Research Project Proposal
Academic year 2021-2022
Máster en Investigación Biomédica

Project Nº 49

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

Department/ Laboratory Laboratory where the project will be carried out indicating Department, Area, Faculty, CUN, CIMA etc.
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 underlies heart failure is myocardial fibrosis, the excessive deposit of extracellular matrix, as it negatively affects cardiac function and patient prognosis. Currently, there are no specific treatments for myocardial fibrosis.

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 relevant mechanism may be 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 the level of 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. Cardiac function parameters as well as fibrotic histological (picrosirius 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. This study will determine if CM272 is a promising novel therapy for the specific treatment myocardial fibrosis in heart failure.

yes	X	Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?
no		