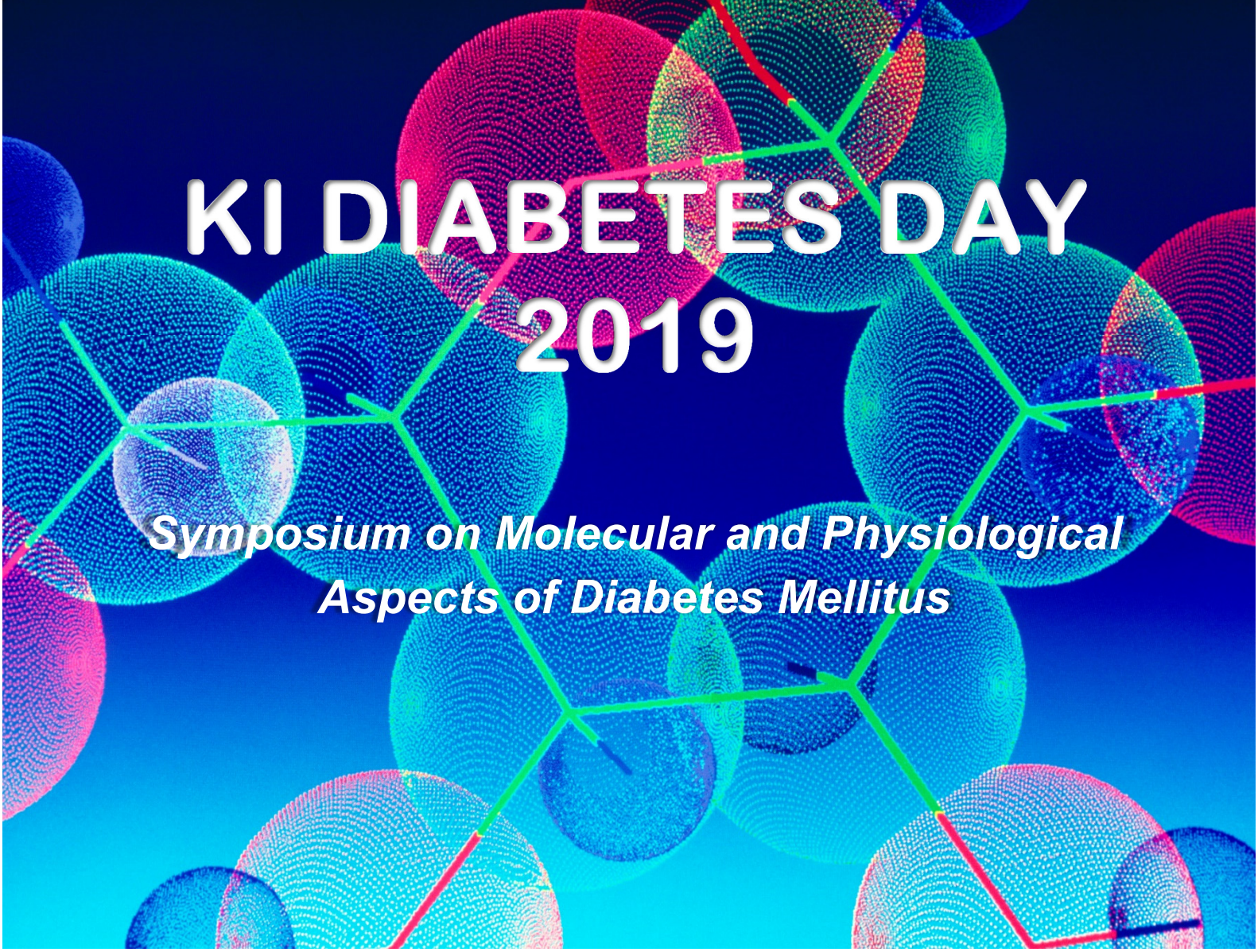

November 14, 2019 | Karolinska Institutet

world diabetes day

PROGRAMME AND ABSTRACTS

SRP DIABETES

Karolinska Institutet

Organiser:

Strategic Research Programme in Diabetes at Karolinska Institutet (SRP Diabetes).

https://ki.se/en/srp-diabetes

SRP Diabetes was initiated 2010 and is based on thirty-five different research groups at Karolinska Institutet and Umeå University. An integrated research environment in the diabetes area has been formed where results are translated between basic and clinical science with the aim to improve the care and treatment of people with diabetes. The overall goal of SRP Diabetes is to improve both prevention and treatment of diabetes by forming a strong, integrated research environment in the diabetes field, rich in collaboration, communication, and scientific exchange.

Specifially, SRP Diabetes activities aim to:

- Develop and support technical platforms such as a Metabolic Phenotyping Centre for Diabetic Animal Models, a Centre for Clinical Metabolic Research in Diabetes, Beta Cell in-vivo Imaging/ Extracellular Flux Analysis (Seahorse) and support for Functional Genomics in Diabetes Research (bioinformatics)
- Increase interactions between the research teams of the programme by supporting collaborative projects and arranging common symposia, meetings and seminars
- Support undergraduate and graduate education within the research areas connected to the programme
- Increase translational research by supporting collaborative projects between experimental and clinical researchers
- Facilitate international contacts
- Increase interactions with the biotech and pharmaceutical industry
- Support commercial utilization by providing in-house expertise and support for business development by liasing with Karolinska Institutet Innovations
- Increase public awarness and inform about current diabetes research

The programme coordinates laboratories possessing substantial expertise and unique technical resources, thus affording a natural point of contact for collaboration within the diabetes area, both for researchers within Karolinska Institutet and Umeå University as well as with external researchers.

SRP Diabetes Management:

Director: Anna Krook (Karolinska Institutet)

Co-Director: Peter Arner (Karolinska Institutet)

Per-Olof Berggren (Karolinska Institutet)

Helena Edlund (Umeå University)

Erik Näslund (Karolinska Institutet)

Juleen Zierath Karolinska Institutet)

Venue: Biomedicum Seminar Hall, Karolinska Institutet, Solna

Web/Twitter: https://ki.se/en/srp-diabetes/diabetes-day / @srp_diabetes

Programme

08.30-09.00	REGISTRATION
09:00- 09:10	Welcome Note - **Anna Krook**
SESSION 1	**Chair: Mikael Rydén**
9:10- 9:45	"*Diabetes and cardiovascular disease: Insights into mechanisms"* **Karin Bornfeldt,** University of Washington, Seattle, WA, USA
9:45- 10:20	"*Hyperglycaemia induces trained immunity in macrophages and their precursors and promotes atherosclerosis"* **Robin Choudhury**, University of Oxford
10:20- 10:50	COFFEE BREAK
SESSION 2	**Chair: Helena Edlund**
10:50- 11:25	"*Organelle dysfunction in pancreatic beta cells: lessons learned from monogenic forms of diabetes"* **Miriam Cnop,** ULB Center for Diabetes Research, Universite Libre de Bruxelles
11:25-12:00	*"Diabetes and Branched Chain Amino Acids"* **Zoltan Arany,** Perelman School of Medicine, University of Pennsylvania, USA
12:00-13:00	LUNCH (Posters mounted)
SESSION 3	**Chair: Juleen Zierath**
13:00- 13:35	"*Communicating Clocks: Circadian Metabolism and Epigenetics"* **Paolo Sassone-Corsi**, UC Irvine School of Medicine, USA
13:35-14:10	*"Emerging roles of bile acid signaling in metabolism and stemness"* **Kristina Schoonjans**, Ecole Polytechnique Fédérale, Lausanne, Switzerland
14:10-14:40	COFFEE BREAK
SESSION 4	**Chair: Erik Näslund**
14:40-15:15	*"Mechanisms of glycemic control improvement after metabolic surgery"* **Geltrude Mingrone,** Catholic University, School of Medicine, Rome, Italy
15:15-15:50	*"Signalling in the Gut-Brain-Pancreatic Axis"* **Fiona Gribble,** University of Cambridge, UK
15:50-16:00	Closing Remarks – **Peter Arner**
POSTER SESSION, Drinks and light bites	
16.00-18.00	Drinks and lite bites served by the Biomedicum entrance
16.15-16.45	Posters with odd numbers will be presented
16.45-17.15	Posters with even numbers will be presented

Speaker abstracts

SESSION 1

Diabetes and cardiovascular disease: Insights into mechanisms

Karin E. Bornfeldt, *PhD, Professor of Medicine, University of Washington Medicine Diabetes Institute, UW Medicine South Lake Union, Seattle, WA 98109, USA*

Atherosclerotic cardiovascular disease (CVD) is a major cause of morbidity and mortality in subjects with type 1 diabetes mellitus (T1DM). Although promising results suggest that CVD risk associated with diabetes is declining in well-controlled patients, overall CVD risk remains increased in T1DM patients, especially in sub-optimally controlled subjects and in subjects with features of metabolic syndrome. Using mechanistic mouse models of T1DM-accelerated atherosclerosis and serum samples from patients with T1DM, we are investigating the roles triglyceride-rich lipoproteins (TRLs) and high-density lipoproteins (HDLs).

