

## DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Cardiovascular diseases, including valvular dysfunctions, are the one of the main causes of mortality in developed countries. One of the most common valvular heart disease is the narrowing of the aortic valve – aortic stenosis. Aortic stenosis can be described as a decrease in aortic orifice area, resulting in obstructed blood flow from the left ventricle into the aorta. Until recently, this disease entity was treated as a degenerative change, characteristic for aging process, but recently scientists suggested that inflammation leads to its development. The inflammation can develop, among other, due to disorders of lipids and carbohydrates transformations, that are directly associated with the risk of cardiovascular diseases.

The nucleotides present in the extracellular space and their cleavage products are involved in the control of inflammation. One of the major enzymes responsible for the nucleotides metabolism is ecto-5'-nucleotidase, also called CD73, converting adenosine-5'-monophosphoran (AMP) to adenosine, which is known for its protective properties. The decrease in adenosine concentration in the extracellular space may be one of the factors leading to exacerbation of inflammation, as well as to disorders of lipids and carbohydrates transformation.

Our results suggest that the lack of CD73 activity, and therefore - decrease in its product – adenosine level, affects the development of aortic valve dysfunction. We also noticed changes demonstrating the disturbances of lipid and carbohydrate metabolism under the influence the CD73 activity deficit. Although numerous studies confirm our results, the role of CD73 in the cardiovascular system is still a controversial. Some researchers noted high expression of this enzyme in the constricted, mineralized valves and indicate its activity as the cause of the disease. On the other hand, convincing evidence can be found indicating the deleterious impact of CD73 activity loss. In patients with a mutation in the gene encoding CD73 severe vascular calcification was observed.

Therefore, the aim of the project is to investigate the impact of the deficit and overexpression of CD73 on the development of valvular disease, and to define the role of lipids and carbohydrates transformations disorders consequent to changes in CD73 activity in the valvular dysfunction. We suggest that the valvular pathologies development may occur largely through the lipids and carbohydrates metabolism disturbances due to changes of CD73 activity.

The objectives of the project will be achieved using mouse models characterized by a reduced and increased activity of CD73. Furthermore, high-fat diet will be applied as additional factor known to cause valve dysfunction. The project envisages assessment of the level of aortic valve dysfunction development in tested animals, and further - evaluation of lipid and carbohydrate metabolism, as well as calcium - phosphate metabolism. All parameters demonstrating disorders in any of the above aspects will be correlated with parameters of the inflammation and aortic valve dysfunction.

Explanation, whether the physiological CD73 activity is optimal for preserving valve function or additional CD73 activation could be beneficial in the prevention of aortic stenosis, is crucial. Implementation of the project could significantly contribute to broadening the knowledge on the valvular diseases pathophysiology. The results can be a base for future innovative therapeutic strategy.