Graves' disease (GD) is a common autoimmune condition resulting in oversecretion of thyroid hormones (known as hyperthyroidism), which is related to the generation of pathogenic autoantibodies stimulating the thyroid gland. Graves' orbitopathy (GO) represents the most common extrathyroidal manifestation of the disease. The peak in the Graves' hyperthyroidism occurrence is between the ages of 30 and 50 years. GD is more common in females than males. Existing medical therapies of GD have remained unchanged for the past several decades and are unsatisfactory. The majority of patients require thyroid ablation as the definitive therapeutic step, which has potentially serious side-effects and results in life-long thyroid hormone replacement therapy. Therefore better understanding of pathogenesis of GD, and development of novel highly effective and well-tolerated therapies are crucial.

Over the last several decades, there has been a dramatic rise in the incidence of autoimmune conditions, including GD. It is believed that changes in modern lifestyles and antibiotic overuse results in changes in the gut microbiome that may trigger autoimmune disorders, as microbiota plays essential roles in regulating immune tolerance. Nevertheless, the role of microorganism and especially microbiota-derived metabolites in GD/GO development is unclear.

Our goal is to elucidate the impact of microbiome and gut metabolites modulation on the GD/GO development using preclinical mouse model of the disease. Selected data will be verified in faecal samples obtained from GD/GO patients and healthy donors.

We will use the mouse model of GD/GO established by genetic immunization to characterize the composition signatures of microbiota and their metabolites alterations at various stages of GD/GO development. Thereafter, oral supplementation of selected, altered metabolites, as well as, faecal transplantation from healthy mouse donors will be performed to evaluate their effect on disease progression. To verify and confront the obtained data from experimental mouse model with GD/GO human subjects, we will perform metabolomic analysis for selected (significantly changed) gut metabolites in stool samples of GD/GO patients compared with healthy volunteers.

Overall, we expect that the proposed studies will provide new insight into the role of microbiota and bacterial metabolites as modulators of host immunity and may result in delivery of novel treatment strategies.