The 60th Annual Meeting of the

Scandinavian Society for the Study of Diabetes

Gävle Concert Hall, 21-23 May 2026

SCANDINAVIAN SOCIETY FOR THE STUDY OF DIABETES

Welcome to SSSD 2026!

Dear colleagues and friends,

Welcome to the 60th Annual Meeting of the SSSD to be held in the beautiful city of Gävle, Sweden, May 21-23. This international gathering will bring together researchers, clinicians, and other stakeholders in the ever expanding field of diabetology to share cutting-edge science, foster collaboration, and inspire innovation.

We have set up a really exciting program, including international key opinion leaders and stellar scientists in the many facets of diabetes. No less than 4 Minkowski awardees will present keynote lectures. The program includes world-leading invited speakers, abstract presentations, industry symposia and several award lectures.

We are so glad that you will join us for a couple days of engaging keynote lectures, interactive sessions, and networking opportunities in one of the arguably hottest areas of medicine. Whether you're presenting your latest findings or exploring new ideas, SSSD 2026 promises to be a memorable and impactful experience.

We warmly welcome you to this excellent opportunity to hear from scientific experts, engage in insightful discussions and network with colleagues and representatives from healthcare, academia, and industry.

For the Scandinavian Society for the Study of Diabetes,

Åke Sjöholm, M.D., Ph.D. Chairman
Professor of Medicine, Senior
Clinical Consultant

Daniel Espes, M.D. Ph.D. Associate
Professor of Medicine, Senior
Clinical Consultant

Sarah-Ålivia Mänd, M.D.
Resident Physician

Gustaf Christoffersson, Ph.D.
Associate Professor, Senior Lecturer

Cover photo of Gävle Concert Hall: Albin Bogren

Practical information

Venue
The conference takes place on 21-23 May in Gävle Concert Hall, address: Kungsbäcksvägen 22, 802 67.

Registration desk opening hours
Thursday 21 May: 11.30-17.00

Name badge
Please keep your name badge on and visible at all times during the entire conference, as it is your ticket for the lectures, coffee and lunches.

Coffee breaks and lunch
The registration fee includes coffee breaks and lunch during the conference, according to the programme. Lunch and coffee will be served in the foyer of Gävle Concert Hall, entrance level.

Welcome reception
On Tuesday May 21 at 19.30, there will be a Welcome reception at Gävle Concert Hall,
address: Kungsbäcksvägen 22, 802 67
Kindly note that this welcome reception is for pre-registered attendants only.

Conference dinner
On Friday May 22 at 19.30, there will be a Congress dinner at Elite Grand Hotel, address: Kyrkogatan 28, 803 11.
Please note that there is no organized transportation, but the location can be easily reached by public transportation or on foot.
Kindly note that the congress dinner is for pre-registered attendants only.

Wifi at Gävle Concert Hall
Network: gavlekonsertguest
Password: Gavlekonserthus

Programme

Thursday 21 May 2026

11:30-13:00 Registration

12:00-13:00 Lunch symposium – Chiesi Pharma AB

Welcome and introduction – Prof. Åke Sjöholm (SE)

Lipodystrophy diagnosis and treatment – an overview –Prof. Baris Akinci, Izmir Biomedicine and Genome Center & DEPARK, Dokuz Eylul University Health Campus, Izmir, Turkey

Experience with lipodystrophy in atypical diabetes – Prof. Åke Sjöholm

13:00-13:10 Opening and welcome remarks – Åke Sjöholm (SE)

13:10-13:55 *Keynote lecture:* Factors affecting the progression rate from seroconversion to autoantibody positivity to clinical type 1 diabetes – Mikael Knip (FIN)
Chair: Daniel Espes (SE)

13:55-14:15 Coffee and visit exhibition

14:15-15:00 Barndiabetesfondens Johnny Ludvigsson Nordic Prize: Early signs of type 1 diabetes – Riitta Lahesmaa (FIN)
*Chair: Johnny Ludvigsson (*SE)

15:00-15:30 Barndiabetesfondens Young Swedish Investigator Prize: Investigations of local immune regulatory mechanisms in type 1 diabetes – Gustaf Christoffersson (SE)
Chair: Johnny Ludvigsson (SE)

15:30-16:30 Abstract session #1A:

Cord Blood Iron Status has Age-specific Role in Future Type 1 Diabetes Diagnosis – Debojyoti Das, *Johnny Ludvigsson*

Epigenetic–proteomic network crosstalk at birth across HLA risk groups in type 1 diabetes – Shamila Darvish Alipoor Astaneh, *Angelica Ahrens, Julia Åkesson, Johnny Ludvigsson*

Integrated analysis of clinical course and proteomics data in DIAGNODE-2 patients – *Debojyoti Das, Indusmita Routray*, Johnny Ludvigsson

Stem cell derived islet organoids attract T cells, resulting in MHC matched organoid destruction by type 1 diabetic patient T cells. – Robin Lindsay, *Xenia Podlipensky, Kina Adjieva, Marleen Bootsma, Svitlana Vasylovska, Anja Ivis, Carl Andersson, Gustaf Chistoffersson, Joey Lau*

Pancreatic islets in mice and humans: unravelling mechanisms driving beta cell proliferation under metabolic stress – Leonie Reible, *Teresa Pereira, Daniel Espes*

Chair: Signe Schmidt (DK)

Programme

Thursday 21 May 2026

15:30-16:30 Abstract session #1B:

Regulation of insulin secretion by Ras signalling in pancreatic β-cells – *Yunjian Xu*, Moa Södergren, *Santiago Echeverry, Per-Eric Lund, Oleg Dyachok, Olof Idevall, Sebastian Barg, Anders Tengholm*

Novel METTL3/14 methyltransferase activators for protecting pancreatic beta- cells in diabetes mellitus – Julia Kiva, *Huini Li, Maria Lindahl*

Increasing the enteroendocrine cells by stimulating secretory progenitors with a Vcp-mediated autophagy activator – Lorenzo Buttò, *Lianhe Chu, Jiarui Mi, Stefan Ebmeyer, Jeremie Charbord, Agnese Kocere, Anna Johansson, Olov Andersson*

The Welander TIA1 mutation dedifferentiates human insulin-producing cells by upregulating MYC, an effect prevented by the GLP-1R agonist liraglutide – *Tongjian Zhao, Jing Cen, Xuan Wang, Mingyu Yang, Joey Lau, Anders Tengholm, Åke Sjöholm*, Nils Welsh

Characterization of glucose tolerance, islet cell function, and insulin sensitivity in patients with Welander distal myopathy – Åke Sjöholm, *Zhanchun Li, Joey Lau, Sarah-Ålivia Mänd, Niklas Dahl, Per-Ola Carlsson, Nils Welsh*

Chair: Daniel Espes (SE)

16:30-17:15 *Keynote lecture:* GRK-biased adrenergic agonists for the treatment of type 2 diabetes and obesity – Tore Bengtsson (SE)
Chair: Åke Sjöholm (SE)

17:15-18:15 Novo Nordisk Foundation Nordic Diabetes Prize – Charlotte Ling
Chair: Lena Eliasson (SE)

18:15-18:30 Short Break

18:30-19:30 Role of VEGF-B signaling in diabetic complications: focusing on fatty liver disease and diabetic stroke – Ulf Eriksson (SE)
Chair: Åke Sjöholm

19:30- Welcome reception

Programme

Friday 22 May 2026

08:00-08:45 Knud Lundbæk Award – Anna Krook
Chair: Elisabeth Qvigstad (NO)

08:45-09:30 *Keynote lecture:* Lipodystrophies and the road to diabetes – Fredrik Karpe (UK)
Chair: Esben Söndergaard (DK)

09:30-10:30 Abstract session #2A:

Anti-CD3 monoclonal antibody modulates gamma-aminobutyric acid (GABA)ergic activity in T cells from healthy and type 1 diabetes individuals – Zhe Jin, *Bryndis Birnir, Jarl Hellman*

Characterization of the human virome in a childhood Type 1 diabetes cohort; focus on circoviruses – *Amanj Bajalan, Edmundo Grisard, Claudia Beck Eichler Jonsson, Tobias Allander,* Björn Andersson, *Johnny Ludvigsson*

Early life islet autoimmunity in type 1 diabetes among children frequently followed in a prospective birth cohort study – Nelli Rönkä, *Tiia Honkanen, Anni Kyrönniemi, Toni Valtanen, Johanna Lempainen, Heikki Hyöty, Jorma Toppari, Jaakko Koskenniemi, Mikael Knip, Taina Härkönen, Tytti Pokka, Riitta Veijola*

Gene Expression Signatures Associated with Disease Progression in Individuals with Newly Diagnosed Type 1 Diabetes: Insights from the INNODIA Study – *Tomi Suomi,* Inna Starskaia, *Omid Rasool, Ubaid Ullah Kalim, Sylvaine Bruggraber, Loredana Marcovecchio, Emile Hendricks, Lut Overbergh, Mark Peakman, Timothy Tree, Søren Brunak, Anke M Schulte, Chantal Mathieu, Mikael Knip, Riitta Lahesmaa, Laura L Elo*

Chair: Gustaf Christoffersson (SE)

09:30-10:30 Abstract session #2B:

Effect of impaired glycogenolysis and glycogen excess on exercise-mediated glucose metabolism in skeletal muscle: Insights from novel mouse models – Dipsikha Biswas, Marianne Agerholm, Joachim Nielsen, Mohd. Syed Ahanger, Elton Zeqiraj, Kei Sakamoto

Exploring predictors for long-term clinical benefit after gastric bypass and sleeve gastrectomy in type 2 diabetes: A Machine Learning Approach – Gudrun Höskuldsdóttir, Ala Mejaddam, Moa Lugner, Hanne Carlsen, Araz Rawshani, Ingrid Larsson, Johan Ottosson, Katarina Eeg-Olofsson, Kerstin Landin-Wilhelmsen, Björn Eliasson

Extracellular Vesicle associated Glycosylated Sphingolipid Alterations in Type 2 Diabetes Impair Adipocyte Glucose Metabolism – Daan Paget, Jutta Jalkanen, Svetlana Michurina, Kirstin MacGregor, Antonio Checa, Niklas Mejhert, Taras Sych, Erdinc Sezgin, Harriet Wallberg- Henriksson, Juleen Zierath,

Anna Krook
Therapeutic Targeting of the ANGPT2/TIE2 Signaling Axis Improves Diabetic Nephropathy in the BTBR OB/OB Mouse – Amanda M. Marks-Hultström, Marie Jeansson

Programme

Friday 22 May 2026

Tuning GRK2-biased β_2 signaling: next-generation muscle-targeted modulators with enhanced metabolic and anabolic profiles – Nodi Dehvari, Anastasia Kalinovich, Carina Halleskog, Hamza Bukhari, Sofia Karlström, Tore Bengtsson

Chair: Helga Sigurjónsdóttir (IS)

10:30-10:50 Coffee and visit to exhibition

10:50-11:35 *Keynote lecture:* Exercise timing and circadian regulation of metabolism in type 2 diabetes – Harriet Wallberg (SE)
Chair: TBN

11:35-12:20 *Keynote lecture:* The insulin-resistant brain – Martin Heni (DE)
Chair: Åke Sjöholm (SE)

12:20-13:20 Lunch symposium - Eli Lilly

13:20-14:05 *Keynote lecture:* Advances in oligogenic diabetes – Amélie Bonnefond (FR)
Chair: Daniel Espes (SE)

14:05-14:50 *Keynote lecture:* Advances in diabetic nephropathy – Peter Rossing (DK) – Online presentation.
Chair: Gustaf Christoffersson (SE)

14:50-15:20 SSSD Young Investigator Award – Mikkel Thor Olsen
Chair: Elisabeth Qvigstad (NO)

15:20-16:05 *Keynote lecture:* Glucokinase as a therapeutic target in diabetes – Elaine Chow (HK)
Chair: Åke Sjöholm (SE)

16:05-16:50 *Keynote lecture:* Diabetes technology: Sensors and pumps – Jarl Hellman (SE)
Chair: Signe Schmidt (DK)

16:50-17:10 Coffee and visit to exhibition

17:10-17:55 *Keynote lecture:* Survival of transplanted allogeneic β-cells with no immunosuppression – Per-Ola Carlsson (SE)

Chair: Gustaf Christoffersson (SE)

17:55-18:55 Abstract session #3A

Ephemeral diabetes after Covid-19 vaccination – Sarah-Ålivia Mänd, *Åke Sjöholm*

Targeted serum proteomics of longitudinal samples from newly diagnosed youth with type 1 diabetes affirms markers of disease – *Robert Moulder,* M.Karoliina Hirvonen, *Tommi Välikangas, Tomi Suomi, Lut Overbergh, Mark Peakman, Søren Brunak, Chantal Mathieu, Mikael Knip, Laura L Elo, Riitta Lahesmaa*

Programme

Friday 22 May 2026

THE INFLUENCE OF PARENTAL ROLE MODELING AND GENDER ON PHYSICAL ACTIVITY PATTERNS IN CHILDREN WITH TYPE 1 DIABETES – Hilla Hannola, *Tytti Pokka, Maisa Niemelä, Marika Paalanne, Raija Korpelainen, Anna-Maiju Leinonen, Päivi Tossavainen*

Treatment with GAD in LADA – follow-up of a clinical trial – Valdemar Grill, *Indusmita Routray, Chandima Balasuyria, Rosaura Casas, Anneli Björklund, Ingrid Hals*

