

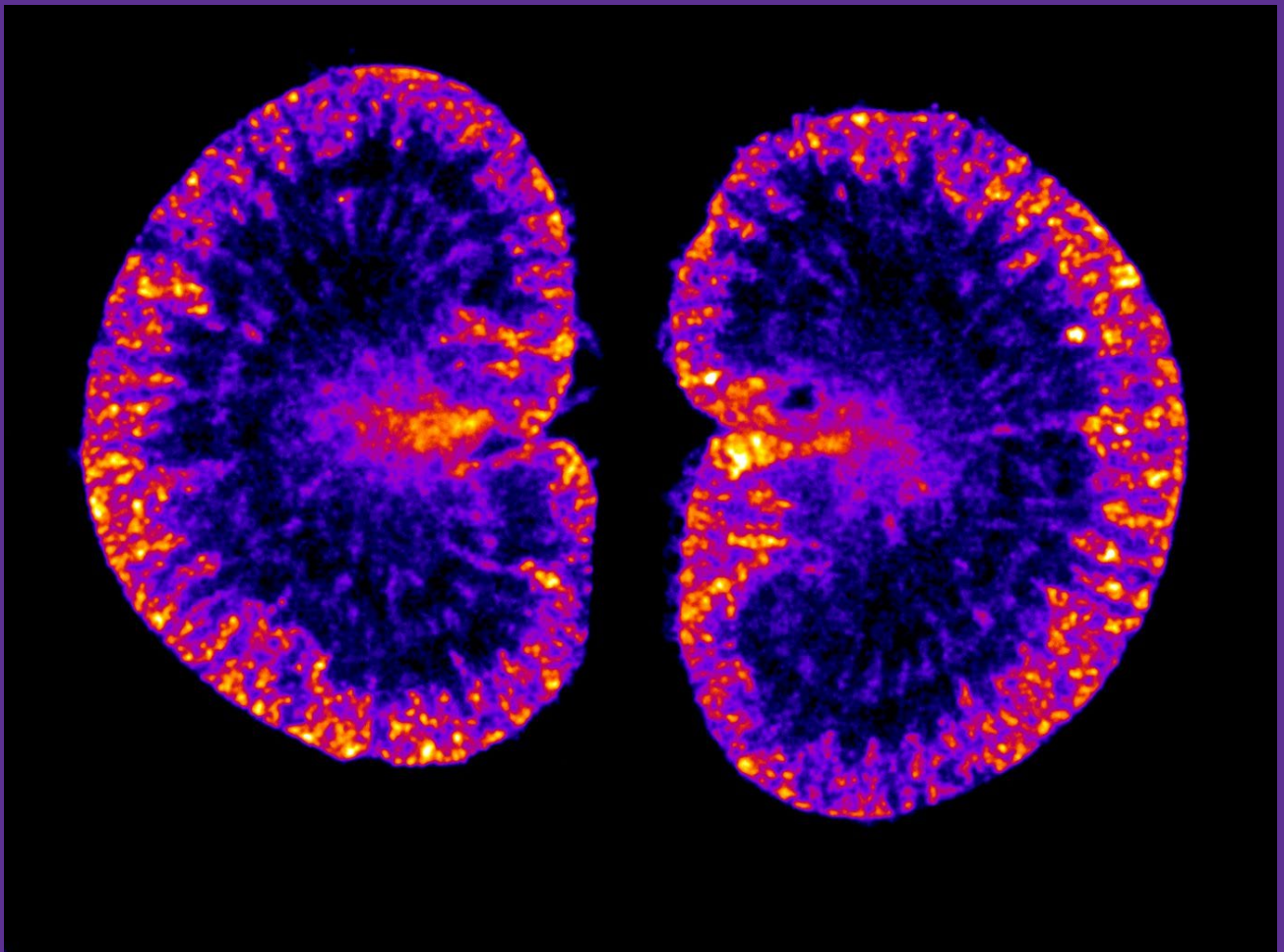


UNIVERSITY OF GOTHENBURG

# Sahlgrenska Academy Junior Researcher Symposium

27<sup>th</sup> – 28<sup>th</sup> of January 2026

Venue: Wallenberg Conference Centre



*Cover image by Charlotte Ytterbrink (Department of Medical Radiation Sciences).*

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# Sahlgrenska Academy Junior Researcher Symposium (SAJRS) 2026

## Abstract Book

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**Sahlgrenska Academy Junior Researcher Symposium (SAJRS)** is an annual scientific meeting organized by *Future Faculty* at Sahlgrenska Academy, providing a platform for junior scientists to present their research, exchange ideas, and foster interdisciplinary collaboration.

**Organizing Committee:** Elin Bernson, Stefanie Fruhwürth, Astrid von Mentzer, Luisa Klahn, Francesco Longo, Bingqing He

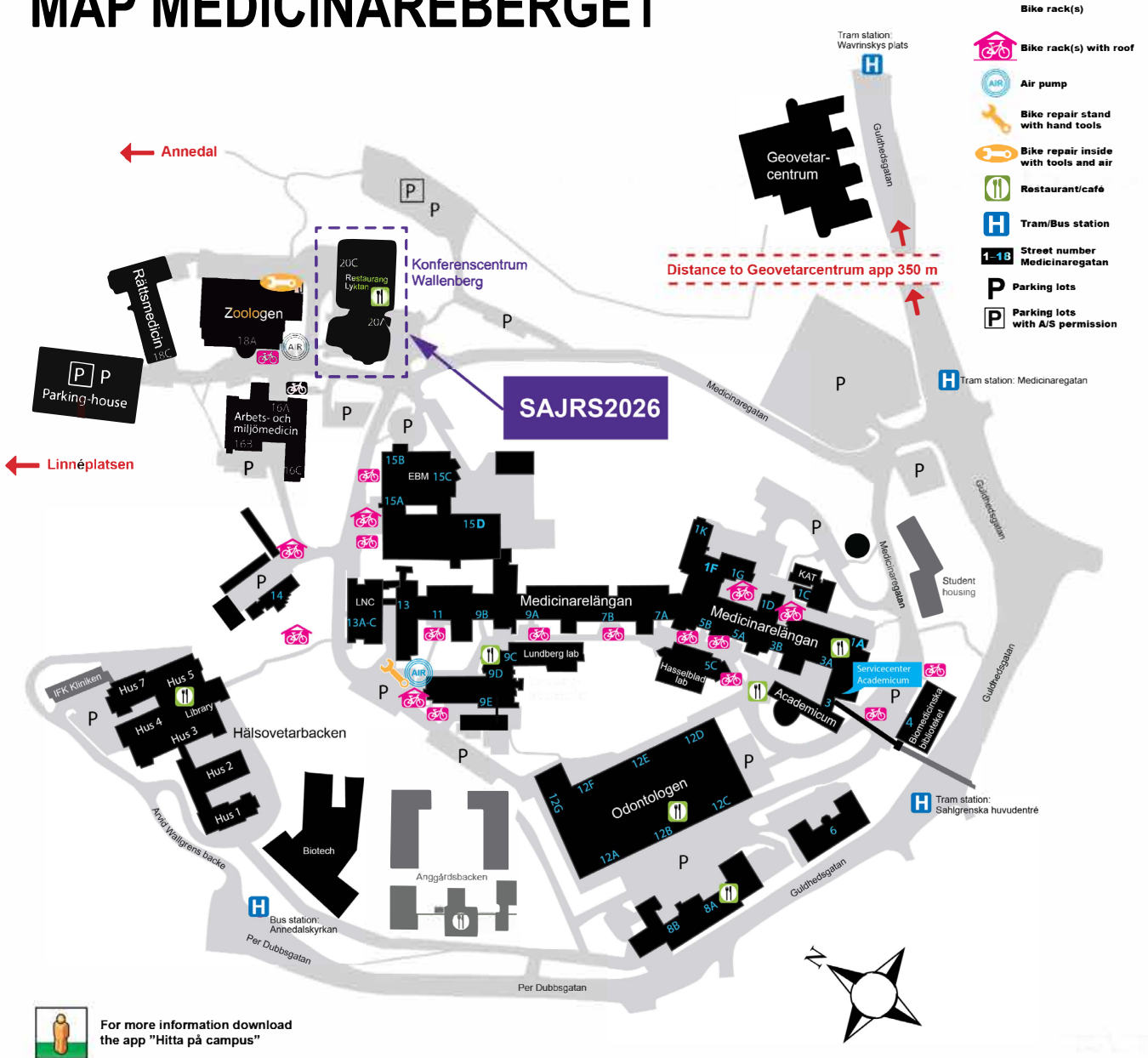
**Cover image:** alpha camera images of the distribution of an antibody labelled with the alpha emitter At-211 in mouse kidney. Provided by Charlotte Ytterbrink from Department of Medical Radiation Sciences.

**Acknowledgements:** The Organising Committee would like to express special thanks to **Johan Tolö** for his valuable support in the preparation and production of this abstract book.

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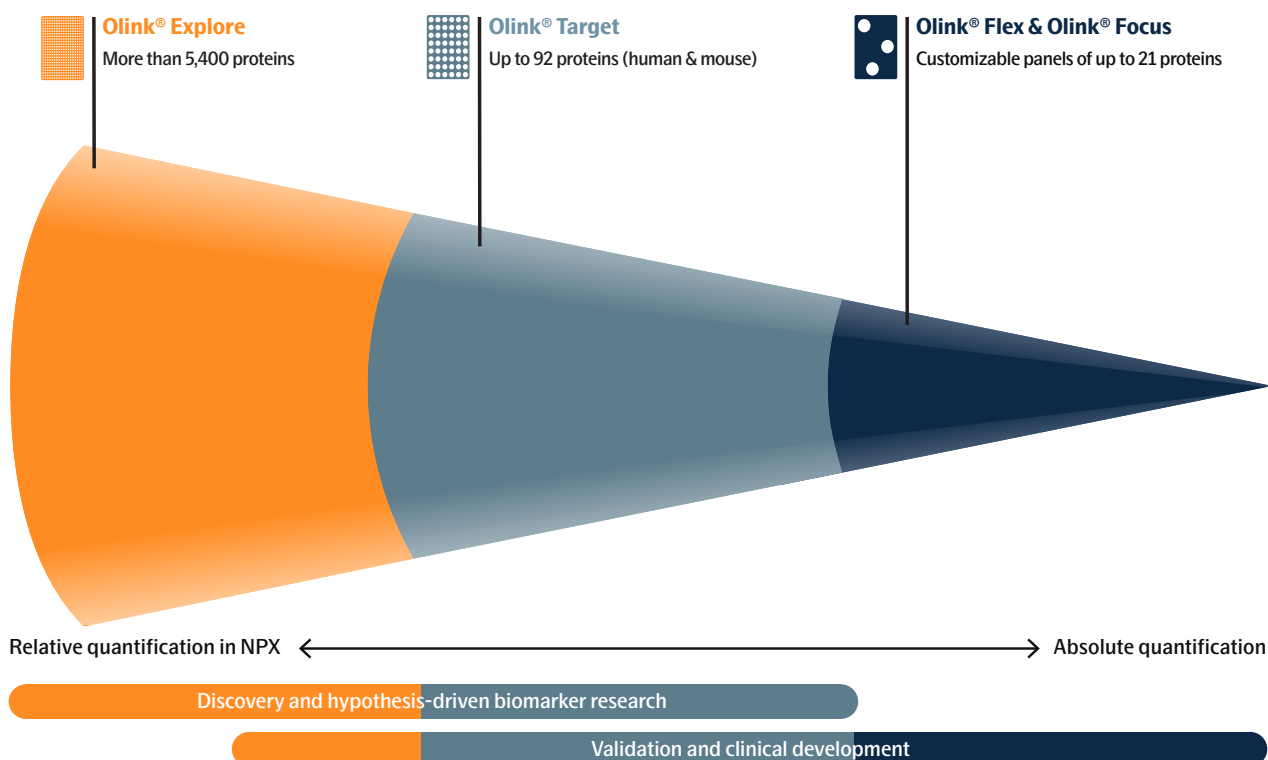
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# From biomarker discovery to clinical utility, on one platform

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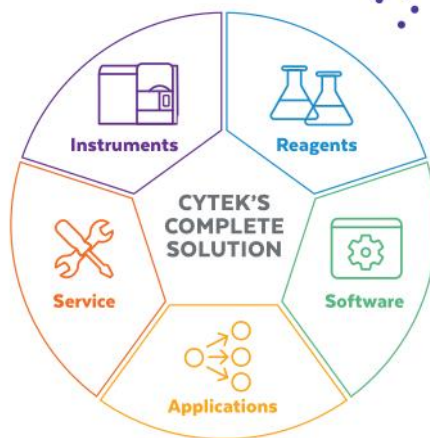
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# Program

# Sahlgrenska Academy Junior Researcher Symposium 2026

<b>Tuesday 27<sup>th</sup> January</b>	
<b>13:00 Opening</b> by Future Faculty and the Dean of Sahlgrenska Academy, Professor Jenny Nyström	
<b>13:15 Keynote</b> lecture: <b>Professor Suzanne Dickson</b>	
<b>14:00 Session 1</b>  Chairs: Kerryn Elliott, Christina Heiss	<b>14:00 Andreas Göteson</b> – <i>Toward molecular staging of schizophrenia and bipolar disorder using cerebrospinal fluid proteomics</i> <b>14:15 Laia Montoliu-Gaya</b> – <i>P-tau205 is a biomarker linked to tau-PET abnormality: A cross-sectional and longitudinal study</i>
<b>14:30</b> Research support office, FIK and GU Ventures	
<b>14:40</b> Fika, networking and sponsor exhibitions	
<b>15:10 Session 2</b>  Chairs: Abi Ghifari, Caitlyn Myers	<b>15:10 Ajay Pradhan</b> – <i>Enzymatic electrochemical biosensors reveal fusion pore dynamics of glutamatergic synaptic vesicles in hiPSC-derived neurons</i> <b>15:25 Caitlyn Myers</b> – <i>Peripheral inflammaging drives neurodegeneration via extracellular vesicles</i> <b>15:40 Vibha Gupta</b> – <i>Improving Equity in ECG-Based MI Detection Using Age-Aware Deep Learning</i> <b>15:55 Neha Kanduri</b> – <i>Spermidine supplementation reprograms cardiac proteostasis in human iPSC-CMs and aged C57BL/6J mice</i>
<b>16:10</b>	Sponsor presentation: Miltenyi
<b>16:30</b>	Poster session 1
<b>17:15 – 19:00 Social</b> networking event at the conference venue	



Wednesday 28 <sup>th</sup> January	
<b>09:00 Session 3</b>  Chairs: Roshan Vaid, Mustafa Kaya	<b>09:00 Nuttida Issdisai</b> – <i>NOX2 inhibition enhances NK cell function and restrains distant metastasis in murine pancreatic ductal adenocarcinoma</i> <b>09:15 Tomás Gómez Vecchio</b> – <i>Healthcare professionals’ perspectives on improving quality of care for patients with malignant glioma and their informal caregivers</i> <b>09:30 Elin Hilpold Berntsson</b> – <i>An scRNA-seq analysis workflow to characterize WNT-modulated mesodermal and hematopoietic trajectories in human gastruloids</i> <b>09:45 Kerry Elliott</b> – <i>UV-mutational signal metrics as predictors of melanoma specific survival</i>
<b>10:00</b>	Sahlgrenska Academy International Office and Core Facilities
<b>10:30 Fika</b> and sponsor exhibitions	
<b>11:00 Session 4</b>  Chairs: Anna Linder, Luisa Klahn	<b>11:00 Tanmoy Dutta</b> – <i>Di-lineage liver organoids from human donors recapitulate steatotic liver disease</i> <b>11:15 Sofia Hammarstrand</b> – <i>Associations between high serum levels of perfluoroalkyl substances (PFAS) and reproductive hormones in children and adolescents, a Swedish cohort study</i> <b>11:30 Melania Aluia</b> – <i>Jejunal Anti-Incretin Pathway in Diet-Induced Diabetes: GLP-1–Targeted Therapies to Mimic Gastric Bypass</i> <b>11:45 Julia Wängberg Nordborg</b> – <i>Endo-SOFT: Study Protocol for a National Multicenter Randomized Controlled Trial: First-Line Surgery vs. First-Line Assisted Reproductive Technologies in Patients with Advanced Endometriosis</i>
<b>12:00 Lunch</b> , networking and sponsor exhibitions	
<b>12:45 Keynote</b> lecture: <b>Professor Fredrik Bäckhed</b>	

<b>13:45 Poster Session 2</b>	
<b>14:45 Session 5</b>  Chairs: Erna Islamagic, Elzbieta Rembeza	<b>14:45 Adhara Gaminde-Blasco</b> – <i>Modeling neuronal hyperexcitability with PTZ reveals microglial activation and impaired microglia–oligodendrocyte interactions in zebrafish larvae</i> <b>15:00 Lenka Nováková</b> – <i>Patients experiencing early PIRA show signs of disturbed remyelination</i> <b>15:15 Neele Levin &amp; Ghadah Al-Wassiti</b> – <i>Unmasking C5aDesArg as a Functional Mediator of Human Neutrophil Activation</i> <b>15:30 Jordan Popovic</b> – <i>Comparative Proteomics Reveal Eosinophilic Protein Enrichment in CD177<sup>pos</sup> Neutrophils</i>
<b>15:45 Prize ceremony and closing remarks</b>	

# Need help to fund your research?

## Sahlgrenska Academy Research Support Office

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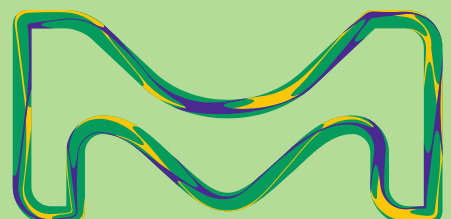
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# Poster Session Schedule

Tuesday 27th 16:30-17:15				
Poster number	Title	First name	Last name	Group (Chair)
1	Decoding m6A Epitranscriptome-Mediated Regulation in High-Risk Neuroblastoma	Roshan	Vaid	A (Luisa Klahn)
2	Early establishment of small intestine neuroendocrine tumors	Alice	Schiller	
3	Surgery-Induced Expansion of Myeloid-Derived Suppressor Cells and Loss of Cytotoxic Lymphocyte Function Predict Poor Survival in Pancreatic Ductal Adenocarcinoma	Olivia	Johnsson	
4	The role of TRAIL/TRAIL-receptor bidirectional signaling for NK-cell cytotoxicity against neuroblastoma cells	Erna	Islamagic	
5	Use of the cell division assay to evaluate T cell toxicity in response to 177Lu-DOTATATE peptide receptor radionuclide therapy	Shaghayegh	Gharaghani	
6	Read-Level Methylation Analysis of cfDNA Using Targeted EM-seq for CNS Tumor Classification	Ryan	Kwan	
7	The mutational landscape of endometrioid ovarian carcinoma	Sara	Schumacher	B (Stefanie Fruhwürth)
8	Tumor Associated Mutations in Liquid Biopsies from the Gynecological Tract	Isabella	Simonsson	
9	Temporal trends in preterm delivery rate over 30 years in a country lacking national preventive strategies: a register-based study	Bin	Han	
10	Targeting dopaminergic dysfunction in fragile X syndrome	Saly	Alsiah	
11	Longer breastfeeding duration is associated with reduced risk of coronary artery calcification	Maja	Sandberg	
12	Targeted delivery of mRNA to the heart via tissue-specific extracellular vesicles or lipid nanoparticles	Muhammad	Nawaz	
13	Aesthetic Treatment With Resin Infiltration In Teeth With Mild Fluorosis – A Long Term Follow-up	Emily	Veen	C (Astrid von Mentzer)
14	The Association of Stress and Periodontitis with Low Birth Weight and Preterm Delivery in Danish Pregnant Women: A Cohort Study	Ammar	Chahda	
15	Bone again: Re-Osseointegration of Disrupted Titanium Implants	Martina	Jolic	

