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HEARTzheimer - Role of Presenilin 2 in cardiovascular physiology: possible implications for Alzheimer's disease pathogenesis

Cardiovascular disease (CD) is the first cause of death in the European Union. A key factor in CD pathogenesis is Ca^{2+}. Indeed, Ca^{2+} plays a crucial role in heart contraction and defective intracellular Ca^{2+} signalling causes severe dysfunctions in failing heart. Interestingly, Alzheimer's disease (AD) patients often show CD and one of the mutated protein associated with the pathogenesis of familial AD (FAD), Presenilin 2 (PS2), is involved in the regulation of Ca^{2+} homeostasis in non-cardiac cells. The present proposal aims to study, for the first time, the role of PS2 in cardiovascular physiology and pathology and determine whether PS2 could be a new molecular link between CD and AD. I will study, the role of PS2 (wild type and FAD-PS2 mutants) in: cardiac cytosolic Ca^{2+} dynamics, sarcoplasmic reticulum-mitochondria coupling, mitochondria function, myocardial function and response to ischemia-reperfusion injury. To achieve these tasks, I will use novel technologies (some of which have not been used in cardiovascular research yet) at whole organ, cellular and subcellular level, using in vitro, in vivo and ex vivo approaches. Dr. Pizzo´s experience in investigating Ca^{2+} homeostasis in AD will be complemented with my knowledge of cardiovascular pathophysiology, to guarantee the fulfillment of all the proposed objectives. This project will not only allow me to mature as a scientific researcher, but also it will have a great impact on the host institution, by developing a new and promising line of research with the generation of new international collaborations. Finally, the obtained scientific results will be transfer to society, providing new knowledge and helping the health system and policy makers in the development of new strategies to fight these diseases.