Apolipoprotein C3 (APOC3) is an abundant apolipoprotein that increases TRLs and their remnant lipoprotein particles (RLPs) in circulation by blocking their catabolism and clearance. Our recent observations indicate that serum levels of APOC3 predict incident CVD risk in patients with T1DM. This prediction was independent of LDL-cholesterol, HDL-cholesterol and non-lipid risk factors, including diabetes duration and HbA1c. Our mouse studies demonstrate that diabetes increases plasma levels of APOC3 through a mechanism dependent on insufficient insulin and not through hyperglycemia. Moreover, lowering APOC3 levels markedly reduced atherosclerosis in diabetic mice. Our data further support the proposal that elevated APOC3 acts in diabetes by promoting the trapping of atherogenic RLPs in the artery wall, which in turn leads to increased accumulation of macrophages and lipid loading of these cells. Accordingly, inhibition of APOC3 prevented macrophage accumulation and necrotic core expansion in atherosclerotic lesions despite persistent hyperglycemia in diabetic mice.

These observations raise the possibility that APOC3 has a heightened importance as a CVD risk factor for atherosclerotic CVD in patients with T1DM, and perhaps in patients with T2DM and hepatic insulin resistance, and that lowering of APOC3 levels might reduce the excess risk for CVD observed in those subjects.

In another recent study, we investigated factors associated with protection from CVD in people with long-standing T1DM (average diabetes duration of 45 years) by using targeted mass spectrometry and analysis of HDL populations. In two distinct cohorts, people without vascular complications exhibited significantly higher concentrations of a specific HDL medium-sized particle population, without differences in HbA1c, as compared with T1DM subjects with vascular complications. People without vascular complications also had higher levels of HDL-associated paraoxonase 1 (PON1), an enzyme that inhibits atherosclerosis in animal models.

Collectively, our studies point to important and hitherto unknown roles of lipoproteins in cardiovascular disease associated with T1DM.

Speaker abstracts

Hyperglycaemia induces trained immunity in macrophages and their precursors and promotes atherosclerosis

Robin Choudhury, *Professor of Cardiovascular Medicine at the University of Oxford; Consultant Cardiologist at the John Radcliffe Hospital and Clinical Director of the Oxford Acute Vascular Imaging Centre, University of Oxford.*

Cardiovascular risk in diabetes remains elevated despite glucose lowering therapies. Given the central role of macrophages in this disease process, we examined whether trained immunity in macrophages could promote persistent pro-atherogenic characteristics. In macrophages, high extracellular glucose promoted pro-inflammatory gene expression and pro-atherogenic functional characteristics, through glycolysis-dependent mechanisms. Bone marrow-derived macrophages (BMDM) from diabetic mice, but cultured in physiological glucose, retained these characteristics, indicating 'hyperglycaemic memory'. Bone marrow transplantation from diabetic mice into [normoglycaemic] Ldlr-/- mice increased aortic root atherosclerosis, confirming a disease-relevant form of trained innate immunity. ATAC-seq and RNA-seq analyses of haematopoietic stem cells and BMDM revealed a diabetic "priming effect" that implicated transcription factor, RUNX1. Macrophages laser-captured from human atherosclerotic plaques were also enriched for RUNX1 targets in diabetes, consistent with a potential role in human disease. Innate immune 'memory' induced by hyperglycaemia may explain why targeting elevated glucose is ineffective in reducing 'macrovascular' risk in diabetes and suggests new targets for disease prevention and therapy.

Speaker abstracts

SESSION 2

Organelle dysfunction in pancreatic β cells: lessons learned from monogenic forms of diabetes

Miriam Cnop, *ULB Center for Diabetes Research, Universite Libre de Bruxelles*

The heterogeneity in clinical presentation of type 2 diabetes points to a complex pathophysiology, with diverse routes leading to β cell failure. Genetic variants, epigenetic factors and environmental stresses, such as diets rich in saturated fats, play an essential role. Our work has focused on the role of saturated free fatty acids in β cell failure. We have used RNA sequencing to map the human islet transcriptome and uncover mechanisms of fatty acid-induced β cell dysfunction and death. We identified endoplasmic reticulum (ER) stress as an important cellular response contributing to free fatty acid-induced β cell apoptosis. Signaling in the PERK branch of the ER stress response in particular leads to lipotoxic β cell demise. Mitochondrial dysfunction also contributes to β cell failure in type 2 diabetes.
Monogenic forms of diabetes can be used a simpler models of organelle dysfunction to dissect disease mechanisms. We have therefore turned to human "knockouts", i.e. patients with monogenic diabetes caused by loss-of-function mutations in genes with a role in ER stress signaling or mitochondrial function. Four monogenic forms of diabetes provide strong human genetic evidence for the importance of PERK signaling in maintaining β cell integrity. Dysregulated eIF2a phosphorylation and mRNA translation in these human diseases leads to β cell demise. We have also studied diabetes pathogenesis in Friedreich ataxia, a monogenic mitochondrial disease, and identified a central role for β cell dysfunction and apoptosis in the loss of glucose tolerance in these patients. The differentiation of patients' induced pluripotent stem cells into β cells provides an exciting disease-relevant model to study molecular mechanisms of β cell failure and test β cell protective therapies.

Diabetes and Branched Chain Amino Acids

Zoltan Arany*, Perelman School of Medicine, University of Pennsylvania, USA*

Branched chain amino acids (BCAAs: leucine, valine, and isoleucine) are essential amino acids, i.e. cannot be synthesize by humans, and yet comprise up to a third of protein content and can be an important source of energy in catabolic tissues. BCAAs have recently moved front and center in the field of diabetes, as unbiased metabolomic profiling studies have shown that serum elevations in BCAAs predict insulin resistance and diabetes as much as 20 years prior to clinical presentation, and Mendelian randomization studies have demonstrated that polymorphisms that cause elevations in BCAAs also predict insulin resistance. How elevations in BCAAs cause insulin resistance, however, remains unexplained. This presentation will review recent advances in our understanding of integrated systemic BCAA physiology, and current hypotheses on the mechanisms by which BCAAs cause insulin resistance.

Speaker abstracts

SESSION 3

Communicating Clocks: Circadian Metabolism and Epigenetics

Paolo Sassone-Corsi, *Center for Epigenetics and Metabolism, School of Medicine, University of California, Irvine - USA.* psc@uci.edu

The circadian clock is responsible for biological timekeeping on a systemic level. The mammalian central pacemaker is localized in the hypothalamus, in a paired neuronal structure called the suprachiasmatic nucleus (SCN). The discovery that all tissues and virtually all cells contain an intrinsic circadian clock revolutionized the field, providing a conceptual framework towards the understanding of organismal homeostasis and physiological tissue-to-tissue communications. The circadian clock controls a remarkable array of physiological and metabolic functions through governing a significant portion of the genome. Furthermore, the clock drives cyclic chromatin remodeling associated to circadian transcription, including spatial nuclear organization. The circadian epigenome shares intimate links with cellular metabolic processes and has remarkable plasticity showing reprogramming during aging and in response to nutritional challenges. We will present findings that reveal specific molecular connections between chromatin remodelers, metabolic pathways and the circadian clock.

Emerging roles of bile acid signaling in metabolism and stemness

Kristina Schoonjans, *EPFL, Lausanne, Switzerland*

The epithelial surface of the intestine constitutes the largest barrier against the external environment. Coordinated renewal and patterning of the intestinal epithelium is dictated by intestinal stem cells (ISCs), which are subject to tight regulation by nutritional cues to fine-tune the balance between self-renewal and cell fate specification. In this context, a number of dietary and metabolic factors have recently been found to act as niche signals to control ISC behavior. Bile acids (BA) are among the most abundant metabolites in the gut, in particular after food ingestion, and act as versatile signaling molecules that relay nutrient availability to a physiological response. The BA responsive membrane receptor, Takeda G-coupled receptor 5 (Tgr5, aka Gpbar1), regulates many of the gut homeostatic functions of BAs, including gut hormone secretion. While its role is well established in particular subpopulations of the intestinal epithelium, such as in the enteroendocrine L cells where TGR5 is known to trigger BA-mediated Glucagon-like protein 1 (GLP-1) secretion, it is unknown whether the BA-TGR5 molecular axis coordinates intestinal cell renewal and specification through regulation of ISC function. Here, I will show an unexpected role of BAs in orchestrating TGR5 mediated intestinal stemness and provide novel mechanistic insights into the relationship between dietary and metabolic cues, intestinal stem cell function and metabolic homeostasis.

