Life Science PhD Meeting 2025

Innsbruck, April 2025

Abstract Book

universität innsbruck

MEDIZINISCHE UNIVERSITÄT INNSBRUCK

This meeting is organized by:

Johannes Wölk, Ilaria Dorigatti, Marina Schapfl

Denise Kummer, Giacomo Gariglio, Francesco Costacurta, Helge Schöppe, Andreas Aufschnaiter, Paul Petermann, Julia Baumann, Felix Eichin, Raphael Gronauer, Francesca Silvagni, Jakob Scheler, Jiri Koutnik, Petronel Tuluc, Maria Troppmair, Lena Denk, Marta Konopka, Taraneh Zavvar, Maria Peteinareli, Mieke Nicolai, Norbert Redlinger

Abstract book designed by Andreas Aufschnaiter and Paul Petermann

Mission Statement

The Life Science PhD Meeting provides a platform for the whole Life Science community, from undergraduate students up to PIs, to share their knowledge, experience and critical thinking. Furthermore we want to encourage all students to present their research to train this important skill for international conferences.

We are proud to present excellent scientific work from numerous fields, which is only possible due to the huge variety of scientific interests of the groups represented in the meeting. Therefore the organizing committee would like to take the opportunity to thank the research programs making it possible to organize this meeting for all the Life Scientists in Innsbruck:

- MCBD
- CBD
- Clinical PhD program
- SPIN
- ARDRE
- CavX
- HOROS
- IGDT
- IIT
- MYCOS

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Life Science PhD Meeting Innsbruck 2025 Program

Location: Biocenter, CCB, Innrain 80/82, Innsbruck

Wednesday, April 23rd

09:00-13:00 (M01.470) - Workshop AI in Biomedicine: Concepts and Application

14:00-18:00 (M.EG.180) - Project Presentations Clinical PhD

Thursday, April 24th

09:00-11:00	M.EG.180	**Opening**		
	Parallel short talk session			
	M.EG.180	Cell Biology, Metabolism and Cell Death Kinz, Lochner, Purwar, Bernar, Siegmann, Kummer	L.EG.220	Neuroscience, Neurology and Psychiatry Roth, Heiss, Maronchuk, Halbedl, Nelles, Schulze
11:00-11:30	*Coffee break with snacks*			
11:30-12:15	M.EG.180	**Plenary Lecture Linda Oyama,** Queen's University Belfast *"Unseen Reservoirs of AMR Transmission and the One Health Challenge "* Chair: Jakob Scheler		
12:15-13:00	*10x Genomics Tech Talk (15min)* *Lunch*			
13:00-15:00	Aula	**Poster Session I** (Odd numbers)		
15:00-15:15	*Coffee break with snacks*			
15:15-17:00	M.EG.180	**Plenary Lecture Federica Benvenuti,** International Centre for Genetic Engineering and Biotechnology (ICGEB) *"Understanding the evolution of type 1 DCs along progression of lung tumors"* Chair: Jiří Koutnik		
	M.EG.180	**Plenary Lecture Stephan Pless,** University of Copenhagen *"Not alone: examples of how heterogenous protein assemblies shape cellular excitability"*		
17:00-17:30	M.EG.180	**Best Paper Awards 2025** (IGDT, MCBD, Neuroscience PhD Program)		
17:30-20:00	*Wine and Cheese in the CCB Foyer*			

Life Science PhD Meeting Innsbruck 2025 Program

Location: Biocenter, CCB, Innrain 80/82, Innsbruck

Friday, April 25th

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	Parallel short talk session			
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11:00-11:30	*Coffee break with snacks*			
11:30-12:15	M.EG.180	**Plenary Lecture Gaia Novarino,** Institute of Science and Technology, Vienna *"From Cells to Systems: Navigating the Complex Landscape of Autism Spectrum Disorders"* Chair: Francesca Silvagni		
12:15-13:00	*PHIO Scientific Tech Talk (15min)* *Lunch*			
13:00-15:00	Aula	**Poster Session I** (Even numbers)		
15:00-15:15	*Coffee break with snacks*			
15:15-17:00	M.EG.180	**IGDT Alumni Talk Marco Rupprich,** FHNW Switzerland *"Scientific Innovation for a Sustainable Future: My Career Journey"*		
	M.EG.180	**Plenary Lecture Hal Drakesmith,** University of Oxford *"Ironsbruck, immunity and meteorites"* Chair: Maria Troppmair		
	M.EG.180	**Poster and Short Talk Awards 2025** **Closing remarks**		
17:30-18:00	M.EG.180	**Sponsors Quiz Awards**		
17:30-20:00	*Dinner at CCB Cafe and party on the 2nd floor*			

Selected short talks

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Alberto	**Galimberti**	19	R1-R2* relaxivity in white matter is associated with survival in glioblastoma patients
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Sub-lethal mitochondrial permeabilisation as a driver of B cell mutagenesis and oncogenic transformation

Mitochondrial outer membrane permeabilisation (MOMP) commits a cell to undergo apoptosis. Despite the dogma that MOMP is the point-of-no-return and occurs in every mitochondria in a cell, recent studies have shown that in cells which encounter a sub-lethal stress, only a limited number of mitochondria undergo permeabilisation, resulting in sub-lethal caspase activation, a phenomenon termed "minority-MOMP". Nevertheless, this caspase activation is sufficient to induce caspase-activated-DNAse (CAD)-dependent DNA damage and oncogenic transformation. Minority-MOMP has mostly been studied in the setting of solid tumors - however, whether minority-MOMP occurs in hematopoietic cells is unclear.

Using in vitro culture systems and pre-clinical mouse models of pre-malignant and malignant B-cell lymphomas, we establish that minority-MOMP and its downstream CAD-dependent effects occur in progenitor B-cells as well as in human B-cell lymphoma cell lines. Exploiting these mouse models, we ask whether minority-MOMP plays a role in B-cell lymphomagenesis.

Employing BH3-profiling, we have classified human lymphoma cells as either apoptosis-primed or unprimed, revealing intricate BCL-2 family relationships. We have correlated sensitivity to chemotherapy to these BCL-2 family member dependencies and also determined whether cancer treatment-induced minority-MOMP generates vulnerabilities which might explain the high relapse rates (~40%) in B-cell lymphoma patients.

Using our B-cell lymphoma mouse models, we show that pre-malignant B-cells from CAD knockout mice are exquisitely sensitive to BMF peptide treatment, which we are currently investigating further.

Altogether, understanding the underlying molecular mechanisms, as well as survival strategies employed by cancer cells that undergo minority-MOMP, will pave new paths for therapeutic intervention.

Nadine Kinz1, Sarah Spoeck1, Johannes Weiss1, Andreas Villunger1, Verena Labi1, Francesca Finotello2, Joel S. Riley1

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2 Institute of Molecular Biology, Digital Science Center, University of Innsbruck, Innsbruck, Austria

Discovering new players in inflammatory cell death

Mitochondrial permeabilisation during cell death can, under certain circumstances, be highly inflammatory. The release of mitochondrial DNA from the mitochondrial matrix contributes to inflammation during cell death via an interferon response during caspase inhibition. Furthermore, chains of ubiquitin decorate mitochondrial membranes after their permeabilisation, resulting in an NF-kB inflammatory response. These mechanisms parallel a cell's response to bacterial infections. Guanylate binding proteins (GBPs) are known to be highly upregulated in an IFNγ-dependent manner and bind to bacterial membranes forming a large multimeric platform. These GBP platforms have a myriad of roles, including co-ordinating the cells anti-pathogen response and destroying the pathogen itself.

We now show that GBPs are recruited to permeabilised mitochondria during inflammatory cell death. Thus, we aim to understand the role of GBPs at these mitochondria, starting at mitochondrial membrane binding partners, membrane disruption and signaling. With these goals we want to further uncover how mitochondria are inflammatory during cell death.

Using super-resolution imaging we show that all members of the GBP family are recruited to permeabilised mitochondria. We also show that this is a general feature of mitochondrial permeabilisation, independent of the activation of BAX/BAK. Additionally, we have determined that ubiquitination of mitochondria is not required for GBP recruitment or assembly. By employing a range of biochemical, imaging and proteomics approaches, we aim to uncover the role of GBPs mitochondrial recruitment during cell death and how this impacts the inflammatory outcomes of cell death.

M. Lochner 1 & J.S. Riley 1

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Organelle-specific assembly of the ESCRT machinery and their role in organellar repair

The endosomal-sorting complexes required for transport (ESCRT) were identified in budding yeast (S. cerevisiae) for directing ubiquitinated transmembrane proteins into the vacuolar lumen for degradation via the multivesicular body pathway. Beyond this role, ESCRTs have now been implicated in diverse processes, such as cytokinesis and autophagy, involving the assembly of ESCRT-III filaments and their interaction with Vps4 (AAA-ATPase) to drive membrane remodeling with similar topological features. Typically, ESCRT machinery catalyzes negative membrane curvature, where the membrane bends away from the cytosol. In contrast, we observed that TORC2 inhibition-induced plasma membrane (PM) stress recruits Snf7 (an ESCRT-III subunit) to PM structures invaginating into the cytosol (positive curvature) in S. cerevisiae. This raises the question of whether the formation of ESCRT-III filament follows a set of general rules or is adapted to perform different biological tasks.

Our first objective is to investigate how ESCRT-0, -I, and -II contribute to the recruitment of ESCRT-III to the stressed PM upon TORC2 inhibition – Rapamycin treatment and hyperosmotic shock. Moreover, we will dissect whether ESCRT-III assembly at PM and endosomes follows similar or different rules. Finally, we aim to identify the physicochemical signals triggering ESCRT-III/Vps4 recruitment to stressed PM. By doing so, we seek to determine whether the ESCRT-III recruitment is a specific response to alleviate PM stress under different conditions or a general response to reduced PM tension.

Our work will expand the understanding of how ESCRT-III is recruited to stressed or damaged organelles and delineate either universal or organelle-specific rules for ESCRT-III assembly.

Astha Purwar (1), Simon Sprenger (2), Oliver Schmidt (2), David Teis (1)

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Unravelling the Role of Coagulation Factors in Hemophilia A-Associated Bone Metabolism

Introduction:

Patients with hemophilia A (HA) face an increased risk of low bone mineral density (BMD), independent of traditional risk factors. Evidence suggests that coagulation factor VIII (FVIII) may influence bone metabolism beyond coagulation, but this relationship remains unclear. This study explores the effects of coagulation factors on bone cells to elucidate their roles in HA-associated bone metabolism.

Method:

Human SaOs-2 osteoblasts and human osteoclasts were cultured with coagulation factors (FVIII, FIX, FX, FXa, vWF, vWF-FVIII complex, thrombin, FVIII-thrombin; 1 U/ml each) in mono- or co-cultures to assess cell viability, mineralization, fluorescent staining, and tartrate-resistant-acid-phosphatase (TRAP) activity.

Results:

In monocultures, coagulation factors did not affect SaOs-2 cell viability, but FX dose-dependently reduced osteoblast mineralization (31% reduction at 0.25 U/ml to 96% at 4 U/ml), confirmed with fluorescent staining. FXa had no effect, indicating the necessity of FX activation. Coagulation factors did not affect osteoclast viability or TRAP activity. In co-culture, FX inhibited mineralization by 40%, similar to monocultures, but distinct effects on osteoclasts were observed with TRAP activity increasing by 35% with FVIII and 55% with FIX.

Conclusion:

FX dose-dependently inhibits osteoblast mineralization, with the effect reversed upon activation, highlighting the importance of FX activation in bone health, particularly in HA. Co-culture models revealed unique osteoclast responses not seen in monocultures, demonstrating the limitations of monocultures in studying complex interactions and underscoring the value of co-cultures. These results highlight the interplay between coagulation and bone metabolism, offering insights for improved therapeutic strategies in HA.

Conflict of interest: None.

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The role of sphingolipids in protein quality control at the Golgi

How cells control the lipid and protein composition of their membranes is a fundamental biological question, essential for maintaining functional membrane integrity. Yet, the underlying molecular mechanisms that coordinate the biophysical and chemical properties of lipids with proteins remain poorly understood. Our recent work (Weyer et al., 2024, Nat. Comms; Schmidt et al., 2019, EMBO J) highlights the role of the Dsc ubiquitin ligase complex as a central player in Golgi quality control. The Dsc complex mediates the selective degradation of orphaned proteins at the sorting center of cells, preventing their spreading across other organelles and thereby preserving cellular membrane protein and lipid composition. Notably, we found that the loss of the Dsc complex not only caused the accumulation of orphaned proteins but also resulted in a specific increase in glycerophospholipids with shorter and asymmetric fatty acyl chains. How these lipids are regulated and how they contribute to Golgi quality control is not understood. To address these questions, I applied a multi-omic approach to comprehensively integrate quantitative proteomic, lipidomic, and synthetic genetic interaction datasets. This analysis clearly indicated that the regulation of lipid metabolism is a pivotal factor in Golgi quality control. Validation experiments revealed that Csg2, a regulator of mannosylinositol phosphorylceramide synthase, is a significant factor in this interaction. Functional biochemical and cell biological experiments support the hypothesis that complex sphingolipids and Golgi quality control are interconnected to ensure cell viability. Future research will explore Golgi protein quality control to advance our understanding of cellular membrane health.

