Expression and function of Regulator of G Protein Signaling (RGS) proteins in physiological and pathophysiological conditions of the intestinal tract

G protein coupled receptors (GPCR) mediate a vast variety of critical biological processes ranging from proliferation and motility to cellular reception and excitability. GPCR signaling pathways are of particular importance for the pharmacy since it is estimated that they constitute approx. 25% of all druggable targets. Importantly, but not surprisingly, even a subtle imbalance in GPCR signaling often leads to profound consequences such as tolerance or nonresponse to drug. While a variety of GPCRs have been found and their role in health and disease has been well characterized, the intricate regulatory dynamics of G protein pathways and its influence on pathophysiology as well as drug-related effects remain elusive. Several major steps have been made in understanding the regulatory network of GPCR signaling in the nervous system, such as basal ganglia and retina however a minuscule attention was paid so far to the function of those mechanisms in the periphery, e.g. in the gastrointestinal (GI) tract.

The key family of regulators of GPCR signaling pathways are the Regulator of G protein Signaling (RGS) proteins. RGS proteins constitute a large family of proteins that promote G protein inactivation by facilitating their GTP hydrolysis thus ensuring timely inactivation of the GPCR responses. Many members of the RGS family have been clinically linked to human disease conditions. Serving as a central control point in GPCR signaling cascades, RGS proteins hold great promises as targets for the drug development. This brings the major emphasis of this proposal on elucidating the function and mechanisms of action of RGS proteins in physiology and pathophysiology of the intestinal tract.

The major groups of GPCRs targeted by drugs in GI diseases are opioid receptors, serotonin receptors and cannabinoid receptors. Agonists and antagonists of those receptors serve in the therapy of disorders, such as irritable bowel syndrome, postoperative ileus, chronic constipation and diarrhea. Little is known about how the effect of those drugs is modulated by RGS proteins. In this project we will examine the expression and function of the members of RGS protein family in the GI tract and by the use of genetic mouse models we will evaluate how certain RGS proteins affect the action of drugs available on the market as well as compounds that did not pass the evaluation in the clinical trials due to their low efficacy or safety. We expect to uncover novel pharmacological targets downstream to GPCRs that could be blocked or enhanced as to achieve additional spatial or temporal selectivity compared with GPCR-targeted drugs. Inhibition of a specific RGS protein might allow for the use of lower agonist doses or a wider therapeutic range or ameliorate pathological conditions that result directly from RGS protein dysregulation.