

ESC Council for Basic Cardiovascular Science

ESC First Contact Initiative Grant Report

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Project: Effects of minicircle-hypoxia inducible factor 1-alpha on pro-angiogenic properties of mesenchymal stem cells (MSCs) in chronic ischemic left ventricular dysfunction

It was a great pleasure for me to receive the ESC First Contact Initiative Grant. With this generous support, I had the opportunity to visit the Laboratory of Asc. Prof. Mariann Gyöngyösi at the Department of Cardiology, Medical University of Vienna. I have spent vivid, convenient and productive time in her laboratory. I was involved in a project on large animal model of chronic left ventricular ischemia and cell therapy treatment. Earlier I fulfilled my PhD studies in pluripotent stem cell field in the Heart and Vascular Centre of Semmelweis University, Budapest. Although I have lot of experiences in molecular biology techniques and stem cell work in vitro, I had quite a few on animal models and in vivo studies. This grant provided opportunity for the laboratories to share their ideas and work together for the first time. Recently even a teaching course on cardiovascular cell therapy was organised for PhD students in Budapest, where Asc. Prof. Gyöngyösi also talked.

Details of the project: Intracoronary and intramyocardial autologous or allogeneic mesenchymal stem cell (MSC) therapy for treatment of acute and chronic ischemic heart disease has shown promising results in preclinical and early clinical trials mainly via the rich paracrine effects of MSCs, in spite of low cell retention rate. Hypoxia-inducible factor-1 α (HIF1 α) is one of the most powerful anti-ischemic factor, modulating over hundreds of angiogenic and regenerative substances. In order to enhance the paracrine anti-ischemic and anti-remodelling efficacy of the cell therapy, porcine allogeneic MSCs were transfected with virus-free minicircle plasmid driving HIF1 α transgene (MSC-MiCi-HIF1 α). Domestic male pigs (n=16) underwent closed-chest reperfused acute myocardial infarction (MI) via balloon-occlusion of the mid-LAD for 90 minutes, followed by reperfusion. One month later (chronic ischemic left ventricular remodelling), the animals were randomized to receive either MSCs alone (n=6) or MSC-MiCi-HIF1 α (n=10). Animals were harvested at different time points to enable detailed time-line follow up of the regenerative effects. Size of myocardial infarction and scar, left ventricular ejection fraction was analysed. In vitro proteome profiling, RT-PCR, ELISA measurements and quantitative immunohistochemistry analyses were performed to

identify angiogenic, anti-fibrotic and anti-apoptotic effects. Furthermore, novel regulators of cardiac regeneration were also identified.

In conclusion in this pre-clinical translational model of chronic post-infarction heart failure, therapy combining MSCs transfected with minicircle plasmid expressing HIF1 α significantly decreases infarct size and improves adverse remodelling via modulation of angiogenic and antifibrotic processes of the heart.

One abstract was submitted to the Heart Failure Meeting of ESC and we plan to publish the detailed results of this project in peer-reviewed journal soon.

Thanks for the motivational atmosphere and the strong and wise leader of the laboratory I could reach my best during my visit. I learned new molecular biology methods (e.g. handling transfected cell culture and cardiopoietic differentiation), I got insight how to plan, organise and perform in vivo large animal studies. I gained extremely useful hands-on experiences on large animal model of chronic left ventricular ischemia.

Back in my home institute I am very happy to share my knowledge with other PhD students and researchers in our laboratory. Moving towards in vivo studies is the dream of my home institute, thus my recent experiences may promote reaching it. Hopefully fruitful collaboration will grow between the Medical University Vienna and Semmelweis University Budapest.