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Plasmalogen catabolism: a new fluorescent HPLC-based Assay

Plasmalogens are a prominent class of glycerophospholipids distinguished by their characteristic 1-O-alk-1'-enyl double bond. Accounting for about 20% of the mammalian phospholipid pool, they have been linked to various human disorders, including Zellweger syndrome, Rhizomelic Chondrodysplasia Punctata, as well as neurodegenerative diseases such as Alzheimer's. While their biosynthesis in peroxisomes and the endoplasmic reticulum has been thoroughly studied, their catabolic processes remain less understood. Plasmalogen degradation involves conversion to 2'-lyso forms, catalyzed by lysoplasmalogenase. TMEM86B, expressed and purified from bacteria, has been confirmed to encode lysoplasmalogenase activity using a coupled optical assay. TMEM86A, although not yet purified, is also suspected to function as a lysoplasmalogenase, supported by indirect lipidomic data from tissues exhibiting altered TMEM86A levels and results near the detection limit of the optical assay.

We developed a novel assay to measure lysoplasmalogenase activity, involving substrate incubation, aldehyde product derivatization, and hydrazone quantification through reversed-phase HPLC with fluorescence detection.

This method is sensitive enough to detect lysoplasmalogenase activity in cells expressing TMEM86A or TMEM86B and distinguishes their response to different substrates. Mutations in putative enzymatically active amino acid residues in both TMEM86A and TMEM86B were generated and the resulting changes in lysoplasmalogenase activity relative to protein expression were analyzed to gain a deeper understanding of the critical enzymatic regions. The assay also effectively assessed lysoplasmalogenase activity in various mouse tissues.

Our assay provided a robust tool for measuring lysoplasmalogenase activity in cells and mouse tissues, aiding the study of plasmalogen catabolism and enhancing the understanding of plasmalogen-associated diseases.

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Optimizing immunomonitoring for oncolytic virotherapy

VSV-GP, a modified vesicular stomatitis virus-based oncolytic virus (OV), is currently in early phase 1 clinical trials. Preclinical studies have demonstrated its potential to induce strong innate and adaptive immune responses. However, upon OV treatment not only anti-tumor but also anti-viral T cells are activated, with the latter representing the dominant T cell pool, making it challenging to assess treatment efficacy. T cell receptor (TCR) diversity has been shown to be a good predictor of treatment response upon immunotherapeutic interventions. This works well in "sterile" settings, but is complicated in pathogen-based therapies due to the presence of anti-viral T cells. To accurately evaluate OV therapies, we are developing a novel TCR deduction approach using single-cell TCR sequencing. This method aims to deduct anti-viral TCR clones from the overall therapy-induced TCR pool, enabling a clearer assessment of anti-tumor immunity.

As a first step, we identified 20 activating VSV-GP CD8+ T cell epitopes in the widely used BL6 mouse model using bioinformatics tools and immune readouts. To validate the TCR deduction approach, we used the MC38 syngeneic mouse tumor model as a proof-of-concept. Here, tumor-specific antigens are known and T cell responses against those as well as against VSV-GP can be monitored using peptide-MHC-I multimers which carry unique DNA barcodes. These barcodes are used to assign the TCR sequences to the anti-viral and anti-tumor T cells. We hypothesize that after anti-viral TCR deduction the post-therapy TCR pool contains TCRs associated with cells labeled with anti-tumor specific multimers.

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The role of Calprotectin in mitochondrial metabolism and inflammation in macrophages

Inflammatory bowel diseases (IBD), including Crohn's Disease (CD) and ulcerative colitis (UC), are characterized by chronic, relapsing episodes of inflammation in and beyond the gastrointestinal tract. While the etiology of IBD remains unclear, dysregulated immune responses to gut microbiota, influenced by genetic and environmental factors, are key contributors.

Fecal Calprotectin, an extensively validated, non-invasive biomarker in IBD diagnostics, is a heterotetrameric protein complex of S100A8 and S100A9 formed in the presence of calcium. However, S100A8 and S100A9 also exist as homo- and heterodimers, which exhibit distinct but incompletely understood functions. Despite extensive research, an explanation for the, in part, contradictive functions of the dimers and heterotetramer remains elusive, especially in IBD. Recent work from our group identified S100A8 and S100A9 homodimers – rather than the S100A8/A9 heterotetramer – as key drivers of gut inflammation in IBD. Building on these findings and driven by results from unbiased approaches, we investigated their impact on mitochondrial function in macrophages, given the emerging link between metabolism and immune activation.

Using in vitro assays and high-resolution respirometry, we demonstrate that exposure to recombinant human S100A8 and S100A9 homodimers, as well as the S100A8/A9 heterotetramer, disrupts mitochondrial energy production in macrophage cell lines and primary macrophages across species. This metabolic dysfunction is accompanied by increased secretion of pro-inflammatory cytokines, suggesting a link between mitochondrial impairment and immune activation following S100A8 and S100A9 exposure. Further mechanistic investigations will elucidate this process, potentially uncovering novel therapeutic targets for IBD.

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An in Vitro Model to Study Pathomechanisms of Autoantibodies in Neuromyelitis Optica Spectrum Disorders

Over the past decades, several rare autoimmune central nervous system (CNS) disorders have emerged, primarily associated with autoantibodies targeting neuronal or glial antigens, such as neuromyelitis optica spectrum disorders (NMOSD). Autoantibody binding triggers immune responses, including complement activation. While in vivo and in vitro models help investigate these mechanisms, animal models are costly and raise ethical concerns, highlighting the need for suitable human cell-based models.

Most in vitro models use HEK293 cells overexpressing target proteins, but these fail to mimic astrocytes expressing AQP4. To address this, we developed a novel cellular system to study AQP4-targeting antibodies in NMOSD. We used AQP4-overexpressing glioblastoma cells (U-87MG-AQP4-ECFP), incubating them with a monoclonal AQP4 antibody (E5415A) and human complement. For comparison, we performed the same experiments on transfected HEK293 cells (HEK293-AQP4-EmGFP) and human primary astrocytes.

We assessed complement-induced cytotoxicity and analyzed transcriptomic changes using RNA sequencing (RNA-seq). Differentially expressed genes were compared with spatial transcriptomic data from a NMOSD rat model. Validation at both gene and protein levels confirmed that U-87MG-AQP4-ECFP best replicated the in vivo model. Our findings suggest this system provides a more physiologically relevant alternative to HEK293-based models for studying NMOSD pathology.

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Vesicular stomatitis virus as mutational tool to predict antiviral resistance

Gain-of-function experiments with dangerous pathogens that require high biosafety-level (BSL-3 or higher) work have been object of heated public discourse. Nevertheless, such studies are extremely important to assess antiviral resistance development. Here, we present two BSL-2 systems based on the Vesicular stomatitis virus (VSV) encoding clinically relevant SARS-CoV-2 proteins. Chimeric VSV encoding the main protease (Mpro) was used to generate protease inhibitor-resistant Mpro variants under selective pressure by nirmatrelvir. Chimeric VSV encoding both Spike and Mpro was used to generate spike mutations in the fusion-core domain under selective pressure by a fusion inhibitor.

The aims of this projects are to: 1) use chimeric VSVs to generate variants resistant against clinically relevant antivirals. 2) assess the role of VSV as a platform for studying evolution and resistance mutations of foreign viral proteins. Chimeric VSVs (VSV-Mpro and VSV-Spike-Mpro) were engineered to depend on these viral proteins for their replication. Serial passaging was conducted in vitro under selective pressure by increasing concentrations of the respective inhibitors to induce mutation in Mpro and/or spike. Dose response, molecular modelling and structural investigation experiments were performed to characterise these mutants. We observed that mutations identified in Mpro conferred reduced susceptibility or complete resistance to nirmatrelvir and mutations in the spike conferred decreased susceptibility to the fusion inhibitor.

This study demonstrates the applicability of chimeric VSVs for investigating antiviral resistance development/evolution in SARS-CoV-2 proteins. Future work can lead to the development of chimeric VSVs encoding viral proteins that belong to other emerging viruses.

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Who am I? CD64+DC Identity Crisis: Unmasking Melanoma's Mysterious Antigen Presenter

Our research has identified a distinct cDC2 phenotype in melanoma mouse models, characterized by FcγRI/CD64 expression - typically associated with monocytes and macrophages rather than DC. CD64+DC are abundant in tumors and tumor-draining lymph nodes, but are rarely found in lymph nodes of tumor-free mice. CD64+DC express both activation (CD40) and inhibitory (PD-L1, PD-L2) markers, suggesting their involvement in initiating and regulating effector T cell responses. Interestingly, some CD64+DC lack the DC-lineage marker Zbtb46, as shown by a Zbtb46-GFP DC-reporter mouse strain, suggesting that CD64+DC originate from both pre-DC and monocytes. Our project aims to understand the developmental origin and function of CD64+DC in tumor immunity.
We have shown that CD64+DC expand in response to FLT3L, a driver of DC differentiation and proliferation, indicating a possible pre-DC origin. Using DC- and monocyte-reporter mice, we are currently investigating their developmental pathways. We used a ZsGreen-expressing melanoma model to study their functional properties, and found that CD64+DC excel in tumor antigen uptake and lymph node trafficking, with CD64 expression correlating with these abilities. Our ongoing research focuses on their ability to present tumor-derived antigens to CD4+ and CD8+ T cells. Our research aims to elucidate the developmental origin and functional role of CD64+DC in tumor immunity and to determine if CD64 could be a biomarker for antigen-experienced DC. This work could potentially lead to novel immunotherapeutic strategies for melanoma treatment and highlights the importance of understanding the functional roles of DC subtypes in cancer immunity.

J. Vierthaler 1, F. Hornsteiner 2, C. Tripp 1, H. Strandt 1, M. Kanduth 2, L. Perro 2, S. Morla 2, G. Wollmann 2,3, P. Stoitzner 1

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Characterizing sex-dependent DC sensing mechanisms and immunometabolism at the tissue barrier during SARS-CoV-2 infection

The mechanism, by which the antigen-presentation capacity of DCs within respiratory tissues during COVID-19 is impaired, is largely unknown. DC numbers are reduced in severe COVID-19 cases and male sex has been identified as a risk factor. Within this study, we aim to generate an immunocompetent respiratory model to investigate the underlying causes for the different afflictions based on sex and the modulation of the DC metabolism upon SARS-CoV-2 infection.
To achieve this, we use lung organoids to incorporate monocyte-derived dendritic cells, optimized with human-based substances to eliminate xenogenic effects. The monocyte-derived dendritic cells will be infected with various SARS-CoV-2 strains via the organoid tissue and separated post-infection via FACS. Furthermore, the differentiation, activation, migration of the monocyte-derived dendritic cells and the inflammation of the lung organoid tissue will be investigated.
This will allow for the in-depth analysis of relevant components and pathways in the dendritic cell metabolism to gain insight into SARS-CoV-2-based modulations. Elimination of xenogenic material and testing of the system with male and female organoids will generate a widely applicable high throughput-capable immune competent system.

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Voltage gated calcium channels in mouse retinal bipolar cells

Sustained glutamate release from photoreceptors is triggered by Cav1.4 L-type calcium channel (LTCC) mediated calcium influx, however the respective voltage gated calcium channels (VGCCs) governing this process remain elusive in rod bipolar cells (RBCs). FACS-sorted RBCs showed transcripts for β2, α2δ-4, Cav1.3, Cav1.4, Cav3.2 and a C-terminal Cav1.1 splice variant, lacking the first 15 exons. Accordingly, whole-cell patch-clamp recordings in wild-type (WT) RBCs confirmed the presence of two distinct calcium currents: a sustained high-voltage activated (HVA) L-type current, measuring -4,5 ± 0,9 pA/pF at a holding potential (HP) of -50 mV and a transient, low-voltage activated T-type calcium current (HP -100 mV -9,9 ± 0,7 pA/pF; n=9, N=9; p<0,0001; unpaired t-test).
Despite substantial Cav1.4 transcript, VGCC current persisted when knocking out Cav1.4 (Current density (CD) [pA/pF] WT: -4,5 ± 0,9 (n=9, N=9), Cav1.4-KO: -2,7 ± 0,6 (n=8, N=5); p=0,0002; unpaired t-test). Using the L-type channel blocker Isradipine (10µM), we confirmed L-type characteristics of the remaining current (CD [pA/pF] WT: -0,6 ± 0,4 (n=8, N=5), p<0,0001; Cav1.4KO: -0,7 ± 0,4 (n=4, N=3); p<0,0001, unpaired t-test). Hence, we assessed the contribution of Cav1.3 channels and employed both a loss-of-function Cav1-3-KO and a gain-of-function CavAG mouse-model. In both mouse-models, anticipated changes in the activation properties were observed, but they as subtle trends, which suggests that Cav1.3 channels have only a minor role in WT RBCs.
The source of the remaining VGCC component will therefore still be explored through additional pharmacological and biochemical experiments.

