

PhD fellowship in metabolomics

Institution:	CIC bioGUNE, Derio, Bizkaia (Spain).
Department:	Metabolomics Platform
PhD supervisors:	Dr. Sebastiaan Van Liempd Prof. José M Mato

Title: Identification and validation of metabolomic-based non-invasive serum biomarkers that diagnose, subtype, risk stratify and monitor non-alcoholic steatohepatitis (NASH) progression

Project: Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of diseases occurring in the absence of excessive alcohol consumption that ranges from isolated hepatic triglyceride (TG) accumulation (steatosis, NAFL), through hepatic TG accumulation plus inflammation (nonalcoholic steatohepatitis, NASH), and ultimately progresses to fibrosis, cirrhosis and potentially hepatocellular carcinoma. NAFLD is a common condition, strongly associated with the metabolic syndrome (obesity, type 2 diabetes mellitus (T2DM) and dyslipidemia). An important brainteaser exists: a significant proportion of the population have NAFLD (10-40%), but only a minority (10-30%) progress to advanced liver disease. The transition from NAFL to NASH and the stage of fibrosis are important discriminators between a relatively benign progression and increased risk of morbidity and mortality. Liver biopsy remains the established although imperfect “gold standard” being invasive, resource intensive, prone to sampling error and carrying a small but significant risk of complications. Liver biopsy is not practical outside specialist practice and is particularly unsuitable with such a large “at risk” population. A lack of tractable non-invasive biomarkers has impeded the diagnosis, risk stratification and monitoring of patients. It has also hampered drug development and the conduct of clinical trials, which still depend on histological effect as an endpoint. Studies in mice and humans have recognized a key role of S-adenosylmethionine (SAME), a key metabolite of one-carbon metabolism (1CM), in the pathogenesis of NAFLD and its progression to NASH. We developed the methionine adenosyltransferase-/- (Mat1a-/-) mouse model, which exhibits chronic hepatic SAME deficiency, and spontaneously develops NASH, fibrosis and hepatocellular carcinoma. We also developed the glycine N-methyltransferase-/- (Gnmt-/-) mouse model where hepatic SAME

accumulates to supraphysiological level and the mice also develop NASH, fibrosis and hepatocellular carcinoma. Although both *Mat1a*^{-/-} and *Gnmt*^{-/-} models develop NASH, they occur through different mechanisms and exhibit liver lipidomic profiles that reflect different activity of enzymes involved in lipid metabolism. We recently demonstrated that around 50% of NAFLD (NAFL and NASH) patients show a serum lipidomic profile similar to *Mat1a*^{-/-} mice (M-subtype NASH). This is the first demonstration of the existence of NASH subtypes in humans, opening the way to develop better prevention and more precise treatment methods. The overarching aim of this project is to develop and robustly validate metabolomic-based non-invasive serum biomarkers that diagnose, subtype, risk stratify, monitor NAFLD and its progression to NASH and the response to treatment. The specific aims of this project are: 1) To identify and define the most accurate and tractable serum metabolomic biomarkers relevant to NAFL and NASH. 2) To identify and define the major metabolic subtypes of NASH. 3) Therapeutic targeting of 1CM metabolism in NASH. This project is funded by the Agencia Estatal de Investigación (NASHDIAGNOSIS project ID: SAF2017-88041-R) and Horizon 2020-EU (LITMUS project ID: 777377).

Duration: 48 months. The student will be enrolled in a PhD program at the University of the Basque Country as the degree awarding institution.

Requirements: The applicant should have a degree in analytical chemistry, be fluent in English and is expected to rapidly take up and develop techniques and concepts from synthetic and analytical chemistry. The candidate should have proficiency in high-resolution chromatography coupled mass spectrometry, be interested in liver metabolism /function and interested in biostatistics and modelling of biological systems. The PhD student should be desired a working knowledge of R and/or Python.

Application: Please send your CV together with a letter of motivation and a minimum of 2 references to rrhh@bicbiogune.es specifying Ref. 43112 RRHH in the subject line until 02.06.2018