The main goal of the project is to investigate the impact of polymorphisms Arg16Gly and Gln27Glu in the β2-adrenergic receptor (β2-AR) on the receptor's functionality and its interaction with drug molecules.

The β2-adrenergic receptor belongs to the important family of G protein-coupled membrane receptors (GPCRs) and is a crucial molecular target for drugs used in the treatment of heart failure, asthma, and prevention of premature miscarriages. β2-AR occurs in approximately eighty polymorphic variants, differing in types of amino acid residues. A genetic change occurring with a frequency greater than 1% is called a polymorphism.

Clinical studies indicate a connection between β2-AR polymorphism and an increased risk of various chronic diseases (e.g., heart failure, hypertension with concomitant obesity, asthma) as well as variable responses to beta-agonists and beta-blockers, exacerbation of the disease, and a faster development of tolerance to the administered drug.

The problem of the impact of β2-AR polymorphism on the above-mentioned phenomena, particularly the molecular differences in the interaction types of β2-AR-drug, β2-AR-G protein, and β-arrestin-β2-AR for different polymorphs, has not been explained so far. In this project, we plan to conduct comprehensive experimental (*in vitro, in vivo*, immunological, genetic, spectroscopic) and theoretical (molecular modeling) studies involving a large group of functionally different compounds (agonists, antagonists, inverse agonists) interacting with selected polymorphs of the β2-AR receptor.

Using zebrafish model of heart failure (HF) and acute respiratory distress syndrome (ARDS) disease we will investigate approximately 24 compounds, derivatives of fenoterol and their stereoisomers, for their cardioprotective effects. Our studies have shown that (*R,R*)-4-methoxynaphthyl-fenoterol exhibits cardioprotective effects at a dose of 10 nM. Through extensive interdisciplinary research, we will explain the differences in the ways polymorphs of β2-AR, such as Arg16Gly and Gln27Glu, interact with functionally different β2-AR ligands. We will examine the impact of polymorphism on the development and course of heart failure and respiratory failure in zebrafish, as well as determine differences in the levels of inflammatory cytokines, gene expression, lipid profile, and protein profile.

Given the crucial role that the β2-adrenergic receptor plays in the physiology of the human body and as a molecular target for a large group of drugs available in the pharmaceutical market, the scientific impact of this project can be very broad and encompass biological, medical, pharmaceutical, and chemical sciences. Furthermore, from the perspective of targeted therapy, our research will answer the question of how patients with different β2-AR genotypes will respond to beta-agonists.