Speaker abstracts

SESSION 4

Mechanisms of glycemic control improvement after metabolic surgery

Geltrude Mingrone, *Catholic University, School of Medicine, Rome, Italy*

Prospective and randomized-controlled studies have shown that bariatric surgery is effective to induce type 2 diabetes remission or at least to significantly improve glycemic control. Since these effects manifest early after surgery before any meaningful change in body weight, a new term has been coined, that of "metabolic surgery", introducing the concept of a weight-independent mechanism of action of gastro-intestinal surgery.

Metabolic surgery, in fact, acts mainly by improving whole-body and hepatic insulin resistance, which are the major player in type 2 diabetes.
Two theories have been postulated to explain the early effects of metabolic surgery on insulin sensitivity and glycemic control, the hindgut and the foregut hypotheses. The former states that the rapid delivery of nutrients into the distal part of the small intestine, i.e. the ileum, enhances signals that improve glucose metabolism. Instead, the foregut hypothesis holds that the exclusion of the proximal gut, and thus duodenum and jejunum, reduces intestinal factor/s that impair the action of insulin.
The major candidate in the hindgut hypothesis is glucagon-like peptide-1 (GLP1) which is secreted by the L-cells prevalently located in the ileum. However, studies using exendin (9-39) after Roux-en-Y Gastric By-Pass (RYGB) show that insulin sensitivity does not worsen again. Moreover, metabolic surgery is effective in reversing experimental diabetes also in GLP-1 receptor knock-out mice and in mice with functional deletion of GLP-1.
The bypass of the duodenum and jejunum in Goto-Kakizaki rats, a strain of corpulent Wistar rats with insulin resistance and type 2 diabetes, in the absence of gastric restriction, is able to reverse diabetes and improve insulin sensitivity independently of body weight reduction. Also, in individuals with obesity, the infusion of nutrients into the mid jejunum significantly improves insulin resistance and reduces glycemia.
Interestingly, an iso-glycemic infusion is associated with a significantly higher insulin sensitivity than an oral glucose administration in insulin resistant subjects with either normal glucose tolerance or impaired glucose tolerance or type 2 diabetes. Indeed, oral glucose administration elicits larger insulin secretion than the intravenous infusion, phenomenon known as "incretin effect". Mathematical simulations shows that hypoglycemia occurs if insulin sensitivity is not reduced by oral glucose stimulation.
Metabolic surgery shows that the duodenum and jejunum play a major role in inducing insulin resistance and that their bypass ameliorates insulin sensitivity. This observation paves the way to the discovery of gut molecular mechanisms implicated in the pathophysiology of insulin resistance and, thus, to the identification of new possible drugs for the treatment of type 2 diabetes.

Speaker abstracts

Signalling in the Gut-Brain-Pancreatic Axis

Fiona Gribble*, Wellcome-MRC Institute of Metabolic Science, University of Cambridge, UK*

The gut endocrine system comprises a collection of enteroendocrine cells scattered throughout the intestinal epithelium, producing hormones that signal locally within the gut and distantly at tissues such as the brain and pancreas. In the field of diabetes and obesity, the best studied gut hormone is Glucagon-like peptide-1 (GLP-1), which has been exploited therapeutically for the treatment of type 2 diabetes and obesity through the development of GLP-1 mimetics and DPP4 inhibitors.
By LC-MS/MS we have identified and mapped the different peptides produced along the length of the mouse and human GI tract, and in pancreatic islets. Following bariatric surgery, we find no changes in the hormones produced by the gut and pancreas, despite the very high post-prandial plasma levels of GLP-1 and PYY observed in these patients. Our results suggest that increased GLP-1 and PYY secretion after bypass surgery is triggered because nutrients are absorbed lower down the gut, where they directly target enteroendocrine cells in that area. We use a variety of techniques to investigate how the enteroendocrine cells detect ingested nutrients, including live cell imaging, electrophysiology and transcriptomics. Sensory pathways of particular interest include those activated by glucose, bile acids and free fatty acids: whereas glucose stimulates enteroendocrine cells as a consequence of its electrogenic uptake, bile acids and free fatty acids target specific G-protein coupled receptors on the cell membrane. We aim that our research will identify new drugs for type 2 diabetes and obesity that act by targeting gut endocrine cells, thus mimicking the gut endocrine consequences of bariatric surgery.

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Presenters of posters with even numbers will be at their posters 16.45-17.15

Poster abstracts

1 Alastair Kerr

Identification of a functional long non-coding RNA in white human fat cells that can alter adipocyte metabolism

Alastair Kerr[1], Kelvin Ho Man Kwok[1], Ingrid Dahlman[1], Mikael Rydén[1], Peter Arner[1] and Hui Gao[1]
1. Department of Medicine (H7), Karolinska Institutet, Karolinska University Hospital, Huddinge, Stockholm 141 86, Sweden

Background and Aim: Long non-coding RNAs (LncRNAs) role in the development of metabolic disease within white adipose tissue (WAT), to date, is not known although some studies have suggested that they may affect generation (adipogenesis) and metabolism of fat cells. We aim to identify and characterize clinically relevant lncRNAs that are able to adjust the metabolic phenotype of the adipocyte as new targets in tackling WAT dysfunction.

Materials and Methods: We have developed a pipeline to screen for functional lncRNAs in the adipocyte. First, we identify differentially expressed lncRNAs in a range of clinical cohorts constructed in this laboratory. The cohorts include; obese versus non-obese (n=28), insulin resistant versus insulin sensitive (n=80) and obese women before and after undergoing bariatric surgery (n=50). LncRNAs of interest are screened via knockdown studies using anti-sense oligonucleotides (ASO) in our human adipocyte derived stem cells (hADSCs), to assess the impact on the metabolic or adipogenic phenotype. To better characterize the altered phenotype, functional genomic analysis after gene perturbation followed.

Results: Through knockdown studies, we identified Adipocyte LncRNA 1 as able to regulate basal (spontaneous) lipolysis and de novo lipogenesis. Microarray gene expression analysis after knockdown identified 1537 genes that were regulated by three different ASOs independently. Identified GO pathways of genes downregulated by knockdown included lipid biosynthesis and metabolism. Further biochemical and molecular characterizations of Adipocyte LncRNA 1 were performed, such as, subcellular fractionation, RNA FISH and RNA-DNA or RNA-Protein interaction. Results will be presented at the meeting

Conclusions:. We identify Adipocyte LncRNA 1 as able to regulate lipid metabolism and perturbation effects the expression of many lipid metabolic genes. Understanding the role of this lncRNA within the adipocyte could lead to the identification of a future therapeutic target.

Poster abstracts

2 Alice Åslund

Acute β-adrenoceptor mediated glucose clearance in brown adipose tissue; a distinct pathway independent of functional insulin signaling

Alice Åslund[#], Jessica M. Olsen[#], Muhammad Hamza Bokhari, Dana S. Hutchinson and Tore Bengtsson
Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, SE-106 91, Stockholm, Sweden.
Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria 3052, Australia.

β-adrenoceptor mediated activation of brown adipose tissue (BAT) has been associated with improvements in metabolic health in models of type 2 diabetes and obesity due to its unique ability to increase whole body energy expenditure, and rate of glucose and free fatty acid disposal. While the thermogenic arm of this phenomenon has been studied in great detail, the underlying mechanisms involved in β-adrenoceptor mediated glucose uptake in BAT is relatively understudied. As β-adrenoceptor agonist administration results in increased hepatic gluconeogenesis that can consequently result in secondary pancreatic insulin release, there is uncertainty regarding the importance of insulin and the subsequent activation of its downstream effectors in mediating β-adrenoceptor stimulated glucose uptake in BAT. Therefore, we have in this study, made an effort to discriminate between the two pathways, and address whether the insulin signaling pathway is dispensable for the acute effects of β-adrenoceptor activation on glucose uptake in BAT.

Using a specific inhibitor of phosphoinositide 3-kinase α (PI3Kα), which effectively inhibits the insulin signaling pathway, we examined the effects of various β-adrenoceptor agonists, including the physiological endogenous agonist norepinephrine on glucose uptake and respiration in mouse brown adipocytes *in vitro*, and on glucose clearance in mice *in vivo*.