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Regulation of the voltage-sensing mechanism in the voltage-gated calcium channel CaV1.1

The skeletal muscle CaV1.1 complex consists of a heterotetrametric alpha-1 pore-forming subunit and auxiliary subunits alpha-2-delta-1, beta, and gamma. Previous studies showed that the alpha-2-delta-1 subunit is crucially involved in modulating the channel's characteristic slow activation kinetics. The alpha-1 pore-forming subunit contains four voltage-sensing domains (VSD I-IV) which are assembled around a common pore. Each of these VSDs is formed by four transmembrane helices (S1-S4) with S4 containing four to five positively charged gating charges. Upon depolarization, these gating charges enable the VSD to sense the changes in the membrane potential, resulting in S4 state transitions and consequently in channel activation. This process is facilitated by transient ionic interactions between the gating charges and negatively charged countercharges in the surrounding helices (S1-S3). In CaV1.1, VSD I has a dominant role in channel gating and its activation properties limit the rate of the channel's activation kinetics. The characteristically slow activation kinetics of the channel are governed by interactions of S4 gating charges with negatively charged countercharges on the extracellular site of VSD I. Additionally, structures revealed an interaction site that links the extracellular part of VSD I with the alpha-2-delta-1 subunit. Here, we use a combination of site-directed mutagenesis of gating- and countercharges, patch-clamp recordings of CaV1.1-null myotubes reconstituted with the mutant constructs and molecular dynamic simulations to analyze how the interactions between gating- and countercharges regulate the voltage-dependence and kinetics of activation and how the alpha-2-delta-1 subunit is involved as a modulator in the speed control of the channel's activation.

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Cross-cultural comparison of treatment delay and stigma in patients with major depressive disorder in Austria and Japan.

Identifying transcultural differences in the social impact of major depressive disorder (MDD) in patients from Austria and Japan could help to understand how the health care system can develop to reduce the burden of mental illness and develop appropriate culturally specific psychosocial programs.

This study examines treatment delay for MDD between patients in Austria and Japan, and influence of spirituality and resilience. It also compares specific dimensions of the social impact of mental illness (SIS), and outcomes such as symptom severity (MADRS), subjective well-being (WHOQOL-BREF) and functional performance (PSP).

The study sample consisted of 101 MDD patients (53% female): 51 from Austria (Mage=36.3±12.3 years) and 50 from Japan (M=47.2±16.9; $p<0.01$). Japanese patients experienced a significantly longer duration of untreated illness (M=0.9±1.8 years, M=4.8±8.7, p=.003), lower symptom severity (M=14.9±11.6, M=25.3±10.1, $p<.01$) and higher perceived spiritual well-being: peace (M=7.9±4.08, M=4.4±3.83, $p<.001$) and faith (M=6.33±3.67, M=4.18±4.64, p=.012) and higher perceived psychological quality of life (t(93)=-2.47, p=.015). In contrast, Austrian patients experienced greater social exclusion (t(97)=2.8, p=.006). Despite these differences, resilience and functional performance were comparable across groups.

Despite lower symptom severity, Japanese study participants reported a significantly longer treatment delay compared to those living in Austria. Whereas resilience did not appear to be relevant in this context, our findings point to significant transcultural differences in the social impact of MDD. This can be partly attributed to differences in spirituality between countries. Findings underscore the need for culturally tailored psychosocial interventions to address region-specific mental health care challenges and reduce the burden of MDD.

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Efficacy of physical therapy in individuals with postural orthostatic tachycardia syndrome (POTS): a systematic review

Physical therapy is recommended as first-line treatment for individuals with POTS by expert consensus. There is a need to identify the evidence base of this non-pharmacological treatment approach.
The present study evaluates the efficacy and safety of physical therapy in improving symptom severity in individuals diagnosed with POTS. Secondary objectives are to assess the physical therapy programs offered to individuals, the assessment of improvement and the compliance to the offered treatments.
We systematically screened the databases PubMED, Clinical Trials and Web of Science until November 11th 2024 combining the following keywords: "Postural orthotstatic taychycardia syndrome" (in variations) "physical therapy", "exercise", "physical activity", "breathing" (selection). Eligible study design included randomized controlled trials (RCTs), comparative non-randomized studies, case series and case reports. Included were adults (aged >18) diagnosed with POTS. We evaluate the supine to standing Δ heart rate (Bpm) (primary endpoint), and – for secondary outcomes – the symptom severity and quality of health.
The search identified 1657 records. We selected 10 studies. 9 out of 10 studies evaluated endurance gradually progressed in time, intensity and posture. Change after exercising was measured by active standing test (n=7) or head-up tilt test (n=4). Mean or highest heart rate response to exercise measured at different timepoints was a common outcome (n=8). Symptom severity improvement was assessed with different autonomic symptom scores. The drop-out rates were between 10 and 59 percent, which corresponds to 304 out of 600 included participants. The study will assess the evidence for physical treatment of POTS patients.

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MR Spectroscopy in well-characterized individuals with and without post COVID condition prior to and following a Yoga breathing intervention- a pilot study

From a clinical perspective we find that many patients with post COVID condition suffer from severe and debilitating shortness of breath, while routine pulmonary investigation cannot find the cause for the experienced problems. If dyspnea is associated with palpitations, dizziness or anxiety the patients are commonly diagnosed as suffering from "dysfunctional breathing". From a psychosomatic perspective the symptom of dysfunctional breathing can be classified under the umbrella term of somatic symptom disorder. Therefore Yoga interventions with special focus on breathing guided relaxation is a promising approach. We aim to explore the psycho-somatic and somato-psychic pathophysiology on a morphological, psychological, functional and biological basis underlying the symptom of dysfunctional breathing. Furthermore, we plan to investigate the mode of action of Yoga intervention on mental and somatic symptom load of participants with post COVID condition. Then, we aim to compare Yoga influence toward another groups- healthy individuals, those with COPD, as well as those with somatic symptoms disorder.

Nelles PA 1 , Hüfner K 1 Sonnweber T 2 , Fanciulli A 6, Karabatsiakis A 3, Singewald N 4, Gostner J 5, Steiger R 6, Kremser C 6, Humpel C 7, Löffler-Ragg J 2, Sperner-Unterweger B 1 , Gizewki E 6

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Subjective well-being in early-phase schizophrenia patients using long-acting injectable vs. oral antipsychotic drugs: data from the European Long-acting Antipsychotics in Schizophrenia Trial (EULAST)

Background: This study aimed to evaluate potential differences in subjective well-being among patients with schizophrenia (SZ) randomly allocated to either long-acting injectable (LAI) or oral antipsychotic medication, as well as the impact of symptomatology, pharmacological side effects, and demographic characteristics on subjective well-being.

Methods: Patients aged ≥ 18 years and meeting DSM-IV criteria for SZ were recruited and followed up for up to 19 months as part of the "European Long-acting Antipsychotics in Schizophrenia Trial" (EULAST) trial. Subjective well-being was assessed using the Subjective Well-being under Neuroleptic Treatment scale (SWN) and possible differences between the type of formulation of antipsychotic drugs regarding subjective well-being were analysed by a linear mixed-effects analysis approach. Multivariable and comprehensive models were implemented to investigate the potential effects of age, sex, symptomatology (Positive and Negative Syndrome Scale [PANSS]), and side effects of medication (Systematic Monitoring of Adverse events Related to TreatmentS [SMARTS], St. Hans Rating Scale for Extrapyramidal Syndromes [SHRS]) on SWN change.

Results: There was no significant difference in SWN change in 364 patients undergoing LAI or oral antipsychotic treatment ($p = 0.1533$) over time. PANSS dimensions (p values < 0.0001), SMARTS ($p < 0.0001$) and several SHRS subscales (subjective ($p < 0.0001$) and objective ($p = 0.0014$) akathisia, parkinsonism ($p < 0.0001$)) showed a significant inverse relationship with SWN scores.

Conclusion: These findings indicate comparable subjective well-being in SZ patients treated with either LAI or oral antipsychotic medication, while symptomatology and medication side-effects work as reliable predictors in this context.

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R1-R2* relaxivity in white matter is associated with survival in glioblastoma patients

INTRODUCTION

Longitudinal relaxation rate (R1) and effective transverse relaxation rate (R2*) mapping are quantitative MRI techniques that allow characterization of tissue composition in vivo. A recent relaxivity model (R1-R2* relaxivity) has been proposed as a marker of iron homeostasis (IH)1. The aim of this study was to calculate R1, R2* and R1-R2* relaxivity in different contratumoral brain regions (ctROIs) of glioblastoma patients before surgical resection and perform correlation analyses with patients' outcomes and neuropathological factors.

METHODS

R1 and R2* maps were computed for each of the thirty-eight glioblastoma patients included in the study before surgery. R1-R2* relaxivity was calculated assuming a linear dependency of R1 on R2* in accordance with 1. T1 images were parcellated using Fastsurfer and parcels were grouped in twelve ctROIs (four cortical [CTX], four subcortical [DGM], four white matter [WM]). Correlation analysis including patients' survival, MGMT methylation status and p53 gene expression was performed in Rstudio.

RESULTS

R1-R2* relaxivity in frontal, occipital and parietal WM discriminated patients based on late or early mortality. R1-R2* relaxivity was associated with MGMT methylation status in temporal WM and with survival at different months after surgery in putamen, frontal and occipital WM.

DISCUSSION AND CONCLUSIONS

R1 and R2* values across non-tumoral brain regions are in accordance with current literature and overall comparable with healthy subjects. R1-R2* relaxivity in WM might represent a marker of patients' survival and an early indication of IH disruption in ctROIs. Larger studies are needed for validation.

REFERENCES

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Alberto Galimberti1,2, Stephanie Mangesius1, Julian Mangesius3, Johannes Kerschbaumer4, Christian Freyschlag4, Ute Ganswindt3, Elke R. Gizewski1,2, Christoph Birkl1,2

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The Therapeutic Potential of a Temporin B Peptide Analog in Skin Infections

Antimicrobial peptides (AMPs) are promising candidates for the development of topical treatments targeting microbial skin infections, including those caused by the Gram-positive human pathogen Staphylococcus aureus. Among the AMPs, Temporin B (TB) is of particular interest. This cationic peptide, consisting of 13 amino acids, is secreted by the granular glands of the European frog Rana temporaria and represents a primary line of defense against invading pathogens. This study aimed to evaluate the antibacterial efficacy of a synthetic TB analog (TBA) against a drug-resistant clinical isolate of S. aureus. The findings demonstrated that TBA exhibited potent bactericidal activity at low micromolar concentrations. Additionally, the peptide showed no toxicity in the in vivo invertebrate mini-host model Galleria mellonella and was well tolerated when applied topically to in vitro three-dimensional (3D) human epidermis equivalents (HEEs). Notably, the therapeutic potential of TBA was confirmed in HEEs infected with S. aureus, where its topical application led to a significant reduction in bacterial load and a decrease in the pro-inflammatory response. These results underscore the strong antibacterial activity and therapeutic promise of TBA in treating S. aureus-associated skin infections.

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Unraveling AKT Isoform Specificity: Profiling Drug Candidates with Cell-Based Reporter Assays

Protein kinases play a crucial role in pathophysiological signal transduction, acting as molecular switches that regulate essential cellular processes, and are regulated by various mechanisms, making them prime targets for drug development. Dysregulation of central kinases such as AKT are linked to a wide range of diseases, including cancer, diabetes, and neurodegenerative conditions. Understanding AKT's involvement in cellular signaling and its isoform-specific functions is crucial for developing targeted therapies that can precisely address specific AKT isoforms and cancer hot spot mutations such as AKT1-E17K [Craven et al., Nature 2025]. Yet, more effective methods for screening and validating new drug candidates are needed. In this project, we first assessed the conformational states of the isoforms AKT1, AKT2, and AKT3 using the cell-based Kinase Conformation (KinCon) reporter system [Kugler et al., eLife 2024]. We discovered major isoform-specific conformation changes of the full-length kinases upon exposure with preclinical and FDA-approved small molecule kinase inhibitors (AKTi). Secondly, the phosphotransferase activity profile of all three AKT isoforms was benchmarked alongside conventional phosphorylation readouts, utilizing FRET reporters [Kunkel et al., JBC 2005] and the newly engineered luciferase protein-fragment complementation assays. We have first evidence that allosteric AKTi alter AKT conformations and activities in an isoform-dependent manner. These cell-based reporter systems will pave the way to systematically analyze further kinase drug candidates. Currently we are evaluating isoform-specific profiles of AKT inhibitors, for predicting their efficacy, potency and specificity in the context of cancer patient-specific AKT mutations.

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Exploring p53-drug interactions: a unique p53 target engagement platform

The tumour suppressor protein p53, often referred to as the `guardian of the genome´, plays a critical role in maintaining genomic stability by regulating cellular stress responses. Mutations in the TP53 gene are observed in nearly 40% of all human tumours with varying frequencies across tissues. Among these, missense mutations are the most common, significantly affecting protein structure and function, leading to aberrant cellular processes and promoting tumorigenesis. The prevalence of p53 mutations offers a promising target for the development of stabilizing and reactivating bioactive small molecules. The goal of my FFG-funded industrial PhD project is to identify and validate chemical entities that reestablish p53 wildtype conformations, for restoring its tumor suppressing function. Here we present a p53 conformation reporter to determine and compare the impact of available small molecule binders on p53 conformations and functions. First, we engineered a genetically encoded monomeric p53 reporter to investigate the conformational dynamics of this intrinsically disordered protein. Second, we demonstrated that certain patient mutations alter the conformation of the protein. Third, small molecules that were postulated to restore the function of mutated p53 were tested and validated using our cell-based target engagement system. Thus, we benchmarked a comprehensive collection of small molecules on their potential in rescuing the functionality of various p53 mutants. Overall, our study shows first evidence that the p53 conformation reporter is suitable for identifying and optimizing future p53-targeted therapeutics. It enables the analysis of mutation-specific drug candidate responses which aim to restore the tumor-suppressive function of mutated p53.

