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The European Heart House
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Lyon, 10th August 2013

Aim: Report for the ESC First contact Initiative Grant.

Criteria for eligibility: Member of the working group of Cellular Biology of the Heart

Dear Council Members,

I would like to thank the European Society of Cardiology for awarding me the First Contact Initiative Grant in February 2013. This grant gave me the opportunity to visit and collaborate with Pr David Sinclair Laboratory (The Paul F. Glenn Laboratories For the Biological Mechanisms of Aging) at Harvard Medical School (Boston, MA, USA) in June 2013, for a period of twelve days.

Pr Sinclair's group has a strong experience in Sirtuins and their role in aging as well as cancer, cardiac diseases, inflammation, neurodegeneration and diabetes. It is one of the most highly published labs in medical research with over a dozen publications in

Cell, Science and Nature over the past 10 years. They have published on the role of SIRT3 in controlling the mitochondrial permeability transition pore and its role in cardiac aging and cardiac failure, a topic that is highly relevant for my project.

During my stay, I have described my current research in Pr Michel Ovize lab to Pr David Sinclair and his team. I benefited from their experience and we discuss the results I have obtained. They help me to define new experiments for my future research. I had an individual interview with each lab's member. We discuss on their projects, and on my project. It was a very enriching experience. Furthermore, I have discovered their specific techniques developed to study Sirtuins and in particular their models available in the lab, with extended techniques, from enzymology and biochemistry to genetics and systems biology but also from mouse models to human genetics. I was very interested by their genetically engineered and mutant mice model of SIRT3 that would gave me the opportunity to develop a mechanistic insight into my research project.

Our lab is specialized in the role of the mitochondrial permeability transition pore in lethal reperfusion injury following a prolonged ischemic insult. It has been proposed that reperfusion causes irreversible myocardial damage through the opening of the mPTP, which is controlled by a matrix chaperone named cyclophilin D (CypD). Recent work has shown that sirtuin 3 (SIRT3), a Nicotinamide Adenine Dinucleotide (NAD+) dependent deacetylase found in mitochondria, is able to regulate mPTP and deacetylate CypD. Our hypothesis is that the protective intervention of mechanical "post-conditioning" could specially activates SIRT3. During my Master 2, I performed hypoxia-reoxygenation experiments (H/R) using the in vitro model of H9c2 cells and I studied SIRT3 activation and its cardioprotective effects on cardiomyocytes. To complete this work, it is important to test our hypothesis *in vivo.* We decided with Pr David Sinclair to launch a collaborative work and I will join his group for one year, doing experimental research during my PhD (from November 2013 to November 2014).

During this first year of PhD I will study the cardio-protective effect of SIRT3 during ischemic post-conditioning *in vivo*. I will use a mice model of myocardial

infarction. I will use wild type, knock out and overexpressing SIRT3 mice models and measure infarct size. Further, I will focus on a new intracellular mechanism of Sirtuin regulation and its role during myocardial infarction and especially mPTP opening. Finally, I will study the effect of a new molecule (a Sirtuin activator) on cell survival after ischemia-reperfusion. This work is very exciting and we hope it will enhance the identification of new therapeutics targets to reduce reperfusion injuries after myocardial infarction.

To conclude, I would like to thank once again the European Society of Cardiology for its support for this enriching experience. I also want to thank Pr David Sinclair and its team for their great welcoming during my stay.

Best regards,

Thomas Bochaton