Chair: Robin Lindsay (SE)

17:55-18:55 Abstract session #3B:

Electrical activity and Ca2+ dependent plasticity in human pancreatic β-cells – Santiago Echeverry, *Per-Eric Lund, Symar Hamdan, Jan Saras, Sebastian Barg*

Epigenetic Impact of GLP-1 Receptor Agonists on Pancreatic β-Cells – *Yuke Wu, Yanying Li,* Xuan Wang

Ex vivo and in vivo experimental investigation of miR-148a-3p as a novel therapy for insulin secretion and type 2 diabetes – Lena Eliasson, *Elaine Cowan, Akira Asai, Jones Ofori, Jonathan Esguerra, Charlotte Ling, Anna Wendt, Mototsugu Nagao*

INHIBITION OF VOLTAGE-DEPENDENT ANION CHANNEL 1 OLIGOMERIZATION AS A TREATMENT OPTION FOR TYPE 1 DIABETES – Ruchi Jain, *Christian C. Lachaud, Cecillia Frej, Cornelia Nilsson, Benoit R. Gauthier, Claes B. Wollheim*

Mitochondria – insulin granule crosstalk controls the early stages of granule maturation – Kousik Mandal, *Styliani Panagiotou, Sofia Amini, Kia Wee Tan, Samuel B. Stephens, Olof Idevall-Hagren*

Chair: Ragnar Grímur Bjarnason (IS)

19:30- Congress dinner – Elite Grand Hotel

Saturday 23 May 2026

08:00-08:30 General assembly of the SSSD

08:30-09:15 *Keynote lecture:* Mechanisms of exocytosis in pancreatic islet cells – Patrik Rorsman (UK)
Chair: Gustaf Christoffersson (SE)

09:15-10:00 *Keynote lecture:* Mechanistic insights and approaches for β-cell regeneration – Olov Andersson (SE)
Chair: Åke Sjöholm (SE)

Programme

Saturday 23 May 2026

10:00-10:45 *Keynote lecture:* Incretin therapy of obesity and diabetes – Jens J. Holst (DK)
Chair: Åke Sjöholm (SE)

10:45-11:05 Coffee and visit to exhibition

11:05-11:50 *Keynote lecture:* Is type 1 diabetes an inflammatory pancreatic disease with its main clinical symptoms due to the loss of the β-cells? - Olle Korsgren (SE)
Chair: Gustaf Christoffersson (SE)

11:55-12:55 Abstract session #4A:

Adenosine deaminase and adenosine monophosphate deaminase 2 delays onset of Type 1 diabetes in mice – Ronja Andersson, *Kailash Singh, Tongjian Zhao, Anongnad Ngamjariyawat, Kina Adjieva, Mudhir Shekha, Averina Octaxena Aslani, Martin Blixt, Zhengkang Luo, Stellan Sandler, Nils Welsh*

Impact of cold ischemia on pancreatic islet function and beta-cell gene expression: studies with brain-dead donor biopsies and human isolated islets – Teresa Pereira, *Joel Gelin, Casian Aioanei, Daniel Espes*

Recapitulating islet vascular remodelling in mouse models of long-standing type 1 diabetes – Casian Aioanei, *Teresa Pereira, Daniel Espes*

The Immunomodulatory Role of Catestatin in Pancreatic Islets: Neuroimmune Interactions and Implications for Autoimmune Diabetes – Dali Epremidze, *Joanna Whittaker, Lucas Hultgren, Simon Ekström, Helena Danielson, Sushil K. Mahata, Elke M. Muntjewerff, Gustaf Christoffersson*

β cell-targeted mesencephalic astrocyte-derived neurotrophic factor gene therapy reverses β cell stress and diabetes in mice – Huini Li, *Julia dsKiva, Marika Itkonen, Liisa Pilv, Maria Lindahl*

Chair: Gudrun Höskuldsdóttir (IS)

11:55-12:55 Abstract session #4B:

Excess risk of cardiovascular disease and mortality following lower-extremity amputation in type 2 diabetes – Karin Bergqvist,Henrik Imberg, Sara Hallström, Jens Michelsen, Hanna Liljebäck, Stefan Franzén, Anna Norhammar, Annika Rosengren, Marcus Lind

Family planning and pregnancy in women with type 2 diabetes – a qualitative prequel to a digitally supported lifestyle intervention (ReproDiaT2D). – Jesini Selvarasa Anurathan, Sandra Dis Steintorsdottir, Astrid Melteig Stalheim, Line Wisting, Cecilie Varsi, Anne-Marie Aas, Elisabeth Qvigstad

Programme

Saturday 23 May 2026

Health and lifestyle habits in dog owners in Sweden – Klara Smedberg, *Erika Roman, Anna Bergh, Sören Spörndly-Nees, Jan W. Eriksson, Lena V. Kallings, Josefin Söder*

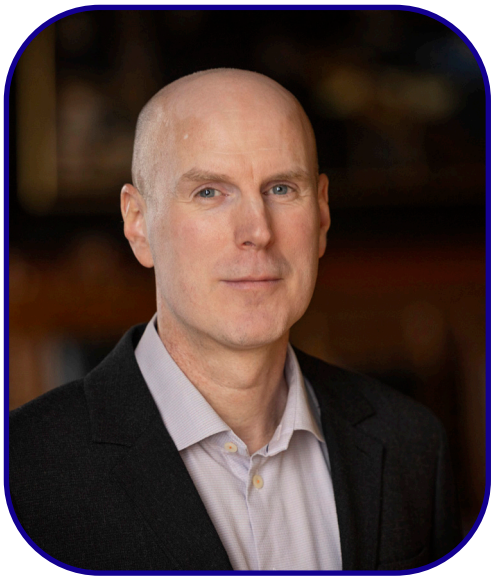
Whole-body magnetic resonance imaging reveals sex-specific anatomical signatures of type 2 diabetes risk in the UK Biobank – Rama Guggilla, *Lars Lind, Susanna Larsson, Robin Strand, Håkan Ahlström, Xiaomei Chen, Yasemin Utkueri, Johan Öfverstedt, Joel Kullberg*

*Chair: Robin Lindsay (*SE)

13:00- Closing remarks and departure lunch – Chair of local organizing committee: Åke Sjöholm (SE)

Keynote speakers

Olov Andersson



Olov Andersson studied pharmacy at Uppsala university, then performed a PhD at Karolinska Institutet regarding TGF-β signaling in development and metabolism using the mouse model. For his postdoctoral work he moved to the lab of Didier Stainier at UCSF and studied the pancreas using the zebrafish model. He set up an independent laboratory at the Karolinska Institutet in 2012 and moved to Uppsala University in 2024, where he is now Professor of Experimental Diabetes Research. Bridging drug discovery, metabolism and β-cell regeneration, his lab screens in the zebrafish model and translate findings to mice and human samples. He has received several awards, among them the ERC consolidator award and the Leif C. Groop award for outstanding diabetes research.

Tore Bengtsson

Tore Bengtsson, PhD, is Professor of Physiology at Stockholm University. His research focuses on metabolism, obesity, and type 2 diabetes, with a particular emphasis on translational physiology and clinically relevant approaches to metabolic disease. His work bridges mechanistic biology and applications relevant to human metabolic health.

Amélie Bonnefond

Amelie Bonnefond graduated as PhD from University of Lille in 2010. Her scientific career has been focused on the dissection of the genetic etiologies of type 2 diabetes and obesity in order to elucidate their pathophysiology towards a better stratification of the patients and a putative identification of new drug targets. She leads the INSERM/CNRS 1283/8199 unit (Lille Pasteur Institute and University of Lille) called METAB-OMICS. She is also the current scientific director of the PIA-funded EquipEx LIGAN-PM platform dedicated to the use of next-generation sequencing in precision medecine. Furthermore, she is a visiting professor at Imperial College London where she teaches in several Master courses. She has published >200 peer-reviewed scientific papers (H Index: 72 [Google Scholar]). She is laureate of the 2012 Rising Star award from European Association for the Study of Diabetes (EASD), the 2018 Auguste Loubatières award from the French-speaking Association for Diabetes (SFD), the 2021 Minkowski Prize from EASD and two European Research Council Grants (Starting 2017-2022 [Reg-Seq] and Consolidator 2022-2027 [OpiO]). She is currently the co-PI of the Horizon Europe Obelisk project (2023-2028) and WP leader of the Horizon Europe Intercept project (2023-2028).

Keynote speakers

Per-Ola Carlsson

M.D., Ph.D. Per-Ola Carlsson is a professor of Medical Cell Biology at Uppsala University, Sweden. He also serves as a senior consultant in endocrinology and diabetology at Uppsala University Hospital and as director of Uppsala Diabetes Centre.

His research focus over the years has been on islet physiology, islet vascular biology, stem cell research, beta-cell replacement and early phase clinical cell therapy trials in type 1 diabetes. Recently, he has translated the concept of immune evasion into a first-in-human study of hypoimmune islet cell transplantation in type 1 diabetes. He has authored more than 200 peer-reviewed publications

Elaine Yee Kwan Chow

Elaine Chow received her medical training in UK and completed her PhD at the University of Sheffield in 2015. She since joined the Chinese University of Hong Kong, where she helped set up glucose clamp and continuous glucose monitoring (CGM) studies at the Phase 1 Clinical Trial Centre. In 2022, she received the Women's Interprofessional Network of the American Diabetes Association abstract award on her work showing dorzagliatin, a dual-acting glucokinase activator increases insulin secretion in beta cell glucose sensitivity in GCK-MODY and recent onset type 2 diabetes. She was awarded the Hong Kong College Physicians Richard Yu Lecture in 2022 and
Sir David Todd Lecture in 2024. She is Associate Editor for Diabetes Research and Clinical Practice and editorial board member for several journals.

Ulf Eriksson

Senior Professor at Karolinska Institutet (2025–present); Professor of Vascular Biochemistry at Karolinska Institutet (2010–2025); Assistant/ Associate/Full Member at the Ludwig Institute for Cancer Research, Stockholm Branch (1988–2009); Council Professor at the Swedish Research Council (Vetenskapsrådet) (2018–2027); Member of the Nobel Assembly at Karolinska Institutet (2012–2024) and its Chair in 2022; Member of the Nobel Committee in 2022; various positions of trust at Karolinska Institutet (2018–2025); Chair of the Board of Comparative Medicine at Karolinska Institutet (2018–2025); Member of the Central Animal Ethics Committee (CDFN) (2022–present).

Keynote speakers

Jarl Hellman

Senior consultant and clinical researcher in diabetes at Uppsala University Hospital.

Head of Diabetes care in adults and coordinator for the Centre of excellence Type 1 diabetes at Uppsala University Hospital.

Excellent Teacher and Program Director for the Medicine Program at Uppsala University and course leader at the Department of Medical Sciences

President of the Swedish Society for Diabetology since 2024, the "Diabetologist of the Year in Sweden 2017".
Research activities mostly focused of implementing new diabetes technology (insulin pumps and continuous glucose monitoring, CGM) and modern treatment methods in clinical practice

Martin Heni

Professor Martin Heni is a physician-scientist in endocrinology and diabetology at the University of Ulm (Germany), where he leads research on brain insulin resistance and its role in the heterogeneity and pathophysiology of type 2 diabetes and unhealthy obesity.
His work further addresses body fat distribution and sex-specific mechanisms, integrating clinical studies with advanced phenotyping and omics approaches to investigate underlying mechanisms and translate these insights into the clinical setting. He has received multiple awards, including the EASD's Minkowski Prize and an ERC Consolidator Grant, and contributes to collaborative research initiatives in the field.

Jens Juul Holst

Jens Juul Holst is Professor of Medical Physiology at the Department of Biomedical Sciences, University of Copenhagen. He is also Senior Group Leader at the Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen.

Professor Holst's scientific work has focused on the regulatory peptides of the pancreas and the gut and their importance in the regulation of the functions of the GI-tract and metabolism. Professor Holst great scientific achievements include the discovery of GLP-1 (glucagon-like peptide 1) a gut hormone regulating insulin secretion and appetite and food intake and his subsequent basic and translational research in this field.

Keynote speakers

Fredrik Karpe

Fredrik Karpe is a physician-scientist who is professor of metabolic medicine at the University of Oxford He leads the Lipid Clinic Service in at the university hospital in Oxford and has a special interest in lipodystrofies.

His main research is in obesity and regulation of human fat distribution in relation to health and disease. He is using genomic and physiological tools to investigate metabolic consequences of dysfunctional metabolism in relation of adipose tissue function.

Mikael Knip

MD, PhD, is Emeritus Professor of Pediatrics and Research Director at the University of Helsinki. His research focuses on type 1 diabetes and other immune-mediated diseases in children and adolescents. Dr. Knip has been one of the Principal Investigators on the Finnish Diabetes Prediction and Prevention (DIPP) study from its start in 1994. Over the last 12 years Dr. Knip and his research group have elaborated an interest in the gut microbiota and its potential role in the development of type 1 diabetes and autoimmunity. Dr. Knip is as well involved in a project aimed at developing an antidiabetogenic Coxsackie B virus vaccine.

Olle Korsgren

Dr Korsgren has served as Senior Consultant at the Department of Clinical Immunology and Transfusion Medicine since 2001. He was appointed Professor of Transplantation Immunology in 2002 and obtained a tenured faculty position as Professor of Cell Transplantation in 2006. He is the founder and principal investigator of the Nordic Network for clinical islet transplantation.