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Development of an immunocompetent 3D bioprinted melanoma-on-chip model

Melanoma remains one of the most aggressive skin cancers, and understanding tumor cell interactions with the immune system is crucial for developing effective treatments. However, tumor immunology research relies heavily on mouse models, but translating these findings to patients is challenging. To address this, we focus on developing a human 3D bioprinted melanoma-on-chip model. As part of this effort, we printed in microfluidic chips and evaluated fibroblast viability, keratinocyte differentiation (confirmed by cytokeratin 1/10 staining), and overall tissue integrity. In parallel, melanoma cell lines (MugMel 2, MugMel 3, and A375) were tested for their growth properties and spheroid formation potential. These spheroids were then incorporated into the 3D bioprinted skin model to establish a 3D melanoma-on-chip model. To incorporate human DC, protocols to differentiate cDC1, cDC2, and pDC from CD34+ hematopoietic stem cells were established. Overall, we confirmed that human cDC1 and cDC2 generated from CD34+ precursors are valuable substitutes for blood DC subtypes to generate bioprinted immunocompetent models. Therefore, we will incorporate them into our 3D bioprinted melanoma-on-chip model and study the interactions between melanoma cells and DC. Further, protocols for generating Langerhans cells (LC) from CD34+ progenitors are currentlytested, and markers CD1a and Langerin are evaluated on LC. Including immune cells and melanoma cells in the 3D bioprinted skin will be a significant step forward in the study of skin immunology and melanoma, offering new opportunities for investigating tumor-immune dynamics and testing therapeutic approaches.

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Microbiome derived products inducing anti-cancer immunity in colorectal cancer

Colorectal cancer (CRC) is largely resistant to immune checkpoint inhibitors (ICIs), except for mismatch-repair-deficient (MMR) tumors, which represent only 15% of cases. Emerging evidence highlights the gut microbiome's role in immune modulation and cancer progression, suggesting potential microbiome-based therapies. Despite this, the precise mechanisms linking microbial metabolites with immune responses in the tumor microenvironment (TME) remain unclear. This study investigates how bacterial metabolites derived from a defined 11-strain gut microbiota consortium influence interactions between intestinal epithelial cells (IECs) and immune cells. Using gnotobiotic germ-free (GF) mouse models, GF organoid models, and bulk RNA sequencing, we identified microbial metabolite-induced upregulation of neutrophil-attracting chemokines, including CXCL1 and CXCL2, in IECs, suggesting activation of immune pathways. Single-cell RNA sequencing of CD8+ T cells from GF mice treated with the bacterial mix and ICIs revealed distinct states (naive, early activ, effector memory, pre-exhausted and exhausted) and developmental shifts supported by markers such as PD1, CD69, ICOS, and CD103 and pseudotime analysis. These findings highlight microbial metabolites as drivers of immune modulation in the colon and link bacterial consortia to immune cell activation and metabolic shifts. Ongoing analysis of cecal metabolomics and spatial transcriptomics aims to further validate these mechanisms. By elucidating microbiome-immune crosstalk, this work identifies potential therapeutic targets to overcome ICI resistance in CRC, advancing microbiome-based cancer immunotherapy.

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5 Cancer Signaling and Microenvironment Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania.

Poster abstracts

- Posters should stay up for the whole duration of the meeting and must be taken down immediately after the poster session on Friday.
- Poster presentations should last approximately 3 min.
- Odd poster numbers on Thursday
- Even poster numbers on Friday
- There will be poster prizes, so stay at your poster during your respective session!

Posters

Odd numbers on **Thursday, even** numbers on **Friday**

Presenting Author		#	Abstract title
Lea Emmy	Timpen	1	The BASP1-E2F1 complex and its role in the regulation of MYC transcription
Leonie	Weber	2	The BASP1 protein interferes with WNT pathway signaling
Fabian	Rabensteiner	3	Novel Role of FoxH1 in Chromatin Scaffolding Events during Early Differentiation
Alexander	Plesche	4	ER lipid homeostasis under mechanical stress
Nikolas	Marchet	5	Alpha-arrestin mediated control of cellular nutrient uptake and its role in metabolic signaling
Lucija	Kucej	6	Golgi quality control and its role in protein homeostasis (proteostasis)
Beatriz	Rodrigues	7	IFRD1 and IFRD2 role in Ifi202b expression and adipogenesis
Adam	Pollio	8	TM9SF4 a cytoskeletal and sorting protein
Doris	Stepic	9	Delineating hepatocytic apical trafficking defects in myoVb associated liver disease
Michaela Maria	Mayr	10	IRE1 is Involved in Translation Control Under Mechanical Stress
Baris	Bekdas	11	Putative novel function of Orm1/2 proteins in ergosterol metabolism
Luca	Szabó	12	The Role of the Retriever in Polarized Plasma Membrane Recycling
Laura	Sammarco	13	Characterization of the Trafficking of VIP36 and VIPL and Identification of New Cargos
Martina A.	Höllwarth	14	Optimization of crosslinking mass spectrometry workflow to unravel the molecular architecture of endogenous BORC complexes
Eva	Rauch	15	Optimisation of an XL-MS/MS workflow to study the architecture of native LAMTOR assemblies
Niklas	Schomisch	16	Functional analysis of novel players involved in Orm2 ER Export

Posters

Odd numbers on Thursday, even numbers on Friday

Presenting Author		#	Abstract title
Isabel	Singer	17	LAMTOR1 phosphorylation orchestrates protein interactions at the lysosome
Florian	Hofer	19	Prognostic implications of recovery of cardiac autonomic dysfuntion after myocaridal infarction: a SMART-MI subanalysis
Simon	Leiter	20	Motivation to participate in the Healthy Brain Aging (HeBA) Tirol study and its association with remotely estimated PD risk
Kai	Zimmer	21	Multi-omics deconvolution of systemic inflammation in the context of clonal hematopoiesis in stroke
Manuela	Ranalter	22	Individualised flow controlled ventilation in a porcine ex vivo lung perfusion model
Felix Julius	Krendl	23	Leveraging normothermic liver machine perfusion as a platform to establish tumour directed ex-situ treatment
Greta	Hemicker	24	Following the Breadcrumbs: Clinical Clues in Huntington's Disease
Daniel	Schwaiger	26	Anticoagulation monitoring in patients receiving elective cardiac surgery
Christoph	Theyer	27	Predicting hyposmia to identify people at-risk for Parkinson's disease: Preliminary baseline data from the population-based HeBA-study
Paolo	Bonatti	28	Ethanol preserved donor corneas as long-term storage for acute tectonic keratoplasties
Matthias	Demetz	29	Exploring Subvisual Protoporphyrin IX Fluorescence in Gliomas
Philipp	Spitaler	30	Stimulated Periodic Repolarization Dynamics as a Predictor of New-Onset Device-Detected Atrial Fibrillation
Lukas	Scherer	31	INNSBRUCK HEALTH PROMOTION PROGRAM (INN.HEALTH)
Michael	Swoboda	32	Technical feasibility of MRI/ultrasound fusion in breast imaging and the characterization of breast foci in contrast-enhanced breast MRI.

Posters

Odd numbers on Thursday, even numbers on Friday

Presenting Author		#	Abstract title
Marta	Konopka	33	Vascular Senescence as a Key Factor in Vascular Damage and Microcirculatory
Lukas	Sigwart	34	Colour changes and surface roughness after air-polishing for tobacco stain removal
Frederik	Eisendle	35	A randomized controlled trial on the effects of respiratory gas shifts to delay asphyxiation in critically buried avalanche victims
Caren	Agreiter	36	The non-canonical function of p27Kip1 in terminally differentiated post-mitotic neurons
Frank	Jagusch	37	Volume reduction of the insular cortex in patients with multiple system atrophy.
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The BASP1-E2F1 complex and its role in the regulation of MYC transcription

The gene regulator MYC controls multiple cellular processes including cell proliferation and differentiation, but MYC is also aberrantly activated in multiple human tumours. For this reason, MYC is considered as major cancer driver representing a promising therapeutic target. However, so far efficient direct MYC targeting has remained unsuccessful. Therefore, indirect strategies targeting the MYC network appears to be a more suitable approach.

One of the downregulated transcriptional targets of MYC is the BASP1 gene encoding a neuronal signalling protein and a transcriptional corepressor. On the other site, ectopic expression of BASP1 suppresses MYC mRNA expression, rendering MYC and BASP1 mutually exclusive. Furthermore, BASP1 overexpression reversed MYC-induced cell transformation.

To investigate the regulation of MYC transcription in the context of BASP1, we performed a reverse chromatin immunoprecipitation (R-ChIP) screen using the colon cancer cell line SW480, and SW480 stably overexpressing BASP1. Here we identified 541 unique proteins binding to the MYC promoter, 107 thereof were specific for BASP1-expressing SW480. Among these, we have identified proteins that are known to interact with the cell cycle regulator E2F1. By performing co-immunoprecipitation (co-IP) experiments we found that BASP1 and E2F1 form a complex. This novel protein complex could be involved in transcriptional MYC regulation using a canonical E2F1 binding site next to the transcription start site.

By investigating the function of the BASP1-E2F1 complex, we expect to gain more insight into oncogenic MYC regulation, which may result in developing novel therapeutic strategies to target MYC.

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The BASP1 protein interferes with WNT pathway signaling

MYC is a transcription factor with oncogenic potential controlling fundamental cellular processes like proliferation, metabolism, differentiation, or apoptosis. While MYC activities in normal cells are essential and tightly regulated, MYC is frequently found to be deregulated in most human tumors, in which this oncoprotein represents both a major cancer driver and a challenging drug target. The transcriptional MYC target BASP1 (brain acid-soluble protein 1) is downregulated in MYC-dependent cancer cells and ectopic BASP1 expression interferes with MYC-induced cell transformation.

Using human colon cancer cells (SW480) featured by high MYC expression and a silenced BASP1 gene, we generated cell lines overexpressing BASP1. BASP1-expressing SW480 display a strongly diminished transformed phenotype accompanied by significant reduction of MYC expression at mRNA and protein level.

Transcriptome, proteome, and interactome comparison of SW480 with our BASP1-overexpressing cell lines was performed using RNA-Seq, Immunoprecipitation, and Liquid chromatography coupled to Mass spectrometry (LC-MS). Genes and proteins downregulated in BASP1- expressing cells are the MYC-associated factor X (MAX) and the metastasis-associated protein 1 (MTA1). Upregulated genes include the metastasis suppressor KISS1 and the kinase STK4, that is known to promote β-catenin degradation. Since the WNT signaling pathway plays a crucial role in cancer development in colorectal cancers we further investigated key proteins of this pathway. The WNT signaling protein β-catenin (CTNNB1), TCF4, or the TCF4-specific kinase TNIK are downregulated upon BASP1 activation. Furthermore, a TCF4 reporter assay confirms that BASP1 expression significantly lowers WNT pathway activity, suggesting that BASP1 directly interferes with established WNT-triggered MYC activation.

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Novel Role of FoxH1 in Chromatin Scaffolding Events during Early Differentiation

Gastrulation with the formation of the three germ layers followed by a step by step fate determination forms a keystone in the development of multicellular organisms. During this early process, cells undergo extensive chromatin remodelling, which alters its structure and regulates gene transcription. FoxH1 is a known major key transcription factor which, during this early embryotic development, controls and fine tunes regulatory gene programs involved in mesoendoderm induction and left-right patterning. Recent studies further suggest FoxH1 as a potential pioneer-transcription-factor with more general function in chromatin remodelling during transition during early cell specification. Recent work from our group in zebrafish revealed interaction of FoxH1 with various DNA-sites lacking the FoxH1 consensus motif, suggesting that FoxH1 might indirectly influence the chromatin state as part of a bigger protein complex. However, how FoxH1 contributes to loci targeting, with which proteins it is interacting and the underlying kinetics during this early remodelling is still unknown. To address these questions, a set of human iPSC cell lines with domain-specific FOXH1 mutations was established. The DNA recognizing FH domain as well as the protein interacting SI domain are thought to be essential for chromatin remodelling events and available data suggests that the absence of either one of them will interfere with FoxH1's function of chromatin-looping. By the usage of these cell lines, the specific functions of each domain can be identified. Additionally, the lines are tagged with a 3xTY1 epitope, which will further be used for a molecular characterization of direct targets.

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ER lipid homeostasis under mechanical stress

Cells within living organisms are exposed to mechanical stresses at all times. These stresses are induces by forces such as stretching, fluidic shearing and confinement. The cell perceives and reacts to these mechanical stimuli via complex signaling cascades, many of which remain poorly understood. Recent work from our group has identified one of the regulators of the unfolded protein response in the endoplasmic reticulum (ER), IRE-1, to be activated following confinement and acting as a master-regulator of translation during this mechanical stress. My research project also centers around the ER during mechanical stress, with a particular focus on changes and adaptations in the lipid homeostasis.

Following confinement, the morphological appearance of the ER changes with an increase of sheet-like structures while the peripheral tubular network is reduced. Accompanying these alterations are changes in lipid groups associated with membrane formation. Next to these large scale alterations, ER exit sites (ERES) which are specialized subdomains for cargo export in the ER, strongly increase under confinement. Treating cells with inhibitors of different lipid synthesis steps changed the effect on ERES, highlighting the importance of lipid composition for the biological functionality of membranes. Furthermore, mitochondria fragment under confinement, a process which was implied in other mechanical stresses to govern multiple downstream processes such as cholesterol production. Future work on the project aims to understand the interplay between mitochondrial fragmentation and lipid homeostasis at the ER under confinement, as well as the upstream signaling events driving ER morphology changes.

