Danish Diabetes Academy

CMN-DDA PhD & Postdoc Course: Metabolic Aspects of the Brain Muscle Axis

3-4 September 2020

Online Course
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## 2. Abstracts – Investigators/Participants

### 2.1 Group 1 – Skeletal muscle /insulin sensitivity/ampk / cancer/ PGC1-α/glucose homeostasis

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Placental structure is affected by maternal obesity, which is not reversed by metformin-treatment

Hufnagel AS¹, Fernandez-Twinn DS¹, Blackmore HL¹, Ashmore TJ¹, Schoonejans JM¹, Wilsmore PK¹, Aiken CE¹,², Ozanne SE¹
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Background/Aims:
Obesity in pregnancy is associated with higher risk of cardiometabolic diseases in the offspring. It is crucial to determine the mechanisms by which this arises and to define interventions to prevent detrimental effects. We hypothesize that the placenta as the main interface for maternofetal communication is important in mediating this developmental programming. The first aim of this study was to investigate effects of maternal obesity on placental structure using a mouse model of maternal diet-induced obesity. The second aim was to assess the ability of the drug metformin to prevent detrimental effects of maternal obesity on the placenta.

Methods:
Mice were fed with chow or obesogenic diet from 10 weeks prior to mating and during pregnancy. A third obese group was supplemented with metformin one week prior to mating and throughout pregnancy. Fetuses and placentae were studied at the end of pregnancy (E19). Placentae were stained for CD31 (immunohistochemistry) and the labyrinth area quantified.

Results:
Compared to fetal weights of control pregnancies (1.15 ± 0.02g), the fetal weights from obese (1.01 ± 0.02g) and metformin-treated pregnancies (0.95 ± 0.04g) were significantly reduced. In the placentae from obese pregnancies, there was a significant (p < 0.01) reduction in the labyrinthine zone (40±2% vs. 46±1%). In addition, calcification was seen in the labyrinth of obese placentae whereas none was observed in the control group. Neither the reduction of the labyrinth nor the calcification were prevented by metformin.

Conclusions:
We conclude that maternal obesity has an impact on the structure of the placenta and promotes calcification potentially associated with impaired placental perfusion. This might lead to the observed fetal growth restriction. Metformin did not prevent the immediate detrimental consequences of maternal obesity on the placenta. However, its ability to prevent long-term detrimental effects of obesity during pregnancy remain to be determined. We are currently in the process of characterising the physiology of the dams further to elucidate all possible mechanisms that might shape the in utero environment, this might be interesting in relation to other research areas as well.

Placental calcification is a well-known sign of an ageing placenta and associated with obesity in human pregnancies, which makes the model clinically relevant. We therefore aim to elucidate this process further.
Development of a screening platform to investigate GLUT4 trafficking

Dr Dougall Norris
IMS, University of Cambridge

Background and aim:
The glucose transporter GLUT4 is a central player in glucose homeostasis, facilitating the disposal of glucose into muscle and adipose tissue. Insulin controls the influx of glucose into these tissues by redistributing GLUT4 from storage vesicles (GSVs) to the plasma membrane. This process is disrupted in metabolic disease. Since we have an incomplete understanding about how insulin signalling regulates trafficking of GLUT4 in health and disease, we established a screening platform to assess the role of genes-of-interest in GLUT4 trafficking.

Material and methods:
We have used high content imaging to measure GLUT4 trafficking responses in a 96-well plate format. We assessed the effect of target gene knockdown on insulin-stimulated GLUT4 trafficking.

Results:
We have set up a workflow for 10-15 target genes, used to identify novel regulators of GLUT4 trafficking in adipocytes. BCL9L knockdown led to increased GLUT4 trafficking responses, suggesting BCL9L is a negative regulator of GLUT4.

Conclusions and discussion:
We are currently working on increasing the throughput of the screen and are interested in any potential targets from collaborators. We aim to migrate the assay into other cell types including myocytes. We are also currently using other methods to further investigate the role of BCL9L in GLUT4 trafficking such as live-cell approaches.
The metabolic perturbations of cancer are accelerated by loss of AMPK activity in skeletal muscle

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Cancer often leads to cachexia and whole-body metabolic perturbations, but the cause of these phenomena is still unknown. AMP-activated protein kinase (AMPK) is a regulator of insulin sensitivity, but increased AMPK activity has also been observed in cachectic muscle. This study aims to investigate the role of AMPK in cachexia and cancer-induced metabolic perturbations.

Wild-type (WT) mice and mice overexpressing a kinase-dead mutant of AMPK (KD-AMPK) in muscle were inoculated with/without cachexia-inducing Lewis Lung Carcinoma cells at the flank. Additionally, WT mice with/without tumor inoculation were treated (300mg/kg/day, intraperitoneal) with the AMPK activator, 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR). Whole-body metabolism was analyzed by magnetic resonance imaging, indirect calorimetry and activity, a glucose (2.0 g/kg, intraperitoneal) and an insulin tolerance test (0.3 U/kg, retro-orbital, anaesthetized).

In pre-cachectic conditions (day 14-16, post inoculation (PI)), only tumor-bearing KD-AMPK mice exhibited glucose and insulin intolerance. In cachectic conditions (day 21, PI), all tumor-bearing mice exhibited insulin intolerance, decreased activity and loss of lean body mass compared to healthy littermates. Only KD-AMPK mice displayed fat loss. In AICAR-treated animals, the cancer-induced insulin intolerance was alleviated. Collectively, we show that AMPK activity may play a protective role against cachexia and the metabolic perturbations of cancer.
The LRPPRC-SLIRP complex as a potential regulatory complex of exercise-induced muscle adaptations downstream of PGC1-α

Tang Cam Phung Pham
Affiliation: Section of Molecular Physiology, Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark

Background and aim:
The progressive decline in skeletal muscle (SkM) function in aging, cancer and diabetes can be decelerated with regular exercise; however, the underpinning mechanisms are not fully understood. We have identified that LRPPRC and SLIRP were upregulated by exercise training (ET) in human and mouse SkM. In non-SkM systems, LRPPRC and SLIRP form a complex and control post-transcriptional gene expression. Thus, we hypothesize that the LRPPRC-SLIRP complex contributes to exercise-induced adaptations in SkM.

