Postdoc **Lasse Bach Steffensen**, Ph.D.

Place of enrolment: Odense University Hospital, Clinical Biochemistry and Pharmacology

Principal supervisor: Professor **Lars Melholt Rasmussen**, Odense University Hospital, Clinical Biochemistry and Pharmacology

Title of project: Uncovering Adipocyte-Driven Risk of Atherosclerosis by Development and Application of a Novel In Vivo Phenotyping

ABSTRACT

The raging obesity and type 2 diabetes pandemic will fortify the position of cardiovascular disease as the leading cause of death worldwide long into the future. New therapeutic options are warranted for these patients to counteract the devastating consequences for global health.

Recent advances in human genetics offer exciting opportunities to obtain novel insight into pathophysiological mechanisms of atherosclerosis, and emerging genetic evidence point to adipose tissue as central in atherosclerosis development with a much greater role than hitherto appreciated. It is conceivable that the mechanisms governing adipose tissue-dependent atherosclerosis risk are aggravated in the setting of obesity and/or type 2 diabetes.

Using sophisticated colocalization analysis based on coronary artery disease (CAD) genome-wide association study metadata and gene-tissue expression data, we unbiasedly identified 8 genes significantly regulated in adipose tissue ($P < 10^{-6}$) by genetic variants with genome-wide significant ($P< 10^{-8}$) association to CAD. We hypothesize that these genes represent mechanisms pivotal for adipose tissue-dependent atherosclerosis risk.

Using recently established technology in our lab, we will identify novel adeno-associated virus (AAV) capsid variants that efficiently transduce adipocytes *in vivo*, which is not possible using currently available native AAV serotypes. This novel tool will be used to knockdown each of the 8 candidate genes specifically in adipocytes in atherosclerosis-prone mice in parallel.

Well-established methods will then be used to assess *in vivo* effects on insulin sensitivity, adipocyte phenotype and atherosclerosis. The 3 candidate genes with the most pronounced effect on these endpoints will be validated by assessing putative correlations between the genotype of the original genetic variant (and if possible, circulating levels of molecules downstream the candidate gene), and metabolic and cardiovascular endpoints in the Danish Cardiovascular Screening Trial (DANCAVAS) (n = 13,500). Moreover, Odense Artery Biobank adipose tissue specimens from obese (BMI > 30, n = 50) and normal weight individuals (BMI < 25, n = 50) will be used to test associations of candidate gene expression (and if possible, levels of downstream molecules) with obesity.

We believe that the unique methodology and novel design described in the proposal represent a powerful approach to translate human genetics into actionable biological knowledge that will ultimately stimulate development of new treatment strategies.