Dr. Korsgren's research activity has been focused on elucidating the etiology of Type 1 Diabetes, PET-imaging, Immuno-Oncology and to make islet transplantation without the need for systemic immunosuppression a possible treatment for patients with Type 1 Diabetes. Dr. Korsgren has authored more than 400 scientific publications.

Keynote speakers

Riitta Lahesmaa

Lahesmaa, M.D., Ph.D. is Professor of Systems immunology and the Director of Turku Bioscience Centre, Turku, Finland (https://bioscience.fi/).

After receiving M.D. and Ph.D. in immunology from the University of Turku, Dr. Lahesmaa was a postdoctoral fellow at Stanford University Medical Center and a Principal Scientist at Roche Bioscience in Palo Alto, California. She has been academy professor and vice-director of the Centre of Excellence in Systems Immunology and Physiology of Research Council of Finland.

Dr. Lahesmaa's research on regulation of immune response and molecular mechanisms of type 1 diabetes and other human immune mediated and inflammatory diseases has resulted in > 250 original papers and reviews. She is an elected member of the Finnish Academy of Science and Letters and EMBO.

Patrik Rorsman

Patrik Rorsman is Professor of Diabetic Medicine (statutory) and Professorial Fellow of Harris Manchester College, University of Oxford.

Patrik Rorsman obtained in PhD at the University of Uppsala in1986. He then moved to the University of Göteborg (Sweden). In 1994 he became Director of Islet Research at Novo Nordisk in Copenhagen. He returned to academia in 1997 when he became Professor of Membrane Physiology at Lund University, where he remained until 2003 when he was elected Professor of Diabetic Medicine at the University of Oxford. Since 2013 he also directs the Metabolic Physiology unit at the University of Göteborg. He is a Member of Academia Europea (since 2006), a Fellow of the Academy of Medical Science (FMedSci; since 2010) and a Fellow of the Royal Society (FRS; since 2014).

Patrik's research focuses on the cellular control of pancreatic hormone secretion, how these processes become impaired in diabetes and their – possible – correction by therapeutic interventions.

Keynote speakers

Peter Rossing

Peter Rossing is a clinician researcher devoted to complications in diabetes with focus on renal and cardiovascular complications. He obtained a specialist degree in internal medicine and endocrinology 2004. Since 2007 he has been a chief physician and manager of the Steno Diabetes Center Copenhagen research team dedicated to the research of micro-and macrovascular complications of diabetes.

Since 2012 Professor in diabetic angiopathy at University of Copenhagen. Peter Rossing has in epidemiological studies investigated key features of the pathophysiology of the diabetic kidney at different stages. He has identified several markers for development of diabetic nephropathy; making it possible to predict the individual risk. He has been involved in several intervention studies in patients with overt diabetic nephropathy aiming at improving the prognosis including DAPA-CKD, FIGARO-DKD, FIDELIO-DKD and FLOW.

He received the Minkowski prize in 2005 and the Golgi prize in 2016 both from the EASD and the E. Bierman award from ADA and the Hormon Medal from European Society of Endocrinology. Past president of the Danish Endocrine Society, and of the European Diabetic Nephropathy Study group and chairman of the Danish National Diabetes Registry and the Independent Research Fund Denmark-Health and Disease.

Harriet Wallberg

Harriet Wallberg, MD, is a professor of physiology at Karolinska Institute and has had a long career in medical research and academic leadership. Her research has primarily focused on metabolism, diabetes, and lifestyle factors affect health. In recent years, her work has been directed toward how circadian rhythms influence blood glucose regulation in people with type 2 diabetes, with a particular focus on time-of-day effects of exercise. Harriet Wallberg has published many groundbreaking scientific papers and been a member of the Nobel Assembly at Karolinska Institute. She has received numerous scientific awards and honorary doctorates from international universities.

Exhibition

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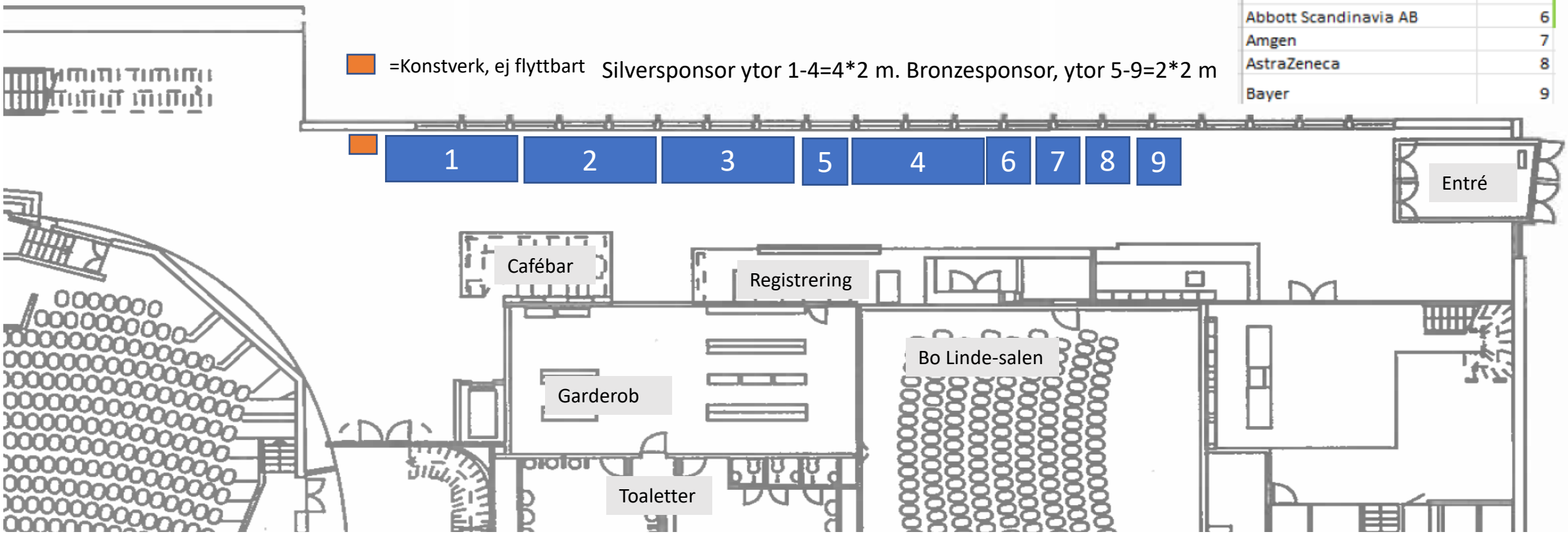

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Referens: Repatha® (evolokumab) Produktresumé, dec 2025 | SWE-145-1224-80009 feb 2026

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Abstract book

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1 - Adenosine deaminase and adenosine monophosphate deaminase 2 delays onset of Type 1 diabetes in mice

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Introduction: Type 1 diabetes (T1D) is characterized by the destruction of pancreatic β-cells, leading to insulin deficiency. Increased intracellular levels of adenosine have been implicated in promoting β-cell death. Adenosine deaminase (ADA) catalyzes the conversion of adenosine to inosine, while adenosine monophosphate deaminase 2 (AMPD2) converts adenosine monophosphate (AMP) into inosine monophosphate; notably, AMP can be converted into adenosine. A previous study using single-cell RNA sequencing demonstrated that ADA and AMPD2 are downregulated in β-cells from T1D patients. Therefore, upregulation of ADA and AMPD2 may reduce intracellular adenosine levels and β-cell death.
Methods: miRNA target site blockers (TSB) were used to enhance the expression of ADA and AMPD2. CD-1 mice were administered streptozotocin (40 mg/kg body weight) over five consecutive days. Mice received two doses of TSB administered before and after streptozotocin treatment. Serum insulin and glucagon levels were measured using ELISA. Experimental groups included control mice (treated with a scrambled miRNA TSB), mice treated with ADA alone, and mice treated with a combination of ADA and AMPD2.
Results: Treatment with ADA and AMPD2 delayed the onset of T1D, defined as blood glucose levels exceeding 11.2 mmol/L. A statistically significant increase in serum insulin levels was observed in both the ADA-treated group and the ADA+AMPD2 group compared to the control group. However, no significant differences in serum glucagon levels were detected.
Conclusions: Upregulation of ADA and AMPD2 delays the onset of Type 1 diabetes in a streptozotocin-induced CD-1 mouse model, potentially through reduction of intracellular adenosine and preservation of β-cell function

2 - Anti-CD3 monoclonal antibody modulates gamma-aminobutyric acid (GABA)ergic activity in T cells from healthy and type 1 diabetes individuals

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Introduction: Glutamic acid decarboxylase (GAD) catalyzes the synthesis of gamma-aminobutyric acid (GABA) and is typically found in neurons and pancreatic beta cells. GAD exists as two isoforms, GAD65 and GAD67. The GAD65 isoform is a major autoantigen in type 1 diabetes (T1D), while GABA acts as an immunomodulatory molecule regulating T cell functions. This study investigated whether human peripheral blood mononuclear cells (PBMCs) and T cells stimulated by anti-CD3 antibody express GAD isoforms, produce, and release endogenous GABA.
Methods: PBMCs and T cells were isolated from blood of healthy and T1D donors sourced from Uppsala University Hospital. Isolated cells were cultured and activated in vitro with anti-CD3 antibody or teplizumab for up to 72 hours, and analyzed using quantitative PCR, immunoblot, immunostaining, ELISA, and patch-clamp recording.
Results: Quantitative PCR revealed that anti-CD3 antibody time-dependently increased GAD67 mRNA expression, partially via NF-κB, in T cells from healthy donors. Immunoblot and immunostaining confirmed GAD67 protein expression in activated T cells. Activated T cells released GABA at sub-micromolar concentrations, which activated GABAA receptor-mediated single-channel currents. GAD67 mRNA and protein expression, along with endogenous GABA production, were also increased by anti-CD3 antibody or teplizumab stimulation in PBMCs or T cells from T1D donors. Furthermore, the GABAA receptor-specific antagonists TPMPA or picrotoxin potentiated IFNγ release from teplizumab-stimulated PBMCs from T1D donors.
Conclusions: These results highlight a potential intrinsic GABA-mediated regulatory loop within T cells, which could have important implications for understanding T cell immunity and inflammation in diabetes.

3 - Characterization of glucose tolerance, islet cell function, and insulin sensitivity in patients with Welander distal myopathy

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Introduction: Welander distal myopathy (WDM) is a dominantly inherited muscular dystrophy caused by a mutation in the RNA-binding protein TIA1. Experimental studies in human β-cells suggest that this mutation induces transdifferentiation toward a diabetogenic phenotype, increasing α-cell formation at the expense of β-cells. These effects were prevented by treatment with a GLP-1 receptor (GLP-1R) agonist. Based on these findings, we hypothesized that WDM patients carrying the TIA1 mutation would exhibit impaired β-cell function and hyperglycemia, potentially treatable with GLP-1R agonists.
Methods: Adults with WDM and their mutation-negative relatives were invited to participate. After fasting, participants underwent a 2-hour oral glucose tolerance test (OGTT). Blood samples were collected at seven time points to measure HbA1c, glucose, C-peptide, insulin, proinsulin, and glucagon.
Results: Ninety-six individuals were enrolled; after excluding those with known diabetes, 87 remained. Surrogate indices of β- and α-cell function and insulin sensitivity were calculated. No significant differences were observed between all WDM and non-WDM participants overall. However, subgroup analysis revealed that a subset of WDM patients exhibited elevated fasting glucagon levels (WDM-High) compared with WDM-Low and non-WDM groups. Despite this, glucose, C-peptide, insulin, and HbA1c levels—both fasting and post-OGTT—were similar across groups. Notably, the WDM-High subgroup showed increased proinsulin levels and higher proinsulin-to-insulin ratios.
Conclusions: The TIA1 mutation in WDM does not appear to impair overall glucose tolerance. However, a subgroup demonstrates hypersecretion of glucagon and proinsulin, indicating possible β-cell dysfunction and partial transdifferentiation toward α-cells. This defect may be masked by altered muscle mass in WDM patients, preserving insulin sensitivity and preventing overt glucose intolerance.

4 - Characterization of the human virome in a childhood Type 1 diabetes cohort; focus on circoviruses

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Introduction: The etiology of Type 1 diabetes (T1D) is complex with both genetic and environmental factors. Several studies have indicated that viral infections play an important role in the development of T1D. Several virus families have been implicated, and recently, both bacteriophages and circoviruses have emerged as candidates.
Methods: Nucleic acids were prepared from plasma and fecal samples collected at birth, and ages 5 and 8, from 36 ABIS (All Babies in South-east Sweden) children who later developed T1D (=prediabetes) and 30 control children, in pools and individually. Half of each was treated with reverse transcriptase, to reveal RNA viruses. All samples were sequenced using deep Illumina sequencing. The reads were analyzed using an in-house metagenomics pipeline, where reads were assembled, classified, and known and unknown viruses were identified.
Results: A broad spectrum of viruses was found to be present in both blood and fecal samples. These included Flaviviruses, Herpesviruses, Papillomaviruses and Poxviruses, as well as picornaviruses. The fecal samples were dominated by bacteriophages, but human infections were also identified. Diverse Anellovirus strains were found in all plasma samples, with higher levels in five-year-olds. The Anneloviruses have been typed using novel tools and analyzed for disease association. Circoviruses were identified in both plasma and fecal samples. We will present data on their typing, distribution and possible disease association.
Conclusions: The metagenomic analysis of viruses in children who later developed T1D has yielded information on virus infections and novel avenues of research into the connection between specific viruses and T1D.