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Alpha-arrestin mediated control of cellular nutrient uptake and its role in metabolic signaling

Entry and exit from quiescence require changes in cellular nutrient acquisition. How quiescent cells reduce nutrient uptake was unclear. Here, we demonstrate that cells entering quiescence select plasma membrane-resident amino acid (AA) transporters for endocytosis and lysosomal degradation, to match AA uptake with reduced translation. The endocytic degradation of the heterodimeric AA transporter SLC7A5-SLC3A2 (LAT1-4F2hc) requires the α-arrestin TXNIP and its interaction with HECT-type ubiquitin ligases. During growth, active AKT phosphorylates TXNIP, maintaining it inactive. In quiescence, reduced AKT signaling licenses TXNIP dependent endocytosis of SLC7A5-SLC3A2 to decrease AA uptake. TXNIP deficiency results in dysregulated AA uptake, enhanced mTORC1 signaling, increased translation, accelerated quiescence exit, and proliferation. Fibroblasts derived from a patient with a novel homozygous loss-of-function mutation in TXNIP, associated with a severe inborn metabolic disease, also failed to downregulate SLC7A5-SLC3A2. These findings highlight TXNIP's role in controlling SLC7A5-SLC3A2 mediated AA acquisition with implications for metabolism and human health (Kahlhofer et al. 2024, bioRxiv).

Based on these results, we now investigate in molecular detail how TXNIP targets SLC7A5-SLC3A2 for endocytic degradation, and aim to define the role of SLC7A5-SLC3A2 in metabolic signaling, and how this could be linked to the regulation of translation and cell proliferation and quiescence.

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Golgi quality control and its role in protein homeostasis (proteostasis)

Proteostasis is essential for healthy cells as defects lead to numerous diseases (e.g. neurodegeneration). To achieve proteostasis, cells have evolved protein quality control checkpoints across different organelles to detect and eliminate dysfunctional proteins. While the quality control functions of the ER, lysosomes, and mitochondria are characterized, the Golgi apparatus remains relatively understudied, despite its critical role in protein sorting and modification. This project aims to bring further insight in the Golgi protein quality control network in mammalian cells, with a particular focus on the retrieval receptor 1, RER1. Previous research in Teis lab has identified RER1 as a key component of the Golgi quality control system in budding yeast. Using a combination of quantitative proteomics, genetics, and advanced imaging techniques, this study aims to identify (1) substrates for RER1 and Golgi quality control, and (2) additional proteins that interact with RER1 to maintain proteostasis.

This work will provide a better understanding of quality control at the sorting center of cells. Therefore, we will define molecular mechanism used to identify orphaned proteins at the Golgi and prevent their accumulation / spreading across the cell. On the long run, it may help to understand how proteostasis defects lead to pathological mechanisms in diseases.

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IFRD1 and IFRD2 role in Ifi202b expression and adipogenesis

Adipogenesis is a complex process requiring interaction of genes at different molecular and cellular levels. In the early stages of this project, we aim to characterize the phenotype of IFRD1/2 dKO adipocytes, and the functional relationship between Ifrd1/2 and Ifi202b genes in the adipogenesis. Mouse Ifrd1 plays a role in adipogenesis regulating transcription and promoting Wnt/β-catenin-signalling. Ifi202b is an obesity gene promoting white adipogenesis via fat storage in lipid droplets. Ifi202b localizes to the nucleus shortly after the induction of adipogenesis, suggesting a regulatory role in expression of adipogenic genes. Mouse Ifrd2 gene, a translational inhibitor of DLK-1, acts as negative regulator of adipogenesis. Ifi202b overexpression decreased the expression of Pref1 (human orthologue of mouse Dlk1), inhibiting adipocyte differentiation. Our preliminary results showed a significant decrease in lipid droplet abundance and size in IFRD1/2 dKO cells. Moreover, RT-PCR analyses identified IFRD1/2-regulated Ifi202b expression, since dKO cells did not express Ifi202b when compared to the WT genotype. However, Ifrd1/2 re-expression in dKO cells did not "rescue" the Ifi202b expression, indicating a missing factor necessary for regulated Ifi202b expression.

In future experiments we plan to characterize the Ifi202b expression in mouse stromal vascular fraction cells, and to analyse the expression of Aim2, a gene known to regulate Ifi202b expression, as a possible link to upstream regulatory mechanisms of Ifi202b in both, in adipogenesis and inflammation.

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TM9SF4 a cytoskeletal and sorting protein

Tm9Sf4 is a poorly understood protein. It actively plays a role in protein trafficking, cancer metastasis, and general cell motility. The exact nature of these phenotypes varies in elucidation. Tm9sf4 in vitro manipulates actin by way of interacting with cofilin and increasing actin depolymerization. Its localization has also been widely reported in various locations of the cell including lysosomes, Golgi, and endosomes. Lastly, it's shown to play a role in trafficking during epithelial polarization. Here we aim to elucidate where Tm9sf4 is subcellularly located and how it might function in the context of epithelial polarity. For this, we use epithelial cells to describe apical basolateral sub-structures and evaluate the transition of cells to a polarized state. We generated a CRISPR-Cas9 based knock-out (KO) of TM9SF4. We used immunofluorescence microscopy for morphological characterization. We characterize changes in cytoskeletal structures and trafficking during the establishment of a monolayer. Lastly, we measure the apical and basolateral surface proteome by quantitative mass spectrometry

The TM9SF4 KO cells migrate slower, and increase the number of focal adhesions. Further, the actin network has more stress fibers in higher density. In KO cells, we see a Golgi apparatus with enlarged cisternae. Finally, we see several proteins differentially expressed on the apical and basolateral plasma membranes. Overall, Tm9sf4 appears to interact with polarization both by manipulating actin during the establishment of a monolayer, and by directly playing a role in trafficking from the Golgi apparatus to the plasma membrane.

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Delineating hepatocytic apical trafficking defects in myoVb associated liver disease

The existence of apical, lateral and basal domains of the plasma membrane in polarized epithelial cells, each with distinct functions and protein composition necessitates targeted protein trafficking. Therefore, disturbed polarized trafficking might result in disease. One example is the intestinal microvillus inclusion disease (MVID) which is characterized by defects in enterocyte polarity and mislocalization of apical proteins. MVID is caused by mutations in the MYO5B, STX3, and STXBP2 genes, which encode the proteins myosinVb (myo5b), syntaxin3 (stx3), and munc18-2, respectively. Myo5b is a motor protein that carries apically destined vesicles, while stx3 and munc18-2 facilitate the fusion of vesicles with the apical membrane. Interestingly, some patients with MVID develop cholestatic liver disease (CLD) characterized by mislocalization of the apical membrane proteins in hepatocytes. The question is how apical trafficking functions in hepatocytes, particularly given that only dominant-negative missense mutations, but not nonsense mutations of myo5b result in CLD and that stx3 is not present. To investigate this, we are using polarized hepatocytic HepG2 cells, from which basis we developed transgenic lines to identify key players in apical protein trafficking in hepatocytes using protein interaction studies. MYO5B knockout cells will allow to identify a possible compensation in the apical trafficking machinery observed in patients. We found that stx2 resides apically and may substitute for stx3 in hepatocytes. Generating a STX2 knockout will enable us to test this hypothesis. Additionally, apical surface proteome studies in various knockout backgrounds will allow us to find out which apical proteins are trafficked via said machineries.

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IRE1 is Involved in Translation Control Under Mechanical Stress

Over the span of their life, cells in the body undergo a plethora of mechanical stresses. Since mechanobiological research usually focuses on the plasma membrane, the cytoskeleton and the nucleus, the mechanobiology of the endoplasmic reticulum remains poorly understood. Here, we show that Inositol requiring protein 1 (IRE1), known for its role in the unfolded protein response (UPR), senses mechanical perturbations of the cell.

Our data shows that confining cells to 3µm for 30min resulted in IRE1 phosphorylation. This activation occurs in the absence of protein misfolding in the ER and does not result in canonical UPR signaling (splicing of XBP1). This indicates a new, UPR independent function of IRE1.

Since a recent paper describes a link between IRE1 and translation, we investigated translation levels in confined cells. Strikingly, SUnSET translation assays show that translation under confinement decreases drastically when IRE1 is inhibited, suggesting that translation under confinement becomes heavily dependent on IRE1. Finally, we explored potential reasons for translation inhibition under confinement. We hypothesized that confinement affects cytoplasmic crowding. To this end, we tracked the movement of fluorescent Genetically Engineered Microparticles (GEMs) to calculate the diffusion coefficient. We found that confinement resulted in an increase of cytoplasmic crowding, a condition that was previously associated with inhibition of translation.

In summary, we propose a model whereby confinement inhibits translation by decreasing cytoplasmic crowding. IRE1 mechano-activation serves to maintain physiological translation levels. Our results highlight an unprecedented role of IRE1 in the control of cellular proteostasis under mechanical stress.

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Putative novel function of Orm1/2 proteins in ergosterol metabolism

Sphingolipids (SLs) are essential for membrane structure and function, with derivatives like ceramides acting as signalling molecules in cell growth, apoptosis, and stress responses. However, intermediates in SL biosynthesis can be toxic at high concentrations and hence, it requires tightly regulation in the endoplasmic reticulum (ER). The conserved ORMDL family proteins (Orm1 and Orm2 in yeast) regulate SL levels by inhibiting the enzyme serine-palmitoyl-CoA transferase (SPT) within the SPOTS complex. When SL levels are low or membrane stress is present, Orm1/2 dissociate from the SPOTS complex, activating SPT. Despite their high sequence similarity, Orm1 and Orm2 exhibit distinct behaviours. For instance, after dissociation, Orm1 remains in the ER, while Orm2 is exported for degradation. It remains unclear whether Orm1 and Orm2 have additional functions beyond their role as SPT inhibitors.

Mass spectrometry-based interactome and co-immunoprecipitation analyses revealed that Orm1 and Orm2 interact with several ER-localized enzymes involved in synthesis of ergosterol, the fungal equivalent of cholesterol. Besides, it demonstrated that Orm2 interaction is more prominent. These interactions likely occur independently of the phosphorylation status of the Orm proteins, which regulates their interaction with the SPT to control sphingolipid homeostasis. Furthermore, mutations in Orm2 result in varying susceptibilities to antifungal drugs targeting sterol biosynthesis. Although previous studies have suggested co-regulation of SL and sterol biosynthetic pathways, the specific molecular mechanisms remain unknown. This project aims to explore a potential new role for ORMDL family proteins in organizing sterol synthesis within the ER and coordinating it with the SL biosynthetic machinery.

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The Role of the Retriever in Polarized Plasma Membrane Recycling

In a CRISPR-knock-out-screen on apical trafficking of DPPIV in Caco2 cells, we found the Retriever subunit dscr3 among the hits, which controls recycling together with mtmr2 (also found among the hits) through the CCC complex. The Retriever complex, a trimeric assembly of vps29, vps35l and dscr3, shares a similar structure and function with the Retromer as they have a common subunit (vps29) and both recycle proteins from endosomes towards the plasma membrane (PM) or Golgi. Crucial difference, however, is that they recognize a different subset of cargoes through different adaptor proteins. It was shown in non-polarized cells that the cargo adaptor of the Retriever is snx17. Up to date, the Retriever complex has not been studied in the context of epithelial polarity, in particular apical and basolateral Retriever cargo segregation.

To address this, we used the epithelial polarity model Madin-Darby Canine Kidney (MDCK) cells and generated WT, VPS35L knock-out (KO), SNX17 KO, MTMR2 KO and CCDC22 KO lines. To study PM cargo recycling, we implemented an unbiased approach where we compared polarized WT and KO clones by selectively biotinylating apical and basolateral PM proteins and identified Retriever-dependent PM cargoes by quantitative mass spectrometry in combination with tandem mass tag (TMT)-labeling.

The ongoing analysis of this dataset with subsequent validation of chosen cargoes via imaging and/or western blotting of biotinylated surface proteins as well as the characterization of the altered endosomal/exocytic system in KO clones aim to provide a comprehensive understanding of Retriever-dependent cargo recycling in polarized epithelial cells.

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Characterization of the Trafficking of VIP36 and VIPL and Identification of New Cargos

The transport of correctly folded secretory glycoproteins out of the ER to the Golgi apparatus is enabled by the COPII vesicles. Soluble secretory proteins are sorted into these COPII vesicles via cargo receptors. This work aims at a better understanding of the intracellular function of two cargo receptors VIP36 and VIPL, transmembrane L-type lectins, which interact with the glycoproteins via their luminal domain.

The first line of research focuses on trafficking of VIP36 and VIPL within the secretory pathway. Both the proteins have a potential cytoplasmic ER exit motif (FY) on their C-termini, while they present different C-terminal ER retrieval motifs. I used the RUSH system in combination with export/retrieval deficient mutants to understand how the trafficking is regulated. The potential role of FY motif as an ER export motif is supported by the slowdown of the export kinetics of the construct upon its substitution by alanines. I also investigated VIP36 and VIPL dependency on SEC24, the major cargo binding module within the COPII coat. Knockdown experiments targeting its four paralogs suggest a major involvement of SEC24 in the trafficking of both VIP36 and VIPL, which is impaired mostly by the depletion of SEC24A and SEC24B paralogs.

