



Research Project Proposal

Academic year 2020-2021

Máster en Investigación Biomédica

Project Nº 39

Title: *In vitro and in vivo assessment of the myocardial antifibrotic effect of a novel epigenetic regulation inhibitor*

Department/ Laboratory :

Program of Cardiovascular Diseases, Laboratory of myocardial remodelling and heart failure

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Summary

Heart failure is a complex syndrome with growing prevalence and bad prognosis despite current treatment. It represents an unmet medical need, for which research on novel specific and safe therapies is essential.

A key pathophysiological mechanism that underlie heart failure is myocardial fibrosis, the excessive deposit of extracellular matrix, as it negatively affects cardiac function and patient prognosis.

Diverse mechanisms contribute to regulate fibroblast-to-myofibroblast transdifferentiation and their overexpression of collagen and the enzymes that metabolise it to produce myocardial fibrosis. One potential mechanism is the epigenetic regulation of the expression of molecules involved in myocardial collagen metabolism. In this regard, CIMA has developed a dual G9a histone-methyltransferase and DNA-methyltransferase-1 inhibitor (CM-272) with hepatic antifibrotic effect.

Our aim is to verify the myocardial antifibrotic effects of CM-272. In *in vitro* experiments, CM-272 will be tested in human adult cardiac fibroblasts against the pro-fibrotic cytokine TGF-beta, and the expression of a transdifferentiation marker (α -SMA), as well as procollagen and collagen-metabolism enzymes (PCP, PCPE, LOX) will be assessed by RT-PCR and western blot. In *in vivo* experiments CM-272 effects will be tested in a murine model of aortic constriction that develops myocardial fibrosis, and cardiac function parameters as well as fibrotic histological (picosirius red staining) and molecular parameters (collagen and collagen-metabolism enzymes, by RT-PCR and western blot) will be studied. In both cases, the levels of CM-272 targets (G9a histone-methyltransferase and DNA-methyltransferase-1 inhibitor) will be assessed.

yes

X

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

no