PI3Kα inhibition in mouse primary brown adipocytes *in vitro*, did not inhibit β-adrenoceptor stimulated glucose uptake, GLUT1 synthesis, GLUT1 translocation or respiration. Furthermore, β-adrenoceptor mediated glucose clearance *in vivo* did not require insulin or Akt activation but was however attenuated upon administration of a β_3-adrenoceptor antagonist.

We conclude that the β-adrenergic pathway is still functionally intact upon the inhibition of PI3Kα showing that the activation of downstream insulin effectors is not required for the acute effects of β-adrenoceptor agonists on glucose homeostasis or thermogenesis.

Poster abstracts

3 Arthe Raajendiran

Identification of metabolically distinct human adipocyte precursor cells

Arthe Raajendiran,[1,2,*] Geraldine Ooi,[4] Jackie Bayliss,[1] Paul E. O'Brien,[6] Ralf B. Schittenhelm,[5] Ashlee K. Clark,[3] Renea A. Taylor,[2,3] Matthew S. Rodeheffer,[6] Paul R. Burton,[4] and Matthew J. Watt1,[1,2]

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[2]*Department of Physiology, Monash Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia*
[3]*Department of Anatomy and Developmental Biology, Monash Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia*
[4]*Centre for Obesity Research and Education, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia*
[5]*Monash Biomedical Proteomics Facility, Monash University, Clayton, VIC, Australia*
[6]*Department of Molecular Cell and Developmental Biology; Program in Integrative Cell Signaling and Neurobiology of Metabolism, Department of Comparative Medicine; and Yale Stem Cell Center, Yale University, New Haven, CT, USA*
[*]*Current Affiliation: Department of Cell and Molecular Biology, Karolinska Institutet, Sweden.*

Unhealthy expansion of adipose tissue (AT) is related to the onset of insulin resistance and understanding the expansion of adipose tissue mass helps to delineate the specific cellular processes promoting health and disease. The adipocytes regulating the mass of an AT depot are differentiated from the tissue-resident adipocyte precursor cells (APCs) whose identity in humans remain largely unknown. We aimed to identify the human APCs located within the regional AT depots obtained from visceral, abdominal subcutaneous and gluteal-femoral regions to assess their adipogenic potential, metabolic properties and correlations with metabolic disease. We have discovered that human AT consists of three transcriptionally (RNASeq) distinct APCs in the lineage depleted ($CD31^-CD45^-$) stromal vascular fraction (SVF) and termed them as $CD34^-$, $CD34^{lo}$ and $CD34^{hi}$ APCs. All three human APCs differentiated into mature adipocytes both *in vitro* and *in vivo* (xenotransplantation into immunodeficient mice).
Rates of lipolysis, fatty acid uptake were higher in $CD34^{hi}$ compared with $CD34^-$ and $CD34^{lo}$ APC-derived adipocytes *in vitro*, the latter having very low fatty acid turnover. Interestingly, only the $CD34^-$ adipocytes displayed enhanced thermogenic potential *in vitro*. Importantly, the proportion of $CD34^{hi}$ APCs was higher and $CD34^-$ APCs were lower in the AT of individuals with type 2 diabetes, suggesting that dysregulated lipolysis commonly observed in these individuals may be attributed to alterations in APC abundance.
Summarily, we have identified three distinct *bona fide* APCs varying in their metabolic capacities and distribution in metabolically healthy and non-healthy adipose tissue depots.

Poster abstracts

4 **Muhammad Hamza Bokhari**

Isothermal microcalorimetric measurements of heat evolution in intact mature brite adipocytes reveals distinct importance of UCP1 but not β_3 adrenoceptor in thermogenesis

M.H. Bokhari[1], C. Halleskog[1], A. Åslund[1], N. Boulet[1,2], R. Csikasz[1], J.M.A. de Jong[1,3], E.-Z. Amri[4], I. Shabalina[1], T. Bengtsson[1];

[1]*The Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholms Universitet, Stockholm, Sweden,*
[2]*Institut des Maladies Métaboliques et Cardiovasculaires, Toulouse, France,*
[3]*Section of Comparative Medicine, Yale University School of Medicine, New Haven, CT, USA,*
[4]*Université cote d'azur, CNRS, Inserm, IBV, Nice, France.*

Recently, the induction and the activation of thermogenesis in brown and brite adipose tissue has gained interest as a druggable target for anti-obesity therapies. However, a major challenge is to develop an assay that can continuously measure thermogenesis in mature floating adipocytes in a multi-well format. Furthermore, since conventional plate based respirometry can only be performed on cultured adipocytes, these measurements may not represent thermogenic responses in fully mature brite adipocytes. We propose that isothermal micro-calorimetry can be used for this purpose and have used this technique to measure adrenoceptor induced heat production in mature brown and brite adipocytes.

Isothermal microcalorimetry is a technique that measures direct heat flux between a microwell containing biological material and a surrounding chamber making it unique tool for the study of cellular bioenergetics. Using this method, we show that β_3 agonist stimulation induces heat production in mature brown and brite adipocytes. However, this effect is absent in adipocytes from UCP1 knockout mice, suggesting no significant contribution of UCP1 independent mechanisms to adrenoceptor mediated thermogenesis in brown and brite adipocytes. Furthermore, in brite adipocytes isolated from β_3 adrenergic receptor knockout mice, isoproterenol - a non-selective beta-adrenergic agonist, can induce heat production thereby showing that in these cells, the β_3 adrenoceptor is dispensable for thermogenic activation. Finally, we report that adrenergic stimulation of human multipotent adipose derived stem cells that had been differentiated to acquire a 'brite-like' phenotype, resulted in increased heat generation showing these cells are functionally thermogenic.

Collectively, our findings suggest that isothermal microcalorimetry can be used to measure thermogenic activity of brown and brite adipocytes ex-vivo. Using this technique, we have shown that the presence of UCP1, but not the β_3 adrenoceptor, is essential for agonist induced thermogenesis in mature brite adipocytes.

Poster abstracts

5 **Noah Moruzzi**

The role of insulin receptor isoforms in selective insulin signaling in physiology/pathology

Moruzzi N., Lazzeri-Barcelo F., Valladolid-Acebes I., Paschen M., Moede T., Leibiger B., Berggren P.O., Leibiger I.
Molecular Medicine and Surgery (MMK), Rolf Luft Center for Diabetes and Endocrinology, Karolinska University/Hospital.

Understanding the mechanisms of β-cell dysfunction, the biological significance of insulin receptor (IR) isoforms, as well as finding IR specific ligands is critical to identify novel treatments for type 2 diabetes mellitus (T2DM). Insulin signaling is initiated by IR-A and IR-B isoforms, which co-exist in β-cells, while classical insulin target tissues or cancer cells express mainly IR-B and IR-A, respectively. Thus, hyperinsulinemia as consequence of insulin resistance can target β-cells causing/contributing to their dysfunction due to different IR isoform affinity and downstream signaling. Moreover, during T2DM development, altered IR isoform ratio might be involved in insulin resistance and disease progression.
Here, we aim to identify timing and molecular mechanisms of β-cell insulin resistance upon different dietary interventions, and IR isoforms changes during development of T2DM using novel tools.
By monitoring dynamics of functional β-cell mass and downstream IR isoform activation *in vivo*, we found that lipotoxicity together with high β-cell work-load led to β-cell insulin resistance during diet-induced T2DM development which can be recovered in the early phase.
By screening the expression of the IR isoforms by using real-time qPCR in genetic and diet-induced obese mice, we found that IR isoform expression changes in selective organs. In the perigonadal adipose tissue (pGAT) the increase in IR-A/IR-B ratio was consistent in all models studied. By pGAT fractionation and using mRNA *in situ* hybridization, we found that the increase in IR-A is due to changes in tissue architecture rather than a splicing alteration in a specific cell type.
Currently, we are evaluating the early changes after diet intervention in circulating glucagon and insulin and gene transcription in islets of Langerhans. Doing so we aim to understand the initiating mechanisms of insulin resistance in β-cells as well as the early factors underlying the hormonal secretory dysregulation.

Poster abstracts

6 **Christina Savva**

Regulation of metabolism by activation of ERβ using a synthetic ligand on male mice.

Christina Savva 1,4, Marcela González-Granillo 1,4, Jan-Åke Gustafsson 3, Bo Angelin 1,4, Marion Korach-André 1,4

[1]Department of Medicine, Metabolism Unit and KI/AZ Integrated Cardio Metabolic Center (ICMC), Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [2] Department of Biology and Biochemistry, Center for Nuclear Receptors and Cell Signalling, University of Houston, Houston, Texas, US; [3]Department of Biosciences and Nutrition Huddinge, Karolinska Institutet, Sweden; and [4]Metabolism Unit, Centre for Endocrinology, Metabolism and Diabetes and Nutrition, Department of Medicine, Karolinska Institute, Huddinge, Sweden.

