# Press release

Please fill in this form and return it to graduateschoolhealth@au.dk in Word format no later than three weeks prior to your defence.

**Basic information**

Name: Signe Mosegaard Email: signe.mosegaard@clin.au.dk Phone: +45 20835507

Department of: Clinical Medicine

Main supervisor: Rikke Katrine Jentoft Olsen

Title of dissertation: Novel insights to fatty acid oxidation disorders - Complex genetics and immunometabolic regulations

Date for defence: 07/01-2022 at (time of day): 15.00 Place: Online via Zoom: https://aarhusuniversity.zoom.us/s/64233978039. Remember to turn off both your camera and microphone when joining the meeting.

Press release (Danish)

## Ny indsigt i fedtsyreoxidationsdefekter - Kompleks genetik og immunometaboliske forstyrrelser

Mitokondriet er den humane celles energiproducerende og mest iltforbrugende enhed, men mitokondrierne er vigtige for meget mere end bare cellulær energiproduktion. Dysfunktion af mitokondrierne kan også føre til frigivelse af faktorer der øger celle død, oxidativt stress (ROS), samt fører til ændringer i cellens metabolisme og metaboliske fleksibilitet. Der er stigende enighed om, at mitokondriedysfunktion der fører til nedsat metabolisk fleksibilitet, spiller en central rolle i bl.a. aldring, cancer, neurodegeneration, diabetes, myocardial dysfunktion, samt sepsis. Foruden mitokondriel dysfunktion med cellulær stress er inflammation også fælles for alle disse forskellige lidelser, og i de seneste år har forskning vist et tæt sammenspil imellem mitokondriefunktion og inflammatoriske responser. I patienter med genetiske defekter i omsætningen af langkædet fedtsyre (lcFAOD), er mitokondriel dysfunktion et centralt cellulært problem der fører til nedsat metabolisk fleksibilitet. Motion og infektioner, der begge aktiverer inflammatoriske responser, er hyppige sygdoms-udløsende faktorer hos patienter med lcFAOD.

I denne afhandling har vi studeret to lcFAOD, Multiple Acyl-CoA Dehydrogenation Defekt (MADD) og Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD). I det første studie har vi benyttet whole exome sequencing (WES) kombineret med transcriptomics og proteomics (såkaldt diagnostisk OMICs) til at undersøge den komplekse genetik af den heterogene lidelse MADD. I et andet studie har vi undersøgt inflammatoriske processer i fibroblaster fra hudbiopsier fra patienter med VLCADD eller MADD. Vi fandt, at både det immunologiske og metaboliske respons var ændret i alvorlig VLCADD og MADD, når vi sammenlignede med mild VLCADD og kontroller. I et sidste studie har vi benyttet massespektrometrisk analyse af plasma acylkarnitiner, en standard analysemetode til diagnosticering af lcFAOD, som et proxymål for temporale forandringer i cellulær FAO i en septisk grisemodel.

Ph.d.-projektet udgår fra Aarhus Universitet, Health. Projektet er gennemført af Signe Mosegaard, der forsvarer det d. 7/1-2022

Forsvaret af ph.d.-projektet er offentligt og finder sted den 7/1-2022 kl. 15 online via Zoom link: https://aarhusuniversity.zoom.us/s/64233978039.

Linket er først aktivt på dagen. Husk at slukke mikrofon og kamera, hvis det ikke allerede er slukket, når du logger på.

Titlen på projektet er ”Novel insights to fatty acid oxidation disorders - Complex genetics and immunometabolic regulations”.

Yderligere oplysninger:
Ph.d.-studerende Signe Mosegaard, e-mail: signe.mosegaard@clin.au.dk, tlf. +45 20835507.

Bedømmelsesudvalg:
Formand: Associate Professor Karin Birkenkamp-Demtröder, Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark.

Professor Francois van der Westhuizen, Human Metabolomics, Faculty of Natural and Agricultural Sciences, North-West University, Potchefstroom, South Africa.

Associate Professor Sander M. Houten, Department of Genetics and Genomic Sciences, Icahn Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, New York, USA.

Press release (English)

## Novel insights to fatty acid oxidation disorders - Complex genetics and immunometabolic regulations

The mitochondrion is the major energy producing and oxygen consuming cellular component and it is important for overall cellular functions. Dysfunction of the mitochondrion may not only affect the cellular energy state but also lead to the release of pro-death factors, increase of reactive oxygen species (ROS) production, and cause a change in metabolic flexibility. Mitochondrial dysfunction with decreased metabolic flexibility is increasingly being recognized as a key element in ageing, cancer, neurodegeneration, diabetes, myocardial dysfunction, and sepsis. Common to all these conditions are also the presence of dysregulated inflammatory responses, and recent years research has revealed that mitochondrial function and inflammatory responses are closely connected. In patients with long-chain fatty acid oxidation deficiencies (lcFAOD), mitochondrial dysfunction is a major cellular issue causing decreased metabolic flexibility, and inflammatory events such as infections and exercise are major disease triggers in these disorders.

This PhD project studied two lcFAOD, Multiple Acyl-CoA Dehydrogenation Deficiency (MADD) and Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD). In the first study we used whole exome sequencing (WES) combined with transcriptomics and proteomics (diagnostic OMICs) to investigate the genetic complexity and heterogeneity of MADD. In a second study we investigated inflammatory processes in both VLCADD and MADD patient derived fibroblasts and detected that both cellular immune and metabolic responses are different in severe VLCADD and MADD, compared to healthy controls and mild VLCADD. Lastly, we, in a preliminary study, used a mass spectrometry diagnostic tool for lcFAOD, plasma acylcarnitine profiling, as a proxy measure of temporal changes in cellular FAO in a porcine sepsis model. The project was carried out by Signe Mosegaard , who is defending her/his dissertation on 7th of January 2022..

The defence is public and takes place on 7/1-2022 at 15.00 online via Zoom link: https://aarhusuniversity.zoom.us/s/64233978039.

The link is only active on the day and remember to turn off your camera and microphone.

The title of the project is Novel insights to fatty acid oxidation disorders - Complex genetics and immunometabolic regulations.

For more information, please contact PhD student Signe Mosegaard, email: signe.mosegaard@clin.au.dk, Phone +45 20835507.

Assessment committee:
Chair: Associate Professor Karin Birkenkamp-Demtröder, Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark.

Professor Francois van der Westhuizen, Human Metabolomics, Faculty of Natural and Agricultural Sciences, North-West University, Potchefstroom, South Africa.

Associate Professor Sander M. Houten, Department of Genetics and Genomic Sciences, Icahn Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, New York, USA.

**Permission**

By sending in this form:

- I hereby grant permission to publish the above Danish and English press releases.
- I confirm that I have been informed that any applicable inventions shall be treated confidentially and shall under no circumstances whatsoever be published, presented or mentioned prior to submission of a patent application, and that I have an obligation to inform my head of department and the university's Patents Committee if I believe I have made an invention in connection with my work. I also confirm that I am not aware that publication violates any other possible holders of a copyright.