16	Carboxymethyl nanocellulose as a bioink for adipose tissue reconstruction	Kristin	Oskarsdotter	
17	The Centre for Cellular Imaging (CCI): Open-Access Microscopy and Image Analysis Services for All Researchers	Rafael	Camacho	
18	Large -scale protein-disease risk association analysis in the UK Biobank: Introducing an extensive and freely available research resource in Olink® Insight	Léocadie	Henry	
19	Specialist palliative care support in primary care: identifying needs and building collaborative models	Susanna	Böling	
20	Suicide Risk in Postpartum Psychosis: A Nationwide Swedish Study (1973–2020)	Elin	Hörbeck	D (Bingqing He)
21	Longitudinal associations between substance use and mental health outcomes in Swedish adolescents - results from the STARS cohort	Frieda	Haselbach	
22	Insulin-like growth factor axis dysregulation is associated with structural brain changes in bipolar disorder	Patrick	Quinlan	
23	Nicotine increases the vulnerability to develop alcohol use disorder like behavior in rat	Davide	Cadeddu	
24	TIMING OF COMPLEMENTARY FOOD INTRODUCTION IS NOT ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE RISK: A PROSPECTIVE BIRTH COHORT STUDY	Ida	Sigvardsson	
25	The influence of genomic contexts on deamination kinetics in human DNA	Linnéa	Ögren	

Wednesday 28th 13:45-14:45				
Poster number	Title	First name	Last name	Group (Chair)
26	NOX2 acts as a driver of M2 macrophage polarization through the activation of NRF2	Mustafa	Kaya	E  (Francesco Longo)
27	Lymphocyte populations in mouthrinse samples from patients with leukoplakia and oral lichen planus	Veronika	Karlsson	
28	m6A-Modified TERRA RNA Drives RNA Condensate Formation and Telomere Maintenance in ALT+ Neuroblastoma	Ketan	Thombare	
29	LRP10-Dependent Regulation of TRAIL Receptors in Cancer	Ebba	Danielsson	
30	Chemical Proteomic Screens identify Serine Proteases (SP99 and SP50) That Regulates Receptor Ligands in Drosophila Neuroblastoma model	Kundan	Kumar	
31	Kidney toxicity after Targeted Alpha Therapy	Charlotte	Ytterbrink	
32	Novel CSF oligodendrocyte biomarkers for Alzheimer's disease	Luiza	Santos Machado	F  (Martina Sundqvist)
33	Development of transgenic zebrafish models via targeted CRISPR-Cas9 knock-in strategy to study App regulation	Maryam	Rahmati	
34	Neuroinflammation in Alzheimer's Disease: linking proteomic signatures with TSPO PET Imaging	Ilaria	Pola	
35	Dysfunction of in vitro urinary bladder contractility and relaxation in the 6-OHDA rat model of Parkinson's disease	Arghavan	Azadi	
36	iPSC-derived microglia exposed to Alzheimer's disease CSF show disease specific phenotypes	Christina	Heiss	
37	Development of perineuronal nets in Zebrafish	Aïssatou Lala	Diakhate	
38	An algorithm for automatic measurement of volar tilt and radial inclination of the distal radius on 3D models: validation against manual 3D and conventional 2D methods	Emilia	Gryska	G  (Elin Bernson)
39	Arterial Elasticity and Cardiac Function: A Population-Based Study in the Vara-Skövde Cohort	Gábor	Száló	

40	Validation of a Plasma GFAP Immunoassay and Establishment of Age-Related Reference Values: Bridging Analytical Performance and Routine Implementation	Burak	Arslan	
41	Evaluating digital lab training via Virtual Reality	Alma	Söderström	
42	An optimized feeder-free protocol for isolation and expansion of functional ILC2s isolated from human peripheral blood	Lina	Andersson	
43	Integrative Multi-Omics and Machine Learning Reveal Predictive Markers of Radiation-Induced Intestinal Injury	Yueling	Peng	
44	Feasibility and efficacy of digitally delivered dietary treatment for irritable bowel syndrome: A pilot study	Kristina	Cullman	H (Catarina Magnusson)
45	Allelic variants of the plasmid-encoded colonization factor CS6 are associated with distinct enterotoxigenic Escherichia coli clades	Marlene	Grimmer	
46	Dissecting the Antiviral Role of AXL During HSV-1 Infection: Beyond Phagocytosis in Microglia	Arketa	Meshi	
47	Distinct plasmid mobility patterns shape the distribution of colonisation factors in enterotoxigenic Escherichia coli strains	Biel	Garcias Puigserver	
48	Sex differences in immune responsiveness and the effect of alpha 7 nicotinic acetylcholine receptor stimulation in PBMCs from a healthy middle-aged population	Rebecka	Wilhelmsson	
49	Cellular senescence impairs insulin-stimulated glucose uptake in human adipocytes	Ida	Alexandersson	

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# Abstracts

## OP01: Toward molecular staging of schizophrenia and bipolar disorder using cerebrospinal fluid proteomics

**Göteson A**, Hörbeck E, Sigström R, Roström M, Pålsson E, Goulding A, Isgren A, Jonsson L, Erhardt S, Cervenka S, Bejerot S, Sellgren CM, Landén M

*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, University of Gothenburg  
- Sahlgrenska Academy*

### **Background:**

Schizophrenia (SCZ) and bipolar disorder (BD) share considerable genetic risk and overlap in clinical presentation, yet the nature and extent of their molecular convergence, particularly in relation to illness progression, remains insufficiently defined. Cerebrospinal fluid (CSF) proteomics offers a minimally invasive approach to characterizing brain biology in vivo and offers potential for biomarker discovery.

### **Methods:**

We analyzed CSF from 400 individuals (160 with SCZ-spectrum disorders, 139 with BD, and 101 controls) across four Swedish cohorts using Olink Proximity Extension Assay targeting 1,152 proteins. A subset (n=186) underwent repeated CSF sampling after a median of 6.5 years. We examined differential protein abundance across diagnostic categories, illness stages, and longitudinal change in relation to manic or psychotic episodes.

### **Results:**

We identified 139 proteins with differential abundance across SCZ and BD subgroups, implicating synaptic and neurodevelopmental pathways, as well as immune, metabolism, and cell-structural functions—some of which map to genes prioritized in BD and SCZ risk loci. Effect sizes were strongly correlated between SCZ and BD subgroups, indicating shared molecular pathology, with larger fold changes in SCZ, particularly in more chronic and treatment-resistant stages. Proteomic alterations in first-episode psychosis later diagnosed with SCZ resembled chronic SCZ. Longitudinal analyses linked changes in immune and synaptic proteins to relapse over the 6.5-year follow-up.

### **Conclusion:**

These findings suggest a progressive and shared molecular pathology across the BD–SCZ spectrum, with early proteomic changes detectable at illness onset in SCZ. If confirmed by longitudinal studies, CSF proteomics could provide a basis for biomarker-informed staging frameworks to guide diagnosis, prognosis, and treatment development in severe mental illness.

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## OP02: P-tau205 is a biomarker linked to tau-PET abnormality: A cross-sectional and longitudinal study

Lantero-Rodriguez J, Janelidze S, Palmqvist S, Sophie Braun-Wohlfahrt L, Vavra L, Bali D, Orduña Dolado A, Mattsson-Carlsson N, Stomrud E, Zetterberg H, Hansson O, Salvadó G, **Montoliu-Gaya L**

*Department of Psychiatry & Neurochemistry, Institute of Neuroscience & Physiology, University of Gothenburg - Sahlgrenska Academy*

Current fluid biomarkers for Alzheimer's disease (AD) track amyloid- $\beta$  ( $A\beta$ ) pathology more strongly than tau, even though clinical and cognitive decline relate more closely to tau. We evaluated cerebrospinal fluid (CSF) phosphorylated tau at epitope 205 (p-tau205), measured using immunoassays, as a biomarker of tau aggregation. A total of 2,069 samples from the BioFINDER-2 (n=1,364) and BioFINDER-1 (n=705) cohorts spanning the full AD continuum were analyzed to assess cross-sectional and longitudinal associations with imaging and clinical measures. CSF p-tau205 levels were elevated in both biologically and clinically advanced disease stages. In  $A\beta$ -positive individuals, cross-sectional p-tau205 correlated with  $A\beta$ -PET ( $R^2=0.26$ ), tau-PET ( $R^2=0.29$ ), cortical atrophy ( $R^2=0.14$ ) and cognition (MMSE,  $R^2=0.14$ ). Baseline p-tau205 predicted subsequent  $A\beta$  accumulation ( $R^2=0.44$ ) and tau-PET uptake ( $R^2=0.33$ ) and increased more steeply over time in  $A\beta$ -positive than  $A\beta$ -negative participants ( $\beta[95\%CI]=0.16[0.12-0.21]$ ,  $p<0.001$ ). Longitudinal p-tau205 change related to cortical thinning ( $R^2=0.32$ ) and cognitive decline ( $R^2\geq 0.41$ ). Incorporating  $A\beta_{42/40}$ , p-tau217 and p-tau205 into a CSF-based staging model, the final p-tau205-positive stage showed the strongest cortical atrophy, cognitive impairment, and risk of incident dementia ( $HR=6.40[4.28-9.59]$ ). These findings support CSF p-tau205 as a valuable marker for biological staging and progression monitoring in AD.

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## OP03: Enzymatic electrochemical biosensors reveal fusion pore dynamics of glutamatergic synaptic vesicles in hiPSC-derived neurons

Pradhan A\*, Wang Y\*, Gupta P, Roselli S, Fruhwürth S, Hodzic DV, Karlsson-Fernberg H, Agholme L, Hanrieder J, Zetterberg H, Cans AS (\*equal contribution)

*Department of Chemistry and Chemical Engineering, Not Applicable, Chalmers University of Technology*

### Background & Aims:

The dynamically regulated release of glutamate, the primary excitatory neurotransmitter in the brain, is an active field of research, especially its aberrant neurotransmission in disease states. Despite its importance, decades of research on glutamate signalling have been limited to the response of postsynaptic receptors to the released glutamate. The main limitation of conventional tools is the extremely high spatial resolution necessary to target the tiny release sites. Additionally, sensitive electrochemical detection methods using ultramicroelectrodes are typically limited to oxidizable molecules like dopamine. Further, the research on exocytotic release of neurotransmitters is mainly limited to non-neuronal secretory cells or rodent neurons. Although our group has previously shown real-time monitoring of glutamate release from rodent brain slices, it is unequivocal that in vitro neuroscience research needs to focus on human neurons for modelling complex human diseases.

### Methods:

In our current work, using advanced electrochemical enzymatic glutamate biosensors, we performed detailed characterization of quantal glutamate release from hiPSC-derived neurons. This technique involves real-time recording of current spikes generated from the reduction of the enzymatically generated hydrogen peroxide from the released glutamate.

### Results:

Our recordings show that these neurons are capable of reliable non-evoked glutamate release and exhibit a continuum of complex fusion pore dynamics, evidenced by the presence of features on the amperometric spikes. The different release modes exhibit differences in kinetics and amount of glutamate released, which is an important facet of presynaptic plasticity and could likely alter during synaptic pathologies. These exocytotic events responded to elevated intracellular calcium levels in the form of higher release frequency and quantal size, and to prolonged KCl stimulation in the form of short-term presynaptic facilitation.

### Conclusion:

Our results validate this hiPSC-biosensor platform as a powerful tool to understand fusion pore dynamics, presynaptic plasticity, and for modelling aberrant glutamate signalling.

## OP04: Peripheral inflammaging drives neurodegeneration via extracellular vesicles

Öberg M, **Myers C**, Saffarzadeh N, Maric I, Murillo-Leon M, Strömberg A, Fabrikova D, Fabrik I, Rivas-Galvez L, Deshmukh MV, Enriquez J, Ali KX, Crescitelli R, Angeletti D, Sayin VI, Jin T, Rafie K, Skibicka KP, Kurzawa-Akanbi M, Paul G, Gekara NO, Härtlova A

*Department of Microbiology and Immunology, Institute of Biomedicine, University of Gothenburg - Sahlgrenska Academy*

All animals age. However, aging is a heterogeneous process, and individual organisms age differently. Moreover, cells or organs do not age at the same time or speed within the same organism. For instance, although neurodegeneration is a key trait of aging, neurological symptoms normally manifest long after multiple indicators of aging appear in peripheral tissues. The genetic determinants of aging are not completely understood. Gain of function (GoF) mutations in leucine-rich repeat kinase 2 (LRRK2GoF) are major genetic risk factors for Parkinson's disease (PD). By analyzing PD patients and mice with LRRK2GoF, we demonstrate that PD is an accelerated aging disease characterized by age-associated inflammation (inflammaging). This STING-dependent inflammaging first manifests in the periphery, then disrupts the blood-brain barrier and progresses to the brain, resulting in neurodegeneration characterized by loss of dopaminergic neurons. Mechanistically, we demonstrate that a primary consequence of aging or LRRK2GoF is endo-lysosomal decline. This results in the cytosolic build-up of extraneous self-DNA and subsequent shedding of DNA-containing extracellular vesicles, thereby triggering the cGAS-STING pathway cell-intrinsically and intercellularly in distant host cells. This study unveils the cGAS-STING pathway and LRRK2GoF as key determinants and potential targets for preventive or therapeutic strategies against accelerated aging, inflammaging, and neurodegeneration.

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## OP05: Improving Equity in ECG-Based MI Detection Using Age-Aware Deep Learning

Gupta V, Rawshani A

*Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg - Sahlgrenska Academy*

### Background:

Myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide, where timely diagnosis via 12-lead electrocardiograms (ECGs) is critical. Deep learning (DL) models have shown strong potential for automated ECG interpretation, but their performance often varies across age groups. Age substantially influences ECG morphology and MI presentation, yet most models only include it as a simple covariate, overlooking its deeper impact on signal interpretation. This limits clinical trust and may exacerbate disparities in diagnosis.

### Methods:

We investigated three age-aware strategies for ECG-based MI detection using a multi-center Swedish dataset of 142,921 ECGs. A convolutional–recurrent baseline network (ECG-BaselineNet) served as backbone, with age incorporated via: (1) age-specialist models trained separately for <50, 50–70, and >70 years; (2) a multi-head architecture with shared features and age-specific outputs; and (3) a Mixture-of-Experts (MoE) model combining age-specialized subnetworks via dynamic routing. Training was performed on two hospitals, with external validation on an independent site. Performance was assessed by AUROC, with sensitivity, specificity, and interpretability as secondary measures.

### Results:

The multi-head model provided the best overall balance across age groups, while MoE achieved the highest performance in elderly patients, and age-specialist models improved sensitivity in younger cohorts. All age-aware models outperformed the baseline in at least one subgroup. Score-CAM visualizations confirmed that strategies attended to clinically relevant ECG regions, such as ST segments and T waves, reinforcing medical plausibility.

### Conclusion:

Explicitly modelling age in DL architectures enhances both fairness and generalization for ECG-based MI detection. While different strategies excel in distinct subgroups, age-aware modelling improves diagnostic equity and interpretability. Such models may support earlier and more accurate MI diagnosis across diverse patient populations, with potential to improve outcomes and reduce disparities in cardiovascular care. This highlights the importance of integrating demographic context into medical AI to achieve equitable clinical practice.

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## OP06: Spermidine supplementation reprograms cardiac proteostasis in human iPSC-CMs and aged C57BL/6J mice

Bauzá-Thorbrügge M, **Kanduri N**, Miljanovic A, Levin M, Gidlöf O, Smith JS

*Department of Molecular and Clinical Medicine, Institute for Medicine, University of Gothenburg - Sahlgrenska Academy*

### **Background:**

Cardiac spermidine levels decline with ageing, coinciding with worsening diastolic function and reduced cellular maintenance capacity. As an endogenous polyamine, spermidine supports cardiac health and has been shown to extend lifespan in model organisms by strengthening cellular upkeep and adaptive responses, thereby preserving contractile performance. Although emerging studies indicate that supplementation can influence these maintenance pathways, their breadth, mechanisms and relevance in the ageing heart remain only partly understood.

### **Purpose:**

To define how spermidine supplementation modulates proteostasis and endoplasmic reticulum (ER) related stress responses in human iPSC-derived cardiomyocytes and aged female C57BL/6J mouse hearts.

### **Methods:**

Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) underwent genetic (ornithine decarboxylase 1, ODC1 silencing) and pharmacological ( $\alpha$ -difluoromethylornithine, DFMO) depletion of endogenous spermidine synthesis, followed by spermidine treatment. Autophagy, the ubiquitin-proteasome system, and ER-related stress pathways were assessed. In parallel, 19-month-old female C57BL/6J mice received 8 weeks of spermidine supplementation (3 mM); cardiac function was evaluated by stress echocardiography, and cardiac tissue was collected for downstream analyses of cellular maintenance pathways.

### **Results:**

In iPSC-CMs, spermidine supplementation countered the effects of genetic and pharmacological polyamine depletion, normalising cellular maintenance signalling with evidence of enhanced autophagy and adjusted ER-related responses. In aged mouse hearts, supplementation produced concordant changes in cardiac maintenance, alongside echocardiographic assessment of function. Together, these findings indicate that spermidine broadly reinforces cellular maintenance networks in the heart.

### **Conclusions:**

Across complementary cellular and animal models, spermidine supplementation enhanced autophagy and adjusted ER-related responses, consistent with improved cardiac proteostasis in ageing. These findings support spermidine as a candidate intervention to mitigate age-associated cardiac decline and mechanisms relevant to heart failure, warranting further mechanistic and translational evaluation.

---

## **OP07: NOX2 inhibition enhances NK cell function and restrains distant metastasis in murine pancreatic ductal adenocarcinoma**

**Issdisai N, Kaya M, Kiffin R, Kristoffer H, Martner A**

*Department of Microbiology and Immunology, Institute of Biomedicine, University of Gothenburg - Sahlgrenska Academy*

Pancreatic ductal adenocarcinoma (PDAC) accounts for >90% of cases of pancreas cancer and is associated with 5-year survival rates below 10%. Its immunosuppressive tumor microenvironment and a desmoplastic stroma contribute to therapeutic resistance and facilitate disease progression and metastasis, underscoring the need for novel strategies. NOX2, an enzyme complex that generates reactive oxygen species (ROS), is predominantly expressed in myeloid cells. Excess production of NOX2-derived ROS can suppress the function of adjacent cytotoxic immune cells, including natural killer (NK) and T cells. However, the role of NOX2 in PDAC remains poorly understood.