Background: Obesity is a pandemic problem affecting more people each year and becoming a burden to worlds economy. Metabolic complications in obesity is sex-dependent and the role of estrogens in these regulations is still unclear. Estrogen receptors (ERs), which include Estrogen receptor alpha (ERα) and Estrogen receptor beta (ERβ), mediate estrogen signalling and are key regulators of metabolic functions. While the role of ERα in energy metabolism is well described, the action of ERβ in metabolism homeostasis is still dubious.
Aim: To Investigate the metabolic function of ERβ activation in obese female and male mice using a synthetic ERβ selective ligand (DIP).

Methods: Wild type C57BL/6J mice were fed with control diet (CD) or high fat diet (HFD) for 6 weeks before being treated with DIP. Lipid metabolism was investigated in vivo using magnetic resonance imaging (MRI) and spectroscopy (MRS) together with deuterium labelling method and/or metabolic cages. At sacrifice, metabolic tissues were harvested and the molecular machinery in response to DIP was investigated.

Results: Both female and male HFD mice gained fat mass as compared to CD but only females lost weight when treated with DIP. Surprisingly, total fat content increased in DIP-treated males as a result to induction of subcutaneous fat content. Liver lipid content was reduced in females and unchanged unchanged in males, but fatty acids composition was reversed towards more unsaturated lipids as compared to HFD baseline in both sexes. The metabolic profile was improved in both sexes after DIP treatment.

Conclusion: ERβ could be a potential target to treat obesity and associated metabolic disorders avoiding the side effects of ERα activation.

Poster abstracts

7 Lucia Coppo

Mitochondrial depletion of glutaredoxin-2 leads to mitochondrial dysfunctions and altered lipid metabolism in mice

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Glutaredoxin (Grx) system is an established defense against oxidative stress and also in physiological signaling, but the mechanism of regulation exerted by Grxs is still poorly understood. Glutaredoxin-2 (Grx2) can glutathionylate/de-glutathionylate several target proteins and can also coordinate an iron-sulfur cluster (2Fe-2S), forming inactive dimers. Two variants of Grx2 are known: Grx2a found in mitochondria and Grx2c, which is located in both the cytosol and nucleus.

AIM: To investigate the role of Grx2a in lipid metabolism, we created a unique mouse model specifically depleted of Grx2a in mitochondria (mGD).

METHODS: Mitochondrial respiration parameters were studied in liver and heart of WT and mGD mice. The major differences were obtained in ROS production, on the mitochondrial membrane potential and on the mitochondrial swelling assay. Determination of the oxygen consumption, assessment of total thiols and analysis of redox compensatory mechanisms were also investigated. Oil-red-O staining and TEM imaging were performed in primary hepatocytes, liver and heart tissue and isolated mitochondria. The level of CoA (total and reduced form) were also measured with an HPLC based method. Gene expression of key proteins in fatty acid metabolism, cholesterol metabolism and other target of interested were analyzed with RT-qPCR.

RESULTS: Remarkably, mGD mice are characterized by 20-30% increase of body weight under normal diet. In particular, liver and heart display dramatic lipid deposits, the morphology of mGD mitochondria is altered and the cristae structure disordered with respect to the WT. Higher generation of ROS production was detected in mGD mice but we did not detected any upregulation of antioxidant system as compensatory mechanism.

CONCLUSIONS: The lack of Grx2 in the mitochondria is responsible for the development of an early-onset fatty liver, a decrease of mitochondrial activity and a disrupted mitochondrial dynamic with iper-fused mitochondria indicating a unique function of Grx2a in regulation of these mechanisms.

Poster abstracts

8 **Mirko E. Minniti**

Reduction of bile acid synthesis and intrahepatic lipid accumulation in liver-humanized mice define the unfavorable pharmacodynamics of LXR agonism in humans

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Background and Aims: The strategy to decrease atherosclerosis by stimulating liver X receptor (LXR) originated in mouse models. However, the first human trial testing a LXR agonist was prematurely terminated principally because of severe hyperlipidemia. We therefore investigated whether liver-humanized mice (LHM), *i.e.* mice repopulated with human hepatocytes, could serve as a translatable human model to explain the negative outcomes of LXR agonism.

Methods: LHM were treated for 4 days with the LXR agonist GW3965. Serum lipoproteins and lipids were separated by size-exclusion chromatography and quantified. Gene and protein expression levels were assessed by qPCR, Western blot or ELISA. Lipoprotein binding to human aortic proteoglycans (haPG) was assayed *in vitro*. Triglycerides, cholesterol composition, and cholesterol and bile acid precursors in liver were assessed by colorimetry, GC-MS or LC-MS/MS.

Results: LXR stimulation in LHM increased cholesterol and triglycerides in VLDL and LDL, despite unaltered hepatic LDLR and circulating PCSK9 levels, and lack of cholesteryl ester transfer protein (*CETP*) expression. haPG binding of lipoproteins was higher after GW3965 treatment, although their binding capacity was unchanged when correcting for serum cholesterol. In liver, LXR stimulation resulted in triglyceride and cholesteryl ester accumulation, and reduced the precursors of bile acid and cholesterol biosynthesis. Down-regulation of *CYP7A1* and of the *SREBF2*-system, and induction of *SREBF1* variant c were observed.

Conclusions: Despite the lack of CETP, LHM displayed severe hyperlipidemia after LXR stimulation, subsequent to a decrease in bile acid synthesis (leading to intrahepatic cholesterol accumulation) and increased triglyceride anabolism. These results endorse for the first time a mouse model recapitulating the molecular mechanisms of LXR agonism occurring in human liver.

Poster abstracts

9 Patricia Recio-López

Apolipoprotein CIII silencing, a novel strategy to combat metabolic disorders

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Background: Apolipoprotein CIII (apoCIII) is a key regulator of lipid metabolism and it has been suggested as a druggable target to combat metabolic disorders.
Aims: 1) Design and screen small-interference RNAs (siRNAs) against mouse apoCIII mRNA; 2) Test *in vivo* these compounds in mice with high levels of apoCIII.
Material and methods: *In silico* approaches were used to design eight apoCIII-siRNAs. *In vitro* dose-response screenings were performed in Hepa 1-6 cells using the Renilla luciferase assay to measure the capacity of each siRNA to lower apoCIII. For *in vivo* studies, 12-week old Ob/Ob mice were given i.v injections of apoCIII-siRNAs (doses: 0-1 mg/kg) during three consecutive days. Control groups received either control-siRNA or sham injections with vehicle. We monitored body weight (BW) and liver, intestine and plasma were collected for evaluation. Quantitative Real-Time PCR was used to measure liver and intestine apoCIII mRNA levels and to determine if the siRNAs had an impact on the apoAI-CIII-AIV cluster gene. Finally, we measured a number of metabolic parameters in plasma from our Ob/Ob-treated mice.
Results: *In vitro* studies showed that the most effective siRNAs exhibited a maximal apoCIII inhibition of ~ 91% and ~93%. *In vivo*, these active siRNAs were able to dose-dependently silence liver apoCIII mRNA up to~99.2% as compared to the control groups. In the intestine, no effect of the siRNAs was observed. ApoAI and apoAIV remained unaltered in both tissues in all treatment groups. ApoCIII silencing did not affect BW in any of the treatment groups. Ob/Ob mice treated with apoCIII-siRNAs significantly improved lipid profiles as compared to those treated with the control siRNA. However, apoCIII silencing did not affect plasma glucose, insulin, c-peptide and ALT levels.
Conclusions: Our findings indicate a therapeutic potential of apoCIII-siRNAs for future treatment and/or prevention of metabolic diseases.

Poster abstracts

10 David Rizo-Roca

Metabolic Crosstalk and the Regulation of Insulin Sensitivity in Type 2 Diabetes.

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Type 2 diabetes is a lifelong disease characterized by chronic hyperglycemia and insulin resistance. Within this context, skeletal muscle, which represents approximately 40% of body mass and is the largest site for glucose disposal, develops insulin resistance arising from impaired signal transduction and glucose transport activity. Moreover, type 2 diabetes is being increasingly associated with a chronic low-grade tissue inflammatory state, leading to impaired tissue metabolism and function. This interplay between metabolic and immunological processes, now recognized as immunometabolism, is extremely complex and involves the integrated communication between different organs and systems. Thus, cytokines, peptides and metabolites produced by liver, skeletal muscle or adipose tissue can exert autocrine, paracrine as well as endocrine responses, integrating the individual organ response with the whole organism. However, the extent of this inter-tissue crosstalk and its role in the development of type 2 diabetes remains to be elucidated.

