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**Title of project:** Mechanisms Underlying Appetite Suppressing and Weight Lowering Effects of Combination Treatment with Neurotensin and GLP-1 Agonists in Mice

## **ABSTRACT**

Global rates of obesity and associated diseases like type 2 diabetes are increasing, but as of now bariatric surgery remains the only obesity intervention inducing sustained weight loss. Bariatric surgery is associated with serious side effects, and thus, there is an unmet need for efficacious anti-obesity agents to combat metabolic diseases. The action of single hormones cannot fully explain the efficacy following surgery, whereby current approaches to novel pharmacotherapy development often involves targeting of multiple gut hormone signaling pathways. Treatments combining in particular glucagon-like peptide-1 (GLP-1) with other hormones are being explored.

Results from studies in our lab and recent clinical trials identifies the gut hormone neurotensin (NT) as an important regulator of appetite that might contribute to the metabolic effects observed after bariatric surgery. Moreover, we have found that protracted long-acting NT agonists act synergistically with very low doses of GLP-1 agonists to induce weight loss of up to 11% after 10 days of treatment in obese mice. The understanding of underlying molecular mechanisms mediating the beneficial metabolic effects of this combination treatment are however rudimentary. Initial studies point to activation of regions in the CNS associated with homeostatic energy balance control and in particular pro-opiomelanocortin neurons of the hypothalamus as central for the observed effects. Further, illumination of the mechanisms underlying the beneficial effects of combination treatment with NT and GLP-1 agonists might reveal novel drug targets that could aid development of pharmacotherapies for treatment of obesity and associated diseases like type 2 diabetes. In the present project, we aim to further investigate the mechanisms underlying the appetite and weight lowering effect induced by NT and GLP-1 agonist combination treatment.