We used murine PDAC cells (PDA30364) carrying *Kras*G12D/+ and *p53*R172H/+. These cells were tagged with luciferase and intravenously injected into wild-type (WT) and *Nox2*-deficient (*Nox2*<sup>-/-</sup>) C57BL/6 mice. In vivo imaging revealed a striking reduction of PDAC lung metastasis in *Nox2*<sup>-/-</sup> animals. NK cell depletion in vivo enhanced the metastatic burden similarly in WT and *Nox2*<sup>-/-</sup> mice, thus highlighting NK cells as key effector cells inhibited by NOX2-derived ROS. Furthermore, IL-15 administration enhanced NK cell activity only in *Nox2*<sup>-/-</sup> mice, suggesting that NOX2 loss creates a permissive environment for NK cell-based immunotherapy and that additional NK cell stimulation is required to fully exploit this potential. Spectral flow cytometry revealed a favorable immune landscape in *Nox2*<sup>-/-</sup> mice characterized by improved NK and CD8<sup>+</sup> T cell activities.

In vitro co-culture assays confirmed that murine NK cells cocultured with PDA30364 cells exhibited significant expression of CD107a, indicating degranulation and cytotoxic activity toward tumor cells. In single-cell transcriptomic analyses, NK cells from *Nox2*<sup>-/-</sup> mice displayed stronger cytotoxic signatures compared to NK cells from WT mice. These findings suggest that NK cells can kill PDAC cells and that they are suppressed by NOX2-derived ROS. Our results point towards therapeutic interventions combining NOX2 inhibition with NK cell-targeted strategies to control or prevent metastatic disease.

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## **OP08: Healthcare professionals' perspectives on improving quality of care for patients with malignant glioma and their informal caregivers**

**Gómez Vecchio T, Henocho I, Schenell R, Nyblom S, Ozanne A**

*Care in Long-Term Conditions, Institute of Health and Care Sciences, University of Gothenburg - Sahlgrenska Academy*

### **Introduction:**

Patients with malignant glioma and their informal caregivers are both significantly affected by care-related unmet needs. By exploring the experiences and attitudes of healthcare professionals (HCPs) across different levels of care, we aim to identify barriers and facilitators to improving the quality of care for patients with high-grade glioma and their informal caregivers throughout the disease trajectory.

### **Material and Methods:**

A total of 12 focus groups were conducted including 44 HCPs active in the geographical area of Region Västra Götalands. The interviews were conducted from November 2024 to March 2025, utilized semi-structured guides. The sample included 35 (79%) participants from four hospitals under county jurisdiction, and 9 (21%) participants from units under municipal jurisdiction. An inductive qualitative content analysis was employed to systematically characterize the gathered material.

### **Results:**

Two categories emerged from the analysis of the manifest content: I. Organization and structural decisions, describing advantages and limitations in the local healthcare system, and II. Interactions and interpersonal dynamics, illustrating interpersonal dynamics and mental attitudes among HCPs. Based on these categories, we identified barriers and facilitators to improving care for patients with high-grade glioma and their informal caregivers. These factors appear to extend beyond interpersonal dynamics, encompassing organizational structures and public health policy levels.

### **Conclusion:**

The findings highlight the need for systemic changes in healthcare delivery to enhance the quality of care for patients with high-grade glioma and their informal caregivers.

---

## **OP09: An scRNA-seq analysis workflow to characterize WNT-modulated mesodermal and hematopoietic trajectories in human gastruloids**

**Hilpold-Berntsson E**, Monsalve-Iguiniz A, Shivalingappa PKM, Hogmalm A, Tesfaye R, Guibentif C

*Department of Microbiology and Immunology, Institute of Biomedicine, University of Gothenburg - Sahlgrenska Academy*

Human pluripotent stem cells (hPSCs) provide a powerful platform to model early hematopoietic development. Embryonic hematopoiesis takes place in different embryonic locations through three overlapping sequential waves: primitive, pro-definitive, and definitive, making it challenging to model using hPSC differentiation. We explore the hematopoietic potential of a gastruloid-based hPSC differentiation system designed to more accurately model emergence of successive mesodermal populations in vitro. Accurate in vitro modelling of human developmental hematopoiesis will provide a new source of clinically relevant cell types such as hematopoietic stem cells, and a platform to study molecular mechanisms of congenital diseases and prenatal transformations leading to childhood leukemia.

WNT signaling regulates the emergence of mesoderm subtypes, leading to distinct hematopoiesis waves. By using the small molecule CHIR99021 (CHIR) at three concentrations (1.8, 3, and 5  $\mu$ M at protocol day 0) we investigate the WNT signaling effect on mesoderm specification and hematopoietic emergence. scRNA-seq is applied to gastruloid samples collected at early developmental stages. Current efforts benchmark an optimal workflow for steps such as quality control, normalization, and cell-type annotation. This approach aims to identify reproducible transcriptional trajectories and define how WNT modulation shapes cell-fate specification in blood development.

Using manual annotation and deep learning-based tool SingleR, we identified a prominent PDGFRA<sup>+</sup>/PRRX1<sup>+</sup> stromal population and a WNT dose-dependent shift in mesodermal lineage composition. At day 3, low CHIR favored splanchnic LPM and NMPs/PSM, whereas 5  $\mu$ M promoted somatic LPM and paraxial mesoderm lineages. By day 8, diverse VCAN<sup>+</sup>/FN1<sup>+</sup>/COL3A1<sup>+</sup>/ADAM12<sup>+</sup> mesenchymal populations emerged, suggestive of a heterogeneous stromal compartment potentially supportive of hematopoietic specification. Importantly, throughout both time-points, we identify the emergence of a subset of endothelial cells, putative developmental precursors to embryonic hematopoietic cells.

These findings show that modulating WNT during gastruloid formation reshapes mesodermal patterning. The workflow provides a robust framework to model human developmental hematopoiesis in vitro.

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## **OP10: UV-mutational signal metrics as predictors of melanoma specific survival**

**Elliott K, Ögren L, Riaz N, Meghadri SH, Tang K-W Ståhlberg, A Olofsson Bagge R, Larsson E**

*Department of Medical Biochemistry and Cell Biology, Institute of Biomedicine, University of Gothenburg - Sahlgrenska Academy*

Despite advances in melanoma prognostication, molecular markers that reflect tumor biology and predict clinical outcomes remain limited. To address this, we designed a UV-sensitive hotspot panel based on known highly UV-mutagenic sites in the genome using error-correcting amplicon sequencing. We then analyzed two mutational metrics in a cohort of 221 primary cutaneous melanomas: the Clonal Peak Score (CPS), defined as the number of high variant allele frequency peaks reflecting tumor mutation burden, and the UV Damage Score (UDS), derived from low-frequency background signals representing cumulative UV-induced mutations in the surrounding skin. Clonal peak and UV damage scores were quantified and examined in relation to T-stage, sentinel lymph node status, recurrence, and melanoma-specific survival. In a subset of 72 tumors, whole-exome sequencing confirmed canonical melanoma driver mutations and allowed for calculation of tumor mutational burden. Our analysis revealed that increasing T-stage was associated with a higher clonal peak score and decreased UV damage score. Interestingly, the UV damage score was the most predictive, and correlated both with sentinel node status, recurrence and melanoma-specific survival in univariable analyses. Notably, in multivariable analysis, the UV damage score remained a significant independent predictor of melanoma-specific survival ( $p = 0.038$ ), even after adjusting for established prognostic factors including age at diagnosis, Breslow thickness, ulceration, gender, and sentinel node status. These results suggest that UV-sensitive hotspot profiling, supported by exome-derived mutation data, can uncover variant metrics with prognostic relevance, offering a potential framework for integrating mutational signal features into clinical risk stratification for early-stage melanoma.

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## OP11: Di-lineage liver organoids from human donors recapitulate steatotic liver disease

Dutta T, Kovooru L, Mancina RM, Romeo S

*Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg - Sahlgrenska Academy*

### **Background and Aims:**

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disorder and a major contributor to liver-related morbidity and mortality. Existing in vitro models either depend on complex differentiation protocols, or hepatocyte-only 3D-models or immortalized cell models that fail to capture fibrosis driven by hepatic stellate cells. Here, we present a di-lineage human hepatic organoid model that represents the key pathological features of MASLD.

### **Method:**

Organoids were generated using primary hepatocytes (PHHs) and primary hepatic stellate cells (PHSCs) from several human donors in a pre-defined 24:1 ratio. Steatosis and fibrotic-like conditions were induced by incubation with a mixture of fatty acids (oleic and palmitic acid in a 2:1 ratio, at a final concentration of 500  $\mu$ M) and TGFB1 (10 ng/ml).

### **Results:**

Our model recapitulated the hallmarks of MASLD, including elevated neutral lipid accumulation, increased COL1A1 deposition, lower  $\beta$ -oxidation and reduced ApoB100 secretion. Transcriptomic and proteomic analyses demonstrated changes in the expression of genes and protein levels associated with extracellular matrix (ECM) and metabolic pathways, key features of MASLD. Results were validated in RNA seq data from people with the entire spectrum of fibrosis severity. Incubation with resmetirom or obeticholic acid reversed lipid accumulation and collagen deposition, consistent with clinical trials.

### **Conclusion:**

This di-lineage human hepatic organoid model offers a physiologically relevant and scalable system that effectively recapitulates the hallmarks of MASLD. Moreover, this model offers a valuable platform for the discovery and validation of treatment for MASLD.

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## **OP12: Associations between high serum levels of perfluoroalkyl substances (PFAS) and reproductive hormones in children and adolescents, a Swedish cohort study**

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### **Background and Aims:**

Perfluoroalkyl substances (PFAS) are persistent chemicals with endocrine-disrupting properties. Evidence regarding effects on reproductive hormones remains limited and inconsistent, particularly in children and adolescents. A local contamination accident in Sweden provides a unique opportunity to study a highly exposed population. The aim was to examine associations between serum PFAS levels and reproductive hormone concentrations in children and adolescents.

### **Methods:**

In 2013, very high PFAS levels ( $>10,000$  ng/L), mainly perfluorooctane sulfonic acid (PFOS) and perfluorohexane sulfonic acid (PFHxS), were detected in drinking water in Ronneby, Sweden. Between 2014–2016, 288 children and adolescents (5–20 years) were enrolled in the Ronneby Biomarker Cohort. Participants were divided into prepubertal girls and boys (5–11 years) and pubertal/postpubertal boys (12–20 years), while pubertal girls were excluded due to limited menstrual cycle data. Regression models, stratified by sex and adjusted for age and BMI used to examine associations between serum PFAS (PFOS, PFHxS, perfluorooctanoic acid (PFOA)) and reproductive hormones; testosterone, prolactin, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG).

### **Results:**

In prepubertal children (5–11 years), prolactin was positively associated with  $\Sigma 3$ PFAS (PFOS, PFHxS and PFOA), both in boys ( $\beta = +0.20$ , 95% CI 0.07–0.34) and girls ( $\beta = +0.25$ , 95% CI 0.09–0.41). Categorical analyses further indicated lower FSH in both sexes and consistently higher prolactin in medium and high exposure groups. In boys 12–20 years, each IQR increase in  $\Sigma 3$ PFAS was associated with lower testosterone ( $\beta = -0.18$ , 95% CI  $-0.33$ ,  $-0.04$ ) and LH ( $\beta = -0.21$ , 95% CI  $-0.37$ ,  $-0.05$ ).

### **Conclusion:**

Higher PFAS concentrations were associated with lower testosterone and LH, consistent with prior studies. Prolactin in children showed a positive association with PFAS, not previously described. Overall patterns are compatible with PFAS-related endocrine disruption of the hypothalamic–pituitary–gonadal axis.



## OP13: Jejunal Anti-Incretin Pathway in Diet-Induced Diabetes: GLP-1–Targeted Therapies to Mimic Gastric Bypass

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### **Background:**

Obesity is a major global health burden associated with type 2 diabetes (T2D) and cardiovascular disease (CVD). Bariatric surgery, such as Roux-en-Y gastric-bypass (RYGB), effectively improves metabolism by restoring incretin glucagon-like peptide-1 (GLP-1) secretion but remains invasive and unsuitable for many patients, while pharmacological alternatives often show limited efficacy. Recent evidence links intestinal ketone overproduction, mediated by upregulated 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2), to impaired GLP-1 release in obesity. Interestingly, HMGCS2 expression markedly decreases after RYGB, suggesting a potential “anti-incretin” role of intestinal ketogenesis in metabolic dysfunction. However, the underlying mechanism remains to be elucidated.

### **Aim:**

to target intestinal HMGCS2 to suppress ketone production and enhance GLP-1 secretion, leading to improved glucose homeostasis and metabolic health.

### **Methods and Results:**

HMGCS2 expression was assessed in gastric and small intestinal mucosa biopsies obtained from obese patients and lean controls following a two-week high-fat diet (HFD) intervention. Based on the observed HFD-induced upregulation of intestinal HMGCS2 expression in humans, a complementary mouse model was established to investigate its functional relevance. C57BL/6J mice (5–6 weeks old) were fed a Western HFD for four weeks and subsequently treated with an AAV9-CRISPR/Cas9 construct targeting HMGCS2 to achieve an intestine-specific knockout. Three days post-injection, intestinal HMGCS2 expression was reduced by approximately 60%, accompanied by decreased HMGCL and PPAR $\alpha$  levels, while hepatic expression remained unchanged. AAV-treated mice exhibited lower blood glucose, reduced body and spleen weight, decreased hepatic plasminogen activator inhibitor-1 (PAI-1) and transforming Growth Factor Beta 1 (TGF $\beta$ 1) expression compared with HFD-fed scrambled controls. Although GLP-1 concentration decreased in serum and plasma, GLP-1 activity appeared enhanced in the liver and small intestine, suggesting tissue-specific modulation of incretin signaling following HMGCS2 inhibition.

### **Conclusion:**

Intestinal-specific HMGCS2 inhibition mitigates obesity-associated metabolic dysfunction and may represent a novel “gastric-bypass-mimetic” strategy to restore incretin function, improve lipid metabolism, and promote cardiometabolic health.

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# **OP14: Endo-SOFT: Study Protocol for a National Multicenter Randomized Controlled Trial: First-Line Surgery vs. First-Line Assisted Reproductive Technologies in Patients with Advanced Endometriosis**

Marklund A, **Wängberg Nordborg J**, Ascitutto C, Elenis E, Francis J, Jokubkiene L, Wennmo Zuk K, Åmark H, Rodriguez-Wallberg K, Sundfeldt K, Forslund M, Brunes M

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## **Background & Aims:**

Endometriosis affects approximately 10% of women of reproductive age and is frequently associated with pain and infertility. Among women with stage III-IV endometriosis, around 80% experience dysmenorrhea, and 45% report dyspareunia. Treatment options for endometriosis-associated infertility include surgery or assisted reproductive technologies (ART). However, evidence is lacking on whether first-line endometriosis surgery before ART improves fertility outcomes compared to first-line ART. Endo-SOFT aims to evaluate whether first-line surgery before ART improves cumulative live birth rates (CLBR) compared to first-line ART in patients with stage III-IV endometriosis. The Swedish Endometriosis Patient Association has been involved in planning the Endo-SOFT trial and has encouraged the study group, since the research question is important to many endometriosis patients.

## **Methods:**

This national, multicenter, non-blinded randomized controlled trial (RCT) includes all four Swedish specialized centers (NHV) for endometriosis surgery and fertility treatments. 350 women (aged 18-38, BMI 18-30) with endometriosis stage III-IV are randomized 1:1 to either first-line surgery followed by ART or first-line ART. Exclusion criteria include previous endometriosis surgery, previous IVF/ICSI cycles, hemato-/hydrosalpinx, clear surgical indications, submucosal fibroids or intramural fibroids >4 cm, uterine malformations, and ART with donor oocytes.

Primary outcome is CLBR within three years. Secondary outcomes include pregnancy rate, miscarriage rate, recurrent implantation failure (RIF) rate, surgical or ART- related complications, quality of life, pain, healthcare costs and obstetric complications. Outcomes will be analyzed based on the intention-to-treat principle. The study will end when all patients enrolled in trial have been followed for three years after first treatment, withdrawn consent, or been lost to follow-up.

Planned start: Fall 2025

Ethical approval: 2024-04293-01

Funding: FORTE, Region Stockholm, ALF funds from Västra Götaland Region

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## **OP15: Modeling neuronal hyperexcitability with PTZ reveals microglial activation and impaired microglia–oligodendrocyte interactions in zebrafish larvae**

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Neuronal network hyperexcitability is increasingly recognized as an early feature of Alzheimer's disease (AD), potentially contributing to cognitive decline. However, how this activity affects glial communication and myelination remains unclear. Here, we modeled hyperexcitability in 5 days post-fertilization (dpf) zebrafish larvae using 2 mM pentylenetetrazole (PTZ) administered chronically for 24 hours. PTZ, a GABA-A receptor antagonist, blocks inhibitory signaling, increasing neuronal excitability and inducing seizure-like activity.

PTZ-treated larvae exhibited hyperactive behavior without experiencing toxicity. Using Rhod-4 AM, we performed calcium imaging of the optic tectum and found that PTZ-treated larvae had significantly larger and more frequent calcium spikes compared to controls, confirming sustained hyperexcitability. Analysis of Tg(apoe:GFP) and Tg(olig2:dsRed) transgenic lines showed no change in microglia or oligodendrocyte numbers, but chronic PTZ markedly reduced microglia–oligodendrocyte contacts. Moreover, PTZ-treated microglia also adopted an amoeboid morphology indicative of activation, accompanied by enhanced phagocytic activity as revealed by Acridine Orange staining.

The P2Y<sub>12</sub> receptor enables microglia to monitor neuronal activity and maintain network homeostasis via purinergic signaling. In AD, P2Y<sub>12</sub> is often downregulated as microglia adopt a disease-associated phenotype, impairing regulation of neuronal excitability and clearance of pathological proteins such as amyloid- $\beta$ . In Tg(Apoe:GFP); p2y<sub>12</sub><sup>+/-</sup> larvae, microglia–oligodendrocyte interactions were reduced to levels observed in wild-type larvae treated with PTZ. PTZ did not further diminish interactions in p2y<sub>12</sub><sup>+/-</sup>, although there was a trend toward a reduction, suggesting that microglia partially rely on this pathway to maintain contacts with oligodendrocytes.

Overall, we establish a subtoxic, functionally effective paradigm to study the impact of neuronal hyperexcitability. Our results indicate that hyperexcitability triggers microglial activation and disrupts microglia–oligodendrocyte connectivity, in part via P2Y<sub>12</sub> receptor. Future studies will examine how this loss of connectivity affects glial function and neuronal network stability, providing insight into early AD pathophysiology.

## OP16: Patients experiencing early PIRA show signs of disturbed remyelination

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### **Background & Aims:**

Disease progression in multiple sclerosis (MS) can be categorized into two distinct profiles: progression independent of relapse activity (PIRA) and relapse associated worsening (RAW). PIRA is a gradual worsening of disability, in which activated microglia and astrocytes cause chronic inflammation and neurodegeneration in the CNS. As MS is a demyelinating disease, it is important to investigate how myelin changes occur during the disease course. In healthy adults, the myelin content normally increases and reaches its peak at age 50. The aim was to study the evolution of the myelin content of PIRA and non-PIRA patients over a 5-year period.

