Myocarditis is a severe cardiovascular disease that can be caused by bacterial, protozoal and viral, among others also COVID-19, infections. The etiology of the disease can also be autoimmunity. Myocarditis often progresses to dilated cardiomyopathy and heart failure. The disease itself is difficult to diagnose as it requires endomyocardial biopsy. Furthermore, the mechanisms controlling the pathogenic process are still not elucidated. Metformin is a common drug which is administered orally to treat type 2 diabetes. Until now, however, very little is known on the possible role of metformin and its targets in autoimmune myocarditis. Although recent studies showed that metformin has a cardioprotective role, the molecular mechanisms were not studied. Our preliminary results from mouse model of experimental autoimmune myocarditis (EAM) point that metformin plays a crucial role in protecting the heart muscle from developing myocarditis. We have shown improved heart function, measured by echocardiography, and ameliorated inflammation of the heart muscle, when metformin was administered during autoimmune myocarditis in the mouse model. We hypothesize that metformin can be used to protect the heart muscle from developing myocarditis but also can be administered as a possible therapeutical agent to stop the progression of the disease. In order to understand molecular mechanisms and to distinguish molecular players and metabolic processes affected by metformin we propose a multifaceted study based on the mouse model of experimental autoimmune myocarditis. In our study we aim to elucidate cardioprotective and therapeutical role of metformin in the mouse model of EAM, to evaluate whether metformin is a molecular regulator of myocarditis and its progression to DCM phenotype and to characterize cell population that is affected by metformin action the most. Moreover, we would like to study metformin action on the protein and metabolomic levels – assay proteins, peptides and small compounds that can be used as a myocarditis mediators. This way, we will describe the complex mechanisms of action of metformin in autoimmune myocarditis and propose mediators that can serve as cardioprotective mechanism.

This project includes several research goals that can be addressed using both basic biological methods as well as advanced molecular assays such as single cell RNA sequencing, spatial transcriptomics, proteomics and metabolomics. By using multi-omics we will be able to evaluate metformin action on a single-cell level which is by far, the most advanced molecular technique available.

This research project will have huge impact for the society and will lead to other studies in the cardiovascular research. As treatment options for patients with inflammatory heart diseases are limited the search for novel biomarkers and drugs is well-justified. Metformin is a pleiotropic drug which is very frequently used in both basic research, pre-clinical and clinical studies as well as a routine treatment protocol for patients with diabetes type 2. However, the impact of metformin on myocarditis and its progression to dilated cardiomyopathy remains unknown. Nothing is known about metformin molecular targets and pathways through which it acts. In this project we will provide a comprehensive analysis of the impact of metformin and its mechanism of action during autoimmune myocarditis on the animal model. The use of combined approaches, as presented in this grant proposal, will allow to identify molecular targets and cell populations affected by metformin on a single-cell level. We will also identify novel biomarkers and molecules which can be used to develop new therapeutical methods and that can help to diagnose the disease or monitor its progression. Understanding molecular mechanisms governing development of cardiac inflammation and its progression to dilated cardiomyopathy and placing metformin as a both cardioprotective and therapeutical agent will substantially broaden our knowledge of the physiopathology of myocarditis. Furthermore, novel data obtained from this project will open new avenues of research in search for new therapeutical agents to treat inflammatory heart disease. Summarizing, with the support from the National Science Centre Poland, we will be able to address very important and internationally competitive questions in cardiovascular research and set the basis for future therapies. We will improve our already established cutting edge techniques (CITEseq approach to single cell omics) as well as develop new methodologies that have never been used previously to monitor inflammatory myocarditis.