Cardiovascular diseases are the leading cause of death worldwide. Development of novel therapies targeting any heart conditions, however, is particularly difficult due to limited availability of cardiac tissue and poor proliferative potential of isolated adult cardiomyocytes. Therefore, new models of human myocardium enabling investigation of molecular mechanism of cardiovascular diseases are needed. Importantly, reprogramming of human somatic cells with defined transcription factors, first described in 2007, provided a novel platform for utilization of stem cells in cardiac disease modelling. This is because hiPSCs generated in the reprogramming process demonstrate the potential for infinite self-renewal and differentiation into any cell type of human body including cardiomyocytes (CM). It has been already demonstrated that patients-derived hiPSCs-CM recapitulate the pathophysiological phenotype of cardiomyocytes observed in several cardiac diseases and thus may serve for investigating molecular basis of a particular heart condition as well as for drug screening. Nevertheless, currently available methods for cardiac differentiation of hiPSCs result in development of immature cells which phenotype resemble fetal rather than adult cardiomyocytes. This limits the potential of hiPSCs-CM for *in vitro* modeling of human myocardium and calls for investigation of factors influencing maturity of hiPSCs-CM.

It has been already observed that regulation of metabolism in hiPSCs-CM can stimulate maturation of these cells. Additionally, long term culture of human embryonic stem cells (hESCs)-derived cardiomyocytes (hESCs-CM) as well as formation of engineered heart tissues which develop adult-like characteristics in hESCs-CM were reported to profoundly regulate several microRNAs (miRNAs) including miRNA-378a (miR-378a) which was described to influence various aspects of cellular metabolism. Nevertheless, the role of miR-378a in maturation of hiPSCs-CM and their therapeutic potential has not been investigated so far. Our experiments revealed that lack of miR-378a in mice impairs the number of blood vessels in muscle tissue further suggesting that this miRNA may be involved in the regulation of muscle and endothelial cell interactions. This in turn may represent another important aspect of human cardiomyocytes maturation which can additionally augment therapeutic potential of hiPSCs-CM in the treatment of myocardial infarction. For detailed analysis of any factor influencing hiPSCs-CM physiology, though, highly efficient monolayer cardiac differentiation of hiPSCs has to be complemented with advanced methods enabling investigation of interactions between different cell types constituting myocardium as well as providing three dimensional structure of heart tissue. Particularly, application of heart-on-chip technology and cardiac organoids allow for comprehensive modeling of human cardiomyocytes properties.

Taking it into consideration the aim of this proposal is to investigate the role of miR-378a in the regulation of metabolism, electrophysiological properties and proangiogenic activity of human induced pluripotent stem cells (hiPSCs)-derived cardiomyocytes (hiPSCs-CM) and thus their maturity and therapeutic potential. Importantly, this project will concomitantly enable investigation of signaling pathways influenced by miR-378a and because of the complexity of action of microRNAs, it may indicate additional novel molecular targets involved in acquisition of adult-like phenotype of human cardiomyocytes. Research on hiPSCs-CM maturity will additionally provide methods improving the enormous potential of hiPSCs-CM in disease modeling, drug screening and regenerative medicine. Additionally, this project will provide novel information on interaction of hiPSCs-CM with endothelial cells which is crucial for proper cardiac tissue physiology and may indicate a possible approach to target various cardiovascular disorders including myocardial infarction.