Pulmonary hypertension (PH) is a fatal and currently incurable disease. This may result from the fact that its pathophysiology is poorly known. Generally pulmonary arteries constrict due to proliferation and contraction of vascular smooth muscle cells forcing the right ventricle (RV) of the heart to work harder to propel the blood through the pulmonary circulation.

Initially this increased burden leads to thickening of the RV wall, making its contraction stronger but with time this compensation breaks down, resulting in RV failure and patient's death.

There is a growing body of evidence that the primary trigger for narrowing of the pulmonary arteries is a protein called PTEN. This protein inhibits cellular proliferation, migration and survival and is extensively tested in tumors as a tumor suppressant. All forms of both human and experimental PH share a common feature: reduced expression and activity of PTEN. Thus we believe that its stimulation could prevent PH or at least slow its progression.

Moreover, once PH develops, fate of the patient depends on his RV. If it fails, he is destined to die. There is a growing body of evidence that the thickened RV becomes hypoxic (i.e. it lacks adequate oxygen), which triggers its failure.

The aim of this project is to test a hypothesis that *myo*-inositol trispyrophosphate (ITPP), a novel effector of hemoglobin that both enhances the oxygen release capacity of hemoglobin and activates PTEN, is beneficial in a rat monocrotaline (MCT) model of pulmonary hypertension due to its dual mechanism of action: (1) by activating PTEN it prevents narrowing of the pulmonary arteries, (2) by increasing oxygen delivery it protects the right ventricle from failing, making both the pulmonary hypertension less severe and right ventricle less prone to failing and improving outcomes.

In the 1st part we will give a single injection of MCT and then divide our experimental rats into two groups: those who are given ITPP and those who are given ordinary saline, trying to prevent PH with ITPP.

In the 2nd part we will give a single injection of MCT and then wait for PH to develop and then start giving ITPP to prevent right ventricular failure.

We will perform echocardiography to monitor pulmonary artery pressure and right ventricular function, hemodynamic studies, histology of the heart and lungs, investigations of isolated cardiac myocytes and cell culture studies to gain insight into possible beneficial mechanism of ITPP on the pulmonary arteries and right ventricle of the heart.