Pulmonary artery hypertension (**PAH**) is still an incurable disease. The currently approved drugs for PAH, are mainly dedicated to reduce a diameter of pulmonary arteries whereas PAH is a complex and multi-factorial disease (Fig. 1). Currently, the European Respiratory Society and the European Society of Cardiology recommends for treatment patients with PAH combination therapy with medications acting at various targets and the effectiveness of such proceedings is confirmed by literature data. **Polypharmacology** is an innovating strategy that involves the use of a single compound to target multiple therapeutic pathways. Such approach is more effective than the use of several drugs and undoubtedly more easy to use by patients.

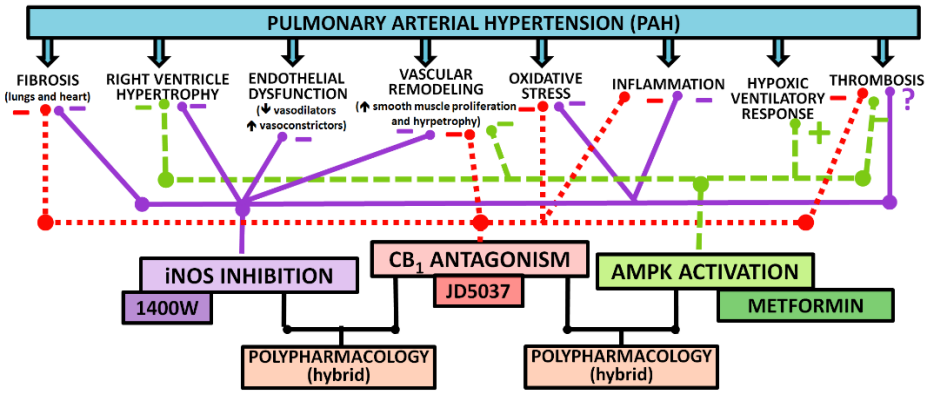

Fig. 1. Potential site of actions for peripherally restricted cannabinoid **CB_1 receptor antagonists**, inhibitors of inducible nitric oxide synthase (**iNOS**) and activators of 5′-adenosine monophosphate (AMP)-activated protein kinase (**AMPK**) in pulmonary arterial hypertension (PAH).

As shown in Fig. 1 **peripheral restricted cannabinoid CB_1 receptor antagonists** (e.g. JD5037), **inhibitors of iNOS** (e.g. 1400W) and **AMPK activators** (e.g. metformin) exert a number of beneficial effects on processes underlying PAH. Novel orally bioavailable and peripherally restricted CB_1 receptor antagonists that simultaneously inhibit iNOS (e.g. MRI-1867) or activate AMPK (e.g. MRI-1891) represent the third generation of CB_1 receptor antagonists. **The aim of our project** is the evaluation of the new combined therapies targeting blockade of peripheral cannabinoid CB_1 receptor plus iNOS inhibition or AMPK activation in two models of experimental pulmonary hypertension. In addition, we plan to compare the effectiveness and beneficial effects of these treatments to the generally accepted gold standard of reference combination for PAH therapy, i.e. ambrisentan (antagonist of endothelin) given together with tadalafil (inhibitor of phosphodiesterase 5).

We will apply the two most accepted preclinical rat models of established pulmonary hypertension: (1) induced by monocrotaline and (2) induced by Sugen/hypoxia [i.e., combined administration of the vascular endothelial growth factor receptor (VEGF) inhibitor Sugen 5416 with exposure to chronic hypoxia]. Compounds will be orally administered both in mono- as well combined polytheraphy. The severity of pulmonary hypertension will be examined using non-invasive echocardiography, invasive hemodynamic studies, histological examination of lungs, hearts (mainly right ventricle) and pulmonary arteries, functional studies of isolated pulmonary arteries, cardiac atria and right ventricular strips as well as biochemical parameters of fibrosis, oxidative stress, inflammation or thrombosis. Functional studies will also be performed on isolated human pulmonary arteries.

The examination of chronic administration of new combined therapies and new hybrid compounds acting simultaneously on various targets and the respective reference compounds on development and severity of PAH allows for the assessment of the effectiveness of tested substances. In addition, in regarding to modern polypharmacology it may also indicate new trends in the treatment of still incurable PAH. Patients with pulmonary hypertension are more susceptible to respiratory infections. PAH symptoms indicated in Fig. 1 occur also in SARS-CoV-2 coronavirus infection. Therefore, it cannot be excluded that in the future, new examined compounds will be beneficial in the treatment of COVID-19.