Material and methods:
LRPPRC and SLIRP abundance were assessed by Western blotting in quadriceps of 12-week voluntarily ET muscle-specific PGC-1α knockout or muscle-specific PGC-1α overexpressing mice (n=9-12) or in gastrocnemius of SLIRP knockout mice (n=4) compared to controls. Immunoprecipitation (IP) was performed against SLIRP in gastrocnemius lysate.

Results:
PGC-1α is not only required for the exercise-induced upregulation of SLIRP and LRPPRC but overexpression of PGC-1α increases their expression by 4-fold and 2-fold, respectively. The interdependent LRPPRC-SLIRP complex exists in SkM shown by IP and by a 90% decrease in LRPPRC upon loss of SLIRP.

Conclusion and discussion:
The LRPPRC-SLIRP complex may play a novel role, via PGC-1α, in orchestrating SkM adaptations to ET. Understanding how ET modifies this process might facilitate forming therapeutic strategies against conditions associated with SkM dysfunction.
Diabetes Risk Index, a Multimarker Based on Lipoproteins and BCAA, is Associated with Incident Type 2 Diabetes in the General Population.

Jose L. Flores-Guerrero
Department of Internal Medicine, Division of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
PhD supervisor(s): Stephan J. L. Bakker and Robin P. F. Dullaart

Background and aim:
The Diabetes Risk Index (DRI) is a nuclear magnetic resonance spectroscopy -based multimarker that relies on the measurements of six lipoprotein parameters and concentrations of plasma branched chain amino acids producing a single score from 0 to 100 that reflects the magnitude of insulin resistance in a given individual. The aim of the study is to evaluate the ability of the DRI to predict incident type 2 diabetes (T2DM) in a large prospective cohort.

Material and methods:
The DRI was developed by combining LP-IR and the branched chain amino acids valine and leucine, all of which have been show previously to be associated with future T2D. DRI scores were calculated in a total of 6134 nondiabetic men and women in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study. Cox proportional hazards regression was used to evaluate the association of DRI scores with incident T2DM.

Results:
During a median follow-up of 8.5 years, 306 new T2DM cases were ascertained. In analyses adjusted for age and sex, there was a significant association between DRI scores and incident T2D with the hazard ratio (HR) for the highest versus lowest tertile being 7.49 (95% confidence interval: 5.01-11.19), P <0.001. After additional adjustment for BMI, family history of T2D, alcohol consumption, diastolic blood pressure, total cholesterol, triglycerides, HDL cholesterol and HOMA-IR, the HR was attenuated but remained significant (HR 1.67 [1.01-2.76], P = 0.04). Similar results were obtained when DRI was analyzed as HR per 1 SD increase (HR 1.37 [1.14-1.65], P = 0.001). The Kaplan-Meier plot demonstrated that patients in the highest tertile of DRI scores presented at higher risk (p-value for log-rank test P<0.001). To assess the performance of DRI, we calculated the Harrell’s C-index (95% CI) for the FOS risk score (a traditional T2D risk assessment tool that takes into account age, sex, family history of T2D, BMI, blood pressure, TG, and glucose) to be 0.870 (0.869–0.870), which increased to 0.876 (0.875–0.877) after addition of DRI, with a statistically significant improvement (P < 0.001). The Net Reclassification Index (NRI) was 0.41 (0.30–0.52; P < 0.001), denoting that when DRI was added to the model, more subjects were correctly re-classified than when the FOS risk score was used alone. The addition of DRI allowed for 42% of the participants who developed T2D during the follow-up to be properly reclassified at baseline from low to medium risk (11%) and from medium to high risk (31%).

Conclusions:
Higher DRI scores are associated with an increased risk of T2DM. The association is independent of clinical risk factors for T2D including HOMA-IR, BMI and lipids. Due its dual biological foundation, DRI could additionally have an application in the evaluation of lifestyle interventions.
## Abstracts

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<td>Oligodendrocytes of the hypothalamic median eminence are highly plastic and regulated by nutritional stimuli</td>
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A recurrent de novo HSPD1 variant is associated with hypomyelinating leukodystrophy

C. Cömert1, L. Brick2, D. Ang3, J. Palmfeldt1, M.F. Meaney4, P. Fernandez-Guerra1, M. Kozenko2, C. Georgopoulos3, P. Bross1

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Hypomyelinating leukodystrophies (HLDs) represent a group of rare heterogeneous disorders that interfere with the myelination in the central nervous system. One of the HLD-related genes is HSPD1, encoding the mitochondrial chaperone heat shock protein 60 (HSP60), which functions as folding machinery for mitochondrial proteins. Disease-causing HSPD1 variants have been associated with two different inherited neurological disorders: a fatal HLD (MIM 612233) and spastic paraplegia (MIM 605280) [1]. In 2018, a de novo HSPD1 variant was reported as a potential disease-associated variant in a patient with HLD [2]. Here, we present another case carrying the same disease-causing heterozygous de novo variation in the HSPD1 gene (c.139T>G, p.Leu47Val) associated with an HLD phenotype.

In this study, we used an E. coli-based complementation assay to demonstrate that the variant protein lacks in vivo function and used mass spectrometry-based proteomics to show the variant HSP60 is stably present in patient's fibroblasts, thus confirming the disease association of the variation. Our initial mitochondrial phenotyping experiments suggest disruption of mitochondrial bioenergetics together with increased glycolysis, and increased mitochondrial superoxide levels.

