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Dear Council Members,

ESC First Contact Initiative Grant Report

I would like to extend my thanks to the European Society of Cardiology and the Council on Basic Cardiovascular Science for their generous award of the ESC First Contact Initiative Grant. This gave me the opportunity to visit the Centro Nacional de Investigaciones Cardiovasculares Carlos III (National Centre of Cardiovascular Investigation, CNIC) in Madrid, Spain, under the supervision of Dr Borja Ibáñez.

The CNIC is a leading centre that combines basic and clinical science to address all aspects of cardiovascular disease, and has an international reputation for outstanding and novel research.

I worked in the Myocardial Pathophysiology Area, that is addressing, in part, the treatment of ischaemia-reperfusion injury, in September 2016. The group are expert in a porcine model of ischaemia-reperfusion and advanced imaging techniques, including MRI, CT and echocardiography. For example, they recently discovered with T2-mapping that myocardial oedema after ischaemia-reperfusion injury is not stable and instead follows a bimodal pattern.[1]

Using these techniques, the group has demonstrated both pharmacological and local ischaemic preconditioning in pigs. This is essential in the context of cardioprotective interventions that have failed to translate to man. For example, cyclosporine has been shown in pre-clinical studies to limit apoptosis, improve functional recovery and limit infarct size in models of ischaemia-reperfusion injury. However, a multi-centre, double-blind, randomised trial of 970 patients with STEMI who received IV cyclosporine prior to PPCI recently failed to meet its primary endpoint of a significant improvement in the composite of all-cause mortality, worsening in-hospital heart failure, rehospitalisation for heart failure or adverse LV remodelling at 1 year.[2] Interestingly, this result might have been predicted based on a systematic review and meta-analysis that showed that while, overall, cyclosporine reduced infarct size, there was no demonstrable benefit in swine.[3] Therefore, pre-clinical models using pigs are fundamental to improving the chances of successfully translating promising pre-clinical cardioprotective strategies. Indeed, this has been acknowledged in a recent ESC Working Group Report.[4]

To this end, the aim of this Grant and my visit to the CNIC was to experience and understand the porcine closed-chest model of ischaemia-reperfusion injury, and be introduced to pre-clinical imaging techniques. I am delighted to report that these aims were achieved and, moreover, the First Contact Initiative Grant has facilitated the foundation of collaborative research between our institutes.

In particular, I have learnt the following:

- Principles of anaesthesia and mechanical ventilation of pigs.
- Femoral arterial and venous access in swine.

- Angiography and selective balloon angioplasty of the left anterior descending coronary artery to confer myocardial infarction.
- Principles of CT to define the myocardial area at risk and MR to delineate oedema, infarction and microvascular obstruction, and ventricular remodelling.

These techniques can be applied to many promising approaches to cardioprotection to maximise their potential to confer benefit in patients suffering cardiovascular disease. Furthermore, the imaging techniques described will be applied to small animal models of ischaemia-reperfusion injury to increase their utility and as part of a reductionist approach to animal research.

When follow-up for these recovery experiments is completed at the CNIC, I look forward to collaborating with respect to the potential involvement of stromal derived factor-1α (SDF-1α), in either infiltrating leukocytes or resident cardiac cells, in the aforementioned myocardial oedema. In particular, I will use a novel antibody to intact SDF-1α to elucidate the co-ordination between and expression dynamics of myocardial CXCR4, CXCR7 and SDF-1α, and leukocyte infiltration, after AMI.

In addition, I have benefitted from the opportunity to observe imaging techniques in translational studies in humans, discuss the exciting research in relation to cardioprotection, and broaden my understanding of research outside my particular field of interest, including cardiotoxicity, neural pathway imaging and MRI sequence design.

In conclusion, I would like to thank Dr Borja Ibáñez and his whole group, especially Austin Benn and Carlos Galán, for their kind hospitality and support in achieving the aims of the Grant, and to re-iterate my thanks to the ESC for their kind support.

Yours faithfully,

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