### **Methods:**

Newly diagnosed patients with relapsing-remitting (RR)MS (n=98) were included in a 5-year prospective study and assessed yearly with neurological examination and synthetic magnetic resonance imaging (SyMRI). As control subjects, we included age and gender-matched symptomatic controls (SC, n=15). The patients were dichotomized in PIRA/non-PIRA. The brain parenchymal fraction (BPF), non-aqueous component (NAC) and myelin content (MyC) were measured by SyMRI with automatic tissue segmentation and volumetric measurements.

### **Results:**

At baseline, patients with PIRA, non-PIRA and SC had similar BPF, NAC and MyC. During the 5-year follow-up, MyC increased in non-PIRA patients (from 11.5 (IQR 10.9-12.3) to 12.1 (IQR 11.5-12.7),  $p=0.005$ ), but no changes were evident in PIRA patients (from 12.1 (IQR 11.0-12.5) to 12.0 (IQR 11.3-12.9),  $p=0.495$ ). MyC also increased in SC (from 11.9 (IQR 11.8-13.5) to 12.7 (IQR 11.7-13.3),  $p=0.031$ ). Despite that the brain atrophy increased over time in both groups, higher BPF at diagnosis reduced the risk of PIRA (OR 0.82, 95% CI 0.74–0.91,  $p=0.0004$ ).

### **Conclusion:**

While SyMRI showed similar rates of brain atrophy in both patients with and without PIRA, only the non-PIRA group showed evidence of increased remyelination. At the five-year follow-up, the myelin content in non-PIRA group was comparable with a healthy adult brain. Thus, pathological processes in PIRA patients appeared to decrease the capacity for remyelination. In early RRMS, the reduction of myelin content appears to be an important explanation for progression.

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## OP17: Unmasking C5aDesArg as a Functional Mediator of Human Neutrophil Activation

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### Background and Aims:

The anaphylatoxin C5a is amongst the most potent inflammatory proteins of the complement system and a potent activator of human neutrophils, orchestrating key effector functions essential for host defence. Its desarginated metabolite, C5aDesArg (cleaved from C5a by carboxypeptidases), has long been regarded as functionally elusive and biologically less active. This study aimed to characterise the functional capacity of C5aDesArg in relation to C5a and to examine how TNF primes neutrophil responses to these ligands.

### Methods:

Human neutrophils were treated with or without TNF to induce priming, then stimulated with C5a or C5aDesArg and assessed for responses including reactive oxygen species (ROS) production, intracellular Ca<sup>2+</sup> mobilisation, degranulation (defined as upregulated surface expression of intracellular granule-localised receptors) and chemotaxis. Surface expression of C5aR1 and C5aR2 following TNF treatment was also analysed by flow cytometry.

### Results:

Both C5a and C5aDesArg induced ROS production, intracellular Ca<sup>2+</sup> mobilisation, upregulation of CD11b, and chemotaxis. TNF priming further enhanced the ROS response to both ligands, an effect commonly associated with increased receptor expression on the plasma membrane. However, flow cytometric analysis revealed no change in surface levels of C5aR1 or C5aR2 following TNF treatment. Instead, TNF appeared to potentiate C5a/C5aDesArg-induced ROS production by increasing the surface expression of flavocytochrome b558 (the membrane component of the ROS-producing NADPH oxidase in neutrophils) and/or by amplifying intracellular signalling pathways that drive NADPH oxidase activation upon stimulation with C5a or C5aDesArg.

### Conclusion:

C5aDesArg elicits the same effector functions as C5a, albeit at higher concentrations for e.g. ROS production, indicating reduced potency yet preserved signalling capability. These findings demonstrate that C5aDesArg acts as a functional mediator of neutrophil activation and reveals a TNF-dependent priming mechanism that enhances complement-driven oxidative responses without upregulation of C5aR1 or C5aR2.

## OP18: Comparative Proteomics Reveal Eosinophilic Protein Enrichment in CD177pos Neutrophils

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### Background & Aims:

Neutrophils are the most abundant immune cells in peripheral blood, serving as the first responders to microbial infection and inflammation. Although traditionally viewed as a uniform population, a growing body of evidence now indicates that neutrophils are a heterogeneous group. CD177 is a marker of neutrophil heterogeneity expressed on 0% to 100% of cells, defining CD177-positive (CD177pos) and CD177-negative (CD177neg) subsets. Increased proportions of CD177pos neutrophils are observed in conditions such as periodontitis, polycythemia vera, systemic lupus erythematosus, and pregnancy. However, broader functional and proteomic distinctions between these subsets remain unclear. We aimed to investigate proteomic differences between CD177pos and CD177neg neutrophils.

### Methods:

High-resolution proteomics was applied to highly purified CD177pos and CD177neg neutrophil fractions. Flow cytometry, enzymatic cleavage of CD177, immunoprecipitation, and immunoblot analyses were used to validate key findings and identify potential protein–protein interactions.

### Results:

The two subsets shared largely similar proteomes, although CD177 was 21 times more abundant in the CD177pos subset, confirming effective separation. Unexpectedly, proteomic analysis revealed enrichment of eosinophil-associated proteins—including eosinophil peroxidase (EPX), major basic protein (PRG2), and galectin-10—significantly elevated in CD177pos neutrophils. Given that these eosinophilic proteins are intracellular and secreted by eosinophils, we hypothesized that they are selectively bound by CD177pos neutrophils. Flow cytometry confirmed detectable EPX signal on purified neutrophils, consistently higher on CD177pos cells. Enzymatic cleavage of CD177, followed by immunoprecipitation and immunoblotting, identified CD177 itself as a binding partner for EPX.

### Conclusion:

Although CD177 subsets share extensive proteomic similarity, CD177pos neutrophils uniquely exhibit enrichment of eosinophil-related proteins. These findings indicate that CD177pos neutrophils bind eosinophil granule proteins, with EPX likely interacting directly with CD177. This reveals previously unrecognized traits of a neutrophil subset with potential implications for immune cell interactions and functional behavior.

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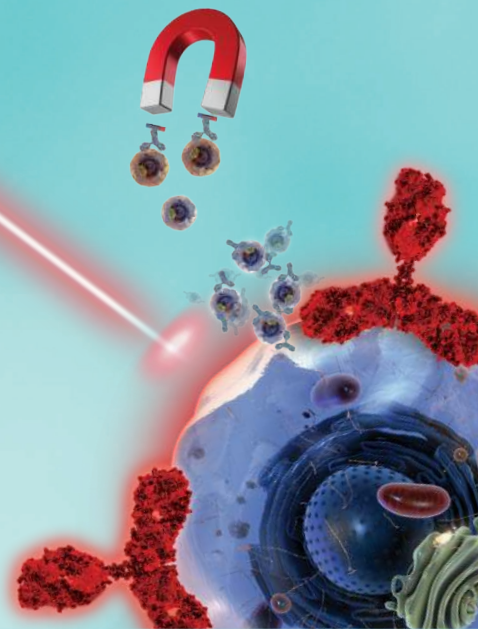
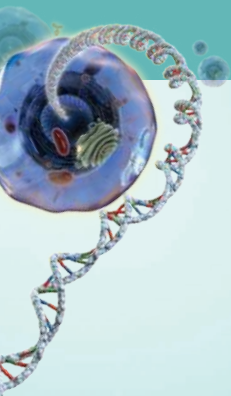
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## PP01: Decoding m6A Epitranscriptome-Mediated Regulation in High-Risk Neuroblastoma

**Vaid R**, Thombare K, Perla P, Mendez A, Lundberg KI, Burgos-Panadero R, Johnson Z, Ayyalusamy R, Djos A Bartenhagen C, Kogner P, Martinsson T, Johnsen JI, Fishcer M, Turner DS, Mondal T

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Epitranscriptomic regulation, particularly via N6-methyladenosine (m6A), plays a pivotal role in RNA metabolism and gene expression control. Although m6A dysregulation has been linked to several cancers, its contribution to neuroblastoma (NB) especially high-risk subtypes remains poorly defined. High-risk NB, frequently driven by MYCN amplification and/or the alternative lengthening of telomeres (ALT) phenotype, remains a clinical challenge due to its resistance to conventional therapies.

To explore m6A's functional role in NB pathogenesis, we established a novel MYCN-driven neuroblastoma model by differentiating embryonic stem cells into trunk neural crest cells (tNCCs) and subsequently into sympathetic neurons. MYCN overexpression in this system faithfully recapitulates the undifferentiated state observed in NB tumors. Leveraging this model, we discovered that MYCN and m6A act in concert to regulate the tNCC-to-sympathoadrenergic progenitor (SAP) cell transition. MYCN-driven dysregulation of m6A pathway genes promotes an undifferentiated, tumorigenic phenotype<sup>1</sup>.

To mechanistically dissect this axis, we optimized a low-input m6A RNA immunoprecipitation sequencing (m6A-RIP-seq) workflow, enabling the first transcriptome-wide m6A landscape analysis in MYCN-amplified NB. Our results demonstrate that NB-relevant transcripts are regulated in an m6A-dependent manner. Pharmacologic inhibition of METTL3 using STM2457 restored differentiation and, when combined with chemotherapy, significantly reduced tumor burden in MYCN patient-derived xenografts.

Furthermore, applying m6A-RIP-seq in ALT+ NB revealed a crucial role for m6A-modified TERRA RNA in telomere maintenance. ALT+ NB cells were particularly sensitive to m6A loss, as demonstrated in vitro and in vivo. Notably, STM2457-mediated m6A inhibition induced telomere damage in ALT+ NB<sup>2</sup>.

Building on these findings, we are now applying a highly sensitive multi-modification profiling method<sup>3</sup> optimized for low-input RNA in scarce clinical NB samples. More broadly, our work uncovers how RNA modifications shape cancer biology, with the ultimate goal of translating epitranscriptomic insights into novel prognostic markers and therapeutic strategies for high-risk NB.

Thombare, K... Mondal, T. et al. EMBO J 43, 6310-6335 (2024).

Vaid, R.... Mondal, T. et al. Nucleic Acids Res (2024).

Erdem Sendinc.... Gudrun Stengel et al, bioRxiv (2024)

## **PP02: Early establishment of small intestine neuroendocrine tumors**

**Schiller A**, Hultmark A, Lindberg M, Socratous A, Lujits T, Van den Eynden J, Elf A-K, Norrdlund RR, Arvidsson Y, Elias E, Larsson E

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Small intestine neuroendocrine tumor (SI-NET) is normally diagnosed late in life and has several unusual properties, including low proliferation rate, low mutation burden, lack of driver mutations, and frequent multifocality in the form of polyclonal tumor clusters. This sets SI-NET aside from other adult cancers and raises questions about the timeline of initiation and progression. Here, we investigated the evolutionary history of multifocal and unifocal SI-NET using whole genome sequencing data, obtaining timing information on primary tumors, metastases and key genetic events. Despite the late onset, the results indicated that major genetic alterations and the establishment of advanced metastatic tumor cell clones can often be traced back to childhood or adolescence in SINET. This was validated by re-examination of archival CT/MR scans, allowing longitudinal tracking of individual tumors up to 12 years prior. Metastases were detected at a high degree of consistency in the historical imaging data and estimated growth rates suggested several additional decades of tumor expansion. Collectively, our data support that slow growth of advanced lesions over half a century or more may precede SI-NET diagnosis in late adulthood.

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## **PP03: Surgery-Induced Expansion of Myeloid-Derived Suppressor Cells and Loss of Cytotoxic Lymphocyte Function Predict Poor Survival in Pancreatic Ductal Adenocarcinoma**

**Johnsson O**, Nilsson MS, Kiffin R, Bourghardt Fagman J, Vilhav C, Bratlie SO, Naredi P, Hellstrand K, & Martner A

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### **Background:**

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with high recurrence rates even after curative-intent resection. Mounting evidence suggests that surgical stress triggers systemic inflammation and transient immunosuppression, potentially facilitating tumor relapse. Myeloid-derived suppressor cells (MDSCs) and dysfunctional natural killer (NK) cells have emerged as key mediators of this process. We hypothesized that surgery-induced immune dysregulation, partly driven by NADPH oxidase 2 (NOX2)-derived reactive oxygen species (ROS), impairs postoperative antitumor immunity and worsens clinical outcomes.

### **Methods:**

Peripheral blood mononuclear cells (PBMCs) from 30 PDAC patients enrolled in the IPEP trial (ethical approval number 057-18) were collected preoperatively and postoperatively (day 1 and days 3–5). Single-cell transcriptomic and proteomic profiling (BD Rhapsody) was performed to characterize immune cell populations and activation states. Frequencies of key immune subsets and surface receptor expression were analyzed longitudinally and correlated with relapse-free survival and overall survival.

### **Results:**

Analysis of 445,152 immune cells revealed major postoperative shifts in circulating leukocyte composition. NOX2-expressing monocytic MDSCs (M-MDSCs) expanded markedly on postoperative day 1 ( $p < 0.0001$ ) and remained elevated through days 3–5. Conversely, cytotoxic CD8<sup>+</sup> T cells and NK cells significantly declined in numbers after surgery ( $p = 0.008$  and  $p = 0.0003$ , respectively), where NK cells in addition showed reduced expression of the activating NK cell receptors NKp30 and DNAM-1 postoperatively. Patients with high M-MDSC frequencies after surgery exhibited significantly poorer overall survival ( $p = 0.017$ ).

### **Conclusions:**

Pancreatic cancer surgery induces profound immunological remodeling characterized by M-MDSC expansion and suppression of cytotoxic lymphocyte function. These changes are associated with adverse clinical outcomes, suggesting that early postoperative immune dysfunction may promote recurrence. Targeting NOX2-dependent immunosuppressive pathways represents a promising strategy to preserve antitumor immunity and improve survival after PDAC surgery.

## **PP04: The role of TRAIL/TRAIL-receptor bidirectional signaling for NK-cell cytotoxicity against neuroblastoma cells**

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### **Background & Aims:**

Neuroblastoma (NB) is the most common pediatric extracranial solid malignancy, characterized by low MHC class I expression and therefore an ideal target for natural killer (NK) cell-based therapies. NK cells kill cancer cells by the release of cytotoxic granules or by ligating death receptors using ligands, such as TRAIL. Recent reports suggest that TRAIL ligation may result in bidirectional signaling. We investigated the role of TRAIL/TRAIL-receptor interplay and reverse signaling for NK cell responses towards NB with the long-term goal of developing novel NK-based immunotherapeutic strategies in neuroblastoma.

### **Methods:**

We performed functional assays using neuroblastoma cells (SK-N-AS or KELLY) incubated with pre-activated NK cells with maximized TRAIL expression. To pinpoint the involvement of TRAIL-Rs in the NK degranulation process, we either disabled the binding to TRAIL with TRAIL-R1/R2-blocking antibodies or knocked down the receptors. To estimate the significance of death receptors for the degranulation process, we independently blocked signaling from NK cell receptors (NKG2D/NKp46/DNAM-1), and compared the results.

### **Results:**

We found that SK-N-AS and KELLY express TRAIL-R2 and that they trigger substantial NK cell degranulation and cytotoxicity. TRAIL-R1/R2 blockade reduced NK cell degranulation more than blockade of the major activating receptors NKG2D and DNAM-1, and to a similar extent as NKp46 blockade. Combined blockade of TRAIL-Rs and activating receptors, almost completely rescued neuroblastoma cells from NK cell killing. Furthermore, the knock-down of TRAIL-R1/R2 molecules reduced neuroblastoma cell death killing and significantly reduced the NK cell degranulation towards neuroblastoma cells. All data point towards a notable role of the TRAIL-TRAIL-R1/R2 complex in NK-cell activation.

### **Conclusion:**

Our findings suggest bidirectional TRAIL signaling upon NK cell interaction with neuroblastoma cells. Blockade/knock-down of TRAIL-R1/R2 did not only reduce NK cell killing of SK-N-AS/KELLY but also strongly reduced granule-mediated cytotoxicity of NK cells, highlighting the importance of TRAIL in NK cell signaling.

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## **PP05: Use of the cell division assay to evaluate T cell toxicity in response to <sup>177</sup>Lu-DOTATATE peptide receptor radionuclide therapy**

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Lyytikäinen A , Hammarsten O , Johansson P

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<sup>177</sup>Lu-DOTATATE therapy improves survival in patients with metastatic neuroendocrine tumors (NETs), but bone marrow toxicity limits treatment dose. There is considerable inter-individual variation in hematological side effects, and current absorbed dose estimates lack the precision needed for individualized treatment planning. This may reflect both technical limitations and intrinsic differences in patient radiosensitivity. However, no routine clinical assay exists to assess this sensitivity.

We previously developed a Cell Division Assay (CDA) to quantify T cell sensitivity to cytotoxic agents. The assay measures cell division as a surrogate for survival and is suitable for suspension cells like peripheral blood T cells. In this study, we applied the CDA to evaluate normal T cell sensitivity to <sup>177</sup>Lu-DOTATATE across a range of activity concentrations. This allows investigation of dose-dependent biological toxicity and may help identify patients at increased risk of hematological side effects, supporting more personalized PRRT planning.

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## PP06: Read-Level Methylation Analysis of cfDNA Using Targeted EM-seq for CNS Tumor Classification

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*Department of Medical Biochemistry and Cell Biology, Institute of Biomedicine, University of Gothenburg - Sahlgrenska Academy*

### Background & Aims:

Accurate classification of central nervous system (CNS) tumors is essential for treatment planning. DNA methylation profiling offers high diagnostic power, and circulating cell-free DNA (cfDNA) enables minimally invasive analysis. We evaluated targeted TWIST Enzymatic Methyl-sequencing (EM-seq) for cfDNA-based CNS tumor classification.

### Methods:

cfDNA data were processed with nf-core/methylseq and MethylDackel to obtain read-level methylation ratios. Methylation windows were analyzed using alpha (read-level) and beta (site-level) metrics, followed by PCA and AUC-based binary classification. Marker filtering with 450K array data was tested to remove blood-derived features.

### Results:

EM-seq profiles correlated strongly with Illumina EPIC arrays ( $r > 0.96$ ) and reflected similar copy number alterations, validating EM-seq as a low-input alternative.

A new outlier approach identified stochastic “pure” tumor signals detectable at moderate sequencing depth. Signal quantification—based on counting discrete clusters normalized to shuffled controls—accurately separated patients from healthy controls. Beta using all reads performed well; beta using short reads was unstable; alpha provided the most robust classification.

Tumor subtype classification performance was moderate: meningioma versus lymphoma ( $AUC > 0.9$ ), IDH-mut gliomas versus lymphoma/meningioma ( $\approx 0.8$ ), and IDH-mut versus IDH-wt gliomas ( $\approx 0.8$ ). Sensitivity was maintained at 5% tumor fraction (specificity 0.81).

### Conclusion:

This study establishes targeted EM-seq as a reliable cfDNA-based methylation assay and introduces an outlier-driven framework for detecting stochastic tumor-specific signals in liquid biopsy.

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## PP07: The mutational landscape of endometrioid ovarian carcinoma

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### **Background:**

Endometrioid ovarian carcinoma (EOC) constitutes approximately 10% of epithelial ovarian cancer and displays a large molecular heterogeneity. Current treatment of EOC adheres to a relatively uniform approach with few personalized therapies available. Mapping the mutational landscape of EOC could contribute to identifying biomarkers linked to personalized therapies and guiding treatment decisions. Herein, we aimed to identify biomarkers for prognostic stratification of EOC using both molecular and clinical data from a cohort of 49 EOC in Western Sweden.