We conclude that de novo variations of the HSPD1 should be considered as potentially disease-causing in the diagnosis and pathogenesis of HLDs. The presence of the same de novo variation in two different patients with similar clinical phenotypes suggests that the p.Leu47Val variant is the consequence of a mutational hotspot in the HSPD1 gene, although the role of HSPD1 in myelination is yet to be understood.
Hypothalamic Mechanisms Underlying Sustained Remission of Diabetes Induced by Fibroblast Growth Factor 1

Dylan M. Rausch1,2,###, Marie A. Bentsen1,2,###, Zaman Mirzadeh3, Kenjiro Muta1,4, Jarrad M. Scarlett1,5, Jenny M. Brown1, Jonatan Thompson2, Kimberly M. Alonge1, Chelsea Faber1, Vicente Herranz-Pérez6,7, Karl J. Kaiyala8, Cecilia F. Ratner2, Birgitte Holst8, Thomas H. Meek9, Yu Zhang9, Thomas Sparso10, Gregory J. Morton1, Birgitte R. Kornum11, José-Manuel García-Verdugo5, Anna Secher10, Rasmus Jorgensen10, Tune H. Pers2*, Michael W. Schwartz1*

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In rodent models of type 2 diabetes (T2D), sustained remission of hyperglycemia can be induced by intracerebroventricular (icv) injection of fibroblast growth factor 1 (FGF1), and the hypothalamus was recently identified as a key target for this effect. To investigate how FGF1 action in this brain area achieves this effect, we combined traditional RNA sequencing (RNA-seq) with single cell and single nuclei RNA-seq to identify >60,000 single cell transcriptomes from the hypothalamus of diabetic Lepob/ob mice obtained both 1 and 5 days after icv injection of either FGF1 or vehicle. In addition to robust effects on tanycytes and neurovascular cell types, icv FGF1 injection also induced a neuroprotective astrocyte phenotype predicted to reduce neuronal excitability. In line with this finding was a broad-based inhibition of hypothalamic neurons, and in the case of Agrp neurons, this inhibitory effect persisted for at least 6 wk. Moreover, the effect of Agrp neuron inhibition to increase hypothalamic melanocortin signaling appears to be required for FGF1-induced diabetes remission, as this response is prevented by either genetic or pharmacological blockade of central melanocortin receptors. These findings collectively implicate glial-neuron interactions in the sustained remission of diabetes induced by the hypothalamic action of FGF1 action.
Metabolic Aspects of the Brain Muscle Axis 2020
The effect of metformin intervention on the programming of adiposity in offspring of obese pregnancy

Schoonejans JM\textsuperscript{1,2}, Blackmore HL\textsuperscript{1}, Hufnagel AS\textsuperscript{1}, Ashmore TJ\textsuperscript{1}, Fernandez-Twinn DS\textsuperscript{1}, Ozanne SE\textsuperscript{1}
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Background and aims:
Metformin is the first-line pharmacological treatment for gestational diabetes mellitus in several countries. However, long-term studies investigating the effects of intrauterine metformin exposure on offspring health are lacking. This study investigated adiposity outcomes in offspring exposed to maternal metformin treatment in an established mouse diet-induced obesity model.

Materials and methods:
Dams were fed a control diet (7% sugars, 3% fat) or high-fat diet (10% sugars, 20% fat) supplemented with sweetened condensed milk (55% sugars, 8% fat). Upon reaching a critical adiposity threshold, obese dams were either directly mated or treated orally with a clinically relevant dose of metformin from one-week pre-mating until E19. Dams were kept on their respective diets throughout pregnancy and lactation. Offspring were weaned at 3 weeks of age onto a control diet fed \textit{ad libitum}. Body weight, food intake and body composition (TD-NMR) of male and female offspring was measured weekly until 12 weeks of age.

Results:
Dams fed the high-fat high simple sugar diet were heavier and fatter at mating and in late pregnancy (p<0.0001). Metformin-treated dams were fatter than control dams but had decreased fat mass (p<0.0001) compared to untreated obese dams despite no difference in caloric intake. Offspring of obese and metformin-treated dams were smaller on postnatal day (PD) 2 (p<0.01) but both groups displayed catch-up growth by PD7 (p<0.001). At 12 weeks of age metformin-exposed offspring were significantly fatter than offspring of control (p<0.001) and obese dams (p<0.01) despite no difference in body weight or caloric intake.

Conclusions and discussions:
Metformin treatment during obese pregnancy lowers maternal adiposity. However, offspring adiposity was increased in both male and female exposed offspring. This study highlights the need to consider both short and long-term effects of metformin treatment during pregnancy on both mother and child. Further studies are therefore required to define the broad metabolic effects across the life-course.
Oligodendrocytes of the hypothalamic median eminence are highly plastic and regulated by nutritional stimuli

Sophie Buller, Clemence Blouet
WT-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom

Although the majority of oligodendrocytes (OLs) are born in early postnatal life, OLs are generated from oligodendrocyte progenitor cells (OPCs) in adulthood in response to specific stimuli such as learning a new motor skill. Adult-born OLs add to the pre-existing OL population and produce myelin, which either ensheathes previously unmyelinated axons or modifies existing myelin structures. Emerging evidence suggests that hypothalamic oligodendrocytes (OLs) may play a role in the regulation of energy metabolism. 

OPCs constitute the main proliferative cell type within the hypothalamus, however the proliferation, differentiation and maturation of this population of OLs has not been previously characterised.

Focussing our study on OLs of the median eminence (ME), a hypothalamic region devoid of a complete blood-brain-barrier that undergoes structural remodelling in response to changes in peripheral energy availability, we show that 1) OPCs of the ME are highly proliferative, 2) newly-formed OLs are continuously and rapidly generated in the adult ME, 3) the OL population here remains stable over time, 4) OLs of the ME rapidly turnover and 5) plasticity of the ME OL population is modulated peripheral energy availability. However, the functional significance of the unique dynamics of OL lineage cells in the adult ME is yet to be fully elucidated.
### 2.3 Group 3 – Skeletal muscle /insulin sensitivity/ampk / cancer/ PGC1-α/glucose homeostasis/Gut & Brain / Adiposity /

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Orla Woodward, Jo Lewis, Fiona Gribble, Frank Reimann
Wellcome Trust-MRC Institute of Metabolic Science – Metabolic Research Laboratories, University of Cambridge, Cambridge, UK