Our aim is to unravel the complex regulation of the communication between liver, skeletal muscle and adipose tissue and to understand how these processes are perturbed in type 2 diabetes. We hypothesize that metabolites, peptides and proteins secreted by these three tissues severely impact insulin sensitivity and glucose metabolism along the course of the condition. To test that hypothesis, we propose three specific objectives: 1) Identify novel liver-, white adipose- or skeletal muscle-derived factors linked to type 2 diabetes in cross-sectional clinical cohorts; 2) Determine whether candidate factors mediate “crosstalk” between these tissues in vitro; and 3) Determine the role of the identified candidates on whole-body metabolism in diabetic rodent models.

These studies will provide evidence for a physiological effect of the tissue-released factors on glucose metabolism in different organs and reveal whether candidate tissue-derived factors influence insulin sensitivity in type 2 diabetes.

Poster abstracts

11 **Elena Caria**

Glutamine regulates skeletal muscle immunometabolism

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Background: The chronic low-grade inflammation associated with obesity negatively affects tissue function and contributes to the pathogenesis of Type 2 Diabetes. While the role of cytokines in immunometabolism has been described, less is known on the signaling role of extracellular metabolites. Adipose tissue explants from obese individuals have decreased glutamine secretion compared to adipose tissue from lean volunteers, and we hypothesized that alteration of glutamine metabolism may contribute to the development of metabolic disturbances and affect skeletal muscle function.
Results: Nine-days exposure of primary human myotubes to high levels of extracellular glutamine (10mM) decreases mRNA levels and protein release of the inflammatory cytokines *IL6* and *CCL2*. *In vivo*, 14 days glutamine injections improves fasted glycemia in 16-weeks high fat diet (HFD) fed mice. In skeletal muscle, glutamine treatment leads to decreased expression of *Ccl2* and other markers of immune cell infiltration. Furthermore, insulin signaling is enhanced in the EDL of HFD and glutamine-treated mice as compared to HFD control mice.
Discussion: Our results reveal that glutamine exposure reduces inflammatory markers in skeletal muscle in cultured muscle cells as well as following in vivo treatment. In cultured muscle cells, the modulation of extracellular glutamine levels affects myotubes inflammatory profile. Glutamine treatment *in vivo* improves glucose homeostasis in HFD mice, associated with increased skeletal muscle insulin sensitivity and decreased inflammation in skeletal muscle. These results suggest that dysregulation of glutamine metabolism plays a role in the development of metabolic perturbations in obese type-2 diabetic skeletal muscle. Deciphering the mechanisms involved could identify new pharmacological targets and potential strategies to improve insulin sensitivity in individuals with obesity or type 2 diabetes.

Poster abstracts

12 **Sander Verbrugge**

Genes Whose Gain- or Loss-Of-Function Increases Skeletal Muscle Glucose Uptake in Mice: A Systematic Literature Review.

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Insulin and exercise increase skeletal muscle glucose uptake, and insulin-mediated glucose uptake is defective in type 2 diabetes patients. To identify genes that regulate glucose uptake in skeletal muscle, we conducted a systematic review to identify genes whose experimental gain- or loss-of-function increases or decreases skeletal muscle glucose uptake in mice. We found that the manipulation of 47 genes increases glucose uptake as measured by accumulation of 2-deoxyglucose in skeletal muscle. The effect size ranged from +10 to +650% and results from the manipulation of the following genes: *Slc2a1, Aifm1, Itga2, Ucp3, Cd36, Stk11, Prkcq, Tp53, Trib3, Pik3c3, Igfbp1, Mtor, Igf1r, Cat, Hbegf, Slc2a4, Hk2, Foxc2, Sphk1, Dgat2, Sirt6, Ptpn1, Mapk8, Tbc1d1, Abhd5, Lipa, Txnip, Nos2, Abcc6, Kcna3, Ptpn6, Slc2a12, Timp3, Camk4, Hmga1, Ddah1, Id2, Gnas, Pik3r1, Fasn, Mstn, Cept1, Rxrg, Apob, Il10, Dgat1, Prkag3.* Furthermore, we found 40 genes whose gain or loss-of-function decreased glucose uptake in muscle ranging from -15% to -70%. These genes are: *Hdac3, Cav3, Irs1, Vegfa, Nob1, Ppargc1a, Agt, Gfpt1, Ptprf, Lpl, Enpp1, Il6, Cpt1c, Sirt1, Tbc1d1, Itgb1, Mmp9, Igf1r, Ankrd26, Insr, Nos3, Igf1r, Inppl1, Stxbp3, Pea15, Ceacam1, Rrad, Tbc1d4, Dgat2, Lnpep, Pparg, Lipe, Dgat1, Rictor, Prkab2, Rab28, Igfbp1, Ptpn11, Igfbp3, Ski.* In summary, glucose uptake is a polygenic trait that is influenced by more than 80 genes in mice.

Poster abstracts

13 Theresa Mader

Metabolic alteration in mice with breast cancer.

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Skeletal muscle function is crucial for our ability to move, and plays an important role for whole-body metabolism. Cancer-induced muscle dysfunction is a broad clinical challenge that is not restricted to palliative or advanced stage patients, but also observed in newly diagnosed patients with low tumor burden. For instance, patients with breast cancer have impaired muscle strength both before and after anticancer treatment. Furthermore, breast cancer patients have an increased risk of developing type II diabetes. However, little is known about the molecular mechanisms underlying cancer-induced muscle dysfunction and altered metabolism. Here we aim to characterize the muscle function and metabolic status in mice with breast cancer.

The breast cancer mouse model MMTV-PyMT (PyMT) was used, which mimics the disease progression observed in human patients. At the age of three months (12 weeks), PyMT mice exhibited large tumors. However, no obvious difference in baseline muscle characteristics, i.e. fiber morphology, fiber diameter or fiber type distribution were observed between 12 weeks old PyMT and WT littermates. Dual-energy X-ray absorptiometry (DXA) measurements displayed an increased lean whole-body mass accounted by the tumor mass, and reduced percentage of fat in PyMT as compared to WT mice. Anti-tumorigenic treatment with CX-5461 (CX, i.p. injections once per week between 8-12 weeks of age, 75mg/kg bw) reduced the tumor volume and prevented the whole-body fat loss in PyMT mice. Comprehensive lab animal monitoring system (CLAMS) was used to assess the metabolic status of the mice. CLAMS showed that treated and untreated PyMT mice consumed more food and water, but moved less as compared with WT mice. Moreover, the respiratory quotient (VCO_2/VO_2) was lower in PyMT than WT mice (but normalized after CX treatment). Live-cell metabolic rate (Seahorse) was assessed using isolated adult muscle fibers from treated and untreated PyMT and WT mice. The energy production and mitochondrial coupling efficiency were lower in PyMT than in WT mice. Thus, the primary tumor as well as anti-tumorigenic treatment affects and alters whole-body metabolism and mitochondrial respiration in muscles of non-cachexic mice with breast cancer.

Poster abstracts

14 **Zhengye Liu**

The role of mitochondrial Ndufa4l2 in peripheral artery disease

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Patients with obesity and type II diabetes exhibit a higher risk to develop skeletal muscle ischemic disease, such as peripheral artery disease (PAD). Thus far, a majority of PAD research has focused on limb collateral vessel development as a way to counteract PAD. However, the hemodynamic impairment associated with PAD does not fully account for the reduced muscle impairment, but point towards that pathophysiologic mechanisms inside the skeletal muscle as contributing factors to reduced muscle function. Nevertheless, there is little molecular insight into how intramuscular dysfunction contribute to the progression of PAD associated with obesity and T2D.
Here we aim to elucidate the role of the hypoxia-sensitive nuclear-encoded mitochondrial Ndufa4l2 protein in PAD-induced muscle weakness. Unilateral femoral artery ligation (FAL), a mouse model of PAD, was induced in C57BL6 mice that had been fed normal chow diet (ND) or on a high-fat diet (HFD) for eight weeks prior to FAL. In ND mice, FAL resulted in reduced muscle force production and increased Ndufa4l2 mRNA and protein expression of fast- and slow twitch hind limb muscle 8 and 15 days after the surgery. The FAL-induced Ndufa4l2 response was blunted in hind limb muscle from HFD mice. Furthermore, force production of muscles from HFD-FAL legs were much lower than the ones from ND-FAL legs, both 8 and 15 days after the surgery. Cross-sectional staining showed that NDUFA4L2 was increased in the interstitial space of muscle fibres in the FAL leg from ND mice 15 days after the surgery, whereas the increase appeared weaker in HFD mice. Moreover, NDUFA4L2 co-localized with type I collagen, a component in fibrosis formation. In summary, eight weeks of HFD prior FAL attenuated the force loss in skeletal muscles. The functional importance of NDUFA4L2 needs to be further clarified, but our preliminary results suggest NDUFA4L2 as an integral player in the aggravated PAD associated with obesity and T2D.

