The androgen receptor is located in many tissues - muscles and bones, gonads, skin fibroblasts, arteries, heart and adipose tissue. Testosterone and dihydrotestosterone (DHT) are the two main androgen hormones acting through the androgen receptor and they are responsible for development of secondary sex characteristics in males, stimulate gametogenesis and regulate sexual behaviour. In recent years, much effort has been put into developing selective androgen receptor modulators (SARMs) - agents that are an alternative to hormone replacement therapy using testosterone derivatives. Currently, a lot of SARM compounds have been synthesized, whose task is the selective activation of androgen receptor in tissues. This allows the promotion of beneficial anabolic functions typical for androgens, while limiting their adverse effects e.g. in the prostate. It is well known that androgens are involved in the regulation of carbohydrate-lipid metabolism. They intensify lipolytic processes, inhibit lipogenesis, and sensitize, among others muscle tissue for insulin improving glucose utilization in the body. Androgen deficiency in men results in an unfavourable metabolic phenotype - obesity, insulin resistance, type 2 diabetes and an increased risk of cardiovascular disease. The cause of insufficient androgen production can be hypogonadism (primary and secondary), as well as cachexia - a state that accompanies many diseases, including cancer. Obesity occurs both as a result of androgen deficiency but also as a cause because obesity has been shown to significantly reduce testosterone production. Obesity also results in tissue hypoxia, which negatively affects the functioning of adipose cells and surrounding tissues - it can cause inflammation and also lead to necrosis. Epicardial fat, which in physiological conditions is necessary for the proper functioning of the heart, in the case of obesity can overgrow the organ and reduce its contractile functions, as well as promote inflammation and hypoxia. This negatively affects cardiac cells, resulting in pathological tissue remodelling. The relationship between obesity and androgens is studied, but the relationship/dependence between the molecular mechanisms of hypoxia, the role of androgen receptor and metabolism is poorly understood.

As part of our research, we hypothesized that enobosarm: i) affects the physiological features of cultured C2C12 cells demonstrating the anti-catabolic effect and improving glucose uptake; ii) affects the physiological features of cardiac cells – primary cardiac fibroblast, iii) affects the metabolism of fat cells - primary preadipocyte cells and 3T3-L1 cells; iv) increases lean body mass, results in body fat loss and improving the parameters of carbohydrate-lipid metabolism in obese male rats.

The main goal of the project is to study androgen receptor modulation using the selected SARM - enobosarm in the context of carbohydrate and lipid metabolism. The main goal will be achieved by studying the effect of SARM on: (1) metabolism and differentiation of the C2C12 myoblast cell line, (2) metabolism and proliferation of primary cardiac fibroblasts, (3) metabolism and differentiation of the 3T3-L1 cell line and isolated rat preadipocytes, (4) metabolism and hormonal profile of rats with normal body weight and with induced obesity and subjected to forced physical activity - treadmill running. Enobosarm was chosen for the experiments because it underwent preclinical studies, in which it was considered safe, and in clinical studies patients did not report dangerous side effects. In addition, many studies have shown that physical activity is an important element in the treatment of obesity. It increases energy expenditure, improves tissue insulin sensitivity, and also increases blood supply, and thus oxygenation of organs - therefore, physical effort is planned in the experiment. The research problem presented is multi-faceted - it will allow a comprehensive assessment of enobosarm activity, providing knowledge about its effects in tissues. In addition, by analysing the metabolism of cells in a hypoxic state, we will broaden our knowledge about androgen receptor function. Finally, an important value of the project is the analysis of the compound, which, despite the lack of acceptance as a therapeutic agent, is already widely available on the black market for abuse in sport as an anabolic agent. Understanding the effect/action of enobosarm is therefore not only a safety aspect of introducing new therapeutic therapies, but may also include preventive and educational activities in the use of doping agents.