Insulin-like peptide 5 (Insl5), secreted from enteroendocrine L-cells in the distal region of the gastrointestinal tract, has been demonstrated to be an orexigenic hormone, with elevated levels of Insl5 following caloric restriction and Insl5 administration increasing food intake. Insl5, and its cognate G protein coupled receptor relaxin/insulin-like family peptide receptor 4 (RXFP4), is therefore thought to play a role in appetite and feeding behaviour. RXFP4 is widely distributed peripherally with some research indicating the central expression of this receptor; however, data thus far has been limited. This study implemented the novel RXFP4-Cre x GCaMP3-reporter mouse as a functional tool to address the precise location of RXFP4 in the central nervous system. Large numbers of GCaMP3 positive cells were detected in the lateral hypothalamus (LH), tuberal nucleus (TN) and paraseptalamic nucleus (PSTN) with smaller numbers observed in the dorsal vagal complex (DVC). Reverse transcription quantitative polymerase chain reaction (RT-qPCR) also demonstrated RXFP4 expression in the hypothalamus and hindbrain. This study provides an initial illustration of RXFP4 distribution in the mouse central nervous system. Expanding understanding of the distribution, physiology and pharmacology of RXFP4 is essential due to the identification of RXFP4 as a potential target for anti-obesity and antidiabetic drugs. Our data suggests the brain may be a key site of RXFP4 action.
Kristoffer J Kolnes1, 2, Daniel S Tangen2, Anders J Kolnes2,3, Egil I Johansen2, Jørgen Jensen2
1 Steno Diabetes Center Odense, Odense University Hospital, Denmark. 2 Department of Physical Performance Norwegian Sport School of Science, Norway. 3 Section of Specialized Endocrinology, Rikshospitalet, Oslo University Hospital, Norway.

Background:
Insulin resistance (IR) is a major cause of the development of T2DM. IR is associated with inactivity and training improves IR. Skeletal muscle takes up the majority of glucose during insulin secretion. Whether oxidative capacity and insulin action in skeletal muscles are connected remains unknown.

Aim:
The aim of was to investigate the effect of training on expression of oxidative enzymes in healthy and dysglycaemic middle-aged males.

Methods:
13 lean health and 13 obese dysglycaemic males (40-65 years) were recruited to a 12 weeks training intervention: 2 endurance and 2 resistance training sessions weekly. Hyperinsulinaemic clamps, muscle biopsies, VO2max and fat oxidation during exercise, were tested before and after the intervention.

Results:
VO2max was higher in lean than overweight, and increased similarly. Glucose infusion rate (GIR) increased in both groups, but remained 50% reduced in overweight. Expression of proteins from the five complexes involved in electron transport was similar in both groups before and after the intervention.

Conclusion:
VO2max and GIR increased similarly in lean and overweight. Expression of oxidative enzymes normalized in overweight, but GIR remained 50% reduced. Insulin-stimulated glucose uptake seems not to be directly associated with oxidative capacity.

Collaboration:
RNA seq have been performed on the biopsies, and collaboration with Giles Yeo and Brian Lam in Cambridge is ongoing with these data.
AMPK is necessary for muscle glucose uptake during recovery from muscle contractions

Nicolas Oldenburg Jørgensen
Molecular Signaling in Muscle Metabolism, Section of Molecular Physiology, Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen. Copenhagen, Denmark.

Background & Aim
Within the field of skeletal muscle physiology it is thought that activation of AMPK during exercise (EX) and muscle contractions (CON) regulates skeletal muscle glucose uptake (GU), however, this is not a consistent finding. A review of the previous publications investigating this revealed that the discrepancy is due to methodological issues. The review unveiled that the majority of papers supporting a role for AMPK measured GU during and after muscle EX/CON, whereas papers not supporting a role for AMPK only measured during muscle EX/CON. The aim of this study was to directly assess the role of AMPK for the regulation of GU during and after muscle CON.

Material & Methods
One leg from wildtype (WT), AMPKα1α2 KO (mdKO), and AMPKγ3 KO (γ3 KO) mice were subject to 10 min of CON through direct nerve stimulation. The contralateral leg served as control. Through I.V. injection of \([3H]2\)-deoxyglucose, GU in m. tibialis anterior was measured for 10 min either during or 30 min after CON.

Results
Skeletal muscle GU was increased in WT, mdKO, and γ3 KO during 10 min of muscle CON. 30 min into recovery GU was maintained in WT mice, ~50% decreased in mdKO muscle, and returned to resting levels in γ3 KO muscle.

Conclusions & Discussion
These findings suggest a central role for AMPK in the regulation of GU in recovery from muscle CON. Specifically it seems like the AMPKα2β2γ3 is the complex regulating this phenomenon. This study serves as an example of how studies using in situ muscle CON can model in vivo EX. This model can serve as a valuable tool for studies of interorgan cross talk during EX e.g. from muscle to brain. Blood sampling and organ dissection can easily be carried out after CON cessation. Measurements of plasma content e.g. myokines, exosomes, extracellular vesicles, or the like, through mass spectrometry, could be ways of implementing this methodology within the interorgan cross talk field.
Deciphering the role of human gut microbiota in choline metabolism using an in-vitro colon model

Day PEW, Shehata E, Saha S, Kellingray L, Narbad A, Kroon PA
Food Innovation & Health, Quadram Institute Bioscience, Norwich Research Park, Norwich, Norfolk NR4 7UQ, UK

Introduction:
Choline, carnitine and their metabolites correlate with metabolic diseases including neurodegenerative diseases and diabetes. Plasma levels of a choline/carnitine gut microbiota metabolite trimethylamine oxide (TMAO) predict death after heart failure. Being essential substrates for the cellular membrane component phosphatidylcholine and the brain signalling molecule acetylcholine and having regulatory roles in lipid and insulin signalling, it is unsurprising that, these substrates correlate with metabolic diseases, although the mechanisms involved are poorly understood. Choline/carnitine utilisation by the gut microbiota may limit the availability of these substrates to the host.

Methods and Results:
Using an anaerobic in-vitro colon model and LC-MS, we show that human faecal microbiota catabolise 100% of choline to produce TMA via the choline TMA-lyase pathway and 100% carnitine via γ-butyrobetaine hydroxylase, a process that forms an intermediate from which TMA is produced. Very small amounts of TMA were produced from betaine and none of the other putative pathways were involved in TMA production from choline or carnitine.

