Title: **The role of inflammatory macrophages in pathophysiology of experimental autoimmune myocarditis.**

Applicant: **Karolina Tkacz, M.Sc.**

Research institute: **Jagiellonian University Medical College**

Popular science summary

Myocarditis – a heart-specific inflammation is a chronic disease that can be caused by virus infection or non-infectious agents. In some patients, myocarditis can progress into dilated cardiomyopathy (DCM) characterized by excessive accumulation of the fibrotic tissue in the myocardium resulting pathological heart remodeling, ventricular stiffness and at the end heart failure. Viral myocarditis can be often associated with damage of heart tissue and releasing self-antigens from cardiomyocytes which can cause autoimmune responses. The autoreactive CD4+ T cells drive development of myocarditis, although majority of heart infiltrating cells constitute myeloid cells. Due to non-specific symptoms and limited treatment options, myocarditis pathophysiology requires thorough investigation.

The mouse experimental autoimmune myocarditis (EAM) model is an interesting option to study mechanisms of myocarditis and its transition into post-inflammatory fibrosis. Transforming growth factor beta (TGF-β) is considered as one of most important profibrotic factors in cardiovascular diseases. As well, during EAM, levels of TGF-β are markedly increased in acute and chronic stage of disease. TGF-β is produced among others by macrophages and can act in autocrine manner. Macrophages are cells responsible for phagocytosis and occur in two subsets: inflammatory M1 and anti-inflammatory M2. In the injured heart, monocytes are recruited to the injury site, produce proinflammatory cytokines and differentiate into inflammatory macrophages. The early phase of inflammation is replaced by repair processes when inflammatory macrophages switch their phenotype into anti-inflammatory and start to produce growth factors inducing production of fibrotic tissue and shifting inflammation into fibrosis. A massive infiltration of macrophages in the progress of the EAM was described, however, their role in the pathophysiology of the disease is not clear. It is not known how TGF-β activates inflammatory macrophages in vivo in this model.

We hypothesize that under the influence of TGF-β inflammatory macrophages infiltrating injured heart can contribute to pathophysiology of the disease. In order to investigate the role of macrophages in immunofibrotic processes in EAM mediated by profibrotic TGF-β signaling we propose research that include 1) addressing the impact of TGF-β on inflammatory macrophages in EAM using mice with lack of TGF-β receptor in myeloid cells 2) sorting inflammatory macrophages and genome sequencing, 3) analysis of molecular pathways involved in EAM dependent on TGF-β. We hypothesize that TGF-β signaling trigger profibrotic responses in inflammatory macrophages including producing of chemokines and cytokines such as CCL7, IL-1β, IL-13. Lack of TGF-β in macrophages may limit fibrotic processes and DCM development in the heart during EAM.

TGF-β and macrophages, play crucial roles in inflammatory cardiovascular diseases, though they can constitute an anchor point for therapy strategies. Understanding the molecular mechanisms of the disease and finding potential therapeutic target is the key to develop effective therapies for myocarditis patients. We believe that research in proposed project may contribute to better understanding mechanisms of myocarditis pathophysiology.