The role of AMP deaminase and effects of its inhibition on cardiac mitochondrial function in the experimental hypoxic and failing heart

Studies that analysed relation between genetic diversity in humans and progression of heart disease found that patients with mutation of AMPD1 gene deals better with heart failure and ischemic heart disease. Previous studies that tried to find out how this works revealed that activity of enzyme AMP deaminase is decreased in the heart which causes increased production of adenosine that protects heart from injury. Furthermore, it was found that another enzyme AMP regulated protein kinase is activated. However, the role of this change is not known. AMP regulated protein kinase is controlling energy turnover in the heart and other organs. Key element of energy turnover is function of intracellular organelles called mitochondria. This project will test therefore how function of mitochondria changes in the heart when activity of AMP deaminase is decreased in the failing heart or when oxygen supply is restricted. This study will be conducted with genetically modified mice that makes it vulnerable to injury during restricted oxygen supply. These mice were further modified to delete gene for AMP deaminase is it occurs in humans. Experiments with these mice will reveal whether mitochondria indeed are functioning better if heart disease develops. Such analyses are not possible directly in humans. Second part of the project will test inhibitors of AMP deaminase that recently become available and are potential candidates for drugs to be used in cardiovascular disease. Finally, inhibitors of AMP deaminase will be tested in cultured human cells and slices obtained from explanted human hearts to compare effects and to confirm whether findings from studies in mice could be applied to human pathology. This project will provide new important information about mechanism of heart disease and how to prevent it. Results of this project will help to find new drugs to treat heart disease.