Conclusion:
Gut microbiota choline/carnitine metabolism may deprive the host of substrates essential for membrane integrity, brain signalling and glucose homeostasis. We highlight strategic pathways that contribute to the gut-brain-skeletal muscle signalling and may be targeted to treat or prevent neurodegenerative diseases and diabetes.
### 2.4 Group 4 – Gut & Brain / Adiposity / CNS/gene variance/drug action /energy metabolism

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Archaeological preserved brain tissue: Biomolecular evidence of ancient metabolic disease?

Alexandra Morton-Hayward, University College London, UK (& Matthew Collins, University of Copenhagen, Denmark / University of Cambridge, UK)

Ancient brain tissue and spinal cord preserve in an unexpected and as-yet unexplained array of archaeological contexts. Since 1790, some 1300 preserved brains have been reported; yet it remains a neglected area of bioarchaeological research with enormous potential for cross-disciplinary investigation of the way in which the human metabolome has changed through time, and between past populations.

Unanswered questions abound: Does the ancient CNS entrap genomic, proteomic or lipidomic profiles of metabolic disorders, or cardiometabolic biomarkers associated with body composition? What might comparative biomolecular and transcriptomic approaches reveal about the ancient brain-muscle axis? Do ancient brains preserve a coherent neural network, and what might we learn about diet- and microbiome-related white matter integrity by visualising it? This collaborative project employs a matrix of analytical methodology to investigate 13th century brain samples (n=5) and preserved spinal cord (n=1) from Aalborg, Denmark, with the aim to create a cohesive, multifaceted dataset of mutual benefit to and informed by fields as diverse as palaeopathology, neurobiology, metabolomics, structural and functional proteomics, medical genetics and clinical biomarker research.
Leucine sensing in the caudomedial hindbrain rapidly inhibits AgRP neurons

Anthony Tsang, Danae Nuzzaci, Tamana Darwish, Emma Roth, Havish Samudrala, Clemence Blouet.
MRC Metabolic Diseases Unit, University of Cambridge Metabolic Research Laboratories, WT-MRC Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, UK.

Accumulating evidence suggest that deregulation of appetite-regulating function of the brain plays a pivotal role in human obesity. Among all macronutrients, protein has the most potent appetite-suppressing effect. However, how protein availability is encoded and detected by the brain to modulate behaviour is unclear. We propose that circulating leucine levels serve as a postprandial signal of protein availability.

We previously showed that leucine sensing in the dorso-vagal complex (DVC) rapidly suppresses hunger, but the neural circuits mediating this response are unknown. Here we combined viral tracing studies and histological assessments to characterise the central pathways engaged downstream from DVC leucine sensing to rapidly suppress hunger.

First, we showed that DVC leucine sensing can rapidly inhibit AgRP neurons in the arcuate nucleus (ARC) in fasted mice. We identified that ARC-AgRP neurons receive poly-synaptic inputs from a distinct subpopulation of catecholamine neurons in the DVC expressing calcitonin receptor (CTR) and prolactin-releasing peptide (PrRP). We found DVC leucine sensing activates this neuronal subset while inhibiting these neurons blunted the anorexic effects of DVC leucine sensing. We then deciphered the neural pathways through which the DVC interoception modulates the activity of AgRP neurons via a relay in the dorsomedial nuclei of the hypothalamus (DMH). Lastly, we confirmed the functional relevance of the DVC -> DMH -> ARC-AgRP circuit in the regulation of feeding behaviour.

Together, these findings shed light in elucidating the central leucine-sensing mechanism and describe a novel neural pathway through which hindbrain nutrient sensing is relayed to key appetite-regulating neurons of the hypothalamus.
Changes in neuroglial interactions on POMC neurons at the meal scale

Danaé Nuzzaci 1, Emmanuelle Nedelec 1, Amélie Laderrière 1, Fabienne Liénard 1, Vincent Gigot 1, Aleth Lemoine 1, Xavier Fioramonti 1, Alexandre Benani 1
1 Centre des Sciences du Goût et de l'Alimentation, AgroSup, CNRS, INRA, Univ. Bourgogne Franche-Comté, F-21000 Dijon, France

The melanocortin system of the arcuate nucleus is one of the best characterized neuronal feeding circuits. This includes POMC neurons which express proopiomelanocortin a precursor of the anorectic peptide α-MSH. In the adult brain, this system can undergo synaptic remodeling in response to change in blood hormones. However this phenomenon occurs during extreme metabolic situations such as 24H-fasting or high-fat induced overfeeding, two situations characterized by large hormonal variations. The physiological role of this phenomenon remains to be clarified. In particular, we still do not know whether or not this synaptic plasticity is recapitulated in response to moderate hormonal fluctuations, such as this occurs at the meal scale.

To examine this possibility, we investigated neuronal and glial interactions onto POMC neurons in the arcuate nucleus in preprandial state (PRE) and postprandial states which correspond to 1H-Standard Diet (1H-SD) and 1H-High Fat Diet (1H-HFD) in adult mouse. These three distinct metabolic situations are characterized by few, if any, variations in hormone levels. Morphometric analysis after electron microscopy and confocal imaging reveals changes in glial interactions on POMC perikarya in 1H-SD fed mice and changes in synaptic configuration in 1H-HFD fed mice. In 1H-SD fed mice, glial changes correlate with an increase of basal activity of POMC neurons. These results show that synaptic and glial plasticity on POMC neurons activity are elicited at the meal scale in adult mouse. Because of their reactivity, these mechanisms might contribute to the regulation of satiety.
Characterising stimulus-secretion coupling of the gastrointestinal hormone motilin in human duodenal organoids

Emily L Miedzybrodzka, Deborah A Goldspink, Rachel Foreman, Pierre Larraufie, Richard G Kay, Fiona M Gribble, Frank Reimann
Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, UK

Background and aim
The gut hormone motilin, released from proximal small intestinal M-cells, regulates gastrointestinal motility and may increase food intake. As motilin is not expressed in rodent models, stimulus-secretion coupling studies have been limited. We aimed to develop novel tools to enable detailed characterisation of human M-cells for the first time.

