Over the last two decades, coronary reperfusion therapy has become the standard treatment for acute myocardial infarction. However, restoring of blood flow to previously ischemic myocardium results in microvascular damage or myocardial stunning and has pathological consequences, referred to as ischemia/reperfusion injury. Some of these cases are fatal. The most important goal of pharmacological prevention and therapy of ischemic heart disease is to improve the oxygen supply/demand ratio for the heart. Currently more than 90% of patients with suspicion of acute myocardial infarction are given aspirin and/or β-blockers. As there is no universally accepted pharmacological approach that gives satisfactory protection from, or treatment of, reperfusion injury, new directions in pharmacological protection and treatment for the injured heart are needed. For this reason, it is important to unravel mechanisms involved in heart injury and develop new pharmacological strategies for the prevention and treatment of heart diseases.

IR injury is mediated principally by oxygen radicals (reactive oxygen species) and neutrophils. While recent studies suggest that pathogenesis of heart injury is based on an increased generation of reactive oxygen species and pressure overload, the precise contribution of different cellular and enzymatic sources of the oxygen radicals involved in cardiovascular pathologies remains unknown. Recently, we showed that reactive oxygen species lead to oxidation, hydroxylation and nitration/nitrosylation of cardiac contractile proteins. We also confirmed that these modifications lead to an increased degradation of contractile proteins caused by an increased proteolytic activity of intracellular enzymes. One of them is matrix metalloproteinase-2 (MMP-2). These discoveries provide support for a new pharmacological strategy aimed at reducing chemical modification of specific substrates of MMP-2 combined with blocking of MMP-2 activity. We propose to use of inhibitory cocktail at subprotective concentrations. The simultaneous prevention with combining drugs at low doses is required thereby limiting unwanted side-effects known to be associated with current single drug approaches. The protective effects of these agents is maintained by synergistic or additive effect.

On the basis of our previous and preliminary studies, initially we will confirm that the administration of combined subthreshold concentrations inhibitors is as effective and protective against heart injury as the same inhibitors given alone at full protective doses. Then, we will check if the same composition of inhibitors will protect the cardiac mechanical function in alive rats. We will use a modern methods for the assessment of heart function, new techniques for detection and identification of proteins modifications, heart structure, markers of injury.

These studies will lay the foundation for development of a drug cocktail useful in the prevention and recovery of heart deterioration in response to heart attack. By combining low, subthreshold doses of multiple drugs targeting multiple pathways, side-effects may be limited or prevented enabling long-term use in high-risk patients. Some of the drugs used in these studies are already approved for use in humans and are being used for other diseases. In this way, the safety of the drugs has already been established so that use of these drugs in patients could happen very quickly. Moreover, these studies are a necessary step that will increase the recovery and the quality of life of patients suffering with heart disease. It also may improve or make the protection of donor's heart stored and prepared for transplantation more efficient.