### **Methods:**

Forty-nine patients diagnosed with EOC (2000-2020) were identified from the biobank at the Department of Pathology, Sahlgrenska University Hospital, Gothenburg. DNA sequencing of all tumors was conducted with GMS560, performed by SciLifeLab, Clinical Genomics Gothenburg and Bioinformatics and Data Centre (BDC). Twenty-two tumors were sequenced using an in-house gene panel, constructed with Simple multiplexed PCR-based barcoding of DNA for sensitive mutation detection using sequencing (SiMSen-Seq), targeting 69 hotspot regions in 17 genes.

### **Results:**

The cohort included 39 low-grade and 10 high-grade tumors (28 FIGO stage I; 9 stage II; 10 stage III; 2 stage IV). Stringent filtering was applied to the GMS560 data, identifying 753 single nucleotide variants across 313 genes. The most recurrently mutated genes were CTNNB1 (34.7%), PIK3CA (28.6%) and PTEN (24.5%). In low-grade/early-stage tumors, CTNNB1 and PIK3CA were the most frequently mutated genes, while TP53 and CTNNB1 were predominant in high-grade/advanced stage tumors. Four tumors exhibited a hypermutated profile with significantly higher tumor mutational burden. The two sequencing approaches showed high concordance, where 20/22 (90.9%) patients had  $\geq 1$  mutation also detected by the in-house gene panel, which successfully detected all GMS560 mutations covered by the included amplicons.

### **Conclusions:**

Collectively, this study offers a descriptive, yet exploratory assessment of genetic variants in EOC, bridging the knowledge gap in prognostic molecular features for this underexplored histotype.

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## PP08: Tumor Associated Mutations in Liquid Biopsies from the Gynecological Tract

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### **Background:**

In recent years, liquid biopsies have emerged as a non-invasive approach to detect cell-free DNA (cfDNA) in various biological fluids, including blood, urine, and saliva. Samples from the gynecological tract can also be utilized to identify cfDNA originating from gynecological lesions such as ovarian cancer and endometriosis. This study aims to evaluate different sample types and conditions in terms of their suitability in detecting cfDNA.

### **Method:**

The cohort consists of 36 women with ovarian malignant (n=13), benign (n=22), or borderline (n=1) lesions. Cervical samples include cytology preservative ThinPrep supernatant (n=15) and ThinPrep pellet (n=26); vaginal samples include DNA preservative Abbott supernatant (n=15), NaCl supernatant (n=15), NaCl pellet (n=15), and Cobas supernatant (n=10). The sample conditions tested are 4°C > 4h, room temperature (RT) > 4h, 4°C for 48h, and RT for 48h. Libraries were generated with UMI SiMSen-seq using a panel targeting mutations associated with gynecological cancer and endometriosis. The median DNA input per reaction was 10 ng (range 1,76–20,58 ng). Statistical analyses were performed using Kruskal-Wallis tests and pairwise Wilcoxon tests with Bonferroni adjustment in RStudio.

### **Results:**

True variants were identified across all sample types and conditions, with VAF between 0,002 and 0,532. Significant differences were observed in coverage ( $p=1,61 \times 10^{-15}$ ), and concentration of libraries ( $p<2,2 \times 10^{-16}$ ) between different sample types. Additionally, there is a significant difference in coverage ( $p=6.44 \times 10^{-9}$ ) between supernatant and pellet, where the pellet generally has higher coverage, but not in concentration of the libraries. Moreover, no significant differences were found between conditions in preliminary results.

### **Conclusions:**

Tumor-associated mutations can be detected in cfDNA from various gynecological sample types. Although sample types differ in DNA yield and coverage, cfDNA remains detectable across tested storage conditions. Liquid biopsies from cervical and vaginal samples show potential for non-invasive detection of gynecological lesions such as ovarian cancer and endometriosis.

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## **PP09: Temporal trends in preterm delivery rate over 30 years in a country lacking national preventive strategies: a register-based study**

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### **Objectives:**

To investigate the preterm delivery rate trends from 1991-2021 overall and by traditional risk factors in Sweden, a country lacking national preventive strategies.

Participants (Instead of patients or subjects) 3,264,146 pregnancies registered in the Swedish Medical Birth Registry with available information on gestational duration and onset of delivery (1991 – 2021).

### **Main Outcome Measures:**

The primary outcomes were the overall, spontaneous and iatrogenic preterm delivery rate among all the deliveries between 1991 - 2021. Using logistic regression model, we investigated whether maternal age at conception, use of artificial reproductive technologies, smoking, parity, and maternal continent of birth affected the observed trends.

### **Results:**

Between 1991 - 2021, we observed an increase in maternal age at conception, use of artificial reproductive technologies and deliveries from women of born in African or Asian countries, and a decrease in smoking prior to pregnancy. The overall preterm delivery rate was stable between 1991 - 2005 (0.055; 95% CI: 0.054, 0.056 in 1991) but decreased thereafter to 0.048 (95% CI: 0.047, 0.049) in 2021. The strongest decline was observed in late preterm deliveries, with a decline from 0.0402 (95% CI: 0.0391, 0.0413) in 1991 to 0.0352 (95% CI: 0.0341, 0.0363) in 2021, followed by moderate preterm delivery (0.0072; 95% CI: 0.0067, 0.0077 in 1991 to 0.0053; 95% CI: 0.0049, 0.0058 in 2021). We observed a decreased preterm delivery rate in women born in European, Asian and African countries, with biggest decline observed in the latter (rate in 1991 = 0.026, 95% CI: 0.017, 0.039; rate in 2021 = 0.017, 95% CI: 0.014, 0.021).

### **Conclusions:**

While the rates of preterm delivery have increased globally, here we show that the rates have decreased in Sweden from 1991 - 2021, despite the lack of any nation-wide preventive strategy.

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## PP10: Targeting dopaminergic dysfunction in fragile X syndrome

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Fragile X Syndrome (FXS) is the most common genetic cause of autism spectrum disorder (ASD), resulting from a mutation in the FMR1 gene that leads to the absence of Fragile X Messenger Ribonucleoprotein (FMRP) and dysregulated protein synthesis. Individuals with FXS frequently display autism-like behaviors, including social deficits, communication impairments, and repetitive behaviors, which have been linked to dopaminergic system dysfunction, particularly in the striatum. This study investigated the potential of a novel dopamine stabilizer with antipsychotic properties, to modulate dopamine regulation and improve behavioral outcomes in a mouse model of FXS. Behavioral assessments were conducted in Fmr1 knockout and wild-type mice to evaluate the effects of (-)-OSU6162 on motor activity, social interaction, and repetitive behaviors. Striatal dopamine levels were also measured to explore the neurochemical effects of the treatment. The results demonstrated that (-)-OSU6162 attenuated dopamine dysregulation in the striatum of Fmr1 knockout mice and was associated with reduced hyperactivity and repetitive behaviors, and improved social interaction. These findings suggest a promising therapeutic approach for addressing core behavioral symptoms in FXS by stabilizing dopaminergic signaling.

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## PP11: Longer breastfeeding duration is associated with reduced risk of coronary artery calcification

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### Background and Aims:

Cardiovascular disease (CVD) is the number one cause of death among women worldwide. While parity increases the risk, breastfeeding is a suggested protector. However, previous literature on the association between breastfeeding and subclinical CVD is limited. We therefore aimed to determine the association between breastfeeding duration on markers of subclinical CVD.

### Methods:

Parous women aged 50-64 years, taking part in the Umeå sub-cohort of SCAPIS (Swedish CARDioPulmonary Bioimage study) were included. Outcomes were presence of carotid plaque, segment involvement score (SIS) ( $\geq 1$  vs. 0), and coronary artery calcification score (CACS) ( $\geq 1$  vs. 0). Participants who completed breastfeeding questions and had valid data for at least one outcome were included. Each analysis was restricted to those with valid data for the respective outcome. For each woman, the average duration of exclusive and any breastfeeding per child was calculated. Associations were assessed using multivariable logistic regression.

### Results:

Among 947 women, 28.6% had CACS  $\geq 1$ . Mean (SD) duration of exclusive and any breastfeeding per child, were 4.6 (2.7) and 8.3 (5.0) months, respectively. Among 928 participants with valid CACS data, longer duration of any breastfeeding per child was significantly associated with lower OR of CACS  $\geq 1$ . Specifically, after adjustment for age, education, smoking, pre-pregnancy BMI, number of births, family history of cardiometabolic disease and reproductive health history, the odds of CACS  $\geq 1$  decreased by 4% (0.96 (0.93;1.00,  $p=0.02$ )) per additional month of any breastfeeding per child. Duration of exclusive breastfeeding per child did not significantly impact CACS. Further adjusting for CVD risk factors in midlife and adult weight change yielded similar results. No associations were observed with carotid plaque or SIS.

### Conclusions:

Longer duration of any breastfeeding per child was associated with reduced odds of CACS in midlife, suggesting potential long-term cardiovascular benefits of breastfeeding.

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## PP12: Targeted delivery of mRNA to the heart via tissue-specific extracellular vesicles or lipid nanoparticles

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Efficient and specific delivery of mRNA to target tissues is critical for maximizing therapeutic benefits while minimizing off-target effects and systemic toxicity. Systemic administration of mRNA using lipid nanoparticles (LNPs) or extracellular vesicles (EVs) typically leads to accumulation in the liver. We hypothesized that cardiac-specific EVs, being adapted to their tissue of origin, could more effectively direct mRNA delivery to the heart, compared to non-cardiac-specific EVs or LNPs. In mice, intravenous administration of cardiac progenitor cell-derived EVs (CPC-EVs) achieved the most efficient delivery of modified mRNA encoding vascular endothelial growth factor A (VEGF-A) to the heart, with minimal liver accumulation relative to non-cardiac EVs and LNPs. Cytokine profiling across eight organs revealed that LNP delivery triggers a widespread pro-inflammatory response, whereas CPC-EVs elicit only a localized and restricted cytokine activation, mainly in the lung and plasma, showing a more favorable safety profile. Furthermore, intracardiac injection of CPC-EVs not only led to efficient mRNA uptake by cardiac tissue and robust VEGF-A protein expression, but also minimal global transcriptomic perturbation, as confirmed by RNA-seq. In contrast, LNPs and non-cardiac EVs induced widespread perturbation in gene expression. Functionally, VEGF-A mRNA delivery via CPC-EVs markedly increased CD31 and  $\alpha$ -SMA expression and vessel formation in ex vivo aortic ring assays, confirming enhanced angiogenic potential. Collectively, these findings suggest that CPC-EVs are superior in cardiac-targeted mRNA delivery, offering enhanced specificity, reduced liver accumulation, minimal off-target transcriptomic perturbation as well as restricted and organ-specific cytokine response and improved functional outcomes.

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## PP13: Aesthetic Treatment With Resin Infiltration In Teeth With Mild Fluorosis – A Long Term Follow-up

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### **Background:**

Dental fluorosis is a developmental defect in the enamel due to systemic exposure to high levels of fluoride during the period of tooth development. The developmental defect is a hypomineralisation, visible as whitish opacities in the enamel leading to a speckled appearance of the tooth. Mild dental fluorosis is not considered to give symptoms nor increase the risk for oral diseases, though affected people might complain on impaired aesthetic appearance. Resin infiltration (RI) is one option for aesthetic treatment, intending to fill the hypomineralised areas in the enamel, thereby masking the signs of the tooth's speckled appearance.

### **Scientific Question:**

How is resin infiltration affecting the aesthetic appearance of teeth with mild dental fluorosis in a long-term perspective?

### **Methods:**

13 patients aged 13-31 years, with mild fluorosis on their maxillary anterior teeth were included. The teeth (n: 74) were treated with ICON infiltrating resin (DMG, Hamburg, Germany). The aesthetic appearance was evaluated by researcher assessing the intraoral photos taken prior RI treatment (T0), immediately after treatment (T1), 2 weeks after the treatment (T2), and 1 year (T3) after the treatment. The aesthetic appearance of all treated teeth was evaluated as: worsened, unchanged, and improved compared to photos prior treatment (T0).

### **Results:**

The analysis showed that 49 teeth were evaluated to have improved aesthetic appearance at T1. At T2 and T3 there were 50 teeth graded having improved aesthetic appearance. There were 22 teeth estimated to be unchanged considering appearance at T1 and T3, and 21 teeth at T2. At T1 and T2 there were three teeth graded as worsened compared to T0, and two at T3.

### **Conclusion:**

For mild dental fluorosis, the aesthetic appearance is immediately improved by treatment with resin infiltration and the result is maintained in the long-term perspective.

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## PP14: The Association of Stress and Periodontitis with Low Birth Weight and Preterm Delivery in Danish Pregnant Women: A Cohort Study

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### **Introduction:**

Pregnancy-related hormonal changes may adversely affect oral health and increase the risk of periodontitis. Periodontitis has been associated with preterm birth (PTB) and low birth weight (LBW). Maternal stress has also been proposed as potential risk factor for adverse birth outcomes, but the combined effect of stress and periodontitis on such outcomes remains unclear.

### **Aim:**

To investigate the association between periodontitis and (PTB and/or LBW) and whether this association is influenced by perceived stress.

### **Methods:**

This prospective cohort study included 552 Danish pregnant women. Demographic data were collected via questionnaire. Stress was assessed using the Perceived Stress Scale (PSS-10), and periodontitis was diagnosed clinically by a trained dentist. Both the survey and clinical examinations were conducted between gestational weeks 11 to 20. Logistic regression and interaction tests estimated crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for PTB and LBW.

### **Results:**

Of the participants, 11% had healthy gums, 56.7% gingivitis, and 32.3% periodontitis. Smoking and lower education were significantly more common among those with periodontitis ( $p < .001$ ). Neither periodontitis (aOR for PTB = 0.95, CI: 0.28–3.17; LBW = 1.44, CI: 0.29–7.15) nor stress (aOR for high stress and PTB = 0.98, CI: 0.42–2.28; LBW = 1.09, CI: 0.39–3.03) was significantly associated with PTB or LBW. No significant interaction between stress and periodontitis was observed.

### **Conclusion:**

This study did not find statistically significant associations between maternal periodontitis, perceived stress, or their interaction and PTB or LBW. However, larger studies are needed to confirm these findings and investigate the possible relevance of dental health and stress during pregnancy.

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## PP15: Bone again: Re-Osseointegration of Disrupted Titanium Implants

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Restoration of skeletal integrity and function often relies on metal implants whose long-term success depends on a direct structural and functional connection between bone and implant, known as osseointegration [1]. Despite high clinical success rate, implant failures still occur. Although re-osseointegration following interface disruption has been reported [2, 3], the biological and biomechanical responses remain insufficiently understood. This study used our new preclinical model [3] to investigate how biomechanical, tissue, and cellular responses contribute to re-osseointegration.

Screw-shaped titanium implants were alkali-modified (5M NaOH, 60 °C, 24 h) and heat-treated (200 °C, 24h) to create a submicron-rough surface. One implant per tibia was inserted into the tibiae of female Sprague Dawley rats. After 28 days of unloaded healing, mechanical overload was induced by surgically exposing and snap-rotating selected implants 90°, then returning them to their initial position. Control implants were exposed but not rotated. Animals were sacrificed immediately or after 3, 7, or 28 days post-disruption. Implant stability was assessed by removal torque testing, while peri-implant tissues were analysed by X-ray micro-computed tomography, histomorphometry, histology, and electron microscopy.

Immediately following disruption, implant stability declined due to loss of bone-implant contact and peri-implant bone damage. Stability was fully restored by 28 days. The regenerative response occurred in stages: at 3 days, a provisional connective tissue matrix and a strong pro-osteogenic response were observed; by 7 days, extensive new bone formation occupied the peri-implant space; and by 28 days, bone had remodelled with no signs of disruption sequelae. Enhanced bone formation indicates that the disruption-response was not merely reparative but adaptive to mechanical trauma.

These findings demonstrate that re-osseointegration of mechanically disrupted titanium implants can occur under non-pathological conditions, where mechanical overload triggers a regenerative cascade restoring bone-implant integrity and stability.

1F.A. Shah et al (2018) Acta Biomater, 84:1-15. 2C-J. Ivanoff et al (1997) Int J Oral Maxillofac Implants, 26(4):310-5. 3M. Jolic et al (2025) Biomater Sci, PMID: 41111326.

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## PP16: Carboxymethyl nanocellulose as a bioink for adipose tissue reconstruction

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3D bioprinted adipose tissue (AT) is a promising option for reconstructive surgery. By generating replacement tissues in vitro, the need for complicated and invasive surgery is reduced. However, there is a need for suitable bioinks, possessing both appropriate biological, mechanical and physiochemical properties. Carboxymethyl cellulose (CMC) is a biocompatible cellulose derivative with reactive carboxyl groups, enabling additional chemical modifications. In addition, it can be dimensionally stabilized through ionic crosslinking, removing the need for additional components added to the bioink to stabilize the printed construct.

In this study, we evaluated CMC as a one-component bioink for reconstruction of autologous adipose tissue through implantation of solid grafts produced through 3D bioprinting.

### **Method:**

Bioink formulations composed of pure CMC, CMC combined with human AT and CMC-AT-alginate (ALG) were prepared and 3D bioprinted using an extrusion-based 3D printer. Scaffolds were crosslinked through ionic gelation ( $\text{Ca}^{2+}$ ), and the implanted in vivo in Balb/c mice. After 30 days, the scaffolds were explanted and studied macroscopically before preserved through chemical fixation pending histological evaluation. Rheological evaluations were performed on scaffolds on the day of implantation and explantation, and the elastic modulus was measured through unconfined compression and nanoindentation.

### **Results:**

The in vivo results demonstrated that 3D printed CMC or CMC-AT scaffolds did not retain its 3D shape in vivo. However, through the addition of ALG, the 3D graft remained dimensionally stable for 30 days in vivo, with excellent retention of fat as indicated by their size and bright yellow colour. Unconfined compression analysis confirmed that although initial stiffness dropped significantly over the time in vivo, the resulting stiffness after 30 days remained within the same order of magnitude as native adipose tissue.

### **Conclusion:**

From our preliminary results, we conclude that CMC is a promising biomaterial as a bioink for 3D printing adipose tissue for soft tissue reconstruction that warrants further study and optimization.

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## **PP17: The Centre for Cellular Imaging (CCI): Open-Access Microscopy and Image Analysis Services for All Researchers**

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The Centre for Cellular Imaging (CCI) at the University of Gothenburg is an open-access research infrastructure providing advanced light, electron, and correlative microscopy services to researchers across disciplines. As part of Core Facilities, SciLifeLab and Euro-BiolImaging, CCI offers cutting-edge imaging technologies and expert support—from sample preparation to data analysis—accessible to all researchers within the Sahlgrenska Academy, the wider University of Gothenburg, and beyond, including national and international academic and industrial partners.

Our services cover the full imaging workflow, including user training for independent access, collaborative projects with expert guidance, and comprehensive project support where facility staff assist with imaging and analysis in close dialogue with users. This collaborative approach ensures that data acquisition and processing align precisely with each project's scientific goals. We also provide consultation for grant applications, assist in the development of novel imaging methods and workflows, and offer data management solutions through our OMERO-based infrastructure to ensure FAIR data practices.

