease.

Specifically, the candidate will infer protein interaction and gene regulatory maps from the data and will integrate them with known models of human metabolism and signalling pathways (Reactome, KEGG etc). This map will be used to identify network signatures that are associated with specific ‘omic’ profiles that are related to the development of NAFLD/NASH. A family of methodologies derived from Flux Balance Analysis (FBA) as well as other pathway modelling and signal propagation approaches (e.g. Gillespie algorithm, Markov Chain Monte Carlo, logic/boolean based modelling or ODE based modeling) will allow the study of the relationship between lipid (or, in general, metabolite) levels and gene/protein activities, providing a mathematical framework to integrate these data. These methods can be used to detect and prioritize mechanism-based biomarkers for validation in subsequent stages of this proposal and also identify key regulatory points that may be attractive targets for drug or diet intervention.

Relevance to health and disease

The proposed project undertaken by the successful EBPOD candidate will provide mechanistic insight for the development of NAFLD/NASH, which can subsequently be verified in cell culture, animal models and larger human cohorts through our international partnerships IMI Litmus and Horizon2020 EPooS (Quentin Ansteen). This will in turn guide the EBPOD fellow to not only identify biomarkers useful for early patient stratification based on their disease outcomes, including interspecies biomarkers, that can be used for pre-clinical trials, but also to contribute to the design of strategies for therapeutic interventions. Therefore, we expect this project to have a significant contribution in our understanding and treatment of NAFLD/NASH.