Research Project Proposal
Academic year 2019-2020

Project Nº 03

Title: *Development of novel engineered forms of fibroblast growth factor 21 (FGF21) for the treatment of metabolic syndrome-associated diseases.*

Department/ Laboratory *Hepatology Program, CIMA.*

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Summary

The metabolic syndrome is a cluster of conditions including hypertension, hyperglycemia, dislipemia and central obesity. The hepatic manifestation of the metabolic syndrome is the so-called non-alcoholic liver disease (NAFLD), a condition associated with the development of diabetes, atheroscleorosis and liver cirrhosis and carcinogenesis. The prevalence of metabolic syndrome is increasing dramatically over the past decades in the western and developing world. Fibroblast growth factor 21 (FGF21), a non-mitogenic hormone, has emerged as a central regulator of energy metabolism. FGF21 is produced mainly by the adipose tissue and the liver in response to feeding status and ketogenic diets and can be also significantly upregulated in this latter organ upon parenchymal injury. FGF21 administration to obese mice or rats promotes a strong reduction in adiposity, lowers blood glucose and triglycerides, reduces liver fat deposition, inflammation and fibrosis, and improves insulin sensitivity, observations also reproduced in non-human primates. Therefore, FGF21 administration may be useful for the pharmacological management of the multiple pathological aspects of the metabolic syndrome. However, the native FGF21 protein has poor pharmacokinetic properties, including a short half-life. Modified variants of FGF21 with increased half-life in circulation are actively being sought after, and a PEGylated FGF21 has recently been demonstrated to reduce liver steatosis in humans. In our laboratory we have developed a platform to generate recombinant chimeric proteins encompassing in a single polypeptide a protein of interest coupled to apolipoprotein A-I (ApoA-I). The ApoA-I moiety allows: i) the incorporation of the protein into HDLs, increasing the half-life of the chimera, ii) targeting to hepatocytes and adipocytes, iii) crossing of the blood-brain barrier, iv) the endowment of the chimeric protein with new metabolic activities mediated through ApoA-I receptors (SR-BI and ABCA1). In this project we will:

1. Analyze the pharmacokinetic properties and tissue distribution of recombinant FGF21-ApoA-I (FA) in mice.
2. Evaluate the *in vitro* biological activity of FA on adipocytes and hepatocytes. Including cell signaling, gene expression regulation and lipid metabolism.
3. Preliminary evaluation of the *in vivo* biological activity of FA in healthy mice.

yes	**X**
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?