Material and methods
Human duodenal organoids were CRISPR-Cas9 modified to express the fluorescent protein Venus or the Ca$^{2+}$ sensor GCaMP7s 3’ to the motilin (MLN) coding sequence. M-cells were purified for qPCR and bulk RNA sequencing by FAC sorting of MLN-Venus organoids and fixed, stained human duodenal epithelium. Single cell Ca$^{2+}$ dynamics were assessed in 2D organoid-derived cultures. Motilin secretion was measured by LC-MS/MS in parallel with other gut hormones.

Results
Expression of MLN and other EEC markers in organoids was significantly increased by the addition of Notch and MEK inhibitors alongside Wnt reduction. In pilot studies, increased cAMP (forskolin/IBMX) evoked motilin secretion and arginine vasopressin elevated M-cell Ca$^{2+}$. Several target receptors have been identified by RNA sequencing and work is ongoing to assess their function.

Conclusions and discussion
Our optimisation of human small intestinal organoid culture is widely applicable for the study of the enteroendocrine system, including developing novel therapeutics. Future work aims to identify physiological factors involved in the stimulation or inhibition of motilin secretion, and mechanisms of M-cell signalling.
## 3. Speakers

### 3.1. List of invited Speakers

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<td>Clemence Blouet</td>
<td>IMS-MRL, University of Cambridge (UK)</td>
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<td>Daniel Fazakerley</td>
<td>IMS-MRL, University of Cambridge (UK)</td>
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<td>Florian Merkle</td>
<td>IMS-MRL, University of Cambridge (UK)</td>
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<td>Heather Blackmore</td>
<td>IMS-MRL, University of Cambridge (UK)</td>
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<td>Jean Farup</td>
<td>Aarhus University (DK)</td>
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<tr>
<td>Lin Lin</td>
<td>Aarhus University (DK)</td>
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<td>Lykke Sylow</td>
<td>University of Copenhagen (DK)</td>
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<tr>
<td>Rasmus Kjøbsted</td>
<td>University of Copenhagen (DK)</td>
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3.2. Biographic sketches - Speakers

Short biography – Christoffer Clemmensen
Christoffer Clemmensen is an Associate Professor at the University of Copenhagen, Denmark. The Clemmensen Lab focuses on understanding central nervous system control of energy homeostasis and metabolic health and on transforming novel insights in the pathophysiology of metabolic diseases into efficacious and safe pharmacotherapeutic options. Christoffer has published 49 scientific papers that has been cited more than 2800 times, and was in 2018 elected into the Royal National Academy of Sciences and Letter for Young Investigators in Denmark.

Short biography - Clemence Blouet
Nutrition physiologist by background, Clemence developed her neuroscience expertise during her postdoctoral training with Dr. Gary Schwartz at The Albert Einstein College of Medicine, with a specific interest in the mechanisms through which the brain detects nutritional and metabolic signals to maintain whole body energy and glucose homeostasis. In 2014, she joined the MRC Metabolic Diseases Unit of the Institute of Metabolic Science at the University of Cambridge and is now on a MRC Programme leader track position. The main focus of her group is to understand how dietary protein create brain representations that regulate hunger and satiety.

Short biography - Daniel Fazakerley
Dr Fazakerley studied for his PhD on GLUT4 trafficking in muscle under the supervision of Professor Geoff Holman at the University of Bath. In 2010, he was awarded a Sir Henry Wellcome Post-doctoral Fellowship to join Professor David James’ group at the Garvan Institute (later University of Sydney) to study GLUT4 trafficking in adipocytes and myocytes in insulin resistance. In 2019, Dr Fazakerley established his own group at the Institute of Metabolic Science, University of Cambridge having been awarded an MRC Career Development Award. His group continues to work on understanding the molecular details of insulin-stimulated glucose transport, and how this process breaks down in insulin resistance.
Short biography – Florian Merkle
Florian is a Sir Henry Dale Fellow, Ben Barres Early Career Investigator, and Robertson Investigator whose group uses human pluripotent stem cells (hPSCs) to model obesity and neurodegeneration. He studied at Caltech before moving to UCSF for graduate school where his work in the laboratory of Prof. Arturo Alvarez-Buylla uncovered the origin and diversity of adult neural stem cells in the mouse brain. For his postdoc, he worked with Prof. Kevin Eggan and Prof. Alex Schier at Harvard University and the Broad Institute of MIT and Harvard as a postdoc to develop hypothalamic differentiation protocols, adapt CRISPR/Cas9 for use in hPSCs, and study the genetic architecture of hPSCs. This experience forms the basis of the Merkle laboratory's efforts to promote the safe and efficient use of hPSCs in disease modelling and regenerative medicine, and to use hPSC-derived cellular models to uncover the mechanistic basis of human neurological diseases with the aim of identifying new therapies.

Short biography – Heather Blackmore
Heather Blackmore is a post-doctoral research associate working with Professor Susan Ozanne. Her research, funded by the British Heart Foundation, assesses the long-term impact maternal obesity has on the cardiovascular health of her offspring. Most recently her work has focused on intervention strategies directed at obese mother, and the associated cardio-metabolic outcomes to both the mother and her offspring.

Short biography – Jean Farup
Jean Farup is did his graduate studies in human exercise physiology at Dept of Public Health Aarhus University from which he obtained his PhD in stem cell physiology in 2014. He then continued into a first postdoc position at Dept of Clinical Medicine, Aarhus University, where he investigated the role of human fibro-adipogenic progenitors in type 2 diabetes. He later joined the lab of Thomas Rando at Stanford University where he worked on the role of Pax3 in the regulation of muscle stem cell quiescence and cell cycle entry. In 2019, he joined the Dept of Biomedicine at Aarhus University as an assistant professor, where he is currently working on human fibro-adipogenic progenitors and their role in maintaining muscle size and function under disease conditions.