The second area of work focuses on the search for cargos for both VIP36 and VIPL. Since an IP based approach could suffer from limitations due to the weakness of lectin-glycoprotein interaction, we combine this approach screening the secretome of VIP36 and VIPL deficient HepG2 cells to gain a more comprehensive picture

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Optimization of crosslinking mass spectrometry workflow to unravel the molecular architecture of endogenous BORC complexes

The BLOC-1-related complex (BORC), an eight-subunit heteromer, regulates lysosomal positioning by recruiting ADP-ribosylation factor-like protein 8 (Arl8), which facilitates lysosomal anterograde movement along microtubule tracks through direct or indirect interactions with kinesins.

We have shown previously that the BORC subunit Lyspersin is the linker between the BORC and the late endosomal/lysosomal adaptor and MAPK and mTOR activator (LAMTOR/Ragulator) complex using chemical cross-linking. The LAMTOR complex functions as a negative regulator for the BORC directed lysosomal transport. The underlying molecular mechanisms of BORC containing assemblies remain largely unknown.

Therefore we aim to unravel the subunit topology of BORC protein complexes, identify specific protein-protein interactions involved and analyse how they rearrange in different physiological conditions. To investigate BORC and its interacting proteins we employ cross-linking mass spectrometry on an endogenously tagged BORC subunit. The native BORC assemblies are isolated by affinity purification and immediately subjected to cross-linking, and then identified by LC-MS/MS.

Using CRISPR/Cas9 ribonucleoprotein-mediated knockin, we generated hTERT-RPE1 cells with N-terminally ALFA-tagged Diaskedin. This enables the targeted purification of endogenous BORC complexes via ALFA-specific nanobody-immobilized agarose-magnetic beads. The purified complexes are subjected to chemical cross-linking and analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). To enhance the detection and identification of cross-linked peptides, we optimized the workflow by incorporating an immobilized metal affinity chromatography (IMAC)-enrichable crosslinker. We are currently refining the workflow to enhance the efficiency of protein complex purification, minimize non-specific background, and achieve greater specificity in crosslink identification.

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Optimisation of an XL-MS/MS workflow to study the architecture of native LAMTOR assemblies

The late endosomal and lysosomal adaptor and MAPK and mTOR activator (LAMTOR) scaffolding complex, resides at the lysosomes where it mediates catabolic and anabolic signalling. The pentameric complex consists of LAMTOR1 whose lipid-modified N-terminal region anchors the complex together with the remaining subunits LAMTOR2-5 in the lysosomal membrane. Previous studies have identified the presence of at least four different LAMTOR assemblies on the lysosomes associated with catabolic or anabolic signalling mediated by its association with Rag-GTPases, SLC38A9, the v-ATPase, AXIN and LKB1. Furthermore, LAMTOR is a negative regulator BORC, a protein complex involved in lysosomal biogenesis and intracellular positioning.

The aim of the project is to investigate the architecture of native LAMTOR assemblies upon different stimuli to understand how a single scaffolding complex can regulate these diverse biological functions. We plan to capture these endogenous protein-protein interactions by employing state-of-the-art crosslinking mass-spectrometry (XL-MS/MS) methods.

I have generated hTERT-RPE1 cells endogenously expressing ALFA-tagged LAMTOR4 and optimised an elaborate AP-XL-MS workflow for the MS-cleavable DSSO crosslinking reagent. Currently I am focussing on integrating the novel IMAC-enrichable crosslinker tBu-PhoX into our workflow. As a complementary tag-free approach I am also working on intact organelle crosslinking of the lysosome enabled by the membrane permeability of tBu-PhoX.

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Functional analysis of novel players involved in Orm2 ER Export

ORMDL family proteins are conserved regulators of sphingolipid biosynthesis, with the main to-date known function to inhibit the rate-limiting enzyme serine-palmitoyl transferase (SPT) in the ER [1]. Dysregulation of SPT activity causes a form of amyotrophic lateral sclerosis, and is genetically linked to several inflammatory diseases. In budding yeast the ORMDL family consists of two members, Orm1 and Orm2. Both are are embedded in a homeostatic system that adjusts sphingolipid levels to cellular demands [1]. However, to-date little is known whether Orm1 and Orm2 differ in function and if they interact differentially with further proteins [2]. Yet, their regulation is different, with Orm2 being subject to regulated ER export and proteolytic turnover via the EGAD pathway, which is not observed for Orm1 [3]. How the specificity of ER export vs. retention of these highly homologous proteins is achieved is unknown. We have been able to determine new factors that could dictate Orm2 export. In an Orm2-interactome we found two p24 proteins, which are known substrate adaptors of COPII vesicles and hence could mediate ER export specificity. Moreover, we found that Orm1 is strongly retained in the ER by intrinsic sequence motifs that are not shared by Orm2. Finally we found several genes that are required for phosphatidylcholine (PC) synthesis in a whole genome screen for ER retention of Orm2. We assume that PC levels have an indirect effect on Orm2 trafficking, whereas p24 proteins could be directly involved in the initiation of Orm2 export.

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LAMTOR1 phosphorylation orchestrates protein interactions at the lysosome

Lysosomes house a sophisticated nutrient-sensing machinery that integrates information about the cell's energy levels, extra- and intracellular nutrient availability, as well as the presence of stress factors and hormones. The LAMTOR-complex serves a central hub in regulating some of these processes by recruiting and/or activating AMPK, MAPK and mTOR on the lysosomal surface. Signaling to and from lysosomes can be catabolic or anabolic, cooperative or mutually exclusive, depending on the associations LAMTOR establishes with other proteins- or protein complexes.

Since LAMTOR1, the membrane anchor of the complex, is highly phosphorylated, we explored posttranslational modifications as a regulatory mechanism. Using recombinant LAMTOR-complex, we confirmed in-vitro, that AMPK phosphorylates LAMTOR1 at S63. While anabolic signaling via LAMTOR is well understood, its role in catabolism remains unclear. Given AMPK's function as a catabolic master regulator, this finding led us to investigate how this phosphorylation affects binding interactions and downstream signaling. A mass spectrometry-based interactome analysis under AMPK-activating conditions, using S63 phosphorylation site mutations, revealed that this site significantly influences LAMTOR's binding affinity to key components of the lysosomal mTORC1 complex. It also uncovered previously unrecognized catabolic functions of LAMTOR that operate independently of mTOR. The current phase of research is dedicated to validating the interactome data and exploring the in vivo effects of the aforementioned phosphorylation site. Through this analysis we expect to improve our understanding of lysosomal signaling pathways and how they are regulated.

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Prognostic implications of recovery of cardiac autonomic dysfuntion after myocaridal infarction: a SMART-MI subanalysis

Background: Periodic repolarization dynamics (PRD) and deceleration capacity (DC) are ECG markers of cardiac autonomic function, with PRD indicating sympathetic and DC parasympathetic activity. These biomarkers predict overall and cardiovascular mortality, especially in post-myocardial infarction (MI) patients. The SMART-MI study showed that post-MI patients with cardiac autonomic dysfunction (CAD) who had ICD implants experienced more arrhythmic events than controls. While PRD and DC have been studied at a single time point, no research has explored their longitudinal progression. This subanalysis investigates the prognostic significance of changes in cardiac autonomic function over time, regarding clinically relevant arrhythmic events.

Methods: The SMART-MI-DZHK trial randomized 400 post-MI patients with reduced left ventricular ejection fraction (36-50%) and CAD signs to telemonitoring with implantable cardiac monitors (ICMs) or conventional follow-up. Follow-up visits occurred every 6 months, and a second ECG was performed at 12 months for risk stratification. CAD was defined as abnormal PRD (≥5.75 deg2) or DC (≤2.5 ms). This subanalysis evaluates the persistence or recovery from CAD at 12 months, relating to the primary endpoint: serious arrhythmic events. A multistate Cox regression model tested the effect of CAD persistence on the endpoint.

Results: Of 272 patients with a second ECG, persistence of CAD was associated with a significantly increased risk of arrhythmic events (hazard ratio = 2.80, p = 0.000452).

Discussion: Persistent CAD after one year significantly increases the likelihood of arrhythmic events, suggesting the need for periodic risk re-evaluation in post-MI patients. However, this post-hoc subanalysis is hypothesis-generating, and the sample size limits generalizability.

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Motivation to participate in the Healthy Brain Aging (HeBA) Tirol study and its association with remotely estimated PD risk

Background: Reasons for participation in population-based studies on risk for Parkinson's diseases (PD) differ between individuals and may be associated with self-perceived symptoms and signs of a prodromal disease state.

Methods: Within the population-based Healthy Brain Aging (HeBA) Tirol study the Movement Disorder Society (MDS) criteria for prodromal PD were calculated utilizing a comprehensive online questionnaire on PD risk and prodromal factors. Home-based smell testing with the University of Pennsylvania Smell Identification Test (UPSIT) was offered to all online participants. Age- and sex-adjusted percentiles were calculated for completed smell tests. Motivation to participate was assessed with a multiple-choice question and differences in scores/percentiles for each reason to participate were analysed.

Results: The question on motivation was available in 1728 online participants, of which 1048 also underwent smell-testing (both median age 61, 60% female). Most common reasons for participation were "supporting research" (76%), "concerns about developing PD/dementia in the future" (42%), and "relatives or friends with PD/dementia" (35%). The MDS prodromal score posttest probability was significantly higher in those concerned about developing a neurodegenerative disease (median 1.05% vs. 0.62%) and lower in those wanting to support research (median 0.71% vs. 0.92%). No significant differences regarding UPSIT raw scores and percentiles were found.

Conclusion: We could demonstrate differences in a PD risk algorithm depending on reason for participation in our study. Whether being concerned about development of future neurodegeneration is truly associated with a higher PD incidence needs prospective investigation.

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Multi-omics deconvolution of systemic inflammation in the context of clonal hematopoiesis in stroke

Introduction: Acquisition of spontaneous somatic mutations in a well defined set of genes (mainly DNMT3A, TET2 and ASXL1) leads to clonal expansion of myeloid cells (Clonal hematopoiesis of indeterminate potential/CHIP). This drives cardiovascular disease via a genetically imprinted pro-inflammatory phenotype. We performed deep molecular phenotyping to identify novel insights to generate hypothesis for mechanistic studies.

Methods: Ischemic stroke patients were included at the time of the acute event. Deep, UMI-based, error-corrected NGS was used to determine somatic variants from blood. Multiparameter flowcytometry and RNA-Seq were performed using whole-blood from ischemic stroke patients. Cytokines were measured from plasma using ultrasensitive assays.

Results: Of n=408 prospectively included patients, 70% (n=276) harbored a somatic variant, with mutations in DNMT3A or TET2 being the most commonly observed. Ultrasensitive cytokine profiling revealed higher levels of IL-6 and TNFa in TET2-mutant vs wildtype individuals. Flow-cytometry revealed a myeloid bias in TET2 mutated individuals. Weighted-Gene Correlation Network Analysis of n=240 bulk RNASeq datasets from freshly obtained whole-blood suggests distinct patterns of inflammatory susceptibility in DNMT3A vs TET2 vs non mutated individuals via distinct dysregulation of innate immune signaling.

Conclusion: Multi-omics deconvolution on genomic, transcriptomic and proteomic level yields insights into possible mechanism of cardiovascular disease mediated by clonal hematopoiesis. Upcoming in-vitro validation experiments will pave the way towards elucidation of potential novel therapeutic targets.

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Individualised flow controlled ventilation in a porcine ex vivo lung perfusion model

Background and Goal of the study

Flow controlled ventilation is a novel ventilation mode with a constant gas flow during the whole ventilation cycle. Combined with direct intratracheal pressure measurement dynamic lung mechanics can be determined and ventilation performed within these limits. These individualised ventilation strategy might reduce the development of ventilator-induced lung injury (VILI), which is of primary interest especially in ventilation of the donor graft during ex vivo lung perfusion (EVLP). Our experimental study investigates if an individualised ventilation strategy is also applicable ex vivo.

Material and methods

After preparation and installation of the donor organ in the EVLP machine, perfusion was started. When a graft temperature of 32 ° C was reached, mechanical ventilation with FCV was established. Ventilator settings were individualised by compliance-guided titration of positive endexpiratory pressure (PEEP) and peak pressure, flow was set as low as possible. With this approach individualised ventilation was performed for 6 hours, which can also be shown by repeatedly recorded pressure-volume loops (p-v-loops).

Results and discussion

An individualised ventilation strategy was feasible in an animal ex vivo lung perfusion model. Recorded p-v-loops show, that ventilation was performed within dynamic lung mechanics. In previous performed studies we could show, that the applied mechanical power was lower with individualised ventilator settings, which is of primary interest especially in extended criteria donor lungs to avoid the development of VILI.

Conclusion

Setting of individualised ventilator parameters is feasible ex vivo as can also be shown by recorded p-v-loops.

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Leveraging normothermic liver machine perfusion as a platform to establish tumour directed ex-situ treatment

Background and Aims: Conventional tumour models fail to replicate the tumour microenvironment, contributing to high drug attrition rates. Normothermic liver machine perfusion (NLMP), originally developed for transplantation, may serve as a platform for more realistic research models. This proof-of-concept study evaluates an adeno-associated virus (AAV) library within an ex-situ tumour perfusion model. AAVs enable targeted gene delivery, offering potential for tumour-specific interventions.