We warmly invite researchers from all fields of biomedical and life sciences to discover how CCI can support their imaging needs. Our goal is to tailor our services to your projects and establish collaborations that advance research through state-of-the-art microscopy and image analysis.

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## **PP18: Large -scale protein-disease risk association analysis in the UK Biobank: Introducing an extensive and freely available research resource in Olink® Insight**

**Henry L, Caster O, Fagerberg L, Andersson H, Grundberg I**

*Olink®, Part of Thermo Fisher Scientific*

With increased sample throughput and highly parallelized assaying capabilities, proteomics has emerged as an indispensable tool in biomarker discovery for the detection, prognosis, and treatment of disease. The UK Biobank (UKB) Pharma Proteomics Project (PPP) is a prime example of large-scale proteomics, with protein-level quantification of plasma samples from more than 50,000 individuals. Using Olink® Explore technology, the UKB-PPP generated data on nearly 3,000 proteins for the >50,000 individuals. The ability to combine proteomic data with e.g., genomic or healthcare data in UKB presents rich research opportunities in biology and medicine. This study aimed to estimate the future risk of a large and diverse set of diseases for all protein biomarkers available in UKB, thus, generating a library of protein disease risk associations freely available to researchers worldwide.

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## **PP19: Specialist palliative care support in primary care: identifying needs and building collaborative models**

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Changes in healthcare organisation have led to regional and municipal primary care assuming an increasingly central role in providing general palliative care for individuals at home and in residential facilities. Specialised palliative care consultation services can serve as a support for primary care by offering expert knowledge and promoting competence development. However, clear guidelines for how such functions should be designed to meet the needs and conditions of primary care are lacking.

### **Aim:**

This study explores the prerequisites for and the need for specialised palliative care consultation services within regional and municipal primary care, as well as to develop a practically applicable model.

### **Method:**

The project comprises four phases: (1) group discussions with healthcare professionals and managers in primary care and palliative consultation teams, (2) descriptive analysis of recordings from the group discussions, (3) interdisciplinary workshops based on the results to develop a practically applicable model, and (4) compilation and reporting of findings for future implementation studies. To date, 26 participants have been included, representing healthcare staff and managers within primary care and palliative consultation teams. Six focus groups and interviews have been completed.

### **Preliminary Results:**

The analysis indicates that both primary care staff and palliative consultation teams identify a need for support in general palliative care. Consultations are seen as a potential tool, but their design must be adapted to the specific context of primary care. Making the palliative consultation services visible is considered essential but is hindered by the large number of actors within primary care. Geographic and organisational variations, as well as a lack of cooperation guidelines, present additional challenges.

### **Conclusion:**

Specialised palliative care consultation services have the potential to strengthen palliative care within primary care, provided they are tailored to local needs and conditions. Visibility and the collaborative structures are crucial to realising this potential.

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## PP20: Suicide Risk in Postpartum Psychosis: A Nationwide Swedish Study (1973–2020)

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### **Background and Aims:**

Postpartum psychosis is a psychiatric emergency that occurs shortly after childbirth, marked by severe mood or psychotic symptoms, rapid fluctuations, and sometimes confusion. The low incidence, of 1–2 cases per 1,000 deliveries, and lack of defined criteria have hampered large-scale studies on prognosis and outcomes. Previous studies have found suicide rates of 4–11% in clinical samples, but large register-based studies on suicide risk are lacking. The aim of this study was to investigate suicide risk in postpartum psychosis in the entire Swedish population over the period 1973–2020.

### **Methods:**

We identified childbirths in the Medical Birth Register. Postpartum psychosis was defined as a psychiatric hospitalization within two months after giving birth, identified in the National Patient Register. Both certain and uncertain suicides were identified in the Cause of Death register. Cox proportional hazards regression was applied to assess suicide risk, with presence or absence of postpartum psychosis, birth date, and country of birth (categorized as within or outside the EU/Nordic region) included as covariates. Survival time was calculated from first childbirth or postpartum psychosis onset to next childbirth, suicide, emigration, or non-suicide related death.

### **Results:**

During the study period 2,103,378 women gave birth to their first child. Of all parous women, 4,786 had died by suicide (0.23%). We identified 3,001 women with postpartum psychosis, of whom 109 had died by suicide (3.6%). In women with postpartum psychosis, the hazard ratio of suicide was 18.8 (95% CI 15.3–23.2) compared with parous women without postpartum psychosis, after adjusting for age at delivery, and country and year of birth.

### **Conclusion:**

Our results confirm a high risk of suicide after postpartum psychosis, comparable to the risk of suicide in major psychiatric disorders such as bipolar disorder and schizophrenia.

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## **PP21: Longitudinal associations between substance use and mental health outcomes in Swedish adolescents - results from the STARS cohort**

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### **Background & Aims:**

Adolescent mental health concerns are increasing, while substance use – though declining – remains a significant issue. To clarify the temporal dynamics between these two constructs during adolescence, we examined the reciprocal associations of substance consumption with stress and psychosomatic symptoms across ages 13 to 18.

### **Methods:**

In the longitudinal STudy of Adolescence Resilience and Stress (STARS) cohort in Western Sweden (n=1255, 62% female), we assessed the prevalence of substance use and conducted a cross-lagged panel analysis, using generalized structural equation models with an ordered logit link function. Over three timepoints (ages 13, 15 and 18) we evaluated if use of substances (low- and high-alcoholic beverages, cigarettes and snus) was associated with subsequent self-reported stress and psychosomatic symptoms and vice versa.

### **Results:**

The prevalence of all forms of substance use increased markedly with age. Substance use differed substantially between the sexes, with females consuming more cigarettes and high-alcoholic beverages while males used more snus, low-alcoholic beverages and illicit drugs. Higher levels of stress and psychosomatic symptoms at age 13 were associated with increased odds of substance use at age 15, especially in females. The association was partially significant between ages 15 and 18. We did not observe any significant predictive relationship between substance use and subsequent stress or psychosomatic symptoms.

### **Conclusion:**

It is important to provide extra support to individuals facing mental health challenges when working toward reducing substance use.



## PP22: Insulin-like growth factor axis dysregulation is associated with structural brain changes in bipolar disorder

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### **Background:**

Insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) are essential for maintaining neuronal health and cortical integrity. Altered IGF signaling and structural brain alterations have both been implicated in the neuropathology of bipolar disorder (BD). This study investigated whether cerebrospinal fluid (CSF) levels of IGF-II and IGFBP-3 are associated with brain morphology at baseline and structural changes over a 7-year follow-up.

### **Methods:**

Baseline levels of CSF IGF-II and IGFBP-3 were quantified in 93 euthymic individuals with BD and 64 age- and sex-matched healthy controls using nanoscale liquid chromatography-mass spectrometry. Magnetic resonance imaging was used to estimate hippocampal, amygdalar, and lateral ventricular volumes, as well as cortical thickness in predefined regions of interest. Longitudinal change was defined as percentage change.

### **Results:**

CSF IGFBP-3 levels were higher in BD than in controls ( $p = 0.03$ ), whereas CSF IGF-II showed a non-significant trend toward higher levels ( $p = 0.055$ ). At baseline, hierarchical linear regression analyses showed that higher CSF IGF-II and IGFBP-3 levels were associated with larger ventricular volumes across participants. Additionally, higher IGFBP-3 was associated with lower cortical thickness in the inferior frontal gyrus and motor cortex. Longitudinally, a significant IGFBP-3  $\times$  group interaction showed that higher IGFBP-3 was associated with higher cortical thickness in BD, but not in controls, across the inferior frontal gyrus, motor, somatosensory, and middle occipital cortices.

### **Conclusions:**

CSF IGFBP-3 was elevated in euthymic BD individuals and, across the cohort, associated with ventricular enlargement and reduced cortical thickness. Longitudinal analyses demonstrated illness-dependent divergence in cortical trajectories, with higher IGFBP-3 associated with cortical thickening and lower levels with cortical thinning in BD only. These findings suggest that IGF axis dysregulation may contribute to structural brain alterations in BD, although the clinical significance remains to be determined.

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## PP23: Nicotine increases the vulnerability to develop alcohol use disorder like behavior in rat

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### **Background:**

Alcohol use disorder (AUD) is characterized by impaired control over alcohol consumption and is thought to involve maladaptive changes in neural circuits, particularly within the medial prefrontal cortex (mPFC). Given its role in decision-making and compulsive behavior, the mPFC represents a crucial target for understanding vulnerability to AUD. Nicotine use is highly prevalent among individuals with AUD, suggesting its role as a risk factor for the development of AUD.

### **Aim:**

The aim of this study was to determine whether sub-chronic nicotine treatment increases vulnerability to developing an AUD-like phenotype. In addition, we aimed to define whether the AUD-like behavioral phenotype is associated with distinct neurophysiological profiles in the mPFC.

### **Method:**

Rats received 15 sub-chronic injections of nicotine (0.32 mg/kg) or saline during a two-bottle choice paradigm in which they could choose between 15% alcohol and water. Animals were subsequently trained for alcohol self-administration in operant chambers for one month and evaluated using a multi-symptomatic 0-3-criteria model of AUD-like behavior. Measures included persistence of responding, motivation, and alcohol seeking despite negative consequences, classifying animals as resilient or vulnerable. Whole-cell and field potential recordings were then performed in mPFC slices.

### **Results:**

Nicotine exposure increased alcohol intake in the two-bottle choice test and alcohol-seeking behavior in operant sessions. Nicotine-exposed rats showed a reduced resilience to developing AUD-like behaviors compared to the saline group. Electrophysiological recordings revealed a trend toward increased inhibitory tone and reduced amplitude of evoked field potentials in the mPFC of nicotine-treated rats. In saline-treated animals, vulnerable rats showed reduced evoked potentials compared with resilient counterparts, an effect that was blunted by a GABAA receptor antagonist.

### **Conclusion:**

Sub-chronic nicotine exposure enhances alcohol seeking while reducing resilience to developing AUD-like phenotype. Electrophysiological recordings further indicate a role for changes in GABAergic neurotransmission in driving these behavioral alterations.

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## PP24: Timing of Complementary Food Introduction is not Associated with Inflammatory Bowel Disease Risk: a Prospective Birth Cohort Study

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### **Background and Aims:**

Complementary feeding, i.e., food introduction besides formula or breast milk, imprints on the developing gut microbiome and immune system, which may have durable influences on disease risk. However, evidence of its role in inflammatory bowel disease (IBD) is limited. We prospectively investigated the association between the timing of complementary food introduction and subsequent IBD risk.

### **Methods:**

We followed 94,238 participants from the All Babies in Southeast Sweden (ABIS; n=11,947) and the Norwegian Mother, Father and Child (MoBa; n=82,291) cohorts from birth (1997–2009) up until 2023. IBD diagnoses were retrieved from national patient registers. The timing of complementary food introduction (<4 months or 4–5 months vs. ≥6 months) was assessed using early-life food diaries and questionnaires. Latent class analyses (LCA) identified four patterns of food introduction across major food groups (e.g., cereals and dairy). Hazard ratios (aHRs) for IBD were adjusted for socio-demographics and parental IBD, and were further adjusted for breastfeeding duration and formula feeding in sensitivity analysis.

### **Results:**

Over 1,562,350 person-years of follow-up, 388 participants developed IBD (ABIS, n=124; MoBa, n=276). The overall timing of complementary food introduction was not associated with IBD (<4 months, aHR=1.04 [95%CI=0.67–1.60]; 4–5 months, aHR=0.83 [0.63–1.10], vs. ≥6 months). Also, aHRs for IBD by LCA-defined feeding introduction patterns approximated one. Results were consistent across cohorts, sensitivity analyses, and Crohn's disease and ulcerative colitis subtypes.

### **Conclusions:**

The findings from this binational birth cohort study indicate that neither the timing nor the pattern of complementary food introduction is a major risk factor for IBD development.

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## PP25: The influence of genomic contexts on deamination kinetics in human DNA

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### **Background:**

Somatic mutations and their distribution across tumor genomes provide a substrate for tumor evolution, influencing cancer progression and treatment response. In skin cancers, the most common cause of somatic mutations is exposure of DNA to UV light. The most abundant UV-induced photoproduct is the cyclobutane pyrimidine dimer (CPD), forming as crosslinks between adjacent pyrimidines (cytosines or thymines), from which C>T mutations can be promoted by accelerated cytosine deamination. However, not much is known about how deamination kinetics is influenced by sequence contexts and other genomic factors such as methylation, and how this shapes the distribution of UV-induced mutations in the genome.

### **Methods:**

To complete the picture of the mutagenic process induced by UV-light and investigate the dynamics of cytosine deamination, we have employed a method called Deamination-sequencing, wherein C>T mutations induced by in vitro deamination of cytosines within CPDs are detected by high-throughput whole genome sequencing.

### **Results:**

From applying Deamination-sequencing to UV-exposed DNA from skin fibroblasts, we were able to determine the deamination half-lives of cytosines within CPDs in different sequence contexts, for example being greatly enhanced in NTCG contexts and hampered by 5' G for specific contexts. We also found that methylated cytosines in RCCR contexts were less prone to deaminate despite a higher CPD formation efficacy. The results were also compared with mutations in melanoma as well as squamous cell carcinoma of xeroderma pigmentosum patients with defective DNA repair, to determine how variable DNA repair times and sequence contexts cooperate with deamination in shaping the distribution and local frequencies of UV-induced mutations in the genome.

### **Conclusion:**

These results give insights into fundamental determinants of UV mutagenesis and highlight a crucial role for variable deamination rates in shaping the heterogenous distribution of somatic mutations across skin cancer genomes.

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## **PP26: NOX2 acts as a driver of M2 macrophage polarization through the activation of NRF2**

**Kaya M, Johnsson O, Issdisai N, Söderberg H, Altinönder I, Kiffin R, Tekpli X, Hellstrand K, & Martner A**

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Macrophages are highly plastic immune cells capable of adopting diverse phenotypes in response to environmental cues, ranging from pro-inflammatory M1-like to anti-inflammatory M2-like states. NOX2, an enzyme that generates reactive oxygen species (ROS), is predominantly expressed in myeloid cells, including macrophages. While NOX2-derived ROS are classically associated with microbial defense and pro-inflammatory responses, their role as signaling molecules in macrophage differentiation and polarization remains poorly defined. In this study, we sought to clarify the role of NOX2 in regulating M2-like macrophage polarization under homeostatic and tumor settings.

Single-cell RNA sequencing of human breast and colon tumors showed that NOX2 is selectively upregulated in M2-like tumor-associated macrophages (TAMs). In NOX2-deficient mouse, lung macrophages exhibited a shift toward a pro-inflammatory phenotype, marked by altered transcription factor activity and enrichment of M1-associated gene signatures. In vitro, inhibition of NOX2 blocked M2 polarization driven by CSF-1 or tumor-conditioned media from breast cancer cell lines, underscoring its role in macrophage reprogramming. Mechanistically, these findings suggest that NOX2-derived ROS activate NRF2-dependent signaling in macrophages, sustaining their anti-inflammatory identity. In two murine models of breast cancer, i.e. orthotopic EO771 implantation and the genetically engineered MMTV-PyMT model, genetic deletion of NOX2 entailed reduced levels of M2-like TAMs, accompanied by enhanced T cell infiltration and decreased tumor growth and metastatic burden.

Clinically, elevated expression of M2-associated markers and NRF2 target genes correlated with poor prognosis in breast cancer patients. Together, these findings identify NOX2 as a critical regulator of macrophage plasticity and suggest that the NOX2–NRF2 axis stimulates immunosuppressive myeloid programming that promotes tumor progression and metastasis.

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## PP27: Lymphocyte populations in mouthrinse samples from patients with leukoplakia and oral lichen planus

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### **Background:**

Oral potentially malignant disorders (OPMDs) are oral mucosal conditions with an increased risk of malignant transformation, among which oral leukoplakia (OL) and oral lichen planus (OLP) are two of the most common. OLP is characterized by T cell-mediated chronic inflammation, whereas the immunopathogenesis of OL remains less well understood. Although natural killer (NK) cells play a crucial role in tumor surveillance, their role in OPMDs has been scarcely studied. A better understanding of immune alterations in the oral cavity during OPMDs may help explain why only some lesions progress to cancer. In this ongoing study, we investigate leukocyte populations, particularly cytotoxic lymphocytes, in mouthrinse and blood samples from patients with OL and OLP, and analyze immunomodulatory factors, including galectin-3, in saliva and plasma.

### **Methods:**

Mouthrinse, saliva and blood were collected from healthy donors and patients with OL and OLP. Leukocytes were characterized by flow cytometry. Galectin-3 levels in cell-free saliva and plasma were measured with ELISA.

### **Results:**

No overall difference in the frequency of oral NK cells among lymphocytes was observed between groups. However, the CD56dimCD16<sup>+</sup> NK cell subset was more prevalent in the oral cavity of OPMD patients than in healthy donors. The frequency of oral T cells was significantly higher in patients with OPMDs when compared to healthy donors. Within the T cell compartment, OPMD patients showed an increased proportion of oral CD8<sup>+</sup> T cells and a decreased proportion of oral CD4<sup>+</sup> T cells. Galectin-3 levels in cell-free saliva differed between OPMD patients and healthy donors but not after normalization to total protein concentration.

### **Conclusion:**

Both CD56dimCD16<sup>+</sup> NK cells and CD8<sup>+</sup> T cells are lymphocytes with high cytotoxic capacity. Detection of alterations in these populations in saliva from OPMD patients suggests that saliva-based immune profiling could serve as a non-invasive tool to study disease-associated immune changes.

## **PP28: m6A-Modified TERRA RNA Drives RNA Condensate Formation and Telomere Maintenance in ALT+ Neuroblastoma**

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Alternative lengthening of telomeres (ALT) is a telomerase-independent mechanism employed by a subset of high-risk neuroblastomas (NB), particularly relapsed cases. A hallmark of ALT+ NB is the upregulation of the telomeric repeat-containing RNA (TERRA), a long non-coding RNA (lncRNA) essential for telomere homeostasis. However, the molecular mechanisms governing TERRA's function in ALT remain largely unknown.

Here, we demonstrate that N6-methyladenosine (m6A) modification of TERRA, catalysed by METTL3, is essential for telomere targeting and maintenance in ALT+ NB. m6A-modified TERRA preferentially associates with R-loops (three-stranded nucleic acid structures), facilitating telomere localization through interaction with hnRNPA2B1. This interaction promotes the formation of TERRA RNA condensates via phase separation, and G-quadruplex (G4) structures present in TERRA RNA play an essential role in this process. These condensates are crucial for sustaining ALT activity, and functional disruption of TERRA m6A or hnRNPA2B1 impairs RNA condensate formation, leading to telomere dysfunction and increased DNA damage. Furthermore, we demonstrate that pharmacological inhibition of METTL3 disrupts TERRA R-loops, leading to telomere dysfunction and DNA damage accumulation in ALT+ NB cells. Strikingly, we observed a synergistic effect of m6A inhibition with ATM kinase inhibitors, significantly reducing ALT+ NB cell viability. These findings reveal a novel RNA modification-driven mechanism underlying ALT and highlight m6A-TERRA condensates as a potential therapeutic vulnerability in high-risk NB.