Short biography – Lin Lin
Lin Lin is currently an associate professor in Department of Biomedicine in Aarhus University. Over the past decades, her main research interest is on the improvement of applied genome technologies such as single cell RNA sequencing and gene editing, and the applications on studying the pathogenesis of human diseases, diseases treatment and the therapeutic potential target discoveries. One unmet medical need, which her research is trying to provide a sustainable solution for, is the greatest shortage of organs for transplantation. This include the islet transplantation for treatment of diabetes. Another research focus is to promote the understanding of diabetic complications and treatment of diabetes patients.
Short biography - Lykke Sylow
Lykke Sylow is Associate Professor and group leader of the Molecular Metabolism in Cancer & Aging Group in the Section of Molecular Physiology at the Department of Exercise, Sports, and Nutrition, University of Copenhagen. Lykke has worked in basic science of muscle metabolism research for 12 years. Her research has focused on the molecular mechanisms by which insulin- and exercise-stimulated glucose uptake is regulated via Rho GTPases. More recently, Lykke’s work has centred on skeletal muscle metabolic dysfunctions in ageing and cancer and molecular causes hereof. Lykke is working on the basic sciences of exercise adaptations that will hopefully allow us to harness the beneficial effects of exercise in ageing and cancer in the future.

Short biography – Rasmus Kjøbsted
Rasmus Kjøbsted received his PhD in the field of molecular physiology from the University of Copenhagen. He is currently working as a DDA-funded postdoctoral fellow at the University of Copenhagen investigating the mechanisms involved in enhancing muscle insulin sensitivity after a single bout of exercise. Prior to his current position Rasmus has trained in 5 international laboratories. He has ~20 publications of which he is lead author on 5 papers published in Diabetes. He has been invited to speak at international conferences and he is part of the committee organizing the Danish Muscle Metabolism Network Workshops. In 2012 he received the August Krogh Centre Scholarship and in 2018 he received the DDA Young Investigator Award.
3.3. Short summary of speaker's talk

Christoffer Clemmensen
The talk will cover major endogenous regulators of energy homeostasis and discuss how external (environmental) factors interact with human biology to determine body weight and metabolic health. We will discuss endocrine, neural and nutritional pathways that are central to energy homeostatic control, as well as potential intervention points for pharmacological interference.

Clemence Blouet
The brain plays a central role in the maintenance of energy balance largely by sensing and integrating dietary signals of nutrient and energy availability and orchestrating behavioural and metabolic effectors eventually determining metabolic health.
This regulation occurs involves specialised neurons in discrete brain areas, including the mediobasal hypothalamus, that can sense food-related signals and engage downstream circuits regulating energy balance.
We are specifically interested in the control of protein intake, the role of protein in the regulation of energy balance and its contribution to the obesity epidemic.

Daniel Fazakerley
Insulin lowers blood glucose, in part, through stimulating glucose transport into muscle and adipose tissues. This is achieved through the regulated trafficking of the glucose transporter GLUT4 to the cell surface in response to activation of the insulin signalling network. This process becomes impaired in insulin resistance.
We study how GLUT4 trafficking is controlled in fat and muscles cells, how insulin signalling intersects with this trafficking machinery to promote GLUT4 cell surface accumulation, and how this process breaks down in insulin resistance. During my talk I will provide background information on what is known about insulin-stimulated GLUT4 trafficking in fat and muscle cells, highlight differences between adipocytes and muscle cells, and present data on the role that mitochondrial reactive oxygen species may play in insulin resistance.

Florian Merkle
Obesity is widely recognised to be primarily a disease of the brain. Due to the inaccessibility of human neurons, the cellular mechanisms contributing to obesity have been largely studied in model organisms. Several years ago, it became possible to differentiate human pluripotent stem cells into hypothalamic neurons, including those that regulate food intake. The study of these cells in vitro has revealed new insights into their functional properties and has opened new opportunities for understanding obesity disease mechanisms that may provide the foundation for developing new treatments.

Heather Blackmore
As obesity rates are rising across the globe, the numbers of women entering pregnancy with a BMI of 30 or more is significant. Obesity in pregnancy is not only associated with immediate adverse consequences to the mother and her developing fetus, but also the long-term health of her offspring. Specifically, offspring born to obese mothers have been shown to have an increased risk of cardiovascular disease and premature mortality than those born to mothers who had a BMI in the normal range. The aim of my talk is to assess the potential impact of a moderate exercise intervention in the obese mother and the consequence to her offspring, using a mouse model of maternal diet induced obesity. My talk will cover the metabolic and cardiovascular impact to the offspring in young adulthood.
Jean Farup
Ageing and age-related diseases (e.g. type 2 diabetes) are associated with a decline in the function and regenerative capacity of multiple key organs such as liver, brain and skeletal muscle. Several of these organs are dependent on tissue specific stem cells to repair and replenish damaged tissue. Seminal studies have shown that the ageing environment markedly impair the functionality of these stem cells. When regeneration fails during ageing or disease, the parenchymal tissue is replaced by fibrotic and adipose tissue, which further disrupts organ function. Fortunately, stem cell function can be rejuvenated by exposure to a healthy young environment. Identification of molecules that may rejuvenate stem cells in key organs such as skeletal muscle holds great potential to change organ regenerative capacity and functionality. Such compounds may ultimately extend healthy lifespan.

Lin Lin
Cell and animal models are valuable resources for understanding the mechanisms causing neurodegenerative diseases and the development of novel treatments. A significant number of studies have been performed based on human induced pluripotent stem cells-derived models. The progression of Huntington’s Disease (HD) involves the loss of striatal projection neurons. Previously, we have reported a 3-steps protocol for promoting the differentiation from neural progenitor cells towards striatal projection neurons. Our optimized method generates MAP2-positive cells, which were 96%, 84%, and 21% positive for GABA, calbindin, and DARPP-32/PPP1R1B, respectively. As a complement approach to the cell-based model, we have in the meantime developing genetically modified pig models for human neurodegenerative diseases. However, the current understanding of regional specific gene expression in the mammalian brain, typically in pigs, are rarely explored. To expand the basic understanding to neurobiology, several brain mapping projects were done on basic organization and regional or cellular gene expression of mammalian brain including mouse and human. For complement the available database, in collaboration with scientists from the SciLifeLab and BGI-research, we have performed a comprehensive, in-depth molecular dissection of various brain regions using multiple transcriptomic methods and antibody-based mapping in human, mouse and pig. This combine approach allows us to identify the regional expression profiles of protein-coding genes, their similarities and differences within or between different regions/species. This Brain Atlas (www.proteinatlas.org/brain) will allow us to explore and compare the expression of individual protein-coding genes in the various parts of the mammalian brain. With the development of single cell sequencing technologies, we aim to map and better understand the cellular organization and molecular signatures underlying the progression of neurogenerative diseases and diabetes using an integrative multi-OMICS approach

