Branch chain amino acids (BCAAs) are essential compounds in the daily diet, considering their crucial role in protein synthesis and energy metabolism. Scientific research has shown that BCAAs act also as signalling molecules that regulate the metabolism of cardiomyocytes. Interestingly, disturbances in BCAAs metabolism are frequently observed in cardiovascular diseases, and elevated levels of BCAAs may lead to an increased risk of cardiovascular incidents, including myocardial infarction. However, therapeutic strategies focusing on BCAAs catabolism demonstrated inconsistent outcomes due to an inadequate understanding of their metabolic and regulatory activities

Our earlier research has demonstrated that a mouse model of dyslipidemia (double knock-out of apolipoprotein E and low-density lipoprotein receptor) exhibited increased susceptibility to myocardial hypoxic damage, which is also observed in humans. Furthermore, in these mice, we observed increased oxidation of leucine in the heart and decreased blood BCAAs concentration. Interestingly, we also noticed reduced BCAAs levels in patients with familial hypercholesterolemia. Moreover, our preliminary studies indicate that a BCAA-enriched diet reduces ischemic heart injury, confirmed by a decreased concentration of troponin T in the serum 24 hours after hypoxia and no changes in the electrocardiography, unlike the control group. In turn, mice on a BCAA-restricted diet exhibited increased hypoxic cardiac cell damage. Therefore, the main research goal of this project is to elucidate the cardioprotective effects of BCAAs in cardiac dysfunction associated with dyslipidemia. Additionally, this project aims to investigate whether the cardioprotective nature of BCAAs is also evident in another model of heart failure (Tgaq*44), not related to dyslipidemia, characterized by significant impairments in the contractile function of the cardiac muscle. Based on the collected data, we aim to identify the direction of BCAAs transformations and their signalling pathways, which may indicate the increased or decreased risk of heart failure progression and sensitivity to hypoxia in animal experimental models, and subsequently analyze them in patients with familial hypercholesterolemia.

This project involves two different animal models of heart failure: vascular origin (ApoE/LDLR KO mice) and myocardial contraction origin (Tgαq*44 mice), at an early and chronic stage of cardiac dysfunction. Mice will be treated for 4 weeks with a standard diet, or a diet supplemented with twice the concentration of BCAAs, or half deprived of BCAAs. Additionally, pharmacotherapy stimulating BCAAs metabolism will be applied. The research plan includes *in vivo* procedures, as well as advanced metabolomic, proteomic, and transcriptomic analyses. Furthermore, our studies will be extended to a comprehensive analysis of BCAAs turnover in patients with familial hypercholesterolemia. The levels of BCAAs, their metabolites, and proteins involved in BCAAs metabolism and signalling will be examined in serum samples. Based on the obtained results, we will be able to identify a cardioprotective pattern of BCAAs turnover and propose BCAAs supplementation in a selected group of patients with active BCAAs catabolism.

To the best of our knowledge, this project represents the first attempt to comprehensively investigate the impact of BCAAs metabolism stimulation in different experimental models of heart failure. Additionally, this project will aid in the identification of a distinctive metabolic and proteomic profile in the serum of patients at high risk of acute ischemic events or suggesting an increased risk of heart failure. The results obtained could also serve as a basis for implementing easy and effective dietary modifications in dyslipidemic patients, aiming to reduce the risk of cardiovascular events.