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**Title of project:** Array-assisted Peptide Drug Discovery for Obesity and Cancer Cachexia.

## Abstract:

Growth/differentiation factor 15 (GDF15), also known as MIC-1, has been implicated in various diseases, including renal and heart failure, cancer cachexia, obesity and type 2 diabetes. Recently, the GDNF family receptor α-like (GFRAL) was identified as the molecular target to which GDF15 is an endogenous agonist. GFRAL is exclusively expressed in the hindbrain and preclinical data suggest that GFRAL stimulation promotes weight loss via a unique mechanism of action, and with an effect that is comparable to that achieved by gastric bypass surgery (~30% body weight loss). Thus, with these reports the GDF15/GFRAL system has emerged as a promising target for the treatment of obesity, and several pharmaceutical companies are now pursuing recombinant protein analogues in clinical development. An important challenge to the GDF15/GFRAL system as a drug target is the technical aspects of developing protein analogues. GDF15 has a relatively complex protein structure, which makes it difficult to produce recombinantly in its active form and in appropriate amounts at a low price. Also, GDF15 analogues may have unspecific effects mediated by other receptors than the central GFRAL. These challenges may unfortunately preclude the development of this very promising target biology into a viable single or combination drug candidate. Here we propose an alternative chemical approach based on small stable peptide fragments that imitate GDF15's binding to GFRAL and therefore serve as synthetic GFRAL receptor agonists. Opposite to proteins, peptides in general offers a relatively straight-forward and cheap drug production, yet with the specificity of a protein. A novel approach – peptide SPOT arrays – will be applied to identify such fragments. Peptide candidates will be tested for weight-modifying potential. Thus, the goal of the proposed PhD project is to identify GFRAL-binding peptides by state-of-the-art peptide arrays and screening methods. Ultimately, this project will lead to highly potent and specific peptide GFRAL agonists suitable for anti-obesity drug development, and in addition potential antagonistic molecules identified may have a relevance in cancer cachexia.

## Abstrakt:

Fedme epidemiens udbredelse og de associerede metaboliske følgesygdomme, såsom type 2 diabetes (T2D) og hjerte-kar-sygdomme, er kraftigt eskaleret de sidste 20-30 år. Det er velkendt at vægttab forbedrer bugspytkirtlens insulinproduktion og insulinsensitivitet i det perifere fedtvæv pga. en reduktion af akkumuleret fedt i organerne og i fedtdepoterne. Glucagon-lignende peptid 1 (GLP-1) baserede lægemidler er godkendt til behandlingen af T2D og fedme. Selvom de effektivt forbedrer kroppens glukosebalance, fører denne stofklasse kun til moderat vægttab. Derfor er der en stor efterspørgsel efter ny og mere effektiv medicin. Peptidhormoner og proteiner udgør en spændende lægemiddelklasse, især inden for det metaboliske sygdomsområde. GDNF family receptor α-like (GFRAL) er fornyeligt blevet identificeret som en oplagt receptor til behandlingen af fedme. Growth/differentiation factor 15 (GDF15) er den endogene ligand for GFRAL. GFRAL er eksplicit udtrykt i en specifik del af hjernestammen, og forsøg i gnavere viser at stimulering af GFRAL kan fører til vægttab på niveau med gastrisk bypass operation. GDF15 har en kompliceret struktur, hvilket betyder at det er meget udfordrende at lave til et lægemiddel. Det er svært at udtrykke rekombinant i dets aktive form og i et brugbart udbytte. Desuden kan GDF15 analoger være associerede med uønskede bivirkninger, der ikke er medieret af centralt udtrykt GFRAL. Et alternativ til rekombinante proteiner er små stabile peptidfragmenter (af 10-20 aminosyrers længde), som kan efterligne den protein-proteininteraktion der finder sted mellem liganden (GDF15) og receptoren (GFRAL). Formålet med det foreslåede Ph.d.-projekt er at identificere fragmenter af GDF15, vha. de nyeste peptidbaserede screeningsteknologier (peptide SPOT arrays), der kan binde med stor affinitet til GFRAL. Ultimativt vil dette projekt fører til små, men specifikke, peptidligander mod GFRAL, som kan danne grundlaget for udviklingen af nye anti-fedme lægemiddelkandidater. Projektet kan også identificere GFRAL-antagonister og disse vil kunne bruges i behandling af cancer-induceret kakeksi.