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## PP29: LRP10-Dependent Regulation of TRAIL Receptors in Cancer

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Natural killer (NK) cells are crucial for recognizing and eliminating abnormal cells, including cancers. The action they take when encountering foreign cells is dependent on the balance of signals from activating and inhibitory receptors. Understanding NK receptor and ligand interactions is therefore important when developing immunotherapies targeting cancer. One of the most important activating receptors is NKp46 that, until recently has been considered an orphan receptor without a known ligand in cancer. However, in screens dependent on NKp46, we identified TRAIL-R1 and TRAIL-R2 as highly important for NK cell recognition, suggesting that these are novel ligands for NKp46.

These findings may have a large impact on immunotherapy development, and studies addressing mechanisms governing TRAIL-R expression are highly warranted. To this end, we performed a genome-wide CRISPR dropout screen where cells were sorted based on their TRAIL-R1 expression. NGS analysis identified the gene LRP10 as the most depleted gene in cells with high TRAIL-R1 expression, suggesting that LRP10 negatively regulates TRAIL-R1 expression. These findings were validated in knockdown experiments, in which siRNA targeting the LRP10 transcripts were shown to enhance TRAIL-R1 expression. Furthermore, other screens in which we engineered the interaction between cancer cells and NK cells to be NKp46 dependent also showed LRP10 as a top 10 gene, that when depleted, made the cells more susceptible to NK cell killing. In addition to the already obtained data knock out experiments will also be performed, and co-immunoprecipitation and split-luciferase assays will assess whether LRP10 physically interacts with TRAIL-Rs and identify the domains involved. Mutant analysis will further investigate functional regions of LRP10. By defining how LRP10 regulates TRAIL-R expression and activity, this work ultimately aims at expanding the knowledge surrounding NK cell receptor and ligand interaction to aid in the design of novel NK cell immunotherapies that improve cancer treatment efficacy.

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## **PP30: Chemical Proteomic Screens identify Serine Proteases (SP99 and SP50) That Regulates Receptor Ligands in Drosophila Neuroblastoma model**

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Oncogenic mutations in anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase drive pediatric neuroblastoma and are associated with poor prognosis. Introduction of an ALK-activating oncogenic mutation ALKY1278S at the *Drosophila melanogaster* Alk locus (AlkY1355S) lead to enhanced Alk signaling output represented by increased numbers of Alk-positive neurons and increased expression of neuropeptide and receptor ligands. The secreted neuropeptides and receptor ligands are often regulated by serine proteases (SPs) belonging to the serine hydrolases (SHs) superfamily in the extracellular space. All SHs use a nucleophilic serine residue in the enzyme active site to perform hydrolytic-type reactions via a two-step ping-pong mechanism and have served as a classical prototype in the development of chemical proteomics techniques such as activity-based protein profiling, to globally interrogate functions in various native, yet complex, biological settings. Our observations led us to hypothesised that SP activities may be deregulated when Alk is oncogenically activated, and to propose that SPs may play role in neuroblastoma and contribute to poor prognosis. To test this, we mapped SH activities in the AlkY1355S neuroblastoma model of *Drosophila* and identified a brain-specific protease SP99 that exhibited increased activity on Alk activation. Using biochemical assays, we defined SP99 as an SP belonging to the trypsin-like enzyme class. Untargeted peptidomics analysis showed that peptides abundance of Jeb, an ALK ligand and Spar, orphan neuroendocrine ligand was downregulated in CRISPR knockout SP99 mutant compared to wildtype control. These findings were further validated using immunoblotting and immunostaining analyses. We also identified SP50, a paralogue of SP99, in a second ABPP screen. Together, our data show that increased SP99 and SP50 activity in oncogenic AlkY1355S models regulate peptide ligand processing and by doing so potentially modulate signaling pathway output in response to Alk activation.

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## PP31: Kidney toxicity after Targeted Alpha Therapy

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Despite recent decades advances in cancer treatment, metastatic cancer and residual disease continue to be a challenge. Targeted Alpha Therapy (TAT) is a up and rising therapy form that uses tumor seeking agents as carrier molecules for alpha-particle emitting radionuclides. The alpha particles are highly cytotoxic and provide high local radiation dose to small volume disease, while sparing surrounding tissue. Compared to other targeted radionuclide therapies that uses beta-emitting radionuclides, TAT is well suited for treatment of small (micro) metastases. In radiotherapy, assessing the radiation dose is crucial for evaluation of treatment efficacy and toxic effects. The radiation dose is usually calculated to whole organs or larger volumes. In many cases, this type of large-scale dosimetry is not suitable to predict the biological outcome of TAT, e.g. in kidney dosimetry. The kidneys are a major risk organ and kidney toxicity can be a dose-limiting factor. After systemic administration, the radiopharmaceutical will have a non-homogeneous distribution in the kidneys. The distribution of the radiopharmaceutical is affected by aspects like charge and molecular weight of the carrier molecule. When predicting kidney toxicity for TAT, it is therefore more suitable to use small-organ dosimetry rather than calculating the radiation dose to whole organ. We are currently conducting a conceptual study to compare whole-organ based kidney dosimetry with small-organ dosimetry. The aim is to assess prediction of kidney toxicity after TAT using carrier molecules with different distribution due to different sizes. Mice were injected with the alpha-emitter astatine-211 labeled to trastuzumab. One group receiving whole antibody (IgG, M.W. 150 kDa) and the other group receiving fragmented antibody (F(ab')<sub>2</sub>, M.W. 100 kDa). The distributions of the radiation in the kidneys were quantified using so-called alpha imaging. Preliminary data shows higher radiation dose to kidney cortex compared to kidney medulla for F(ab')<sub>2</sub> but not for IgG.

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## PP32: Novel CSF oligodendrocyte biomarkers for Alzheimer's disease

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### Background:

Oligodendrocytes are glial cells implicated in amyloid  $\beta$  ( $A\beta$ ) pathology and Alzheimer's disease (AD) pathophysiology. Despite growing evidence for their involvement, biomarkers assessing oligodendrocyte changes in AD are under investigated. We aimed to identify novel oligodendrocyte biomarkers in CSF and evaluate their association with AD amyloid pathology.

### Methods:

Oligodendrocyte- and oligodendrocyte precursor cell (OPC)-enriched genes were identified using single-cell and single-nucleus transcriptomic datasets from the Allen Brain Atlas and SEA-AD consortia. CSF proteomic data from 663 ADNI participants (SomaLogic platform) were analyzed, focusing on proteins encoded by these genes. Group comparisons were performed in cognitively unimpaired (CU) versus cognitively impaired (CI) individuals and in  $A\beta^+$  versus  $A\beta^-$  groups (ptau181/ $A\beta$ 42 cut-off = 0.028) using linear regression. The differentially expressed proteins (DEPs) had their trajectories across centiloid-defined stages examined with regression models. Voxelwise association analyses were then conducted between DEPs and regional [ $^{18}F$ ]AV45-PET uptake. Models were adjusted for age and sex, with random field theory correction applied to imaging results and false discovery rate correction for linear regressions.

### Results:

Were identified 1081 oligodendrocyte- and/or OPC-enriched genes, of which 267 were measured in CSF proteomics. In CI versus CU individuals, 37 DEPs were identified, whereas 68 proteins differed between  $A\beta^+$  and  $A\beta^-$  individuals. Across centiloid stages, 16 proteins showed positive and 8 negative associations with  $A\beta$  burden. Voxelwise analyses confirmed regional associations between these proteins and  $A\beta$  burden, particularly in the cortex.

### Conclusion:

This study identifies 86 oligodendrocyte-enriched CSF proteins altered in AD, including 24 associated to cortical  $A\beta$  burden. These findings provide candidate biomarkers for oligodendrocyte-related pathology in AD and will be further validated in an independent cohort.

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## **PP33: Development of transgenic zebrafish models via targeted CRISPR-Cas9 knock-in strategy to study App regulation**

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Alzheimer's disease (AD), the most prevalent form of dementia, is pathologically characterized by the accumulation of amyloid precursor protein (APP)-derived amyloid- $\beta$  plaques in the brain. Consequently, individuals with APP duplications, APP mutations, or those with Down syndrome (DS), carrying three copies of APP, are at higher risk of AD. Therefore, reducing APP expression may represent a viable strategy for AD prevention, particularly in individuals at elevated genetic risk. Zebrafish (*Danio rerio*) is increasingly recognized as a powerful animal model for drug screening due to its unique combination of features that bridge the gap between in vitro studies and mammalian models. Human APP in zebrafish has two orthologues, Appa and Appb. In this study, we established appa and appb transgenic zebrafish models using a CRISPR/Cas9-mediated targeted knock-in approach. The models incorporate a fluorescent protein (either GFP or Scarlet), to facilitate screening of positive carriers, and NanoLuciferase (NLuc) reporter immediately upstream of the endogenous translation start site of the app genes, enabling real-time, in vivo quantification of App expression. Inserted proteins in our transgenic models are separated by two different 2A peptides. Introducing "self-cleavage" 2A peptides is a strategy which enables co-expression of multiple genes in one vector.

The expression patterns of appa and appb in our transgenic models were confirmed by confocal microscopy and the correct in frame integration was validated via sequencing in F2 offsprings. To assess the sensitivity of the models to detect changes of App protein level, larvae at 48hours post-fertilization (hpf) were exposed to different compounds and post-treatment luminescence signal, corresponding to the App protein level, was quantified by Luminescence reader. Our data indicates that the app-transgenic models provide a sensitive and scalable platform for high-throughput screening of compounds that modulate APP transcription and translation.

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## **PP34: Neuroinflammation in Alzheimer's Disease: linking proteomic signatures with TSPO PET Imaging**

**Pola I**, Ashton NJ, Povala G, De Bastiani MA, Rahmouni N, Tan K, Machado LS, Di Molfetta G, Stevenson J, Therriault J, Pascoal TA, Blennow K, Zetterberg H, Zimmer ER, Rosa-Neto P, Benedet AL

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### **Background:**

Emerging evidence has highlighted neuroinflammation as a key driver in the progression of Alzheimer's disease (AD), contributing to both amyloid- $\beta$  (A $\beta$ ) and tau pathology. While TSPO PET provides valuable insights into brain inflammation, it remains crucial to explore the underlying molecular mechanisms driving these changes. Proteomic studies of cerebrospinal fluid (CSF) and plasma immune-related proteins offer a complementary approach, for deeper understanding of the inflammatory processes in AD.

### **Methods:**

Participants from the TRIAD cohort incorporating within the AD spectrum, and with available A $\beta$  ([18F]AZD4694), tau ([18F]MK6240) and TSPO ([11C]PBR28) PET data (positivity = 2 SD > mean ROI-SUVr of young participants), had CSF (n= 103) and plasma (n= 151) samples analyzed with the NULISA technology (Alamar Biosciences®). Inflammation-related proteins (n= 268) from CNS and inflammation panel were included in our analysis, which differential expression was evaluated with linear models contrasting TSPO groups. After FDR correction, the protein levels of the differentially expressed proteins at different disease stages, were correlated with the PET uptake of anatomical brain regions.

### **Results:**

Our analysis identified 33 CSF inflammation-related proteins significantly associated with TSPO PET signal, which we organized into functional groups reflecting different stages of AD pathology. Specifically, some protein profiles aligned with the early disease stage, or "A $\beta$  phase," while others corresponded to the later stages, or "tau phase." Building on the CSF findings, we also identified a smaller number of corresponding plasma proteins of interest and evaluated their potential as peripheral markers of neuroinflammation and as proxies for TSPO PET imaging.

### **Conclusion:**

These findings delineate the CSF and plasma proteomic landscape of neuroinflammation in AD, highlighting potential biomarkers of neuroinflammation in the AD scenario.

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## PP35: Dysfunction of in vitro urinary bladder contractility and relaxation in the 6-OHDA rat model of Parkinson's disease

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### **Background and Aims:**

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, characterized by the loss of dopaminergic neurons in the substantia nigra and primarily recognized for its motor symptoms. However, PD is also accompanied by debilitating non-motor symptoms, among which bladder dysfunction, manifesting as frequency, urgency, and nocturia, is highly prevalent. The underlying mechanisms driving urinary disturbances in PD remain poorly understood, and effective pharmacological treatments are lacking, making this condition a research priority. In the present study, we aimed to investigate local changes in urinary bladder smooth muscle in the unilateral 6-hydroxydopamine (6-OHDA) rat model of PD.

### **Methods:**

Rats received stereotaxic injections of either 6-OHDA or saline into the medial forebrain bundle. Four weeks post-surgery, the animals were sacrificed, and their urinary bladders were collected for in vitro functional experiments or histological analysis. Smooth muscle responses to electrical field stimulation (EFS), the cholinergic agonist methacholine, the purinergic agonist ATP, and the adrenergic agonist noradrenaline were evaluated using organ bath setup.

### **Results:**

Contractile responses to EFS and methacholine were significantly reduced in 6-OHDA animals compared with sham-operated controls. The relaxation response to noradrenaline was also significantly impaired. Furthermore, histological analyses demonstrated a significant downregulation of muscarinic M3 and adrenergic  $\beta 3$  receptors in the urinary bladder smooth muscle of 6-OHDA rats.

### **Conclusions:**

Unilateral nigrostriatal dopamine loss in the 6-OHDA rat model of PD induces both functional alterations and receptor downregulation in urinary bladder smooth muscle, providing insights into the peripheral mechanisms underlying bladder dysfunction in PD.

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## **PP36: iPSC-derived microglia exposed to Alzheimer's disease CSF show disease specific phenotypes**

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Alzheimer's disease (AD), the most common form of dementia, poses a high social and economic burden, with estimates predicting it will affect up to 3.5% of the European population by 2050. Activation of microglia, the resident immune cells of the brain, plays a central role in AD pathology and has therefore emerged as a primary target in ongoing clinical trials. However, the diverse microglial subpopulations, which have recently been described and their specific functions, are still not fully understood. Dissecting microglial subpopulations and their functional significance holds great potential for developing new targets to modulate beneficial microglial responses in AD. Cerebrospinal fluid (CSF) from individuals with AD exhibits distinctive alterations, notably in tau and amyloid- $\beta$  levels - key components of an AD milieu.

Here we establish a novel human in vitro disease-relevant microglial model by exposing hiPSC-derived microglia to AD-CSF and analyze microglial phenotypes and transcriptional states in contrast to microglia exposed to CSF from non-AD patients. The pooled CSF samples used in this study show AD-typical differences in protein levels. We find that exposing microglia to CSF, does not reduce viability or increase cytotoxicity. When analyzing phagocytic capacity, we observe a reduced uptake of E.coli particles in AD-CSF-exposed microglia compared to controls. Applying a previously published morphology analysis pipeline, we observe clear morphological differences between the two groups. Our sequencing analysis reveals significant differences in transcriptional states of control-CSF and AD-CSF-stimulated microglia.

Overall, our data suggest that exposing microglia to patient-derived CSF enables the creation of a disease-specific model, providing a promising tool to study functionally relevant microglial states in AD.

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## PP37: Development of perineuronal nets in zebrafish

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### **Background:**

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by social communication difficulties, restricted, and repetitive behaviors. Despite the importance of social communication deficits for individuals with autism, we lack a comprehensive understanding of how social preference develops. Perineuronal nets (PNNs) are specialized extracellular matrix structures that surround specific neuronal populations (e.g. parvalbumin neurons). PNNs participate in the regulation of brain plasticity and learning across species and are known to be crucial for the stabilization of synaptic connections and the regulation of critical periods of brain development. Dysregulation of PNNs is present in neurodevelopmental conditions, including ASD. Zebrafish, as an animal model, offers significant advantages due to its genetic similarities to mammals, transparent larval stage, and early emergence of social behaviors. This makes it an ideal model for investigating fundamental brain processes relevant to ASD. Nevertheless, the localization and developmental patterns of PNNs in the zebrafish brain remain largely uncharacterized. Understanding the spatial and temporal dynamics of PNNs in zebrafish is therefore a critical first step to explore their potential involvement in social behavior.

### **Method:**

To visualize the PNN we collected zebrafish at different developmental stages, from one week post fertilization to adulthood. Initially, adult brains were fixed, and sectioned into three different orientations: coronal, horizontal, and sagittal, followed by an immunostaining procedure with CS-56 antibody. The samples were mounted and examined using fluorescence microscopy to analyze the localization of PNNs. In ongoing studies, we are investigating PNNs during development and co-localization with parvalbumin.

### **Results:**

PNNs were localized in different regions throughout the zebrafish adult brain. We observed PNNs notably within the telencephalon, as well as in other brain regions previously described to contain parvalbumin cells.

### **Conclusion:**

The zebrafish seems to be a good model for the investigation of PNNs and the critical periods mechanisms.

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## **PP38: An algorithm for automatic measurement of volar tilt and radial inclination of the distal radius on 3D models: validation against manual 3D and conventional 2D methods**

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Accurate assessment and correction planning of distal radius malunions traditionally rely on two-dimensional (2D) radiographic parameters such as volar tilt and radial inclination. However, 2D imaging is limited by projection errors, image quality, and landmark ambiguity. With the increasing use of three-dimensional (3D) models in preoperative planning, more precise quantification of these parameters has become possible. This study presents and validates an algorithm for measuring volar tilt and radial inclination on 3D virtual models of both malunited and healthy radii.

The algorithm defines a 3D coordinate system and anatomical landmarks that replicate conventional 2D measurement definitions, ensuring compatibility with established clinical standards. Virtual models from 16 participants were analysed. Automatic 3D measurements were compared with manual measurements in 2D radiographs obtained by three surgeons in a consensus meeting, and on 3D models obtained independently by two raters. Agreement was evaluated using Bland–Altman analysis, and test–retest reproducibility and landmark placement discrepancies were quantified.

The algorithm demonstrated 100% reproducibility. Mean differences between automated 3D and 2D measurements were small: for volar tilt, 0.6° in malunited and 2.9° in healthy radii; for radial inclination, 1.5° and 2.3°, respectively. Landmark discrepancies between the algorithm and manual raters ranged from 0.5 to 2.8 mm, and the maximum deviation of the longitudinal axis placement was 2.5°.

This open-source algorithm enables reproducible, knowledge-based measurement of distal radius alignment directly on 3D models. Its strong agreement with standard 2D assessments and elimination of inter-rater variability support its potential for clinical integration and automated deformity evaluation.

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## PP39: Arterial Elasticity and Cardiac Function: A Population-Based Study in the Vara-Skövde Cohort

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### **Objective:**

To examine the associations between small artery elasticity and cardiac function in a large, population-based Swedish cohort.

### **Design and Methods:**

Between 2002 and 2005, 2,816 randomly selected individuals aged 30–75 years were examined for early cardiometabolic signs. In a substudy, 1,035 participants underwent echocardiography using the GE VingMed S5 system. After excluding incomplete data, 991 individuals (men = 488) were included. Small artery elasticity (C2) was measured via radial applanation tonometry (Pulsewave CR-2000). Linear regressions assessed associations between standardized C2 and cardiac outcomes—ejection fraction (EF), cardiac output (CO), and cardiac index—adjusting for demographic, clinical, and lifestyle factors. Analyses were stratified by sex.