5 - Cord Blood Iron Status has Age-specific Role in Future Type 1 Diabetes Diagnosis

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Introduction: Iron is known to have a direct role in diabetes pathogenesis mediated both by beta cell failure and insulin resistance. Although, the underlying molecular mechanisms mediating these effects are not fully understood, they include oxidant stress and signal transduction pathways. We investigated the association of cord blood iron status with future risk of type 1 diabetes.
Methods: Participants were included from the All Babies in Southeast Sweden (ABIS) birth cohort with 17055 registered children and followed prospectively until 2023. Cord blood ferritin and soluble transferrin receptor (sTfR) were measured in a nested case–control sample (83 with future T1D diagnosis, and 296 controls) for the study. Cox proportional hazard model was used to calculate the adjusted hazard ratios (aHR) for T1D.
Results: Neither cord blood ferritin had any association with T1D risk (aHR 1.001; 95% CI 0.999–1.002), nor did sTfR (aHR 0.907; 95% CI 0.773–1.065). The ratio of the two, TfR-F index, also did not show any significant association (aHR 0.883; 95% CI 0.671–1.161). However, landmark analysis revealed a significant protective association of sTfR **(aHR 0.567; 95% CI 0.375-0.858)** and the TfR-F **(aHR 0.461; 95% CI 0.219-0.97)** index during ages 5–10 years, suggesting a potential age-specific effect.
Conclusions: sTfR and the TfR-F index have a putative age-specific effect on future type 1 diabetes diagnosis.

6 - Early life islet autoimmunity in type 1 diabetes among children frequently followed in a prospective birth cohort study

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Introduction: Type 1 diabetes (T1D) can develop through various pathways of autoimmunity, differing by the first emerging islet autoantibody (IAb) and sequential spreading of autoimmunity to multiple IAb. Frequent measurement of IAb during early life is pertinent for grasping the initiating IAb signature.
Methods: We investigated IAb patterns among HLA-susceptible children followed since birth in the Finnish DIPP study according to the renewed DIPP Novum protocol between 2019–2025 by frequent measurement of IAA, GADA, IA-2A and ZnT8A (n=2,460) in relation to age, sex, and familial history of T1D.
Results: By median follow-up of 3.0 years, 59 (2.4%) children developed positivity for a single IAb, 77 (3.1%) for multiple IAb, and 46 (1.9%) progressed to T1D. Multipositive children mostly initiated with multiple IAb (n=37), followed by IAA (n=21), GADA (n=15), IA-2A (n=2) and ZnT8A (n=2). Among multipositive progressors (n=35), initiation with multipositivity reflected shorter time from seroconversion to diagnosis and younger age at diagnosis than initiation with a single IAb (1.2 vs. 2.1, and 2.4 vs. 3.3 years, respectively). Children with a diagnosed first-degree relative progressed more often than children without one (12/24, 50.0% vs. 25/112, 22.3%), and multipositive boys initiating with IAA only progressed more often than girls (10/17, 58.8% vs. 1/4, 25.0%).
Conclusions: Multiple IAb at seroconversion, having an affected first-degree relative, and male sex combined with initiation with IAA only contribute to higher risk of progression among young Finnish children. Our results emphasize the importance of frequent and early screening of IAb for estimating T1D risk accurately.

7 - Effect of impaired glycogenolysis and glycogen excess on exercise-mediated glucose metabolism in skeletal muscle: Insights from novel mouse models

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Introduction: Since exercise improves glycemic control by restoring glucose metabolism in insulin-resistant (IR) skeletal muscles, identifying regulators of exercise-stimulated glucose utilization is critical for effective type2 diabetes (T2D) treatment. Muscle glycogen phosphorylase (PYGM) is a key exercise-responsive enzyme regulating glycogen breakdown. While prior studies have linked muscle glycogen content to glucose uptake, the specific contribution of PYGM-mediated glycogenolysis remains unclear. This study aims to elucidate the distinct roles of impaired glycogenolysis and glycogen excess in regulating muscle glucose metabolism during exercise.
Methods: We generated PYGM S15A knock-in (S15A) mice by selective targeting of phosphorylation-mediated activation of PYGM, resulting in 6-fold higher muscle glycogen. To normalize glycogen levels while harboring blunted glycogenolysis, S15A mice were crossed with a muscle-specific/tamoxifen (TMX) inducible glycogen synthase knock-out mouse ($GYS1^{fl/fl}$-HSACre), generating S15AxGYS1$^{fl/fl}$-HSACre mice. Treadmill running exercise was employed to assess exercise-induced glycogen utilization. Exercise-mediated *in vivo* U-^{13}C-glucose oxidation was evaluated using an isotope gas analyzer.
Results: S15A muscles exhibited increased glycogen particle number, size, and content. 6-12weeks TMX treatment normalized muscle glycogen levels to near WT levels in the S15AxGYS1$^{fl/fl}$-HSACre mice. Exercise-mediated glycogen degradation was impaired in both mouse models, despite preserved exercise performance, suggesting that phosphodeficiency at PYGM Ser15 rather than aberrant glycogen amount is instrumental in blunting exercise-induced glycogen utilization. Exercise-stimulated *in vivo* ^{13}C glucose oxidation in the S15A mice was comparable to WT mice.
Conclusions: PYGM-mediated glycogenolysis, and not muscle glycogen content, is the limiting factor for exercise-induced glycogen utilization. Our unique mouse models provide a platform to investigate the contribution of impaired glycogenolysis to exercise-mediated glucose metabolic defects in the development of skeletal muscle IR.

8 - Effects of Repeated Dorzagliatin Treatment on β-cell Function and Incretin Effect in Intermediate Hyperglycaemia and Type 2 Diabetes

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Introduction: Dorzagliatin, a dual-acting glucokinase activator, enhanced β-cell function after a single dose in people with diabetes. The effect of repeated dorzagliatin administration on β- cell and incretin function in type 2 diabetes (T2D) and intermediate hypeglycemia (IH) remains unknown.
Methods: In this single-centre, open-label mechanistic study, 13 T2D (mean±SD age 53.5±4.8, HbA1c7.1±0.6%, diabetes duration 3.6±2.4 years) and 7 IH participants underwent 270-minute hyperglycaemic clamp-OGTT before and after 4 weeks of dorzagliatin treatment (T2D: 50mg bd or IH:25mg bd respectively). Dorzagliatin was omitted on the morning of the clamp-OGTT. Insulin secretion rates (ISR) were estimated based on C-peptide deconvolution. The incretin effect was calculated as the difference in postprandial (100-270 minute) and pre-prandial (60-90 minute) C-peptide response.
Results: On-treatment blood glucose was lower during dorzagliatin treatment in both subject groups. Steady-state clamp-OGTT blood glucose was well matched between baseline and end-of-treatment visits. Basal ISR (ISRb) was similar pre and post treatment in IH (363±160 vs 390±136 pmol/min/m²) and T2D (297±123 vs 328±135 pmol/min/m²) groups. In IH, incremental second phase insulin secretion (ISR2inc) was numerically lower pre and post treatment (459±239 vs. 361± 190 pmol/min/m²) but similar in T2D group (272±249 vs 245±196 pmol/min/m²). β-cell glucose sensitivity and clamp-derived incretin effects were greater in IH than in T2D, but did not change pre and post dorzagliatin treatment.
Conclusions: In this interim analysis, chronic dorzagliatin treatment preserved β-cell secretory function under controlled hyperglycaemic conditions but did not consistently augment dynamic insulin secretion or clamp-derived incretin responses. Further data and integrated analyses combining with incretin hormones are needed to confirm these preliminary findings.

9 - Electrical activity and Ca2+ dependent plasticity in human pancreatic β-cells

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Introduction: Electrical activity of pancreatic β-cells results in Ca^{2+}-influx that triggers efficient, pulsatile exocytosis and insulin release during hyperglycemia. Exocytosis is well-synchronized to the moment and location of Ca^{2+} entry, and triggers exocytosis from a pool of release-ready insulin granules situated at the plasma membrane. The size of this pool is also regulated by Ca^{2+}, in addition to the effects of cAMP or diacylglycerol signaling. This potentiation of exocytosis by subthreshold Ca^{2+} is mediated by the Ca^{2+}-dependent priming protein Munc13 and involves distinct priming and rapid facilitation components.
Methods: To understand the physiological relevance of these Ca^{2+}-dependent effects, we imaged electrical activity and single granule release events in β-cells. Later, we used capacitance recording in human β-cells to measure exocytosis facilitation, simulating the native electrical activity of β-cells.
Results: Elevated glucose elicited bursting electrical activity, and exocytosis occurred during these bursts, which were well-synchronized with individual action potentials. Neither priming nor facilitation was stimulated by imposed trains of short membrane depolarizations that simulated action potentials (26ms, 0mV at 0.33-10 Hz), and there were no changes in the release kinetics of individual exocytosis events. In contrast, frequency-dependent facilitation was observed in INS1 cells that overexpressed Munc13-1. We observed that human β-cells tend to facilitate exocytosis during trains of long depolarizations (200ms, 2.5Hz), which was further enhanced by increased intracellular Ca2+ concentrations (250 and 400 nm).
Conclusions: We conclude that electrical activity at moderate stimulation frequencies is insufficient to induce secretory plasticity in human β-cells. We hypothesized that Ca2+-dependent facilitation is involved in paracrine signaling, where intracellular Ca2+ is elevated by release from the endoplasmic reticulum.

10 - Ephemeral diabetes after Covid-19 vaccination

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Introduction: After the onset of the Covid-19 pandemic, several case reports appeared describing new-onset diabetes, both type 1- and type 2-like, in close connection with the SARS-CoV-2 infection. It is, however, virtually impossible to rule out that these persons would have acquired their diabetes anyway and that it just coincided with the SARS-CoV-2 infection, *i.e.,* the virus would not be a causative agent but rather an innocent bystander.
There are also anecdotal reports in the literature of cases in which diabetes developed after vaccination against Covid-19.
Methods: We report a case of new-onset, non-autoimmune, non-ketotic and non-insulinopenic type 2-like diabetes in a previously normoglycemic middle-aged man debuting after vaccination against Covid-19.
Results: This was not a mild or short-lived glucose intolerance, but severe and long-standing hyperglycemia with a high glycated hemoglobin (HbA_{1c}) level. However, the course of the diabetes was highly atypical and surprising in that it spontaneously disappeared after a few months and did not recur despite the patient being off all antidiabetic drugs for several months.
The mechanisms by which severe diabetes unfolded and later remitted in this patient remain elusive. Nonetheless, and notwithstanding whether or not there was a cause-effect relation between the vaccinations and his diabetes, the highly atypical course of spontaneously remitting non-autoimmune diabetes lends itself to mechanistic efforts aimed at understanding the biology and pathophysiology of insulin-producing β-cells in health and disease.
Conclusions: This case report should not be construed as vaccine skepticism or deter anyone from vaccination against Covid-19. However, it calls for increased vigilance for unusual and unexpected metabolic effects of Covid-19 and its vaccines.

11 - Epigenetic Impact of GLP-1 Receptor Agonists on Pancreatic β-Cells

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Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used in type 2 diabetes (T2D). However, the epigenetic impact of GLP-1RAs, particularly on DNA methylation in β-cells, remains poorly defined. DNA methylation is a key regulator of β-cell function and stress adaptation in T2D, yet whether pharmacological treatments modulate these epigenetic states is largely unknown. Drug-induced methylation changes may contribute to treatment durability and inter-individual variability.
Methods: To investigate GLP-1RA-associated methylation in β-cells, we employed an integrative multi-omics approach. EndoC-βH1 cells were treated with GLP-1RA across multiple time points. DNA methylation was profiled using the Infinium MethylationEPIC v2.0 array, with matched transcriptomic analysis by RNA sequencing. Spatial protein–protein interactions related to methylation processes were assessed using in situ proximity ligation assays, enabling characterization of the spatiotemporal dynamics of GLP-1RA-induced epigenetic remodeling.
Results: In EndoC cells, 475 DNA methylation sites exhibit alterations after 24h Liraglutide treatment, with 98 sites located within 1500 base pairs upstream of the transcription start site (TSS). Liraglutide treatment was associated with significant demethylation at the secretagogin (SCGN) locus. SCGN is a calcium-binding protein that functions as a calcium sensor and plays a key role in insulin granule trafficking and secretion. Spatial protein-protein interaction network analysis revealed a previously unknown involvement of DNA methyltransferase 1-associated protein 1 (DMAP-1) in GLP-1R signaling. DMAP1 interacted directly with ARRB1 in cytoplasm and the interaction was further confirmed by molecular dynamics simulation.
Conclusions: GLP-1RA treatment induces significant DNA methylation remodeling in human β-cells. These findings provide new insight into the molecular basis of GLP-1RA action and support the role of epigenetic modulation in therapeutic response.

