Enhancement of heart repair after myocardial infarction by means of genetically improved cardiomyocytes and endothelial cells differentiated from induced pluripotent stem cells

Cardiovascular diseases are the main cause of death globally, and they are also the leading cause of death in Poland and China. Although myocardial infarction (MI) is currently effectively treated in many patients, the significant number of MI victims develop the heart failure (HF). HF is also caused by other conditions, like atherosclerosis, hypertension, atrial fibrillation, valvular heart disease, excess alcohol, infections, like influenza and various cardiomyopathies.. The survival of patients with HF is even worse than of many cancers, being 50% at 5 years. Heart transplantation is thus awaited by many patients, however, it is available only for about 10% of them.

HF develops because the regenerative capacity of the heart is very limited and there are no stem cells in the heart. After myocardial infarction, dead myocardial cells (cardiomyocytes), which up to one billion are lost, are replaced by fibrotic tissue. Intensively acclaimed strategies were applied in which cells that are not precursors of cardiomyocytes are injected into the heart, such as bone marrow cells or so called mesenchymal stem cells. However, no real long-term improvement in cardiac function and patient health has been demonstrated. Therefore, it is reasonable to develop biologically justified therapies based on human cardiomyocytes produced in vitro from real pluripotent stem cells, such as induced pluripotent stem cells (hiPSC). Importantly, preclinical studies have shown that the administration of cardiomyocytes to the heart of mice (including our published data), pigs or primates (macaques) significantly improved cardiac function after myocardial infarction. However, implantation of hiPSC-derived cardiomyocytes (hiPSC-CM) is still not fully effective, and the risk of arrhythmia caused by contracting cells injected into the heart requires testing of new strategies before clinical applications occur.

The aim of the project is to examine the effectiveness of improved hiPSC-derived progenitor cells demonstrating the ability to differentiate into hiPSC-CM and endothelial cells (hiPSC-EC) to augment heart function after myocardial infarction. Based on the previous experience of Polish and Chinese team, we hypothesize that overexpression of heme-1 oxygenase- 1 (HO-1), the cytoprotective, anti-apoptotic, anti-inflammatory, proangiogenic and immunomodulatory protein will increase the survival of cells injected into damaged myocardium. In addition, we will examine the possibility of using regulated HO-1 expression, applying safe and already tested in the clinic AAV vectors, into which we will insert the HO-1-coding sequence under the control of the HRE segment, activated by the HIF transcription factor (hypoxia inducible factor). On the other hand, the use of progenitor cells (and not contracting cardiomyocytes), which, after maturation in the heart, will be able to synchronize their contractions with the contracting cardiac muscle and contribute to better vascularization of the damaged tissue, may reduce the risk of arrhythmia, and thus increase the safety of applied therapy. Additionally, in frame of this project, three-dimensional tissue patches will be prepared with hiPSC-CPC and an appropriate substrate, providing conditions for better integration of administered cells with damaged myocardium. The study will be conducted in NOD-SCID mice whose impairment of the immune system enables the adoption of human cells. Studies in mice will show the efficacy and safety of transient HO-1 expression, and long-term observation will allow to evaluate the safety of such therapy. We suppose that the increased but also hypoxia-regulated HO-1 activity will facilitate the integration of maturing cardiomyocytes into the heart, reduction of inflammation and improve vascularity, and may also increase cell implantation. The result of the project will be expanding knowledge about the mechanisms of implantation and improvement of cardiac function by cardiomyocytes and endothelial cells obtained from hiPSC-CPC and demonstrating the legitimacy of the proposed regenerative strategies. The acquired knowledge will be useful in the future for the development of new, effective and safe methods of heart failure treatment.