Gastrointestinal stromal tumours (GISTs) are the most common mesynchemal tumours located in gastrointestinal tract, mainly in stomach and small intestine. In the case of vast majority of GISTS, the neoplastic process is caused by a mutation in KIT gene, encoding receptor tyrosine kinases. In cancer cells these proteins are constitutively activated, which leads to the cell growth and proliferation in an uncontrolled manner. The therapy of GIST was revolutionised in 2002 when a new drug, namely imatinib, was approved for the treatment of patients with KIT-positive unresectable or metastatic GISTs. *Time* magazine hailed imatinib as a 'magic bullet' to cure cancer. Unlike traditional chemiotherapy, imatinib is targeted specifically at cancer cells, regulating tyrosine kinases activity. Unfortunately, with the duration of treatment, most patients develop resistance to imatinib, determined by secondary KIT gene mutation.

The aim of the project is to gain insight into molecular changes in GIST tumour tissue under the influence of imatinib treatment. It can be achieved by applying one of the systems biology tools, metabolomics. Metabolites are the downstream products of biochemical processes taking place in an organism, so they are an excellent, direct reflection of the physiological or pathophysiological state of an organism under particular conditions. Metabolomics research usually includes two research approaches: metabolic fingerprinting and targeted metabolomic analysis, and the most popular biological materials for the study are urine, blood, cell or tissue extracts.

The first part of the project aims at determination of the highest possible number of metabolites present at different levels in the GIST tumour of untreated and treated mice. Samples will originate from GIST mouse model, which is obtained by subcutaneous injection of human tumour tissue to a mouse. In this proposed project, we will utilize four GIST models with different KIT gene mutation corresponding to different sensitivity to imatinib treatment. Untargeted metabolomics analysis will be perfomed by means of two complementary analytical techniques, gas chromatography and liquid chromatography coupled with mass spectrometry. The untargeted analysis will result in selection of metabolites that may play a role in the tumour response to imatinib treatment. Subsequent targeted analysis of the selected compounds will validate the differences in the metabolites levels between treated and untreated GIST tumour.

Results of the project may be an important step towards elucidation of the metabolic background of imatinib responsiveness and resistance in GIST. Insight into altered biochemical pathways is also a path to uncovering new molecular targets in GIST therapy.