12 - Epigenetic–proteomic network crosstalk at birth across HLA risk groups in type 1 diabetes

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Introduction: Type 1 diabetes (T1D) arises from genetic predisposition, where early-life biological events may contribute to later disease development. We recently reported cord blood DNA methylation differences between high- and low-risk HLA genotypes in individuals who later developed T1D, suggesting that distinct molecular mechanisms may underlie disease development across genetic risk groups. Here we examine whether these epigenetic alterations are functionally linked to circulating protein pathways at birth.
Methods: We integrated cord blood DNA methylation (Illumina EPIC850K) with neonatal serum proteomics (Olink Explore 384) from ABIS cohort T1D cases (N=32; HR/LR HLA-stratified) versus controls (N=48). Differentially methylated genes and serum proteins were mapped onto high-confidence STRING protein–protein interaction networks to identify epigenetic–proteomic crosstalk across HLA risk groups.
Results: Network analysis revealed distinct epigenetic–proteomic architectures that may preconfigure T1D susceptibility. HR versus LR carriers showed centralized, immune-dominated networks linking cytokine signaling with DNA damage response and antigen-presentation pathways. Compared with controls, HR infants displayed highly immune-centered networks enriched in HLA class II interactions. In contrast, LR versus controls exhibited more distributed modules involving chemokine signaling, inflammasome activation, cellular stress responses, and vesicle trafficking associated with β-cell function and metabolic regulation.
Conclusions: Coordinated epigenetic–proteomic networks are evident at birth, long before islet autoimmunity develops. Distinct architectures across HLA risk groups suggest genetic predisposition shapes early immune signaling, offering a framework for neonatal T1D risk stratification.

13 - Ex vivo and in vivo experimental investigation of miR-148a-3p as a novel therapy for insulin secretion and type 2 diabetes

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Introduction: Several microRNAs are dysregulated in type 2 diabetes and play essential roles in β-cell function. Our previous work showed that miR-152 affects insulin secretion, and miR-148a-3p is the most abundant member of the miR-148/152 family in human islets. We therefore investigated the role of miR-148a-3p in insulin secretion and glucose metabolism using *ex vivo* and *in vivo* diabetes models.
Methods: MiR-148a-3p expression was measured in islets from Goto-Kakizaki (GK) rats (6, 11 and 13.5 weeks). LNA-mediated silencing (LNA-148-3p) was performed in islets from 7-week-old GK rats to assess insulin secretion and content. In vivo studies were conducted in 11-week-old GK rats and 13–16-week-old ON-DP mice treated with LNA-148-3p (20 mg/kg, s.c. on Days 2 and 7), followed by ipGTT on Day 9.
Results: MiR-148a-3p was significantly upregulated in GK islets, with expression increasing with age. LNA-148-3p achieved 56% knockdown *ex vivo* in GK islets, enhancing glucose-stimulated insulin secretion 2-fold without affecting insulin content. *In vivo*, LNA-148-3p reduced islet miR-148a-3p expression by 28% in GK rats, with no effect on glucose tolerance. In ON-DP mice, blood glucose was significantly reduced despite only 10% islet knockdown; this effect was associated with substantial miR-148a-3p suppression in liver (98%), muscle (76%), and adipose tissue (72%).
Conclusions: MiR-148a-3p expression increases with diabetes progression. Effective, islet-specific silencing improves insulin secretion *ex vivo*. Limited *in vivo* islet targeting likely explains the minimal metabolic effects, though improved delivery to the islets could make LNA-148-3p a promising therapeutic strategy.

14 - Excess risk of cardiovascular disease and mortality following lower-extremity amputation in type 2 diabetes.

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Introduction: People with type 2 diabetes are at high risk for peripheral artery disease and neuropathy, often leading to foot complications and lower-extremity amputation. While amputation indicates advanced disease, its long-term effects on cardiovascular outcomes are not fully understood. This study examined the association between lower-extremity amputation and subsequent cardiovascular events and mortality in a nationwide Swedish cohort.
Methods: We conducted a retrospective, population-based cohort study using the Swedish National Diabetes Register linked with the National Patient Register and Cause of Death Register. Individuals with type 2 diabetes who underwent major and minor lower-extremity amputation between 2006 and 2019 were identified and matched to four controls without prior amputation by age, sex and calendar time. Cox Proportional hazards models were used to estimate adjusted hazard ratio (aHRs), accounting for relevant clinical risk factors
Results: The study included 3,485 individuals with amputation and 13,940 matched controls. Lower-extremity amputation was associated with markedly higher risks of all-cause mortality (aHR 2.46, 95% CI 2.31-2.61), cardiovascular mortality (2.43, 2.18-2.71), heart failure (2.13, 1.92-2.36), myocardial infarction (1.79, 1.55-2.08), and stroke (1.52, 1.31-1.76). The risk of all-cause death was more than threefold higher during the first year post-amputation and remained approximately 50% higher after five years.
Conclusions: Lower-extremity amputation in type 2 diabetes carries a substantially increased risk of cardiovascular events and mortality. These findings highlight the critical importance of proactive cardiovascular risk management both before and after amputation.

15 - Exercise timing and circadian regulation of metabolism in type 2 diabetes

Harriet Wallberg

Introduction: The circadian system regulates daily rhythms in metabolism, substrate utilization, and hormone secretion through coordinated molecular clock networks. In type 2 diabetes, disrupted clock gene oscillations—particularly in skeletal muscle—contribute to impaired metabolic flexibility and glucose dysregulation. Insulin resistance, mitochondrial dysfunction, lipid accumulation, and chronic low-grade inflammation further exacerbate this circadian misalignment.

Exercise is a potent zeitgeber capable of modulating peripheral clocks and restoring metabolic rhythmicity. While its benefits are well established, the role of exercise timing has only recently gained attention. Emerging evidence shows that, in individuals with type 2 diabetes, afternoon and evening exercise elicit greater improvements in glycemic control, insulin sensitivity, and postprandial glucose responses than morning exercise. These effects likely reflect diurnal variation in muscle metabolism, hormonal environment, and clock-related signaling pathways, with additional modulation by exercise intensity and feeding–fasting state.

Aligning exercise timing with endogenous circadian rhythms may therefore offer a practical strategy to improve metabolic health. However, variability in chronotype and lifestyle suggests that personalized timing approaches may be necessary. This presentation will highlight key mechanisms and discuss the translational potential of circadian-informed exercise interventions for type 2 diabetes.

Methods:

Results:

Conclusions:

16 - Exploring predictors for long-term clinical benefit after gastric bypass and sleeve gastrectomy in type 2 diabetes: A Machine Learning Approach

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Introduction: Identifying clinical predictors for outcomes after bariatric surgery remain a challenge. The aim of the study was to examine which pre-operative clinical features were associated with favourable long-term outcomes after bariatric surgery in individuals with obesity and type 2 diabetes (T2DM), applying machine learning methods to national registry data.
Methods: Individuals with obesity and T2DM that underwent Roux-en-Y gastric bypass or sleeve gastrectomy were identified by cross-matching the Swedish National Diabetes Registry and the Scandinavian Obesity Surgery Registry (n=8399). The primary outcome was a favourable composite weight loss outcome (≥20%) at five years post-surgery and no recorded adverse events during the same period. An extreme gradient boosting model was developed using standard procedures for internal validation and performance assessment. SHAP values and plots were used to assess and visualise feature importance. Separate models were also created for optimal weight loss at five years, malabsorption and micronutrient deficiency, depression and anxiety, and alcohol and other drug use disorder.
Results: For the primary composite model, 5253 individuals with weight-loss data approximately five years after surgery were included in the analyses. The primary composite model showed modest discriminative ability, with a ROC AUC of 0.65 [95% CI 0.61–0.68]. The domain-specific models, except for optimal weight loss, performed better. Across models, the most consistent predictors comprised four domains: psychiatric comorbidities, metabolic and renal markers, somatic symptom burden, and sociodemographic factors.
Conclusions: Predicting multidimensional outcomes is difficult; however, individuals with obesity and T2DM and a more complex psychosomatic and metabolic profile before surgery may need more structured, long-term follow-up and comprehensive multidisciplinary support.

17 - Extracellular Vesicle associated Glycosylated Sphingolipid Alterations in Type 2 Diabetes Impair Adipocyte Glucose Metabolism

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Introduction: Dysregulated metabolism in type 2 diabetes is underlined by disrupted interorgan signalling. Extracellular vesicles (EV) facilitate intercellular communication through their protein and lipid cargo. However, the lipid composition of EV and its functional implications in type 2 diabetes are incompletely understood. This study aims to characterize the lipid species alterations in EV from individuals with vs. without type 2 diabetes and investigate how these lipid changes influence metabolism in target tissues.
Methods: Serum was collected from diet-controlled age and BMI-matched men and women with or without type 2 diabetes (n=46 total, n=11-12 per group). EVs were isolated from serum using size-exclusion chromatography and the EV sphingolipidome was profiled using liquid-chromatography with tandem mass spectrometry. The function of lipid targets was validated *in-vitro* by measuring glucose metabolism in human and mouse adipocytes.
Results: There were distinct clusters indicating the EV sphingolipidome was altered in both men and women with vs. without type 2 diabetes. There was a reduction in glycosylated sphingolipids, hexosylceramides and lactosylceramides, and an increase of deoxydihydroceramides in EV from individuals with vs. without type 2 diabetes. To assess function, HexCer(d18:1/16:0) treatment lowered basal glucose uptake (23±17%, p=0.04) in both mouse and human adipocytes. These findings were recapitulated when cells were treated with liposomal formulations mimicking the incorporation in EV (21±13%, p=0.04).
Conclusions: These findings demonstrate that glycosylated sphingolipids were lower in serum EVs from individuals with vs. without type 2 diabetes and modulated glucose metabolism in adipocytes. This study reveals a novel role for EV-associated lipids in glucose metabolism and suggest that such lipid species constitute functional components of intertissue communication.

18 - Family planning and pregnancy in women with type 2 diabetes – a qualitative prequel to a digitally supported lifestyle intervention (ReproDiaT2D).

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Introduction: Women with type-2 diabetes (T2D) have increased risk of pregnancy complications, low rates of pregestational counselling (PGC) and delayed antenatal care. Insights into perceptions and experiences of family planning and pregnancy are limited, especially among women with immigrant backgrounds.

Objective: To explore experiences related to family planning and pregnancy in women with T2D.
Methods: Semi-structured interviews were conducted at a diabetes outpatient clinic. Data was analyzed using thematic analysis.
Results: 26 women with T2D (28–46 years), with varying ethnicity, parity, BMI and proficiency in Norwegian, were contacted and invited to participate in the study, of whom 14 accepted.

I Generally: Participants felt a sense of stigma, and emphasized a healthy lifestyle, distancing from the notion of "deserving" T2D. Partners were relaxed regarding T2D.

II PGC and fertility: Few reported being informed to plan pregnancies; prescribing contraceptives was not linked to such consultations. No information regarding T2D and pregnancy complications was recalled. Pregestational HbA1c was rarely measured.

III Pregnancy: They were satisfied with antenatal follow-up, and secure planning for pregnancies. The focus on blood glucose diverted attention from other care and made follow-up feel less personalized. They wished for partners to be more included. Having T2D did not influence planning more children.

IV Postpartum: they reported little follow-up for T2D and challenges with weight reduction.
Conclusions: The women experienced challenges regarding family planning and pregnancy, indicating a need for improved information and follow-up. There was considerable individual variation in experiences, underscoring the importance of empathetic communication and tailored information throughout the reproductive stages.

19 - Gene Expression Signatures Associated with Disease Progression in Individuals with Newly Diagnosed Type 1 Diabetes: Insights from the INNODIA Study

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Introduction: Accumulating evidence indicates substantial heterogeneity in post-onset insulin secretion decline in newly diagnosed type 1 diabetes (T1D). We previously showed in the First 100 INNODIA cohort that gene expression changes between diagnosis and 12 months were associated with decline in C-peptide at 24 months. We aimed to validate these findings in an independent INNODIA follow-up cohort and to characterise transcriptomic changes during the first year after diagnosis in the combined INNODIA dataset.
Methods: We analysed whole-blood transcriptomes collected at diagnosis and at 1-year follow-up from 168 individuals with newly diagnosed T1D in the INNODIA follow-up cohort, and integrated these data with the previously analysed First 100 cohort. Longitudinal differential expression analyses and associations with disease progression, assessed by the slope of the fasting C-peptide/glucose ratio over time, were performed using adjusted linear mixed-effects and survival models.
Results: The observed gene expression changes showed consistent directional patterns across both cohorts, with six genes also reaching statistical significance in the follow-up cohort ($p<0.05$). In the combined analysis of 456 samples, longitudinal transcriptomic changes between baseline and 1 year were observed. More rapid disease progression was associated with younger age and lower relative neutrophil abundance at 1 year. In addition, changes in the expression of several genes were associated with the rate of disease progression.

Conclusions: These findings validate progression-associated transcriptomic changes in an independent INNODIA cohort and support heterogeneity in early post-diagnosis T1D. Whole-blood gene expression changes during the first year after diagnosis may help identify molecular signatures associated with progression and support patient stratification.
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20 - GRK2-Biased β_2-Adrenergic Agonism: Development of ATR-258, a First-in-Class Oral Therapy Targeting Skeletal Muscle Glucose Uptake in Type 2 Diabetes

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Introduction: Skeletal muscle insulin resistance is central to type 2 diabetes (T2D), yet no approved therapy directly targets muscle glucose uptake. Over the past decade, we mapped a non-canonical β_2-adrenergic receptor (β_2AR) pathway in which GRK2, by acting as a scaffold independent of its kinase activity, activates an mTORC2-centered signaling network, driving GLUT4 translocation independently of insulin, PI3K/Akt, and cAMP.
Methods: By profiling upwards of 15 transducer pathways, we identified ATR-258, a GRK2-biased β_2AR partial agonist with 10-fold selectivity for GRK2 recruitment over Gαs activation. Crucially, ATR-258 promotes a β_2AR/GRK2 complex that does not phosphorylate the receptor C-terminus, preventing β-arrestin recruitment and receptor internalization thereby avoiding the tachyphylaxis that has limited chronic use of conventional β-agonists. Phosphoproteomics in murine muscle bundles confirmed on-target activation of mTORC2, TBC1D1 phosphorylation, and AMPK signaling bypassing insulin-resistant nodes entirely.

