**PhD student Sarina Gadgaard, MSc**

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**University:** University of Copenhagen, Health Sciences.
**Principal supervisor:** Bolette Hartmann, Bainan Biotech.
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**Title of project:** Treating diabetes induced osteoporosis using a new GIP/GLP-2 dual agonist.

## Abstract:

Diabetes mellitus is associated with an increased risk of bone fractures. Clinical studies show a higher risk of any kind of fractures in patients with both type 1 [1] and type 2 diabetes [2-9] resulting in substantial morbidity, hospitalization, high health care costs, impaired quality of life, disability, and death [10]. We have shown that the peptide hormones GIP and GLP-2 (both secreted from endocrine cells in the intestine upon meal intake) have beneficial effects on the bone turnover [11]. Our overall aim at Bainan Biotech is to develop a dual-receptor targeting drug for the treatment of bone-related diseases including diabetes-induced osteoporosis. At present, we have both short and long-acting GIP/GLP-2 dual agonists for human GIP-R and GLP-2R receptors. These have been designed based on a chimeric approach from the peptide backbones of GIP and GLP-2 with lipidations at selected positions.
During the cause of this PhD project, the best dual agonist will be tailored towards that rat GIP-R and GLP-2R using the same approach as for the human receptor systems. The best long-acting rodent GIP/GLP-2 dual agonist will be evaluated by Sarina Gadgaard (PhD student). Sarina will use two rodent systems as she will test the impact of our long-acting GIP/GLP-2 dual agonist in an ovariectomized (OVX) rat model for osteoporosis in parallel with testing the effect in a Zucker Diabetic Fatty Rat (ZDF) type 2 diabetes rat model [12]. The skeletal characteristics of the ZDF rats are well studied making ZDF rats an ideal model to study the bone-related changes after treatment with our duel GIP/GLP-2 agonist. The study design is in both cases long term treatment (4 months) with the dual GIP/GLP-2 agonist. Blood samples will be collected regularly during the study to measure bone turnover markers. At the end of the study, bones (femurs, tibias and vertebrae L1-4) will be collected for a series of biomechanical testing. Whole bone mechanical strength will be assessed by three-point bending and vertebrae will be subjected to compression test. Besides, the microarchitectural structure will be measured by microcomputed tomography (micro-CT) scans. Finally, we will investigate the effect of long term treatment on the bone structure by histomorphometric analyses. In summary, this PhD project, which has been granted an Innovation Foundation PhD-stipend to Sarina Gadgaard and the biotech company Bainan Biotech, will focus on the link between diabetes and osteoporosis. During the project, dual GIP/GLP-2 compounds will be tested for their beneficial effects in OVX rats (osteoporosis) and in the ZDF (diabetes) rat models.

## Abstrakt:

Diabetes mellitus er forbundet med forhøjet risiko for knoglebrud. Kliniske studier viser en forhøjet risiko for alle typer brud hos patienter med både type 1 og type 2 diabetes. Dette resulterer i forhøjet sygefravær, hospitalisering, høje sundhedsomkostninger, nedsat livskvalitet, handicap, og i værste tilfælde død. Vi har vist, at de naturlig forekommende hormoner GIP og GLP-2, som begge er frigives fra tarmen, har en gavnlig effekt på knogleomsætningen. Vores overordnede mål i Bainan Biotech er at udvikle et lægemiddel til behandling af knogle-relaterede sygdomme, inklusiv diabetes-induceret knogleskørhed. På nuværende tidspunkt har vi både kort- og lang- tidsvirkende varianter med virkning på både GIP og GLP-2 systemerne i mennesker. Gennem dette PhD projekt vil den bedste humante- GIP/GLP-2 såkaldte co-agonist blive optimeret med hensigt på at virke på rotte GIP-R og GLP-2R systemerne. Den bedste langtidsvirkende GIP/GLP-2 co-agonist i rottesystemet vil blive evalueret af Sarina Gadgaard (PhD student). Sarina vil anvende to forskellige rottemodeller til at teste langtidseffekten af den udvalgte co-agonist. Først vil Sarina teste effekten i den ovariektomerede (OVX) rotte model, som er en model for knogleskørhed. Dernæst vil hun teste effekten i en Zucker Diabetic Fatty Rat (ZDF) type 2 diabetes rotte model, som er optimal til at studere knogle-relaterede effekter. Blodprøver vil blive udtaget løbende under en 4 måneders behandlingsperioden for at måle knoglemarkører. Til slut i studiet, vil vi udtage knogler (femur, tibia and vertebra L1-4) til undersøgelse af biomekaniske egenskaber og mekanisk styrke ved 3-punkt test af rørknoglerne og kompressions test af ryghvivlerne. Derudover vil vi undersøge den mikroarkitektonisk struktur ved brug af microcomputed tomography (micro-CT) scanning, med andre ord vil vi undersøge

styrken og structuren af knoglerne efter behandling. Med dette PhD projekt, som har modtaget et erhvervsPhD-stipendium fra Innovationsfonden til Sarina Gadgaard og biotek virksomheden Bainan Biotech, fokusere på koblingen mellem diabetes og knogleskørhed. Gennem projektet vil co-agonister (GIP/GLP-2 agonister) vil blive testet for knogle-beskyttende effekt i to rottemodeller: OVX (knogleskørhed) og i ZDF (diabetes).