Poster abstracts

15 Ingrid Nilsson

Energy substrate partitioning and regulation in endothelial cells

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Regulation of energy substrate handling in endothelial cells (ECs) is poorly understood, but the strategic localization of the endothelium suggests that ECs may direct energy substrate transport and utilization in an organotypic manner. Many functions related to EC physiology and pathology are ascribed to Vascular endothelial growth factors (VEGFs). With regard to energy metabolism, a tight correlation between the expression of the VEGF-B isoform and the expression of mitochondrial genes involved in oxidative metabolism has been observed. VEGF-B downstream signalling engaging both VEGF receptor 1 and neuropilin-1 in ECs promoted uptake and transcytosis of fatty acids (FA) from the bloodstream to the underlying tissue for oxidative use. We further identified a novel mechanism of how VEGF-B by impeding low-density lipoprotein receptor-mediated cholesterol uptake reduced plasma membrane cholesterol content. Decreased membrane cholesterol loading by VEGF-B negatively impacted GLUT1-facilitated glucose transport. Targeting VEGF-B *in vivo* was accordingly linked to reconstitution of membrane cholesterol content and induction of glucose uptake and tissue glucose availability, of particular relevance for conditions inferring insulin resistance. In summary, our study provides insights into energy substrate uptake, transport and utilization at the level of the endothelium, and highlights the impact of membrane cholesterol for the regulation of endothelial glucose transport.

Poster abstracts

16 Nataliya Östberg

Neutrophil Proteo-Interactome: Tracking Neutrophil-Derived Messages in Health and Disease

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Metabolic syndrome, a cluster of risk factors for metabolic disorders, affects about a quarter of the world's adult population. The immune system is tightly connected to metabolism and known to be altered in people with metabolic syndrome. Crosstalk between cells is required for the immune system to function properly. Neutrophils primarily initiate the crosstalk in inflammation. Our hypothesis is that the altered neutrophil microenvironment in acquired metabolic disorders leads to disruption in their crosstalk and in turn dysregulation of immune responses.

To test the hypothesis, we aimed to develop a proteomics-based assay that allows tracking the whole spectrum of neutrophil-derived proteins in complex environments. The assay is based on the SILAC approach (stable isotope labelling with amino acids in cell culture). The proteins are labelled upon differentiation of the neutrophil precursor murine HoxB8 cell line (HoxB8-PMN). The labelled proteins are released following stimulation, received by co-incubated cells, and can be distinguished in the proteome of the latter ones using mass spectrometry.
The workflow of the assay was established with macrophage cell line RAW264.7 as a cell-receiver and PMA as a stimulus for HoxB8-PMN. The majority of the 404 proteins identified as transferred to RAW cells are known to be released from cells, including neutrophils (e.g. MIF, HSPs, histones, annexins, S100A8/9). Next, we applied isolated leukocytes as cell-receivers. Mouse monocytes, T- and B-cells were sorted after co-incubation with HoxB8-PMN and one of four stimuli: heat killed S. aureus, fMLP, TNF, or CXCL1. The 20-160 transferred proteins included the known neutrophil-derived (e.g. S100A8/A9, MIF, calmodulin) and cell receiver-specific proteins (e.g. plastin-2 in T cells).
In this study we have developed the assay that is able to track neutrophil-derived proteins in other cells. The assay will be applied to compare the neutrophil crosstalk in blood from diabetic and wild-type mice.

Poster abstracts

17 **Xiaowei Zheng**

Impaired adaptive hypoxia responses in patients with diabetes

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The main therapeutic challenge in diabetes is represented by the devastating complications of the disease. Tissue hypoxia is common in most organ and tissues in diabetes and plays an important role in diabetes complications. A central pathogenic role has been identified in the impaired response of Hypoxia-inducible factor-1 (HIF-1) which functions as a master regulator of the adaptive responses to hypoxia and is inhibited by hyperglycemia in diabetes. In this study, we aim to investigate the change in the adaptive responses to hypoxia in patients with diabetes.

15 patients with Type 1 diabetes and 15 healthy matched controls were exposed to intermittent hypoxia (IH) for one hour, consisting of five hypoxic episodes (13% O_2, 6 min) followed by normoxic episodes (20.9% O_2, 6 min). Upon IH exposure, patients with diabetes had significantly lowered baroreflex sensitivity (BRS). Higher plasma SDF-1alpha levels were induced by IH in healthy controls, but not in patients with diabetes. The number of endothelial progenitor cells (EPC) in circulation increased in healthy subjects after IH, but decreased in patients with diabetes. Before IH exposure, patients with diabetes had significantly higher ROS levels in blood than healthy controls. IH did not change ROS levels in healthy controls, but significantly increased ROS levels in patients with diabetes. Transcriptome profiling of peripheral blood mononuclear cells (PBMC) revealed significant changes in gene expression in healthy subjects, but not in diabetes.

These data showed significantly complex impairment of the responses to hypoxia in patients with diabetes upon exposure to intermittent hypoxia. The impaired adaptive responses to hypoxia may play a pivotal pathogenic role for the development of diabetes complications.

Poster abstracts

18 **Sampath Narayanan**

HypoxiamiR-210 accelerates wound healing in diabetes by improving cellular energy metabolism

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Diabetic foot ulcer (DFU) is a debilitating complication of diabetes whose pathophysiology is still being unraveled. An impaired response to hypoxia due to inhibition of hypoxia inducible factor-1 (HIF-1) has been proposed to be a central mechanism in impaired wound healing in diabetes. microRNA-210 is a HIF-1 target which regulates several cellular processes central to wound healing. In this study, we aim to study the role of microRNA-210 in diabetic wound healing.
The miR-210 expression was evaluated *in vitro* (human dermal fibroblasts (HDF) and *in vivo* (DFU and wounds of diabetic db/db mice). miR-210 was reconstituted in the wounds of db/db mice by intradermal injection of a mature miR-210 mimic on the wound edges.
miR-210 levels in DFU were significantly reduced compared to venous ulcers. While miR-210 was increased in wounds from control mice, wounds from db/db mice showed reduced miR-210 levels. Local miR-210 mimic application in the wounds led to a specific improvement in wound healing rate in db/db mice but not in control non-diabetic mice. This was due, at least partially, to an increase in the proliferation and angiogenesis. Transfer of miR-210 was followed by normalization of the oxygen consumption rate and ROS levels in the wounds of db/db mice as consequence of modulation of several mitochondrial targets. *In vitro*, high glucose levels inhibited miR-210 in hypoxia in HDF. Transfection of miR-210 mimic resulted in a decrease of the oxygen consumption rate and of ROS production, followed by improvement of the migration and proliferation. In conclusion, reconstitution of the decreased levels of miR-210 in diabetic wounds improves wound healing by modulating the mitochondrial metabolism.

Poster abstracts

19 **Edit Szodorai**

Secretagogin interactome conveys calcium signaling of insulin release, β-cell identity and survival

Edit Szodorai[1,2,3], Katarzyna Malenczyk[2,4], Robert Schnell[1], Gert Lubec[3], Tomas Hökfelt[4] and Tibor Harkany[2,4]

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Calcium-binding proteins (CBPs) are essential mediators of intracellular calcium (Ca^{2+}) concentration-dependent cell signalling. Extracellular stimuli driven transient Ca^{2+} spikes allow precise modulation of CBPs, so called Ca^{2+} sensors. Upon binding, they undergo conformational changes enabling formation of protein-protein interactions which assure rapid, dynamic decoding of short-lived intracellular Ca^{2+} signals.

Secretagogin (SCGN), a hexa EF-hand Ca^{2+} sensor, has been shown to be predominantly expressed in the central nervous system and in endocrine glands playing crucial role in hormone and neuropeptide secretion. It is one of the most abundant proteins of endocrine pancreatic β-cells and suggested to regulate insulin release via interaction with cytoskeletal proteins and components of vesicle-mediated trafficking. Accordingly, SCGN loss-of-function correlates with decreased insulin secretion and leads to diabetic phenotype.