In diet-induced obese mice, oral ATR-258 improved body composition and glycemic control without cardiac hypertrophy or myocardial pathology. Combined with empagliflozin, ATR-258 produced greater improvements in glucose tolerance than either agent alone. Combined with liraglutide, it enhanced fat loss while preserving lean mass thereby resulting in improved body composition.
Results: In ATTRACTIVE-1 (NCT05409924), once-daily oral ATR-258 was safe and well tolerated in healthy volunteers and T2D patients. Early efficacy signals were observed: healthy volunteers showed reductions in fasting plasma glucose, and T2D patients undergoing metformin withdrawal demonstrated lower insulin levels during oral glucose tolerance, consistent with improved insulin sensitivity.
Conclusions: These data establish GRK2-biased β_2AR agonism as muscle-targeted approach that couples metabolic and anabolic benefits while circumventing both the cardiovascular liabilities and the desensitization associated with classical β-agonists.

21 - Health and lifestyle habits in dog owners in Sweden

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Introduction: Dog ownership is associated with higher levels of physical activity (PA) and cardiovascular health benefits. However, dog owners newly diagnosed with type 2 diabetes have also been shown to be less likely to achieve treatment goals, highlighting the complexity of dog ownership as a possible health factor. The aim of this study was to explore dog ownership in relation to health by mapping lifestyle habits and health among dog owners in Sweden.
Methods: A questionnaire was distributed to a simple random sample of 2,000 dog owners from the mandatory dog register. To enable crude comparisons with the Swedish population, questions from the national public health survey were used. The response rate was 32%. Results were adjusted for age and gender.
Results: Preliminary results indicate higher PA levels among dog owners; 85% met recommendations of 150 minutes of PA per week, versus 66% in the general population. Additionally, only 15% reported more than 10 sedentary hours/day, compared to population levels of 25%. However, a slightly higher BMI was reported; 57% had a BMI over 25, versus 51% in the general population. Self-reported diabetes prevalence was 5.3%, compared to 6.8% in the population. Dog owners reported less problems with anxiety, stress and loneliness, and spent more time in green spaces.
Conclusions: The findings support previous evidence of high PA levels and suggest mental health advantages among dog owners. These effects may contribute to a reduced risk for development of type 2 diabetes. Results should be interpreted with caution, as they have not been adjusted for confounders such as socioeconomic status.

22 - Impact of cold ischemia on pancreatic islet function and beta-cell gene expression: studies with brain-dead donor biopsies and human isolated islets

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Introduction: Human islets are extensively used to investigate endocrine cell physiology, study diabetes, and, most importantly, to transplant to diabetic patients. After retrieving the pancreas from the donor, the organ is maintained at 4 °C until islet isolation is initiated. This interval of time is the period of cold ischemia. Here, we have investigated the impact of cold ischemia on beta-cell RNA profile and islet function.
Methods: GeoMx DSP was used to investigate the RNA profile of beta-cells in biopsies of brain-dead donors. In GeoMx DSP, the spatial profile of the whole transcriptome is done in populations of cells identified by antibody staining. Isolated islets were cultured for a period of two weeks, and the impact of cold ischemia was investigated using batch insulin secretion assays and quantitative RT-PCR.
Results: RNA profiling of beta-cells from brain-dead donor biopsies showed that in short-cold ischemia (<10 h), there is an enrichment of beta-cell identity genes, while pathways related to inflammation, apoptosis, and hypoxia are enriched in long-cold ischemia (>10 h). In isolated islets, we observed that even after culturing the islets for a period of two weeks, exposure of the biopsy to long-cold ischemia impacts insulin secretion. Finally, quantitative RT-PCR of isolated islets in culture showed that the expression of several genes relevant to beta-cell function and maturity is affected by the interval of cold ischemia.
Conclusions: Our studies show that exposure to long-cold ischemia changes the beta-cell RNA landscape and impacts the phenotype of islets in culture.

23 - Increasing the enteroendocrine cells by stimulating secretory progenitors with a Vcp-mediated autophagy activator

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Introduction: Pharmaceutical products based on incretin hormones gained increasing popularity in the recent years, putting the enteroendocrine cell system into the spotlight for the treatment of diabetes and obesity. Here, we identified SMER28 as a small molecule increasing the enteroendocrine cell density and clarified its cellular mechanism.
Methods: We employed an established transgenic zebrafish line monitoring the expression of Glucose-dependent Insulinotropic Peptide (*gip*) to screen >3.000 small molecules from two chemical libraries. To investigate the developmental origin of enteroendocrine cells, we employed CRISPR-Cas9 to knock-in a p2a-EGFP-t2a-creERT2 cassette into the *dld* locus. We explored the molecular mechanism of SMER28 by overexpressing its target protein Vcp and co-treating reporter zebrafish with SMER28 and autophagy inhibitors.
Results: We found the mTOR-independent autophagy activator SMER28 to be capable of increasing the number of incretin-expressing cells in larval and juvenile zebrafish, with a potent glucose-lowering effect. We established the combined reporter/lineage tracing line zebrafish TgKI(p2a-EGFP-t2a-creERT2) and confirmed that *dld* the functional zebrafish orthologue of the mammalian gene DLL1, labelling secretory progenitors in the intestine. SMER28 increased the number of *dld*+ secretory progenitors and their lineage-traced descendants, including *neurog3*+ endocrine progenitors and several mature enteroendocrine cell types. The effect we observed on enteroendocrine cells depends on SMER28's target protein Valosin Containing Protein (VCP) and its role in mediating autophagy: overexpressing Vcp furtherly increased the effect on *gip*, while inhibiting autophagy downstream of Vcp abolished it.
Conclusions: Our findings add significant knowledge to the field of exploiting enteroendocrine cells to ameliorate glucose control, with potential implications for new diabetes treatments.

24 - Incretin-based therapy of obesity and diabetes, recent advances

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Introduction: GLP-1 is an incretin hormone enhancing postprandial insulin secretion, but GLP-1 also inhibits glucagon secretion, resulting in a dual glucometabolic activity with powerful antidiabetic effects. In the SURPASS trials with tirzepatide, 15 mg for 40 weeks lowered A1c below 5.7 % in more than half of the patients, and over 176 weeks reduced the risk of developing T2DM by 94 % in patients with prediabetes and obesity (Surmount1 extension). A cardiometabolic benefit of GLP-1 Receptor Agonism (GLP-1RA) has been demonstrated in T2DM since 2015 and reproduced in meta-analyses and in the 2023-4 SELECT and FLOW trials. This effect may be related to effects on the endothelium of the blood vessels (possibly receptor-mediated) and the anti-inflammatory actions (e.g. strong reductions in hsCRP). But probably the most important mechanism is the weight loss which now approaches surgical levels.The GLP-1RAs inhibit appetite and reward, effectively maintaining body weight reductions for at least 4-5 years, and this may be their most important action, since similar cardiometabolic benefits are seen after bariatric surgery (life expectancy prolonged by 9 years in patients with T2DM). Heart failure, with reduced or preserved ejection fraction is prevented/ameliorated, and there is also beneficial effects on MASH and Sleep Apnea. As expected, the risk of obesity-related cancers is reduced. Because of the inhibition of reward mechanisms GLP-1 therapy is also associated with lower incidence of alcohol and opioid use disorders. Therapy should be focused on those with increased morbidity and mortality because of the metabolic syndrome. Efficient paradigms for long-term therapy are needed.
Methods: nothing to add
Results: nothing to add
Conclusions: nothing to add

25 - INHIBITION OF VOLTAGE-DEPENDENT ANION CHANNEL 1 OLIGOMERIZATION AS A TREATMENT OPTION FOR TYPE 1 DIABETES

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Introduction: Type 1 diabetes (T1D) is a chronic inflammatory disease characterized by autoimmune destruction of pancreatic β-cells, leading to insulin deficiency and hyperglycemia. Recent reports suggest that upto 50% β-cells escape the immune attack if the disease debuts after the age of 6 years. However, these β-cells have impaired glucose-stimulated insulin secretion (GSIS), but once extracted from the pancreatic pro-inflammatory environment, they show physiological biphasic GSIS invitro.

VDAC1 is ubiquitously expressed channel protein on the outer mitochondrial membrane, transporting calcium ions in the closed state and ADP/ATP and lipids in the open state. In β-cells, VDAC1 is also expressed on the cell membrane. In pathophysiological conditions, VDAC1 oligomerizes, leading to mitochondrial dysfunction and promoting inflammasome assembly at the mitochondrial membrane. This process occurs across multiple cell types, including immune cells and pancreatic islet cells.
Methods: The methods used are immunofluorescence staining followed by confocal microscopy, ELISA, western blot, and invivo mouse studies.
Results: In the present study, we show that VDAC1 is upregulated in β-cells of T1D organ donors and in diabetic NOD mice. In rat insulinoma cells, pro-inflammatory cytokines induce VDAC1 oligomerization and translocation to the plasma membrane. Further, proinflammatory human macrophages show VDAC1 oligomerization, and treatment of these macrophages with the small-molecule VDAC1 oligomerization inhibitor, VBIT4 reduced the secretion of proinflammatory cytokines. Finally, RIP B7.1 mice, an experimental model of T1D, treated with VBIT4, were completely refractory to the development of hyperglycemia.
Conclusions: Therefore, inhibition of VDAC1 oligomerization in T1D offers an attractive two-pronged approach for the prevention and treatment of T1D.

26 - Integrated analysis of clinical course and proteomics data in DIAGNODE-2 patients

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Introduction: Previously the DIAGNODE-2 Phase II trial showed preservation of beta cell function by intralymphatic GAD-alum in GAD-positive individuals presenting with Type 1 diabetes in the HLA DR3-DQ2 haplotype subgroup. Here we aim to see whether protein biomarkers can improve prediction of positive response to the treatment.
Methods: Data from 109 patients before treatment (at baseline) were compared with data after treatment (6 months later). Linear mixed-effects models were used to assess associations between stimulated C-peptide AUC measured at Mixed Meal Tolerance Test before and 6 months after treatment and normalized protein expression (NPX) measured by Olink, to identify candidate inflammatory protein biomarkers, adjusting for sex and age at onset of type 1 diabetes.
Results: Among 291 inflammatory proteins analyzed, two proteins, CSF1(adj.p.val = 0.003) and ITGB6 (adj.p.value = 0.012) were significantly associated with MMTT C-peptide AUC after Benjamini–Hochberg correction (False Discovery Rate <0.05). These associations were not significant in the HLA DR3-DQ2 haplotype subgroup. Additionally, three proteins (TOP2B, NBN, and HCLS1) showed significant visit–treatment interaction effects, suggesting differential longitudinal responses between treatment groups.
Conclusions: Our preliminary findings identify candidate inflammatory protein biomarkers associated with beta-cell function and longitudinal changes in individuals with type 1 diabetes. Further analyzes should be done.

27 - Mitochondria – insulin granule crosstalk controls the early stages of granule maturation

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Introduction: Insulin is produced by pancreatic β-cells and packaged into granules. Only a small number of these granules obtain release competence and contribute to glucose regulation, while the vast majority are instead stored or degraded. Changes in granule release probability contribute to β-cell dysfunction in diabetes, but the molecular determinants that specify the maturation trajectory of newly formed granules remain poorly defined.
Methods: We employed a live-cell microscopy-based approach using mouse islets and clonal mouse β-cells expressing custom-made biosensors for the detection of granule age, organelle interactions, granule turnover, and organelle physiology.
Results: We identified a rapid physical association between newly formed insulin granules and mitochondria that required both the voltage-dependent anion channel (VDAC) and the vesicular ATP transporter (VNUT). VNUT depletion disrupted VDAC recruitment to newly formed granules and redirected these vesicles toward autophagy-dependent lysosomal degradation. VNUT knockdown produced a threefold expansion in lysosomal area and a fourfold increase in lysosomal granule content ($P < 0.0001$, $n > 200$), phenocopying pharmacological VNUT inhibition with clodronate. Loss of VNUT resulted in ~50% reduction in insulin content and a marked impairment in glucose-stimulated insulin secretion ($P < 0.0001$, $n > 200$). Autophagy inhibition with SAR405 restored insulin content in VNUT-deficient cells, demonstrating that lysosomal degradation is the principal fate of granules that fail to engage mitochondrial contact sites.
Conclusions: These data establish mitochondria–granule interactions as an essential checkpoint in the earliest stages of granule maturation, ensuring selective progression of nascent insulin granules into the regulated secretory pathway rather than autophagic elimination.

