DESCRIPTION FOR THE GENERAL PUBLIC

As shown in numerous studies, in acute myocardial infarction significant changes occur in plasma concentrations of, inter alia, osteoprotegerin (OPG), tumour necrosis factor alpha (TNF-alpha) and TNF-related apoptosis-inducing ligand (TRAIL). It has been confirmed that, in this group of patients, high levels of OPG and high ratios of OPG/TRAIL are associated with a greater risk of post-infarction left ventricular remodelling, heart failure and increased mortality in both short- and long-term observation. In patients with high plasma levels of OPG in the acute phase of myocardial infarction it was also found that a smaller amount of MSC was recruited from bone marrow, and consequently a smaller amount of MSC was circulating in the peripheral blood. From in vitro studies, we also know, that the ability of MSC to migrate depends largely on the stimulating effect of TRAIL. This stimulus on the migration of MSC by TRAIL activity is significantly inhibited by high concentrations of osteoprotegerin and is completely destroyed at the high OPG/TRAIL ratio of 6:1. Such a high ratio of OPG/TRAIL was detected in a group of patients with acute myocardial infarction who developed, in subsequent weeks of observation, unfavourable post-infarction left ventricular remodelling and heart failure. Moreover, this was the group of patients with the worst prognosis following a myocardial infarction. In vitro studies also demonstrated that neutralising osteoprotegerin by means of specific anti-OPG antibodies restores the stimulating effect of TRAIL in relation to the mesenchymal stem cells as well as the migration activity of MSC.

Based on this data we plan to do research in order to verify the hypothesis that in vivo, low plasma concentrations of osteoprotegerin and a low ratio of OPG/TRAIL are required to maintain the stimulating effect of TRAIL on MSC, which allows greater mobilisation of mesenchymal stem cells from bone marrow into the peripheral blood and their potentially greater involvement in the repair processes during myocardial infarction. This stimulation of mesenchymal stem cells results in their migration and increased mobilisation from the bone marrow to the peripheral blood. The aim of this study is not only to verify this hypothesis but also to demonstrate if the potentially beneficial processes described above result in reduced necrosis or left ventricular remodelling and a diminished development of heart failure in the post-myocardial infarction period. To this end an experiment is planned using a murine model of myocardial infarction. In the experiment the mice with KO gene of OPG (OPG -) and mice with normal expression of osteoprotegerin (OPG +) will be used. An experimental myocardial infarction will be triggered by ligating the left anterior descending coronary artery (LAD). The coronary artery ligation procedure will be performed in the same manner in both groups of animals. Additionally, in both groups the plasma concentrations of OPG, TRAIL, tumour necrosis factor (TNF-alpha), receptor activator of nuclear factor kappa-B (RANK) and its ligand (RANKL), among other things, will be measured at the outset, during acute myocardial infarction and post myocardial infarction. The number of mesenchymal stem cells in the blood will be monitored in both groups of animals. In addition, twenty-eight days after the myocardial infarction an NMR of the heart will be performed to assess, such parameters as: the left ventricular ejection fraction (EF), infarct size, myocardial viability of the left ventricular and the level of disruption to the microvascular flow (microvascular obstruction - MO) and remodelling of the left ventricle. At the end of the experiment histopathological and immunohistochemical studies of the heart will be performed on all the research animals. In a separate part of the research carried out in vitro, the migratory ability of murine and human mesenchymal stem cells at different concentrations of OPG and at different ratios of OPG/TRAIL will be assessed; these concentrations will be the equivalent to those established in the first part of the study where the mice (OPG+ and OPG-) experienced experimentally induced myocardial infarction.

This multiple assessment will allow a better understanding of the complex relationship between changes in the concentrations of the above mentioned laboratory parameters during an acute myocardial infarction and its consequences in the form of post-infarction left ventricular remodelling and heart failure. This may contribute to a better understanding of the defence mechanisms that protect against the development of post-infarction cardiac remodelling.