Method: Hepatectomy specimens from HCC patients undergoing liver transplantation were flushed with HTK solution, reconstructed, and perfused via NLMP. Tumour and cirrhotic liver biopsies were taken, with viability assessed using real-time confocal microscopy (RTCM) and histology. Precision-cut liver slices (PCLS) from cirrhotic and tumour tissue were infected with a library of 49 AAV capsids. DNA extraction, PCR amplification, and nanopore sequencing enabled the assessment of individual capsid tropism by normalizing barcode counts against the AAV library input.

Results: Three HCC-bearing livers were perfused for 24, 36, and 96 hours, maintaining high viability (RTCM scores 0–1). RTCM correlated well with histology. Nanopore sequencing showed heterogeneous AAV distribution in cirrhotic PCLS, whereas HCC PCLS displayed a more uniform pattern. AAV capsid #45 consistently appeared at higher levels across all HCC samples.

Conclusion: NLMP maintained viability in cirrhotic and HCC tissue for up to 96 hours, supporting its use as a tumour model. AAV capsid #45 emerged as a promising candidate for targeted HCC therapy, warranting further investigation.

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Following the Breadcrumbs: Clinical Clues in Huntington's Disease

Introduction

Huntington's Disease (HD) is a neurodegenerative disease characterized by progressive motor, cognitive and psychiatric symptoms. Existing data on disease progression is inconsistent and highlight the need for further research to develop targeted treatment strategies. Symptoms such as falls and weight loss are associated with increased morbidity and mortality and represent a particular challenge in patient care.

Research question

Can clinical assessments such as the measurement of weight, muscle mass and sarcopenia, eye-tracking analyses, neuropsychological examinations predict relevant correlations regarding the progression of Huntington's disease?

Methods

In this prospective study, various clinical parameters are being collected from patients at the specialized Chorea Outpatient Clinic (Department of Neurology) in Innsbruck in order to investigate potential correlations regarding the progression of HD. The assessments carried out include bioimpedance analysis to assess body composition, calf circumference measurements and the 'Timed Up and Go Test' to assess muscle mass and mobility. In addition, various questionnaires are used to assess sarcopenia, as well as eye-tracking analyses to record eye movements and neuropsychological tests.

Discussion

This study aims to assess specific changes in clinical parameters such as muscle mass, weight loss and eye movements in patients with HD throughout the course of the disease. A better understanding of these parameters could contribute to the development of personalized symptomatic treatment approaches. As there are currently no disease-modifying therapies available for HD, the identification of disease stage-dependent markers could provide an important basis for targeted interventions. This includes both pharmacological approaches and non-pharmacological therapies.

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Anticoagulation monitoring in patients receiving elective cardiac surgery

Background

Systemic anticoagulation is required during cardiopulmonary bypass (CPB) and is typically achieved using unfractionated heparin (UFH). At bedside, it is monitored using a high-range activated clotting time (ACT) and reversed with protamine at the end of CPB. In the postoperative period various methods are used to monitor residual anticoagulation and potential UFH-rebound, including ACT, activated partial thromboplastin time (aPTT), anti-FXa assays, and viscoelastic tests. However, evidence supporting these monitoring tools remains limited, conflicting, and often derived from retrospective data.1–7

Study Design and Population:

Following approval from the Ethical-Review-Board (EK-Nr: 1291/2023), this trial is a single-center-prospective-observational study including patients undergoing cardiac surgery.

Inclusion Criteria: Adults with written informed consent, scheduled for elective cardiac surgery with CPB requiring UFH

Exclusion Criteria: Known pregnancy, emergency surgery

Sample size after power calculation: 400 patients

Methods

A total of 8 blood sampling points are collected over a 24-hour period, starting before the induction of general anaesthesia and continuing until postoperative day 1. The coagulation status will be assessed using ACT, aPTT, anti-FXa levels, viscoelastic testing (ROTEM®), and impedance platelet aggregometry (Multiplate®).

Objectives & Endpoints

The primary objective is to identify the most appropriate anticoagulation monitoring tool for UFH-therapy by comparing different modalities, focusing on the occurrence of bleeding or thrombosis. Secondary objectives include assessing the relationships between anticoagulation levels measured by ACT, aPTT, ROTEM® and anti-Xa, the occurrence of UFH-rebound, protamine substitution, blood loss, mortality, and the correlation between these monitoring tools.

Timetable/Progress:

Planned recruitment phase: 2 years. Study start: June 2024

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Predicting hyposmia to identify people at-risk for Parkinson's disease: Preliminary baseline data from the population-based HeBA-study

Introduction: Hyposmia affects up to 80% of people with Parkinson's disease (PD) and can be present years before diagnosis. Therefore, olfactory testing may serve as an optimal tool for identifying people at-risk for PD in large-scale population-based cohorts.

Methods: The present study was conducted within the multicenter Healthy Brain Ageing (HeBA) initiative, where participants without a prior PD diagnosis over the age of 50 were invited to complete an online survey on demographics and simple PD risk factors. Olfactory testing was then performed remotely using the 40-odor University of Pennsylvania Smell Test (UPSIT). We used baseline olfactory data from the Innsbruck HeBA site to identify simple different PD risk markers associated with hyposmia using the raw UPSIT scores and age- and sex-adjusted percentiles according to Brumm et al. 2023.

Results: A total of 1514 participants with a mean age of 62.0±7.7 years and 60.4% female submitted their UPSIT results. 16.8% of the participants reported a positive PD family history, 10.2% reported subjective hyposmia, and 18.1% reported symptoms suggestive of dream enactment behavior. Raw UPSIT scores were higher in female and younger participants, whereas the opposite was found using age- and sex-adjusted UPSIT-percentiles. Negative family history and subjective hyposmia predicted worse UPSIT raw scores and only subjective hyposmia predicted lower adjusted UPSIT-percentiles.

Discussion: The associations between easily assessable risk factors and olfactory performance may help to better identify people at-risk for hyposmia. Follow-up visits will tell whether this holds true also for the prediction of incident cases of PD.

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Ethanol preserved donor corneas as long-term storage for acute tectonic keratoplasties

Purpose

Acute corneal perforation is a sight-threatening emergency requiring immediate closure. Large defects unsuitable for gluing or amniotic membrane transplantation require tectonic keratoplasty. Due to the global corneal tissue shortage, ethanol-preserved grafts offer a viable alternative. This study evaluates the outcomes of ethanol-stored corneoscleral tissue in emergency tectonic keratoplasty.

Setting

A monocentric, retrospective chart review at the Department of Ophthalmology, Medical University of Innsbruck (MUI).

Methods

Patients undergoing tectonic keratoplasty for corneal perforation (2018–2022) were included. Ethanol-stored corneoscleral tissue not suitable for keratoplasty was stored in 95% ethanol, by the MUI eye bank and provided for emergency surgery. Data on demographics, underlying disease, graft size, and surgical techniques were collected. Postoperative analysis focused on graft durability (Intact Globe Restitution Interval).

Results

Twenty-one procedures were performed on 16 patients (6 female, 10 male) with a mean age of 79.5±12.3 years. Underlying diseases that caused the perforation were: neurotrophic (38%), peripheral ulcerative (38%), metaherpetic (19%), and infectious ulcers (5%). The mean graft diameter was 4.2±1.2 mm. The mean globe restitution interval: 16.3±14.6 months. Epithelial closure was observed after 22.4±24 days. Twelve cases required no further surgery, nine needed re-surgery: 2 for visual rehabilitation, 1 for enucleation, and 6 due to re-perforation. Final visual acuity results to 1.6±0.8 logMAR.

Conclusion

Ethanol-stored corneal tissue is a feasible alternative for emergency tectonic keratoplasty, ensuring long-term globe integrity and enabling elective keratoplasty for visual rehabilitation.

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Exploring Subvisual Protoporphyrin IX Fluorescence in Gliomas

The detection of Protoporphyrin IX (PpIX) fluorescence during 5-aminolevulinic acid (5-ALA)-guided surgery has revolutionized glioma resection by enabling improved visualization of tumor tissue. However, the phenomenon of subvisual fluorescence (fluorescence not detectable by conventional microscopes but present in tumor tissue) remains underexplored. Investigating subvisual fluorescence has the potential to uncover critical insights into glioma biology and refine surgical strategies, ultimately improving patient outcome.

Over the past year, we have been systematically collecting tumor samples from glioma patients, preserving them as fresh frozen tissue to ensure optimal quality for advanced molecular analyses. This year, we aim to evaluate these samples using state-of-the-art spatial transcriptomics to elucidate gene expression patterns within the microenvironment of subvisual fluorescence regions. Furthermore, immunohistochemical staining will be employed to characterize protein expression and validate findings at the cellular level.

By integrating spatial transcriptomics with immunohistochemistry, we hope to identify molecular signatures associated with subvisual fluorescence and its potential correlation with tumor progression and heterogeneity. This study has the potential to deepen our understanding of glioma biology, paving the way for innovative diagnostic and therapeutic approaches. Our findings may also enhance the precision of 5-ALA-guided surgeries, benefiting glioma patients by improving the extent of resection while minimizing damage to healthy tissue.

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Stimulated Periodic Repolarization Dynamics as a Predictor of New-Onset Device-Detected Atrial Fibrillation

Background

Periodic Repolarization Dynamics (PRD) is a novel ECG-based marker reflecting low-frequency oscillations in cardiac repolarization caused by efferent sympathetic nervous system activity. Elevated PRD (≥5.75 deg²) predicts malignant arrhythmias and sudden cardiac death in both, ischemic and non-ischemic cardiomyopathy. Its relationship with atrial fibrillation (AF) remains unclear despite evidence of autonomic dysfunction in AF pathogenesis. This study investigates the association between PRD and device-detected AF (DDAF) in pacemaker patients.

Methods

In the ACasA trial, pacemaker patients were enrolled at the University Hospital of Innsbruck. PRD was calculated from high-resolution ECG under native (AAI) and stimulated (DDD) conditions. Cardiac autonomic dysfunction (c-AD) was defined as native PRD ≥5.75 deg² and stimulated PRD >4.3 deg². DDAF episodes (≥6 minutes) were identified via continuous telemedical pacemaker monitoring. Time to first DDAF episode was analyzed using Kaplan-Meier curves and Cox regression, adjusting for confounders.

Results

Among 233 enrolled patients, 111 without prior AF (median age 76, 44% female) were analyzed over 13,801 patient-days. Of these, 60 had c-AD (median stimulated PRD: 7.7 [5.7–8.6] deg²), and 51 did not (median stimulated PRD: 3.8 [2.0–7.3] deg²). DDAF occurred in 41.2% of c-AD patients compared to 21.7% without c-AD (HR 3.3; 95% CI 1.3–8.5; p = 0.009). Native PRD showed no significant association with DDAF (HR 1.27; 95% CI 0.4–4.0).

Conclusion

Elevated stimulated PRD predicts DDAF in pacemaker patients without prior AF, underscoring autonomic dysfunction's role in arrhythmogenesis. Stimulated PRD may provide superior predictive value compared to native PRD.

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INNSBRUCK HEALTH PROMOTION PROGRAM (INN.HEALTH)

Background:

Cardio- and cerebrovascular diseases are leading causes of death and disability. Exemplary, the STROKE-CARD study (Böhme, Neurology 2019) found that 80% of Tyrolean patients with high-risk TIA (ABCD2-Score ≥ 4) or ischemic stroke had untreated risk factors. Combined, this highlights the need for effective primary prevention. Despite existing prevention guidelines, evidence-based intervention programs are limited.

Objectives:

The INN.HEALTH study investigates whether a single health assessment with personalized counselling and subsequent bi-monthly motivational newsletters improve vascular health over one year in Tyrolean adults, measured using Life's Essential 8 cardiovascular health (CVH) score.

Methods:

This interventional study will involve 1,000 adults from Innsbruck and surroundings and is planned to take a total of 29 months, commencing in March 2025. Participants will undergo baseline assessments including biometrics, blood tests, neurovascular ultrasounds, and questionnaires. Based on the results, participants will receive a one-time health counselling session, followed by newsletters with health promotion tips every two months. Follow-up evaluations 12 months later will mirror baseline procedures.

Statistical Analysis:

Changes in Life's Essential 8 CVH score will be analysed using paired t-tests or non-parametric alternatives. Mixed-effects models will be employed for subgroup analyses, specifically age groups and sex. Models may adjust for confounders such as education and socioeconomics.

Outcomes:

Primary outcome will be changes in Life's Essential 8 CVH score between baseline and follow-up. Secondary outcomes include changes in individual CVH components and longterm health outcomes tracked via data linkage to national registries.

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Technical feasibility of MRI/ultrasound fusion in breast imaging and the characterization of breast foci in contrast-enhanced breast MRI.

Background:

Multiparametric contrast-enhanced breast MRI is a highly precise and valuable method for detecting and characterizing breast cancer (1). However, it frequently reveals small incidental contrast-enhanced foci, which present an interpretative challenge (2). In most cases, additional ultrasound examination is necessary to further evaluate MRI-detected breast lesions. Real-time MRI/ultrasound fusion enables the synchronous visualization of both modalities in real-time and can enhance the sonographic detection rate of MRI-suspected lesions (3).

Objective/Hypothesis:

The study aims to characterize and analyze the outcomes of contrast-enhanced breast MRI foci. The hypothesis is that a more precise MRI characterization of foci provides additional diagnostic value. Furthermore, the feasibility of MRI/ultrasound fusion imaging is assessed regardless of the breast lesion size. The hypothesis is that fusion sonography in the supine position improves lesion localization after conducting a contrast-enhanced MRI in the prone position.