28 - Novel METTL3/14 methyltransferase activators for protecting pancreatic beta- cells in diabetes mellitus

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Introduction: RNA methylation of N6-adenosine (m^6A) is a common reversible RNA modification, involved in various biological processes, e.g. RNA stability, splicing, translation. Research show that dysregulated m^6A mRNA levels in islets is associated with diabetes, suggesting increasing m^6A mRNA levels as a valuable target for beta-cell protection.
Methods: We aim to elucidate mRNA m^6A and their regulating protein levels in diabetes pathology and to study the effect of METTL3/14 activator compounds to protect beta-cells.
Results: Our data demonstrated that expression of m^6A writers *Mettl3* and *Mettl14* is downregulated with disease progression in islets of NOD mice in accordance with previously published data. However, when mRNA was isolated directly from mice without recovery, NOD islets showed higher expression of these genes. Therefore, we are studying if 1) inflammation can induce expression of *Mettl3* and *Mettl14*, and 2) if there is difference in inducing m^6A writers' expression in response to inflammation in NOD mice.
We also measured the expression of m^6A regulators in islets of 5-week-old db/db mice and observed a trend for decreased expression of *Mettl3* and *Mettl14* in db/db mice compared to db/+ mice. Importantly, a correlation between elevated m^6A levels and increasing blood glucose levels was detected in the liver of db/db mice. Currently, we are treating db/db and control animals with METTL3/14 activator compound CHMA1004 to test whether it can stop or slow down diabetes progression in these animals.
Conclusions: Current project is at the beginning of unveiling m^6A role in diabetes and exploring its potential as therapeutic target.

29 - Pancreatic islets in mice and humans: unravelling mechanisms driving beta cell proliferation under metabolic stress

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Introduction: Regenerating human beta cells by promoting their proliferation is a crucial area of research that holds great therapeutic potential for both T1D and T2D. Whilst mouse islets display a higher proliferation rate, human pancreatic beta cells exhibit low levels of proliferation. One factor contributing to the low proliferation rate in beta cells is that, with age, they can become senescent. In this state, cells cease to divide but remain metabolically active, with an altered secretory phenotype. Senescence has recently been reported to contribute to T2D. Senolytics such as Fisetin and Quercetin selectively kill senescent cells and are currently being tested in clinical trials.
Methods: We are using mouse and human islets to investigate beta cell proliferation under metabolic stress and to study the effect of senolytic treatment on cell division using Quantitative RT-PCR and immunohistochemistry.
Results: Quantitative RT-PCR data demonstrated that in islets from 6-month-old mice, the expression of senescence markers such as Cdkn1A/p21 is increased compared to that in 3-month-old mice. However, immunohistochemistry with EdU showed that under metabolic stress, beta cells of 6-month-old mice retain their proliferative capacity. Furthermore, 24 hours of exposure to high glucose upregulates both Chrebp isoforms, necessary for glucose-stimulated proliferation, as well as the senescence marker Cdkn1A/p21.
Conclusions: Treating mouse and human islets with senolytics indicates that proliferation was not inhibited by senescence. We plan, therefore, to further investigate gene expression after 24 hours of high-glucose exposure using RNA sequencing of both mouse and human islets to determinewhich factors inhibit beta-cell proliferation in humans.

30 - Recapitulating islet vascular remodelling in mouse models of long-standing type 1 diabetes

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Introduction: Pancreatic islets feature a dense, fenestrated capillary network that supports glucose detection and hormone release, sustained through interactions among endothelial cells, pericytes, and endocrine cells. However, in long-standing T1D, this environment is disrupted, with the islet vasculature exhibiting endothelial dysfunction and perivascular fibrosis, yet the exact mechanism remains elusive. These vascular changes have been linked to beta-cell loss, hyperglycemia, immune injury, or a combination thereof. Additionally, most animal studies focus on early-stage disease, whereas human samples originate from cadaveric donors. We aim to better understand islet vascular dysfunction in long-standing T1D.
Methods: We employed both a high-dose streptozotocin-induced model in immunodeficient and immunocompetent mice and a spontaneous autoimmune diabetes model (NOD). The multiple model approach was used to isolate the effect of hyperglycemia from the aforementioned factors. Animals were maintained in a hyperglycemic state for 5–8 weeks after onset to model long-standing disease, receiving intermittent exogenous insulin. Islet vasculature was assessed using immunocytochemistry and electron microscopy.
Results: Animals displayed strain and model-specific differences but consistently exhibited increased islet capillary areas positive for Laminin α and Collagen IV compared with healthy controls, indicating extracellular matrix accumulation. Electron microscopy revealed that islet capillaries often lacked RBCs, had collapsed lumens, and thickened basement membranes, consistent with increased extracellular matrix observed by immunocytochemistry. These structural changes point to impaired vascular function, similar to that observed in human T1D islets.
Conclusions: Developing representative murine models of long-standing T1D islet vasculopathy is essential for understanding disease mechanisms and could inform therapies aimed at preventing endocrine failure beyond beta-cell autoimmunity.

31 - Regulation of insulin secretion by Ras signalling in pancreatic β-cells

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Introduction: Insulin secretion from pancreatic β-cells is controlled by the intracellular messengers Ca^{2+} and cAMP. The cAMP effector protein Epac2 binds to granule docking sites at the plasma membrane via its Ras association domain, indicating a potential role for Ras GTPases in exocytosis. This study aimed to determine whether the plasma membrane-localized isoform K-Ras4b is involved in insulin secretion.
Methods: The dominant-negative K-Ras4b S17N mutant (Ras-DN) was expressed in dispersed MIN6 and primary mouse β-cells. Human islets were dissociated, infected with Ras-DN or control adenoviruses and reaggregated in hanging-drop culture during 7 days. Cytoplasmic Ca^{2+} was recorded with fluorescent indicators. Exocytosis was quantified using total internal reflection fluorescence (TIRF) imaging of VAMP2-pHluorin labelled granules and patch-clamp recordings of membrane capacitance. Insulin release from perifused islets was assessed with ELISA.
Results: Depolarization-evoked exocytosis (30 mM K^+) was reduced by 36% ($P<0.001$) in Ras-DN-expressing MIN6-cells, without differences in granule density or cytoplasmic Ca^{2+} responses compared to control. A corresponding impairment in exocytosis (43%; $P<0.001$) was observed in Ras-DN-expressing mouse β-cells based on capacitance responses to voltage-clamp depolarizations. Perifusion experiments with reaggregated human islets from two donors indicate reduction of insulin secretion at both low (3 mM) and high (11 mM) glucose in Ras-DN islets (49% and 58% of control, respectively).
Conclusions: Our findings identify a previously unrecognized role of K-Ras4b in the regulation of insulin secretion. By revealing this new function of Ras signalling, the study highlights a potential mechanistic link between altered Ras activity and impaired insulin secretion in diabetes.

32 - Role of VEGF-B signaling in diabetic complications focusing on fatty liver disease and diabetic stroke

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Introduction: Vascular endothelial growth factor B (VEGF-B) plays a fundamental role in systemic lipid homeostasis by regulating both the release of stored lipids—primarily as non-esterified fatty acids—from adipose tissue through lipolysis, and lipid uptake in peripheral tissues such as the heart and skeletal muscle.
Methods: In this lecture, I will discuss the role of VEGF-B in two well-known diabetic complications: fatty liver disease and diabetic stroke. We demonstrate that VEGF-B expression in adipose tissue controls lipolysis and thereby regulates lipid uptake by the liver. Targeting VEGF-B signalling by genetic or pharmacological approaches across several dietary models reduces hepatic lipid accumulation and protects the liver from inflammation, fibrosis, and the development of hepatocellular carcinoma.
Results: Diabetes is associated with an increased risk of ischaemic stroke. Using experimental mouse models of stroke, we show that inhibition of VEGF-B reduces both infarct size and the risk of intracerebral haemorrhage. This effect is attributable to reduced ectopic lipid accumulation in the cerebrovasculature. Notably, targeting VEGF-B signalling in animals subjected to ischaemic stroke followed by delayed thrombolysis with tissue plasminogen activator (tPA) protected against excessive haemorrhage and significantly improved survival. The protective effect of VEGF-B inhibition in late tPA-mediated thrombolysis was due to suppression of tPA-induced lipolysis, thereby preventing increased ectopic lipid accumulation in the cerebrovasculature. The ability of tPA to stimulate lipolysis is a novel finding and may help explain the narrow therapeutic time window of approximately 4.5 hours following the onset of stroke symptoms.
Conclusions: In summary, this work highlights VEGF-B-mediated lipid homeostasis as a key mechanism underlying several diabetic complications.

33 - Stem cell derived islet organoids attract T cells, resulting in MHC matched organoid destruction by type 1 diabetic patient T cells.

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Introduction: Stem cell-derived islets (SC-islets) are capable of replacing lost β-cells resulting from autoimmune attack during type 1 diabetes (T1D). SC-islets can be transplanted into individuals and restore normal glucose control. However, they are vulnerable to immune mediated destruction from both alloreactivity and autoimmune recognition by T cells. Broad immunosuppression treatments can block the immune response, but have severe side effects that prevent widespread use of SC-islet transplantation.

T cells are critical for immune mediated destruction of SC-islets through recognition of both mismatched MHC molecules and β-cell autoantigens presented on MHC matched cells. T cells must be present in SC-islets in order to exert effector functions and induce β-cell death.
Methods: Using an *in vitro* live cell imaging system, we evaluated if T cells enter SC-islets.
Results: Our results demonstrate that T cells are attracted toward SC-islets *in vitro*, including T cells from T1D patients. This results in rapid entry into the SC-islets within 24 hours and significant cell death after 48 hours in MHC matched SC-islets. The rapid location and entry into SC-islets is not contact dependent, suggesting that the SC-islets secrete chemokines that attract T cells.
Conclusions: Chemokines are produced by SC-islets from multiple stem cell lines, making these the likely source of the T cell attraction and entry. Future work will determine which chemokines are responsible for T cell entry into the SC-islets, if other immune cell types are also attracted to chemokines from SC-islets, and if specific subsets of T cells are attracted to and selectively recruited to SC-islets.

34 - Targeted serum proteomics of longitudinal samples from newly diagnosed youth with type 1 diabetes affirms markers of disease

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Introduction: With growing concerns for the increasing worldwide incidence of type 1 diabetes, there is a need for markers that can be used to monitor the progression, treatment and remission of the disease. In the present study, targeted mass spectrometry was used to evaluate the utility of a panel of 85 proteins previously associated with T1D progression.
Methods: Selected reaction monitoring (SRM) mass spectrometry was used to measure the levels of 85 T1D-associated proteins from longitudinal serum samples of under 18-year-old youth newly diagnosed (ND) with T1D (n=86). To understand associations with beta cell function, the measurements were compared with changes in fasting C-peptide/glucose levels. Additional comparisons were made between the data from ND individuals and cross-sectional measurements obtained from autoantibody-negative unaffected family members (UFMs, n=194). The samples series were from the first 100 ND individuals recruited in INNODIA, with the subsequent validations made with samples from the next 150 ND individuals (n=146) and UFMs (n=272).
Results: Eleven proteins showed significant associations with fasting C-peptide/glucose changes, and 13 proteins differed between ND and UFMs. Among these were apolipoproteins, insulin-like growth factor-family members, coagulants and proteins involved in oxidative stress and beta cell function and integrity. These 21 significant proteins were further validated in ND youth and UFMs subsequently enrolled in the study. Here, most differences between ND and UFMs were replicated and association with C-peptide/glucose was confirmed for three out of the eleven targets.
Conclusions: Our study highlights a panel of protein markers reflecting changes accompanying T1D progression and their potential to monitor beta cell function.

35 - The Immunomodulatory Role of Catestatin in Pancreatic Islets: Neuroimmune Interactions and Implications for Autoimmune Diabetes

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Introduction: Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by immune-mediated destruction of pancreatic β-cells. Intra-islet immune responses, particularly macrophages, contribute to disease progression. Catestatin (CST), a chromogranin A–derived neuropeptide, regulates the sympathetic nervous system via α7nAChR. This study investigated CST's role in islet homeostasis and macrophage function in T1D.
Methods: ELISA was used to measure CST levels in patients with T1D, and CST presence in the non-obese diabetic (NOD) mouse model was assessed by immunofluorescence. Pancreatic islet morphology was analyzed in CST-KO, CgA-KO, and WT mice using histological approaches. CST–receptor interactions were investigated in silico docking, Surface plasmon resonance (SPR), and hydrogen–deuterium exchange mass spectrometry (HDX-MS). Immunofluorescence analyses were performed to assess islet nerve organization, and spatial mass spectrometry was used to analyze neurotransmitters and related metabolites.
Results: CST was detected in pancreatic islets of the NOD mouse model during disease progression, and patients with T1D showed increased plasma CST levels. CgA-KO mice exhibited reduced islet density and circularity, while both CST-KO and CgA-KO mice showed an increased α- to β-cell ratio. Interaction between CST and α7nAChR was confirmed by SPR, with Arginine15 identified as critical for binding. HDX-MS further mapped a specific CST binding region on α7nAChR. Additionally, reduced intra-islet nerve density, decreased macrophage–nerve interactions, and altered neurotransmitter metabolism indicate impaired neuroimmune communication in the absence of CST.
Conclusions: Together, these findings identify CST as a potential key immunomodulatory neuropeptide. By modulating macrophage activity through α7nAChR, CST may play an important role in regulating islet homeostasis, highlighting its potential as a therapeutic target in T1D and other autoimmune diseases.