### **Results:**

Mean age was 50.7 years. Significant sex differences were observed in C2 and cardiac index ( $p < 0.001$ ), but not in EF. In fully adjusted models, a one standard deviation (SD) increase in C2 was associated with higher EF in the total study population ( $B=0.9$ , 95% CI: 0.2–2.2;  $p=0.011$ ), and in men ( $B=1.1$ , 95% CI: 0.05–2.1;  $p=0.041$ ). Among women, the association was significant in Model 1 but attenuated after full adjustment. EF was highest in the top C2 quartile (Q4: 75.1%, 95% CI: 74.0–76.3), with significant differences between Q4 and Q1 ( $\Delta EF=2.0\%$ , 95% CI: 0.05–2.0,  $p=0.044$ ).

C2 was significantly associated with CO across all models ( $B=0.17$ , 95% CI: 0.10–0.24,  $p < 0.001$ ), especially in men ( $B=0.14$ , 95% CI: 0.04–0.24,  $p=0.007$ ). In women, significance was lost after full adjustment. CO differences between C2 quartiles were significant in Model 1 but not in Model 3. No significant associations were found between C2 and cardiac index in fully adjusted models.

### **Conclusions:**

Small artery elasticity is positively associated with systolic cardiac function, particularly EF and CO, with stronger effects observed in men. These findings highlight the vascular–cardiac interplay in cardiovascular health.

## **PP40: Validation of a Plasma GFAP Immunoassay and Establishment of Age-Related Reference Values: Bridging Analytical Performance and Routine Implementation**

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### **Background & Aims:**

Glial fibrillary acidic protein (GFAP) is a biomarker of astrocytic activation associated with neurodegenerative diseases, neuroinflammatory conditions, and traumatic brain injury. As interest in blood-based biomarkers increases, robust analytical validation and reliable reference values are essential for clinical implementation. This study aimed to validate the MSD S-Plex® GFAP immunoassay for plasma and establish age-stratified reference intervals in a healthy population.

### **Methods:**

The study was performed in two phases. First, analytical performance—repeatability, intermediate precision, measurement range, interference testing, and sample stability—was evaluated following Clinical and Laboratory Standards Institute (CLSI) guidelines. Second, plasma from 579 apparently healthy individuals aged 17–91 years was used to define reference intervals via a right-sided non-parametric percentile approach, with upper limits calculated for three predefined age groups. A continuous age-dependent centile model was also applied.

### **Results:**

The MSD S-Plex® GFAP assay showed strong performance, with coefficients of variation for repeatability and intermediate precision below 12%. After accounting for the 1:2 dilution, the validated measurement range was 0.425–1760 ng/L, with calibration residuals within  $\pm 15\%$ . GFAP levels were unaffected by hemolysis ( $p = 0.85$ ) and stable for up to 7 days at 4 °C and under frozen storage. Age-specific upper reference limits were 38 pg/mL (18–<50 years), 73 pg/mL ( $\geq 50$ –<70 years), and 156 pg/mL ( $\geq 70$  years). From age 50, females had higher concentrations than males. GFAP levels correlated strongly with age (Spearman's  $r = 0.832$ ,  $p < 0.0001$ ).

### **Conclusions:**

The MSD S-Plex® GFAP assay demonstrates excellent analytical performance and provides robust age-specific reference values. These findings support its suitability for clinical use and its integration into biomarker-guided strategies for diagnosing and monitoring central nervous system disorders.

## **PP41: Evaluating digital lab training via Virtual Reality**

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In a Gothenburg cross-sector collaborative initiative, a new advanced therapies training and collaboration center named SCALE will be established. SCALE will focus on meeting the upskilling requirements of small and medium enterprises, and facilitating collaboration between industry, academia and healthcare.

As part of this effort, the project team will be evaluating emerging digital training infrastructures, specifically the use of virtual reality (VR) technologies. In a planned pilot study, the focus will be on the FourPlus software suite, which offers immersive training modules for cleanroom behavior, aseptic techniques, and lab bench protocols. The goal is to assess whether VR-based training can better prepare experienced staff for new tasks, and whether it can accelerate the learning trajectory for untrained individuals entering a lab environment for the first time.

The SCALE partners are Sahlgrenska Science Park, University of Gothenburg, Chalmers University of Technology, and CCRM Nordic. Funding is provided by the Environmental and Regional Development Committee of Region Västra Götaland, in partnership with the European Union through the European Regional Development Fund (via Tillväxtverket).

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## **PP42: An optimized feeder-free protocol for isolation and expansion of functional ILC2s isolated from human peripheral blood**

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### **Background:**

Innate lymphoid cells (ILCs) are tissue-resident innate counterparts of T cells. Group 2 ILCs (ILC2s) produce cytokines such as IL-5 and IL-13 in response to alarmins including IL-25 and IL-33. However, ILC2s are rare in human peripheral blood, making their isolation and expansion for functional studies challenging. Existing methods commonly rely on flow cytometry-based cell sorting, which requires large sample volumes, expensive reagents, and considerable hands-on time. Moreover, in vitro expansion protocols often depend on feeder cell lines and recombinant cytokines or alarmins.

### **Aim:**

Design a simple and efficient flow cytometer-free method for isolating and expanding human ILC2s from peripheral blood, without the need for feeder cells or external alarmins.

### **Method:**

Human ILC2s from either buffy coat or density gradient isolated PBMCs from 9 mL peripheral blood were isolated using immunomagnetic positive selection (EasySep™ Human ILC2 Isolation Kit). ILC2s were then cultured in a 96-well round-bottom plate in media containing a combination of cytokines IL-2, IL-7, and IL-15 along with 10% human AB serum (hAB serum).

### **Results:**

Large scale ILC2 isolation resulted in 30x expansion from day 7 to 21 with a final yield up to  $2 \times 10^6$ , while the small-scale protocol yielded up to  $1 \times 10^6$  cells. Sustained viability and purity was ascertained through flow cytometric staining and mRNA analysis. ILC2s functionality was determined through CellTrace based proliferation test and signature cytokine quantification in response to alarmins IL-25 and IL-33. ILC2s remained functional after cryopreservation, albeit less proliferated cells and lower levels of cytokines.

### **Conclusion:**

The protocol yields pure and viable ILC2s from both large and small blood volumes. Expanded ILC2s responded robustly to alarmin stimulation by proliferating and producing signature cytokines and retained functionality after cryopreservation. Together, this method provides a user-friendly and cost-effective alternative to current ILC2 isolation and expansion protocols.

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## PP43: Integrative Multi-Omics and Machine Learning Reveal Predictive Markers of Radiation-Induced Intestinal Injury

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### **Background:**

Pelvic radiotherapy (PRT) can lead to radiation-induced intestinal injury (RIII) with persistent bowel symptoms—urgency, leakage, gas/mucus discharge, and rectal bleeding—that impair quality of life. Patient-level molecular correlates of symptom burden remain insufficiently defined.

### **Aim:**

To identify transcriptomic markers associated with RIII symptom severity through integrative multi-omics analysis and machine learning, and validate their biological relevance at protein and single-cell levels.

### **Methods:**

21 RIII patients and 4 healthy controls completed symptom questionnaires. During endoscopy, rectal mucosa was sampled at 5 cm and 25 cm from the anal verge (P5/P25 in patients; C5/C25 in controls) for multi-omics profiling. Bulk RNA-seq underwent normalization/QC. Module–symptom relationships were assessed by WGCNA. Differential expression compared P5 vs. P25 to nominate candidates; pathway activity was estimated by GSVA. For classification, we compared two machine-learning approaches: a cross-validated sparse logistic model (LASSO) and a linear SVM-RFE baseline. Public intestinal single-cell datasets and site-matched proteomics were used for cross-layer validation.

### **Results:**

WGCNA identified a symptom-linked module (MEpink) most strongly associated with mucus discharge and rectal bleeding. P5 vs. P25 yielded 39 differentially expressed genes, forming a transcriptomic signature that correlated positively with angiogenesis and EMT. A compact LASSO panel classified high vs. low symptom intensity (LOOCV AUC 0.854; accuracy 0.76; F1 0.700), outperforming the linear SVM-RFE baseline (AUC 0.729). Proteomic validation (n=10) demonstrated elevated CFL2, CNN1, CSRP1, and SYNPO2 at high-dose (P5) versus low-dose (P25) sites. Consistently, single-cell analysis revealed the upregulation of these genes in post-irradiated SSC2 stem cells.

### **Conclusions:**

An integrative analysis links bowel symptom burden to transcriptomic programs and nominates a compact marker set (CFL2, CNN1, CSRP1, and SYNPO2), with single-cell and proteomics support consistent with smooth muscle/myofibroblast activation and matrix remodeling in post-radiation injury. LASSO provided strong small-sample performance for symptom classification.

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## **PP44: Feasibility and efficacy of digitally delivered dietary treatment for irritable bowel syndrome: A pilot study**

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### **Objectives:**

Two carbohydrate reduced diets, the low FODMAP diet and the low-carbohydrate diet, are efficacious in relieving symptoms in patients with irritable bowel syndrome (IBS). Traditional dietary counselling has limitations for both patient and care-provider, including accessibility and time restraints. Digital interventions offer a cost-effective and scalable solution. Here, we assessed the feasibility and efficacy for digitally delivered dietary treatments.

### **Methods:**

Participants were recruited from May - October 2024 via clinical referrals and social media advertisement. Eligible participants had a clinical IBS diagnosis without other conditions explaining their symptoms. After screening, participants received their choice of treatment, either a low-carbohydrate or low FODMAP diet. They were given access to the treatment website, which included recipes, and were prompted to follow the diet for four weeks. Digital questionnaires were completed at baseline and week four to evaluate changes in gastrointestinal symptoms (IBS-SSS), extra-intestinal symptoms (PHQ-15) and psychological distress (HADS). A treatment evaluation was completed at week four where self-reported adherence to the diet was assessed.

### **Results:**

Out of 30 participants who initiated treatment, 24 completed the four-week treatment. Reasons for drop-out included diet adherence difficulty (n=4) and loss to follow up (n=2). Both diets demonstrated good feasibility with 80% completion rate and 89% adherence. At week four, a mean score reduction of 149 on the IBS-SSS was observed ( $p<0.01$ ), with no difference between the groups. Reduced severity of psychological distress and extraintestinal symptoms was also obtained (both  $p<0.01$ ). Participants highlighted accessibility and convenience but requested more recipes, weekly menus and a chat function for consultation with a dietician.

### **Conclusion:**

This pilot study demonstrates feasibility and suggests efficacy of digitally delivered dietary treatments, indicating an accessible and cost-effective delivery of evidence-based dietary treatment. Future research should focus on the implementation in large scale trials with long-term follow-up to establish efficacy and sustainability.

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## **PP45: Allelic variants of the plasmid-encoded colonization factor CS6 are associated with distinct enterotoxigenic Escherichia coli clades**

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Enterotoxigenic Escherichia coli (ETEC) is a leading cause of diarrheal disease in low- and middle-income countries with persistent morbidity and rising antimicrobial resistance despite declining mortality, especially affecting children under five. A key virulence factor is the plasmid-encoded colonization factor (CF) coli surface antigen 6 (CS6). It is one of the most prevalent ETEC CFs and a component of several vaccine candidates. Allelic variation within the CS6 structural subunits, *cssA* and *cssB*, has previously been linked to differences in adhesion, expression, and virulence. However, knowledge of its genetic diversity and the implications remain limited. To address this gap, we screened more than 2.5 million bacterial genome assemblies for the presence of CS6 genes and identified 1,617 high-quality, non-redundant E. coli genomes containing at least one CS6 gene. Phylogenetic analysis of these isolates, combined with protein sequence clustering, revealed extensive genetic diversity across all four genes of the CS6 operon. In total, 24 allelic variants were identified across all four genes, which occurred in eleven distinct operon combinations. Mapping these onto a core genome phylogeny showed that specific CS6 combinations are associated with distinct ETEC clades, suggesting that CS6 diversity is both functionally significant and evolutionarily structured. These findings substantially expand the known diversity of the CS6 locus beyond the two structural subunits, provide further evolutionary context, and highlight the need to assess whether allelic variation may influence the efficacy of CS6-based vaccines.

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## PP46: Dissecting the Antiviral Role of AXL During HSV-1 Infection: Beyond Phagocytosis in Microglia

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### Background:

Herpes simplex virus type 1 (HSV-1) infects 60–90% of the population and typically establishes lifelong latency in neurons. In rare cases, however, the virus can spread to the central nervous system, leading to life-threatening herpes simplex encephalitis (HSE). While latency is achieved in neurons, microglia play a crucial role in antiviral defense through viral sensing pathways and the release of type I interferons (IFN-Is). IFN-Is induce a wide range of interferon-stimulated genes (ISGs), which coordinate antiviral responses. One such ISG is the microglial receptor AXL—a phagocytic receptor involved in innate immune processes, including clearance of apoptotic cells. The role of AXL in antiviral defense during HSV-1 infection is, however, unknown.

### Aims:

The aim of this study was to investigate the role of the microglial receptor AXL during herpesvirus infection and further explore soluble AXL (sAXL) as a potential biomarker for HSE.

### Methods:

Human induced pluripotent stem cell (iPSC)-derived microglia and neurons were used to model HSV-1 infection in vitro. AXL knockout (KO) iPSCs were generated using CRISPR-Cas9 technology.

### Results:

AXL KO microglia displayed normal differentiation and marker expression compared to controls. AXL expression was strongly induced in microglia upon IFN $\beta$  stimulation alone as well as HSV-1 infection. Since HSV-1 primarily replicates in neurons, we investigated viral replication in neuron-microglia co-cultures. Co-cultures of neurons with AXL KO microglia exhibited significantly increased viral replication. Moreover, AXL KO microglia adopted a more circular, amoeboid-like morphology in co-culture, suggesting altered activation states. Cerebrospinal fluid (CSF) analyses revealed significantly increased sAXL levels in HSE patients, with a potential correlation to disease severity.

### Conclusions:

Our findings identify AXL as a key mediator of microglial antiviral defense during HSV-1 infection, likely contributing to viral sensing and uptake. Furthermore, sAXL shows promise as a potential biomarker for HSE, possibly reflecting microglial activation during viral encephalitis.

## **PP47: Distinct plasmid mobility patterns shape the distribution of colonisation factors in enterotoxigenic Escherichia coli strains**

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The pathogenicity of enterotoxigenic Escherichia coli (ETEC), an important cause of diarrhea, is driven by plasmids encoding colonization factors (CFs) which enable adhesion, and toxins. ETEC is distinguished by its broad repertoire of CFs, which are key targets in diagnostics and vaccine development, yet the plasmids encoding them remain largely unexplored. As a result, the broader diversity and evolutionary history of ETEC virulence plasmids are still unclear.

Here, we generated the largest collection of hybrid sequenced and assembled ETEC genomes (n=479), complemented with additional complete genomes from public databases (n=59). The plasmidome was clustered using Pling, based on sequence similarity and rearrangement distances, and the resulting plasmid-clusters were analysed in context with ETEC phylogenetic lineages. A database of CF-positive plasmids was used to screen AllTheBacteria database to validate our findings using Quast.

A total of 2603 plasmids were identified and annotated, whereof 903 were virulence plasmids harbouring genes encoding ETEC toxins and/or CFs. We reveal that plasmids encoding toxins are present in multiple different plasmids and that distinct CFs are harboured by specific plasmid clusters. Three evident plasmid-lineage patterns emerged: i) CFs located on a single non-mobilizable plasmid restricted to one lineage, consistent with vertical clonal expansion, ii) CFs located on a single conjugative plasmid spread across multiple lineages via horizontal plasmid transmission followed by clonal expansion, and iii) specific CF variants associated with distinct plasmid clusters suggesting parallel evolution. Analysis of all publically available CF-positive ETEC genomes confirmed these patterns but also revealed that for certain CFs, the associated plasmid cluster could not be identified, suggesting the existence of yet uncharacterised plasmids and highlighting a gap in the current plasmid repertoire. This study improves our understanding of ETEC evolution and by which routes virulence traits spread.

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## **PP48: Sex differences in immune responsiveness and the effect of alpha 7 nicotinic acetylcholine receptor stimulation in PBMCs from a healthy middle-aged population**

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### **Background and Aims:**

Sex influences immune responses, yet whether the anti-inflammatory effects of  $\alpha 7$  nicotinic acetylcholine receptor ( $\alpha 7$ nAChR) stimulation differ between sexes remains unclear.  $\alpha 7$ nAChR activation has been shown to modulate inflammation, but sex-specific responses have not been systematically studied. Thus, this study aims to compare the inflammatory response in peripheral blood mononuclear cells (PBMCs) from healthy middle-aged men and women and to investigate whether there is a sex difference in the inflammatory response upon stimulation of the  $\alpha 7$ nAChR.

### **Methods:**

PBMCs were isolated from a healthy, well-defined, middle-aged population including 27 women and 28 men. Gene expression of *CHRNA7*, the gene coding for the  $\alpha 7$ nAChR, was assessed using RNA sequencing. The PBMCs were challenged in vitro with lipopolysaccharide (LPS, 8.33 ng/ml) and treated with the  $\alpha 7$ nAChR agonist PHA 568487 (83  $\mu$ M) and the inflammatory response was determined by measuring 17 cytokines using a multiplex immunoassay.

### **Results:**

*CHRNA7* expression did not differ between men and women. Upon LPS stimulation, PBMCs from men produced higher levels of IL-2 and TNF $\alpha$  compared to women. In PBMCs extracted from men, treatment with PHA 568487 significantly reduced levels of six cytokines (IL-1 $\beta$ , IL-2, GM-CSF, IFN- $\gamma$ , MCP-1, TNF $\alpha$ ) and increased the level of IL-6. In contrast, in PBMCs from women, treatment with PHA 568487 increased IL-5 and IL-6 levels, with no significant reductions observed.

### **Conclusions:**

Our findings reveal sex-specific differences in the immunomodulatory effects of  $\alpha 7$ nAChR stimulation. PBMCs from men exhibited a more pronounced anti-inflammatory response to  $\alpha 7$ nAChR activation than those from women. These results underscore the importance of considering sex as a biological variable in immunological studies and suggest that sex may influence the efficacy of therapies targeting the cholinergic anti-inflammatory pathway.

## **PP49: Cellular senescence impairs insulin-stimulated glucose uptake in human adipocytes**

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Cellular senescence is a stress-induced state of cell-cycle arrest. Senescent cells are characterized by morphological and metabolic changes, altered gene expression and the development of a pro-inflammatory secretome. Cellular senescence has emerged as a contributor to age-related diseases such as type 2 diabetes. In adipose tissue, senescent cells accumulate with age and in obesity and are associated with impaired adipose expansion. Recent evidence indicates that adipocytes - which are considered postmitotic cells - can undergo senescence; however, the understanding of how cellular senescence impact adipocyte metabolic functions remains limited. By using three different models, the impact of cellular senescence on human adipocyte function was assessed. Successful induction of senescence was confirmed by evaluating senescence markers (p21, p53, SA- $\beta$ galactosidase and senescence-associated secretory phenotype). Utilizing these models, we demonstrated that senescent human adipocytes exhibit a robust decrease in insulin-stimulated glucose uptake. Insulin signaling remained largely unaffected, but levels of the main glucose transporter in adipocytes, GLUT4, were markedly reduced. In contrast, senescent adipocytes retained responsiveness to lipolytic stimuli. Taken together, these results indicate that cellular senescence selectively impairs adipocyte function by attenuating insulin-stimulated glucose uptake while not affecting stimulated lipolysis. Our results suggests that senescent adipocytes may contribute to metabolic dysfunction observed in obesity and type 2 diabetes.

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