

Congenital heart defect (CHD) is the most common birth defects and a major cause of heart diseases. In Europe, CHD occurs in about 8 of 1000 live births. Among CHD cases, 10% result in fetal death or termination of pregnancy. In a survey of CHD cases between 2001 and 2005 in the European population, close to 90% of patients with CHD can survive, in many cases through adulthood, however, need continual treatment and monitoring. Notably, thanks to medical advances over the past 75 years, many of fatal childhood heart problems have changed to chronic medical conditions. Social burdens including education, employment and insurability, which increase the societal costs of adult CHD, are now being recognized for adults living with CHD (Seckeler M. et al. 2016). Further research studies are therefore needed to hamper the morbidity and mortality of CHD patients in Poland and EU.

As prognosed by Centre for Economics and Business Research (UK, cebr.com) the cost of cardiovascular disease (CVD), which includes coronary heart disease, heart failure, CHD and strokes, will increase in Europe to around 102.1 billion euros annually by 2020. According to European Heart Network (Townsend et al. 2016), of the total cost of CVD in the EU, around 54% is due to health care costs, 24% due to productivity losses and 22% due to the informal care of people with CVD. Therefore, research on different aspects of CVD are constantly supported by the European Commission's framework programmes (FPs). Research on this is estimated to be over € 163 million (ec.europa.eu) under Horizon2020.

The increasing survival rate of CHD patients necessitates better diagnosis and understanding of pathophysiology to improve preventive strategies and develop new treatments. CHD is caused by abnormalities in the process of heart development. Genetic determinants of CHD are largely components of molecular pathways regulating cardiogenesis. A comprehensive knowledge of heart development is therefore an essential step in understanding the mechanism of CHD. The lack of understanding on the regulatory network driving heart development, often hinders the diagnosis of CHD and development of novel therapeutic strategies.

Therefore, the main scientific goal of this project is to identify novel functional transcripts and changes in gene regulatory networks of heart development in order to understand the molecular mechanism of CHD. This knowledge will be crucial in designing novel diagnostic and therapeutic strategies in the future. In order to achieve this goal, the project integrates multiple state-of-the-art approaches including functional genomics, *in vivo* biological models, bioinformatics algorithms, and clinical data. Our preliminary data in zebrafish has allowed us to establish the regulatory networks responsible for heart development. By using established zebrafish mutant models for various CHD conditions, we also identified genes which become affected in zebrafish with malformed hearts. In the current project we plan to integrate this data with results obtained by applying genome-wide association studies (GWAS) and whole-exome sequencing (WES) in patients with CHD. This integrative genomics approach will maximize the output of clinical data and data obtained from model organisms.

This study will identify novel factors associated with CHD and further test their function in heart development of zebrafish. In the long run, the knowledge generated from this study will provide invaluable insights into the identification of novel biomarkers of CHD which will enable early non-invasive diagnosis of cardiovascular anomalies and lower risk treatment methods. The knowledge resulting from this study is therefore envisaged to significantly contribute to the advancement of the understanding of CHD biology and the applicability of the gained knowledge in clinics including accurate prenatal genetic tests and novel diagnostic and therapeutic strategies which will decrease the cost related to CHD healthcare. Finally, the project will ensure the development of highly-qualified researchers familiar with cutting-edge research technologies such as next-generation sequencing, live *in vivo* imaging, bioinformatics and personalized medicine.