Lykke Sylow
Exercise-stimulated glucose uptake by muscle occurs independently of insulin signal transduction. This feature makes exercise an excellent non-pharmacological method by which to decrease hyperglycaemia in insulin-resistant states, including obesity and type 2 diabetes mellitus. Yet, the mechanisms that regulate exercise-induced glucose uptake have remained elusive; however, emerging evidence suggest that the Rho GTPase RAC1 is implicated in this process. The difficulty in identifying master signal transduction pathway that mediate exercise-stimulated glucose uptake probably reflects the complexity and partial redundancy of an evolutionarily well-conserved system to ensure sufficient glucose delivery to the working muscle. Knowledge of the molecular mechanisms that mediate glucose uptake during exercise might provide novel therapeutic options in the future to benefit diseases associated with metabolic dysregulation.

Rasmus Kjøbsted
Exercise is an effective strategy for the prevention of lifestyle-related diseases including cardiovascular disease, diabetes, certain cancers, muscle wasting and cognitive impairment. Thus, physical activity may be viewed upon as a superior medicine. But how exercise works is only vaguely known. Obtaining this
knowledge enable us to gain the full advantage of physical activity in how and to whom it should be prescribed. More importantly, it will illuminate novel pharmacological possibilities, which either alone or in combination with (lesser) physical activity will promote health for physical disabled individuals or the many for whom physical activity is not attractive. Therefore my talk will revolve around the ability of exercise to enhance muscle insulin sensitivity and the molecular mechanisms involved that is central to the health beneficial effects of exercise

4. Moderators/Co-hosts

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<tr>
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<td>Institute of Metabolic Science in Cambridge (UK)</td>
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<tr>
<td>Jørgen Jensen</td>
<td>Norwegian School of Sport Science (NO)</td>
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<td>Niels Ørtenblad</td>
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<td>Niels Jessen</td>
<td>Aarhus University (DK)</td>
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5. Programme

Thursday 3 September

09:00–09:30  Welcome & Meet & Greet

Education Manager Jette Husum, DDA (DK)

Moderator: Professor Frank Reimann, Institute of Metabolic Science in Cambridge (UK)

09:30–10:40  Key points from webcasts & Questions & Answers

Neural Integration of Peripheral Metabolic Signals Regulating Energy Homeostasis

Associate Professor Christoffer Clemmensen, University of Copenhagen (DK)

Central Nutrient Sensing in the Control Of Appetite and Metabolism

Programme Leader Track, Dr Clemence Blouet, IMS-MRL, University of Cambridge (UK)

The Skeletal Muscle Niche and the Role of Non-Myogenic Cells in Maintaining Muscle Homeostasis

Assistant Professor Jean Farup, Aarhus University, (DK)

Studying Obesity with Human Hypothalmic Neurons

Senior Research Associate, Dr Florian Merkle, University of Cambridge, (UK)

10:40–10:50  Tea & Coffee break

10:50–11:30  Group work and discussion – next challenges in the field
11:30-11:45  Follow up on the group work
Co-host: Professor Jørgen Jensen, Department of Physical Performance, Norwegian School of Sport Sciences (NO)

12:00-13:30 Lunch

13:30-14:25 Poster pitches & presentations I
Moderator: Professor Frank Reimann, Institute of Metabolic Science in Cambridge (UK)

14:20-14:30 Closing remarks
Moderator: Professor Frank Reimann, Institute of Metabolic Science in Cambridge (UK)

Friday 4 September

09:00-09:20 Welcome & Networking

09:20-09:50 Key points from webcasts
Moderator: Professor Niels Ørtenblad, University of Southern Denmark (DK)

An Integrative Approach to Explore and Better Understand the Mammalian Brain
Associate Professor Lin Lin, Aarhus University (DK)

Insulin-Stimulated Glucose Transport in Health & Insulin Resistance
Senior Research Associate, Dr Daniel Fazakerley IMS-MRL, University of Cambridge (UK)

Muscling In On the Mechanisms Underlying Exercise’s Beneficial Effects on Health –and Some Methodological Considerations
Assistant Professor Lykke Sylow University of Copenhagen (DK)
AMPK and TBC1D4 - Linking Exercise to Muscle Insulin Sensitization
Postdoctoral fellow Rasmus Kjøbsted University of Copenhagen (DK)

Maternal Exercise Intervention in Obese Pregnancy and the Associated Cardiovascular Outcomes in the Adult Male Offspring
Research Associate, Dr Heather Blackmore IMS-MRL, University of Cambridge (UK)

09:50-10:00 Tea & Coffee break
10:00-10:45 Panel discussion
   Moderator: Professor Niels Ørtenblad, University of Southern Denmark (DK)
10:45-10:55 Tea & Coffee break
10:55-11:35 Group work and discussion – next challenges in the field
11:35-12:00 Follow up on group work
   Co-host: Professor Niels Jessen, Aarhus University (DK)
12:00-13:30 Lunch
13:30-14:25 Poster pitches & presentations II
   Moderator: Professor Niels Ørtenblad, University of Southern Denmark (DK)
14:20-14:30 Summary & Closing remarks
   Moderator: Professor Niels Ørtenblad, University of Southern Denmark (DK)
6. Organising Committee

**Clemence Blouet** Dr. PhD, Programme Leader Track, Wellcome-MRC Institute of Metabolic Science- Metabolic Research Laboratories, IMS-MRL, University of Cambridge (UK)

**Niels Jessen** Professor, Head of Research, Department of Clinical Medicine and Department of Biomedicine, Aarhus University (DK)

**Maria Adams** Director of Research Operations, Wellcome-MRC Institute of Metabolic Science-Metabolic Research Laboratories, University of Cambridge, (UK)

**Jørgen Jensen** Professor, Department of Physical Performance, Norwegian School of Sport Sciences, (NO)

**Angela Lumsdon** Network Coordinator, Cambridge Metabolic Network, (UK)