Obesity is a worldwide health issue with occurrence steadily increasing during recent decades. It should not be viewed as only esthetic imperfection as it leads to numerous other disorders, such e.g. type 2 diabetes, atherosclerosis, chronic kidney disease, non-alcoholic liver steatosis, hypertension and certain types of cancer.

Recently new therapies for obesity emerged. Among them, there are drugs mimicking the effects of hormone, glucagon-like peptide 1: liraglutide and semaglutide (GLP-1 analogs). These drugs were primarily developed to treat type 2 diabetes, however it was observer that they also lead to the significant reduction of body mass. GLP-1 analogs are indicated in the treatment of obesity in patients with body mass index (BMI) ≥ 30 or ≥ 27 if they have at least one comorbidity. Contrary to registered indications for these drugs, many patients without clinical obesity misuse GLP-1 analogs to achieve rapid reduction of body mass without dietary and lifestyle modifications. This phenomenon emerged in 2022, after many celebrities embraced on social media use of Ozempic (semaglutide) for weight loss. In such situations patients often use GLP-1 analogs in repeated cycles varying in duration. Some of misusers of GLP-1 analogs obtain their drugs from illegal sources or by using forged prescriptions. After each successful, "seasonal" reduction of body mass, many of these people experience "yo-yo effect". Rapid reduction of body mass is often accompanied by the loss of not only adipose tissue, but also lean mass (muscles) and slowing down of metabolism, which leads to lower energy expenditure. On the other hand, when people regain the mass, it is usually mostly adipose tissue, which leads to increased burden on the musculoskeletal system.

So far most clinical and preclinical studies on GLP-1 analogs focused on their effects after continuous treatment using different long-term schedules (up to 24 months in humans) and observation was usually limited to the short time after cessation of therapy. To the best of our knowledge there is no published data on effects of intermittent, cyclic use of GLP-1 analogs on human or animal health. As GLP-1 analogs have been prescribed to treat obesity for relatively short time, potential long term side effects are currently unknown.

Mechanism of action of GLP-1 analogs include stimulation of insulin release from pancreas in response to food. It is similar to mechanism of another, older group of antidiabetic drugs: sulfonylurea derivatives (SUR), which stimulate insulin release from already overloaded pancreas in patients with type 2 diabetes which is often accompanied by insulin resistance. This leads to late inefficiency of SUR, as after several years of treatment pancreas is no longer capable of insulin production. Thus, it still remains a question whether GLP-1 analogs, similarly to SUR, will negatively affect the function of pancreas after long term use or after the use in repeated cycles.

This project aims at assessment of long term efficacy and safety of GLP-1 analogs, using semaglutide as a representative, administered in repeated cycles to obtain quick reduction of body mass in a preclinical mouse model of diet-induced obesity.

In this project obesity will be induced in laboratory mice by feeding them with commercially available high-fat diet, providing 60% of total calories from fat. The schedule of the project consists of 6 cycles, each including 8 weeks of feeding + 3 weeks of treatment with semaglutide or saline.

The project will assess effects of such treatment with semaglutide in mice on: (1) body mass, fasting glucose levels, glucose tolerance and insulin tolerance, (2) muscle strength and physical fitness, (3) muscle atrophy, (4) histopathological changes in the liver, pancreas and visceral adipose tissue, (5) memory and learning, (6) expression of markers of synaptic plasticity and neuroinflammation in memory-related brain structures, (7) expression of markers of glucose and lipid metabolism in the visceral adipose tissue and blood, (8) inflammatory status in the liver, pancreas, visceral adipose tissue and blood.

The project will use methods such as a set of commonly used behavioral tests, measurement of fasting glucose levels and its changes after injection with either glucose solution or insulin, analysis of histopathological changes in organs and tissues, accompanied by analysis of gene and protein expression, measurement of blood levels of various markers related to inflammation, metabolism and liver damage.

Based on the findings of proposed project new guidelines for the use of GLP-1 analogs may be introduced.