The effect of *Hmmr* gene and its interaction with the endogenous opioid system as a novel mechanism and a therapeutic target for blood pressure regulation

Hypertension is described as a chronic elevation of systolic and diastolic blood pressure and it is a major risk for many common causes of morbidity and mortality including stroke, myocardial infraction, congestive heart failure and end-stage renal disease worldwide. According to the Global Burden of Disease Study 2010, hypertension is responsible for 9.4 million deaths per year. It is predicted that by the year 2025, the prevalence of hypertension will increase globally by 10%, despite better patients' awareness and more effective anti-hypertensive therapies. Therefore a new mechanisms involved in blood pressure regulation need to be discovered. We have focused on endogenous opioid system as a possible system involved hypertension pathogenesis. This system in human organism controls pain, rewarding and but also addiction. It is an endogenous system, which means that in this system opioids are produced by its own organism. Endogenous opioids are released mainly by neurons. Then they bind with opioid receptors in brain and cause an effect. Opioids are mainly used in pain management, however long term usage may lead to addiction. One of the endogenous opioids exerting powerful effect is β-endorphin. β-endorphin strongly stimulates opioid receptors, what leads to euphoria, feeling good, and pain relief. B-endorphin is also responsible for phenomenon known as a "runner's high", simply it happens when after intense physical exercises you will feel euphoria. However this properties of opioid system are already well known, less obvious is fact that opioids may regulate activity of immune system and vascular function, both influencing blood pressure level. In our preliminary research we have found one gene to be significantly upregulated in artery after opioid receptor blockade. Higher expression of this gene corresponded with increase of blood pressure, vascular dysfunction and increase of endothelium potential to attracts immune cells. This data strongly encouraged us to conduct pioneer studies on the role of *Hmmr* gene in hypertension development.

Aim of the project is investigation of *Hmmr* in regulation of blood pressure with focus on vascular function, remodelling and inflammation. Moreover in this project we are planning to generate a small molecule which will block HMMR and could be used as possible regulator of blood pressure in hypertension. We believe to characterize novel mechanism dependent on endogenous opioid system involved in blood pressure regulation.

Experiments which will be performed, will build our knowledge about *Hmmr* role in hypertension development and how it affects inflammation and vascular dysfunction related to hypertension. Main experiments will be performed using model with non-functional *Hmmr* gene. Deficiency of this gene will allow us to understand for which processes this gene is responsible. To check protective effect of *Hmmr* deficiency in this model we will induce hypertension by norepinephrine. During this experiment blood pressure will be monitored. Next we will try to decrease blood pressure using novel chemical compound (which will be synthetize in the project) inhibiting HMMR in two models of hypertension. Using two different models of the same disease will allow as to translate obtained results to conditions of disease with different aetiology. We will also conduct *in vitro* experiments, where using particular system we will evaluate *Hmmr* dependent migration properties of immune cells towards chosen chemotactic proteins. It will allow us to describe role of *Hmmr* in inflammation development. Summarising we aim to describe novel pathway involved in regulation of blood pressure. Moreover novel HMMR inhibitor synthetized in the project will be tested for potential antihypertensive properties.