Ca^{2+}-dependent SCGN interaction network in pancreas was investigated to provide a more comprehensive picture on SCGN-mediated signal transduction. In INS-1E cells the analysis revealed 13 proteins involved in protein folding including members of the chaperonin containing T complex. Moreover, we detected enzymes of deubiquitination such as ubiquitin carboxyl-terminal hydrolase USP9X and USP7. These findings pinpoint abnormal protein folding and degradation with subsequent β-cell loss that may explain impaired insulin secretion in SCGN knock downs (1). In a second study, we described SCGN interacting proteins in mouse embryonic pancreas and identified subunits of the 26S proteasome complex. Ca^{2+}-dependent interaction of SCGN with the 26S proteasome modulates proteasome activity which determines availability of transcription factors defining β-cell identity (2).

Taken together, our results indicate SCGN to be a pivotal molecular hub in many fundamental cellular processes conveying Ca^{2+} signals in the endocrine pancreas. Furthermore, we address that detailed one on one analysis of putative partner proteins has the potential to depict molecular background and functional consequences of these interactions.

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Poster abstracts

20 Hanna Kunina

Morbidity and Mortality Modelling in Type 2 Diabetes Accounting for Competing Risks

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Objectives: Type 2 diabetes (T2D) is associated with comorbidities e.g. chronic kidney disease (CKD) and cardiovascular disease (CVD) and an increased risk of death [1]. The increased risks of comorbidity and mortality are potentially competing, as the onset of a comorbidity may change the risk of the other comorbidity, and death. This project aimed to investigate competing risks of morbidity and mortality, with a multistate, Markov-model [2], using data from the Swedish National Diabetes Registry (NDR).

Methods: Adults with T2D, registered in NDR between 2005 and 2013, without prior CKD and/or CVD were investigated. The high-risk groups of the Renal Association Guide [3] were defined as CKD and the presence of stroke and/or ischemic heart disease as CVD. The model included five clinical states: T2D without comorbidity, CVD, CKD, CVD&CKD and death, with the competing risk of CVD/CKD. The hazards were described with Gompertz-Makeham equations. The following hypotheses were tested: 1) CKD-independent risk of CVD 2) CVD-independent risk of CKD and 3) comorbidity-independent mortality. Hypotheses were investigated using morbidity (MobAS) and mortality (MotAS) age-shifts.

Results and Discussion: The mortality was found to depend on comorbidities. The MotAS was estimated to be 7, -1.9, -2.4 and -10 years, for T2D, CVD, CKD and dyad state, respectively. The risk of CKD was higher for patients with prior CVD: MobAS was -7.9 years. Surprisingly, the hazard of CVD was unaffected by prior CKD. Patients without comorbidities were thus estimated to have a lower risk of dying than the general population, while any comorbidity increased the mortality hazard. The MobAS potentially implies that treatment in CKD is sufficient to prevent CVD, while more could be done to prevent CKD in patients with CVD. Caution should, however, be exercised when interpreting the results of epidemiological data.

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Poster abstracts

21 **Inès G. Buzirukanyo**

Pharmacokinetics of metformin in critically-ill patients

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Aims: The primary aim of this study was to investigate metformin pharmacokinetics in critically-ill patients using a model-based approach. The secondary aim was to investigate the contribution of metformin erythrocytes pharmacokinetics to plasma pharmacokinetics.

Methods: Data of plasma and erythrocyte metformin concentrations came from a published study by Kajbaf et al, where 12 critically-ill patients were hospitalized due to lactic acidosis, supratherapeutic metformin concentrations and in most cases severely impaired renal function [1]. A published population pharmacokinetic model of metformin in normal to slightly impaired renal function was re-used, in which glomerular filtration rate (eGFR) affected both filtration and net secretion clearance [2]. Differences in parameters between previously studied patients and these critically-ill patients were investigated. Models were evaluated by objective function value (OFV) and visual predictive checks (VPCs).

Results and conclusion: A larger V_d has previously been reported in critically-ill patients for several hydrophilic drugs related to fluid shift [3]. When using only plasma observations, the central volume of distribution (V_d) in critically-ill patients was 6 times higher than in previously studied patients. Additionally, removing eGFR from net secretion improved the fit to the data. However, when adding erythrocytes data and distribution of erythrocytes to plasma pharmacokinetics, the estimated V_d decreased compared to plasma alone, and could without loss in fit be fixed to previously published V_d. The inter-individual variability was nonetheless 3.5 times higher for V_d. This indicates that for critically-ill patients, the apparent high V_d can partly be explained by erythrocytes distribution.

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Poster abstracts

Engineered silica particles reduce metabolic risk factors in humans by entrapping digestive enzymes

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Background: Obesity is a major risk factor for cardiovascular disease and diabetes. We have previously shown that engineered mesoporous silica particles reduce body weight and adipose tissue in mouse models. The aim of this single blinded uncontrolled pilot study was to evaluate safety and tolerability of precisely engineered mesoporous silica. Follow-on preclinical investigations aim to understand the mechanism-of-action.

Methodology: We report results of a First-in-Man clinical trial evaluating SiPore; precisely engineered mesoporous silica particles with controlled surface area, pore volume, pore size, particle size and morphology, as a dietary supplement in 10 obese and 10 normal weight male volunteers. We hypothesized that SiPore acts as a trap for digestive enzymes, sequestrating biomolecules in the gastrointestinal tract and thereby reducing and slowing down the digestion of food. Therefore further *in vitro* studies were performed investigating the interaction between SiPore and key digestive enzymes.

Results: The clinical effects of SiPore included significant reduction in several metabolic and cardiovascular risk factors. HbA1c and LDL-C was reduced from baseline, both clinically meaningful reductions. Adverse events observed were mild and transient. The promising results led to further investigations of SiPore's mechanism of action. *In vitro,* SiPore significantly sequestered α-amylase and lipase while smaller pore size silica particles had no effect. SiPore successfully reduced lipase and α-amylase from more complex biological matrices, such as porcine pancreatic and murine intestinal fluid. Further studies of α-amylase depletion *in vitro* confirmed that pores size is a critical parameter for enzymatic sequestration.

Conclusion: SiPore's mechanism of action, combined with its promising safety profile, makes it an exciting candidate for prevention and treatment of metabolic diseases, particularly prediabetes and type 2 diabetes. SiPore is currently being investigated in an ongoing proof of concept clinical trial in 39 prediabetic and newly diagnosed diabetic subjects (NCT03823027).

Poster abstracts

23 **Indranil Sinha**

Functional Genomic Technologies in Diabetes Research

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The Functional Genomic Technologies in Diabetes Research facility is located at the Department of Biosciences and Nutrition in the new NEO building at the KI south campus in Huddinge. The facility provides expertise in functional genomics technologies and associated bioinformatics data analysis. We work in close collaboration with the Bioinformatics and Expression Analysis core facility at Karolinska Institutet (BEA) to support the use of various genomic analysis platforms, such as microarray and high throughput sequencing, for various applications. For example, the applications that we support include genome wide DNA methylation analysis (the methylome), global gene expression analysis (the transcriptome) and global DNA-binding analysis (the cistrome). All applications are supported with established bioinformatics analysis pipelines. The facility can assist during all steps of a project from experimental design to data analysis and will give advice on which technology is best suited to address a particular research question. Examples of research questions that can be addressed include differences in DNA-methylation, gene expression and transcription factor binding between tissue samples from human diabetes and control as well as between different diabetic mouse models and controls as a means to approach molecular mechanisms responsible for the development of diabetes. It is important to emphasize that the facility will provide bioinformatics support also for projects where the assays have not been run at BEA.

Poster abstracts

24 **Patrick Müller**

Bioinformatics and Expression Analysis core facility

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BEA – the core facility for Bioinformatics and Expression Analysis (www.bea.ki.se) located in NEO, Karolinska Institutet Campus Flemingsberg offers access to genomic technologies to help scientists, investigators and the biotech community to conduct and explore their research in the most efficient and economical way. Specifically, BEA provides services and consultation for genomic analyses based on the latest Affymetrix, Agilent, Illumina and ABI platforms for microarray analysis, massive parallel sequencing and qPCR. Our goal is to provide high quality and internationally competitive infrastructure with services and education in genomic technologies including associated data analysis. We offer comprehensive solutions from experimental design to completion of data analysis. BEA implements and provides services on scientist demand, which has proven to be a successful concept. The number of different types of analysis has continuously increased and BEA handles approximately 250 individual projects yearly which corresponds to >6000 individual samples/year. The turnover for 2018 was approximately >20 MSEK. At present, the core facility is financed by grants from KI/SLL and by user fees.

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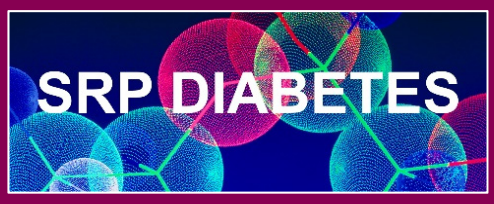

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