36 - THE INFLUENCE OF PARENTAL ROLE MODELING AND GENDER ON PHYSICAL ACTIVITY PATTERNS IN CHILDREN WITH TYPE 1 DIABETES

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Introduction: Many children with type 1 diabetes (T1D) do not meet the recommended 60 min/day of moderate-to-vigorous physical activity (MVPA). This study aimed to evaluate the total physical activity (PA) among children with T1D and their parents, and to explore whether parent's PA predicts their child's PA.
Methods: Children aged 6–17 years with T1D from the Oulu University Hospital Pediatric Diabetes Outpatient Clinic, and their parents, participated in the study. PA was assessed using a questionnaire and 7-day accelerometry. The amount of child's accelerometer-based PA was explained by the amount of parent's PA using regression analysis. Children and parents, respectively, were categorized into three groups (low active, active, highly active) based on MVPA recommendations. Within family, consistency in these three groups was evaluated using the McNemar–Bowker test.
Results: A total of 57 children (mean age 10.9, SD 3.1 years), and one of their parents, participated. The average accelerometer-measured MVPA was 82 (SD 32) min/day, with 79 % of the participants meeting the recommendation. Girls (N= 28) accumulated on average 18 minutes less of accelerometer-measured MVPA (95 % CI: -35; -1.7) and 33 minutes less of self-reported MVPA per day (95 % CI: -52; -14) compared with boys. No significant relationship was found between parents' and children's PA, including the MVPA recommendation-based evaluation.
Conclusions: While the average MVPA level exceeded recommendations, a notable gender gap was observed. Parental PA did not predict their child's PA. These findings highlight the need for strategies to encourage PA, particularly among girls with T1D.

37 - The insulin-resistant brain

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Introduction: Insulin acts not only on peripheral organs but is also transported into the brain, where it regulates key aspects of behavior, cognition, and whole-body metabolism, including the coordination of postprandial energy metabolism. Intranasal insulin delivery enables preferential targeting of the brain with minimal systemic spillover and has provided direct evidence that brain insulin action modulates whole-body glucose metabolism, influences eating behavior, and affects cognitive function. These central effects complement direct peripheral insulin action and contribute to the integrated regulation of postprandial metabolism.

However, these effects are markedly attenuated in individuals with overweight or obesity, indicating the presence of brain insulin resistance. This phenotype is characterized by impaired insulin-induced responses in hypothalamic and reward-related circuits and a reduced ability of brain insulin action to acutely modulate peripheral metabolism, including pancreatic insulin secretion and hepatic glucose production. In parallel, brain insulin resistance is accompanied by unfavorable body fat distribution. In line, longitudinal data indicate that brain insulin sensitivity predicts future changes in body weight and body fat distribution and modulates the response to lifestyle interventions.

Importantly, brain insulin sensitivity is not static. Reduced responsiveness during the luteal phase of the menstrual cycle demonstrates that brain insulin action is dynamically regulated and physiologically modifiable, with potential relevance for metabolic control in women.

Together, these findings position brain insulin sensitivity as a dynamic regulator linking acute metabolic control with long-term changes in body composition. Targeting brain insulin action may therefore represent a promising strategy to improve metabolic health, reduce complication risk, and modulate brain function.
Methods: .
Results: .
Conclusions: .

38 - The Welander TIA1 mutation dedifferentiates human insulin-producing cells by upregulating MYC, an effect prevented by the GLP-1R agonist liraglutide

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Introduction: The RNA-binding proteins TIAR and TIA1 have been reported to affect beta cell insulin production and viability. The missense E384K TIA1 autosomal dominant mutation is known to cause Welander distal myopathy. The aim of this study was to study the effects of the TIA1 E384K mutation in human insulin-producing EndoC-βH1 cells.
Methods: The prime editing technique was used to generate EndoC-βH1 cell clones with the homozygous E384K TIA1 mutation.
Results: The E384K TIA1 mutation did not affect basal or high glucose + palmitate-induced stress granule formation and cell death. Instead, the mutated cells respired and proliferated faster than wild-type cells. This was paralleled by a higher *MYC* mRNA and protein level, a profoundly reduced GLP-1 receptor mRNA expression, increased expression of "disallowed" beta cell genes, a proinsulin-to-insulin processing defect, a decreased insulin content and release, a decreased *PAX4/ARX* mRNA ratio, and an increased glucagon production. The TIA1 mutation reduced *MYC* mRNA binding to TIA1. Downregulation of *MYC* mRNA levels normalized insulin/glucagon and *PAX4/ARX* mRNA ratios. Long-term treatment of TIA1-mutated cells with the GLP-1R agonist liraglutide restored insulin production and reversed beta cell dedifferentiation.
Conclusions: It is concluded that the TIA1 E384K mutation, via increased *MYC* levels and cell proliferation rates, causes beta cell dedifferentiation. Thus, dysfunction of RNA-binding proteins may, at least in certain cases, contribute to the impaired insulin production observed in diabetes. A better understanding of RNA-binding protein-mediated control of beta cell differentiation, and the protective impact of GLP-1 receptor agonism, could facilitate the development of new treatment strategies in diabetes.

39 - Therapeutic Targeting of the ANGPT2/TIE2 Signaling Axis Improves Diabetic Nephropathy in the BTBR OB/OB Mouse

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Introduction: Diabetes is a chronic disease affecting more than 530 million people worldwide and is associated with serious complications including diabetic nephropathy, cardiomyopathy, and atherosclerosis. Diabetic nephropathy, is a leading cause of chronic kidney disease (CKD) and substantially increases cardiovascular risk. Current therapies primarily target metabolic risk factors and inflammation; however, additional vascular mechanisms beyond atherosclerosis contribute to disease progression and remain underexplored.

The connection between Type 2 diabetes (T2DM) and CKD, is driven by common biological processes involving the Angiopoietin-2 (ANGPT2) and TIE-2 signaling pathway. In T2DM, hyperglycemia and advanced glycation end-products disrupt TIE2 signaling, leading to increased ANGPT2 expression and endothelial dysfunction. Elevated circulating ANGPT2 levels correlate with kidney disease severity and help identify the ANGPT2–TIE2 axis as a potential therapeutic target in diabetic nephropathy.
Methods: This study evaluated the therapeutic value of a novel humanized antibody that binds ANGPT2 and restores TIE2 signaling. 4-week-old, BTBR ob/ob diabetic mice received weekly injections of ABX (25mg/kg) or vehicle control, until 11-weeks of age. BTBR WT mice served as a non-diabetic, lean controls.
Results: Diabetic nephropathy was evaluated using blood urea nitrogen (BUN) and urinary albumin and creatinine ratio (uACR). ABX treatment prevented diabetes-induced renal dysfunction, stabilizing BUN and uACR levels. It also preserved renal cortical capillary density (ERG immunostaining), maintained endothelial fenestrations in peritubular capillaries (electron microscopy), and reduced glomerular hypertrophy compared with vehicle-treated diabetic mice.
Conclusions: Taken together, these findings suggest that targeting ANGPT2 with ABX mitigates diabetic nephropathy and preserves renal microvascular structure in experimental type 2 diabetes.

40 - Treatment with GAD in LADA – follow-up of a clinical trial

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Introduction: Encouraging effects by treatment with glutamic acid decarboxylase, GAD, against beta-cell demise are reported in type 1 diabetes. To broaden experience of such treatment to other forms of autoimmune diabetes we performed a 12-month clinical trial in LADA patients who were clearly impacted by autoimmunity as implied by above-median levels of anti-GAD. Inguinal node injections with GAD-alum were accompanied by effects on immunological and beta-cell variables; these we have followed up 2-3 years afterwards.
Methods: Eight out of 14 original participants underwent the same tests of beta-cell function as in the original trial. Tests employed were C-peptide measurements during a mixed-meal tolerance test (MMTT) and during a glucagon stimulation test (GST). Cells secured as PBMC were stimulated in vitro with GAD.
Results: C-peptide responses declined vs. the original trial in 4 out of 8 participants. Decline or no decline was reflected to a similar extent in MMTT and GST and similarity extended to fasting levels of C-peptide. Decline or no decline correlated also with baseline levels of anti-GAD in the original trial. The original positive response (increase in lymphocyte replication) to 7 days culture with GAD was lost in PMBCs from the follow-up. The magnitude of the original PMBC responses did not correlate with C-peptide responses during follow-up testing.
Conclusions: Beta cell decline in LADA is heterogeneous also in the face of strong autoimmune activity, 2) decline is equally well reflected in stimulation tests as in fasting C-peptide, 3) PMBC responses to GAD are not prognostic of C-peptide decline.

41 - Tuning GRK2-biased β_2 signaling: next-generation muscle-targeted modulators with enhanced metabolic and anabolic profiles

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Introduction: Skeletal muscle is central to glucose disposal and lean mass, but classical β_2-agonists are limited by Gs-driven cardiovascular side effects and poor pathway selectivity. GRK2-biased β_2 activation offers a way to retain metabolic and anabolic benefits while minimizing these liabilities.
Methods: We generated a chemically related panel of β_2-adrenergic receptor modulators within a single chemotype and optimized them to span a range of signaling bias toward GRK2 versus Gs and β-arrestin. Muscle metabolic effects were evaluated in differentiated skeletal myotubes by measuring glucose uptake and activation of downstream anabolic signaling markers. Selected compounds were then advanced into rodent models of diet-induced obesity, type 2 diabetes and muscle atrophy, where oral dosing regimens were used and outcomes included glucose tolerance, fasting glycemia and body composition and lean mass assessed.
Results: Across cellular systems, next-generation GRK-biased β_2 modulators displayed distinct signaling fingerprints that were associated with durable stimulation of muscle glucose uptake and activation of anabolic pathways. In preclinical models of obesity, type 2 diabetes and muscle atrophy, several compounds produced superior reshaping of body composition, with preferential reduction of fat mass, preservation or gain of lean mass, and additional improvements in glycemic control compared with vehicle treatment.
Conclusions: By extending metabolic and muscle benefits within a single chemotype, these follow-on candidates demonstrate that tuning GRK-biased β_2 signaling can yield differentiated pharmacology. GRK2-selective β_2 modulation emerges as a powerful and flexible platform for tailoring treatments that couple glycemic control with favorable effects on body composition and muscle health in type 2 diabetes, obesity and sarcopenia.

42 - Whole-body magnetic resonance imaging reveals sex-specific anatomical signatures of type 2 diabetes risk in the UK Biobank

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Introduction: Body-mass-index-based obesity metrics miss anatomical heterogeneity in fat distribution and tissue structure that contributes to type 2 diabetes risk. We mapped sex-specific, whole-body anatomical signatures of diabetes using magnetic resonance imaging.
Methods: We analysed participants in the UK Biobank with whole-body water–fat magnetic resonance imaging at the first imaging visit (2014–2020). Two imaging exposures were derived after non-linear registration to sex-specific reference templates: fat fraction (lipid content) and a relative local volume metric (local structural expansion or contraction). Type 2 diabetes was defined using a validated algorithm. Sex-stratified logistic regression assessed associations, adjusting for age, ethnicity, alcohol use, smoking, diet, physical activity, and total adipose and lean tissue volumes. Family-wise error was controlled using permutation-based threshold-free cluster enhancement.
Results: Among 40,296 imaged participants, 32,139 (16,043 males; 16,096 females) were included in fully adjusted analyses; 1,337 (4.2%) had type 2 diabetes (6.0% males; 2.4% females). Higher fat fraction was associated with higher diabetes odds in visceral adipose depots (including pericardial and mesenteric regions), liver, pancreas, and vertebral marrow, while higher fat fraction was associated with lower odds in gluteofemoral and posterior-thigh subcutaneous adipose tissue and femoral marrow. Spatial patterns were sex-dimorphic, with more extensive protective gluteofemoral subcutaneous associations in females. The relative local volume metric identified adverse expansion in constrained visceral depots and axial marrow and protective expansion in gluteofemoral regions.
Conclusions: Whole-body imaging reveals reproducible, sex-specific anatomical signatures of type 2 diabetes risk that persist beyond total adiposity, supporting anatomically grounded phenotyping for diabetes risk stratification.

43 - β cell-targeted mesencephalic astrocyte-derived neurotrophic factor gene therapy reverses β cell stress and diabetes in mice

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Introduction: Endoplasmic reticulum (ER) stress and mitochondrial oxidative stress contribute to inflammation and β cell death in type 1 diabetes (T1D). Mesencephalic astrocyte-derived neurotrophic factor (MANF) is an ER stress-regulating factor with protective and immunomodulatory roles. MANF knockout (*Manf*$^{-/-}$) mice develop diabetes due to sustained ER stress and β cell loss. In humans, MANF-deficiency is associated with syndromic diabetes. We recently demonstrated that elevated MANF in β cells protects against streptozotocin-induced T1D *in vivo* by reducing islet β cell ER and oxidative stress, immune responses and p53-mediated senescence.
Methods: Doxycycline-inducible β cell-specific INS-MANF mice were crossed with *Manf*$^{+/-}$ mice to generate INS-MANF::*Manf*$^{-/-}$ mice. Mechanisms underlying the protective effects of MANF in β cell mitochondria are being investigated by RT-qPCR, immunocytochemistry, confocal imaging and assays measuring reactive oxygen species.
Results: Prenatal β cell-specific human MANF overexpression in INS-MANF::*Manf*$^{-/-}$ mice reversed diabetes in global MANF-deficient mice. This was associated with increased insulin staining, β cell mass and proliferation. Glucose tolerance and insulin sensitivity were comparable to control mice. Furthermore, β cell-specific overexpression restored serum insulin levels, reduced ER stress, and increased expression of β cell identity markers in islets. Given the oxidative stress observed in β cells of *Manf*$^{-/-}$ mice, we will further elucidate the protective effects of MANF in mitochondrial dysfunction, oxidative stress, and mitophagy.
Conclusions: Prenatal β cell-targeted MANF gene therapy reverses diabetes, restores β cell function and alleviates ER stress in MANF-deficient mice. These findings highlight a promising therapeutic strategy for β cell protection and regeneration in T1D.

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