Methods and Statistics:

A retrospective data analysis will be conducted. The primary endpoints include the characteristics of foci and the successful localization of lesions between contrast-enhanced MRI in the prone position and fusion sonography in the supine position. Planned statistical methods include the chi-square test, descriptive statistics, ANOVA for multiparametric continuous variables with correction for multiple testing in the case of normal distribution, non-parametric tests for non-normally distributed data, and binary regression analysis.

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Vascular Senescence as a Key Factor in Vascular Damage and Microcirculatory

Cochlear implants are among the most successful sensory prostheses worldwide, enabling the restoration of auditory function in individuals with severe hearing loss. However, their efficacy varies significantly, particularly in elderly patients, highlighting the need for a deeper understanding of the underlying biological and anatomical factors that influence outcomes.

This whole study focuses on the role of spiral ganglion neurons (SGNs) and the cochlear microcirculation in optimizing cochlear implant performance. By employing advanced imaging techniques such as microCT and immunohistochemistry, we aim to elucidate the interplay between vascular health and neural degeneration in the cochlea. Preliminary data suggest that vascular senescence and microvascular dysfunction significantly contribute to the decline in SGN viability, which is crucial for cochlear implant efficacy.

Our findings will pave the way for targeted therapeutic interventions, such as neurostimulation and vascular modulation, to enhance implant outcomes. This research holds the potential to improve device performance and patient quality of life, particularly in geriatric populations.

By bridging gaps in our understanding of cochlear biology, this study seeks to inform the design of next-generation cochlear implants that address the unique challenges of aging auditory systems.

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Colour changes and surface roughness after air-polishing for tobacco stain removal

Introduction and Aims

This study aimed to assess the effectiveness of air-polishing in restoring the original colour of tobacco-stained tooth specimens.

Methods

Seventy-two tooth specimens (half dentine, half enamel) were exposed daily to cigarette smoke in an automated chamber for four 14-day cycles. After each cycle, specimens were cleaned using either air-polishing with erythritol or sodium bicarbonate, or a rubber cup with pumice as the control. Colour changes (ΔE) and surface roughness were measured before and after each cycle. Specimens were stored in artificial saliva throughout the study to mimic oral conditions.

Results

All cleaning methods effectively removed tobacco staining, but none restored the original tooth colour. After four cycles, no significant difference in tooth colour was found between erythritol and sodium bicarbonate air-polishing on enamel ($p > .05$). ΔE differences were significant between the air-polishing and control groups ($p < .001$). For dentine, no significant ΔE difference was observed across groups ($p > .05$). Additionally, no significant changes in surface roughness were observed after air-polishing with erythritol ($p > .05$).

Conclusions

Erythritol air-polishing removed tobacco stains as effectively as sodium bicarbonate air-polishing or polishing with pumice, without affecting tooth roughness. Tobacco stains did not reoccur more quickly after air-polishing than with traditional polishing methods.

Clinical Relevance

Erythritol air-polishing is a safe, effective, and minimally abrasive option for removing tobacco-induced discolourations, supporting its use in dental practices for managing extrinsic stains.

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A randomized controlled trial on the effects of respiratory gas shifts to delay asphyxiation in critically buried avalanche victims

Avalanche fatalities are often caused by asphyxia, with buried victims typically dying within 35 minutes. This highlights the need for strategies to delay asphyxiation. Our study tested the Safeback SBX, a new avalanche safety device that delivers airflow from surrounding snow debris to the victim's airways without requiring oxygen or a mouthpiece. Conducted in northern Italy in winter and spring 2023, this randomized, double-blind trial involved 24 volunteers aged 18–60, who underwent simulated snow burials. The intervention group used the Safeback SBX, while the control group used a sham device. Burial durations were capped at 35 minutes for controls and up to 60 minutes for the intervention group. Vital signs like oxygen saturation (SpO_2), carbon dioxide (CO_2), and oxygen levels were monitored. The results showed that the Safeback SBX significantly prolonged survival by maintaining SpO_2 above 80% and stable CO_2 and oxygen levels, indicating effective ventilation.

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The non-canonical function of p27Kip1 in terminally differentiated post-mitotic neurons

The eukaryotic cell cycle is one of the most well-understood processes in mammalian cells. It involves a series of oscillating protein-protein interactions in the nucleus regulated by phosphorylation and proteasomal breakdown. The key players are cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors (CKIs). The CDK-inhibitory activity of p27Kip1 depends on the phosphorylation state of specific tyrosine residues, including the site Y88. Phosphorylation of this particular residue activates the cyclinD/CDK4 and 6 complexes thereby initiating the cell cycle. Neurons are terminally differentiated cells that individually persist throughout the entire lifespan of 70 to 80 years. Therefore, it is not expected that p27Kip1 would be expressed in adult neurons, let alone phosphorylated at Y88. Yet what we detected in adult sensory neurons are not only high expression levels of p27Kip1 that extend from the nucleus to the cytoplasm, but also exceptionally high levels of phosphorylation at Y88 compared to proliferating cells. The question that arises is why neurons afford the expression of a cell cycle regulator in a strictly post-mitotic state, included its costly phosphorylation. We hypothesize that p27Kip1 may have a non-canonical function in adult neurons related to stress management and/or the maintenance of their elaborate morphology. To investigate the role of p27Kip1 in adult neurons we examined its subcellular localization, expression levels, and the phosphorylation status of Y88 under various stress paradigms. We also used a specific mouse mutant of p27Kip1 that has Tyr 88 substituted by Phe and explored the consequences of this loss-of-phosphorylation mutation on axonal outgrowth.

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Volume reduction of the insular cortex in patients with multiple system atrophy.

Background: Differentiating early Parkinsonian syndromes, like Parkinson's disease (PD) and multiple system atrophy (MSA) is challenging. Quantitative MRI-analyses of subcortical regions have proven diagnostically valuable, while earlier studies observed insular cortex atrophy in MSA versus PD. This study examines its role in MRI-based differentiation.

Methods: This retrospective study included MSA-patients (≤70 years) from the department of neurology, Innsbruck, who underwent 3T MRI with 3D-T1 sequences (June 2018-2022) and were matched to a PD cohort using propensity scores (sex, age). Atrophy in the insular cortex, putamen, and cerebellum were determined through automated analysis of T1-weighted MRI-images using FreeSurfer software. Deviations from healthy subjects were calculated using sex- and age-adjusted Z-transformation, with a Z-score ≤-1.96 considered as significant atrophy. Clinical data were collected from medical records, excluding cases with poor image quality or incomplete documentation.

Results: In total, 32 patients (PD=16; MSA=16; no sex differences, p=1.000) were included, with a mean age at MRI of 60.3±4.7 years (MSA:59.6±5.0 years; PD:61.0±4.5 years, p=0.421). Significant volumetric differences between MSA and PD were found in the putamen (p=0.002), cerebellar white matter (p=0.001), cerebellar cortex (p=0.020) and insular cortex (p=0.049). Putaminal atrophy was observed in 8 MSA-(50.0%) and in 1 PD-patient (6.3%). Cerebellar white matter atrophy occurred in 12 MSA-(75.0%) but no PD-patients; cerebellar cortex atrophy in 9 MSA-(56.3%) and 3 PD-patients (18.8%). 2 MSA-patients (12.5%) showed isolated atrophy of the anterior insular cortex without statistically significant diagnostic association ($\chi 2=2.133$, p=0.144).

Conclusion: Isolated insular atrophy did not allow diagnostic classification, but findings suggest MRI-defined MSA-subgroups, requiring validation in larger cohorts.

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tRNA superwobbling - Comparing the decoding of valine codons in M. capricolum and E. coli

Transfer RNAs (tRNAs) are crucial adapter molecules decoding the genetic code during the process of protein synthesis. Although similar in their characteristic L-shaped structure, they are variable in their sequences and modifications. tRNAs are highly modified molecules harboring about 100 different RNA derivatives at different sequence positions. Depending on the type and location of the modifications, ranging from simple methylations to highly complex modifications, they influence structure and stability of the tRNA molecule as well as decoding. To determine and to study the impact of the tRNA sequence and their modifications on aminoacylation and decoding, tRNAs can be generated by splinted ligation of chemically synthesized RNA oligonucleotides. Thereby, tRNAs from different organisms with defined tRNA sequence and defined modifications are characterized. A recombinant translation system combined with different reporter messenger RNAs (mRNAs) provide a suitable setting to test decoding of these individually modified tRNAs. In this project we will compare the decoding capacity of the "standard" E. coli tRNAValUAC with the superwobbling tRNAVal UAC from M. mycoides. By introducing modifications into the each tRNAs individually, we aim to assess the impact of the modification on both tRNAs and determine to what extend the modifications contribute to the potential differences in the decoding capacity of a standard or superwobbling tRNA.

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Antifungal secondary metabolites of an endophytic fungus isolate from the leaves of Gentiana clusii

Plant fungal pathogens pose a significant threat to global agriculture and forestry, causing crop yield losses, quality degradation, and even jeopardizing food security. It is estimated that fungal diseases account for annual crop yield losses of approximately 10% to 28%. Moreover, with the exacerbation of climate change, the spread and severity of fungal diseases are further increasing. Therefore, the search for novel antifungal agents is of high importance for targeting these phytopathogens. Endophytic microorganisms are one of the under-explored, yet promising sources for discovery of novel bioactive lead antimicrobial compounds. In a screening campaign for discovery of antifungal substances from endophytic microorganisms of alpine plants, we have identified an endophytic fungus, belonging to Ascomycota phylum, from the leaves of Gentiana clusii, displaying a promising bioactivity against B. cinerea (MIC = 25 µg/mL). The fungus was upscaled on rice medium, followed by extraction using ethyl acetate. The extract was further systematically separated by chromatography techniques on silica gel and Sephadex LH-20, yielding six secondary metabolites. The structures of compounds isolated were elucidated by spectroscopic methods (1&2D NMR, HRMS), leading to the identification of two novel phomoidride derivatives, named phomoidride I (1) and phomoidride K (2), a new diastereomer of phomoidride A, named phomoidride J (3), and a known secondary metabolite, phomoidride B (4), along with two known xanthone derivatives (5-6). Their absolute configuration was established using electronic circular dichroism (ECD) and computational methods. The antifungal activity of the compounds isolated was assessed against B. cinerea, revealing moderate to promising bioactivity.

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Antifungal activity of secondary metabolites of the endophytic fungus, Paraleptosphaeria sp., against Botrytis cinerea

Botrytis cinerea is one of the most common agricultural pathogens which imposes significant economic loss of between 10 to 100 billion dollars annually. This necrotrophic pathogen can infect over 200 plant species such as wine trees, causing grey mould, evident as grey fluffy mycelium. Recent studies indicate that B. cinerea can develop resistance against conventionally used fungicides. Therefore, there is an increased demand for discovery of new potential fungicides to combat B. cinerea. An alternative approach for discovery of new antifungal agents against this emerging pathogen is utilizing the natural products derived from fungal endophytes. These symbiotic microbes are underexplored sources of bioactive substances and therefore hold a great potential for discovery of novel antifungals. In this study, we aimed for isolation and identification of the bioactive metabolites of Paraleptosphaeria sp., an endophytic fungus isolated from the needls of Picea abies, and assessment of their antifungal activities against B. cinerea. The fungus was upscaled on a rice medium, then extracted using ethyl acetate. Subsequently, the extract was systematically separated by various chromatography techniques using silicagel, Sephadex LH-20, and C18, which ultimately yielded seven compounds. The structures of the compounds isolated were identified by 1&2-D NMR spectroscopy methods and LC-ESI-HRMS, resulting in three new (1-3) and three known (4-6) chromophilones, and a new versiol-like terpenoid (7). The absolute configuration of the compounds was established by comparison of experimental and calculated circular dichroism spectra. Ultimately, pure compounds were evaluated for their bioactivities against B. cinerea, among which compound 7 displayed promising bioactivities.

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Insights into 6-Pentyl-α-Pyrone Biosynthesis in Trichoderma atroviride

Trichoderma atroviride is a fungus widely recognized as a biocontrol agent utilized to combat crop diseases caused by other fungi. This is due to its production of diverse specialized metabolites (SMs) with a broad range of bioactivities and its mycoparasitic ability to invade and degrade phytopathogenic fungi for nutrient acquisition. One of the most prominent SMs of T. atroviride is 6-pentyl-α-pyrone (6-PP), known for its role in inhibiting bacterial and fungal growth as well as promoting plant development. Although 6-PP was identified in the 1970s, the biosynthetic pathway remains largely uncharacterized. In this study, we aimed to identify the core gene responsible for 6-PP biosynthesis and investigate its role in fungal antagonism. Transcriptomic analysis revealed that pks1 is significantly upregulated under dark conditions compared to light, which correlates with peak 6-PP production in darkness. Using CRISPR/Cas9, deletion mutants lacking the pks1 polyketide synthase gene were generated and functionally characterized. HPTLC confirmed that Δpks1 mutants cannot produce 6-PP, validating its polyketide nature, while LC-MS further confirmed this and identified putative precursors absent in the deletion strain. Although pks1 deletion strains exhibited morphology and growth similar to the WT, a significant reduction in mycoparasitic activity and inhibition against host fungi such as Botrytis cinerea and Rhizoctonia solani was observed demonstrating that pks1 is essential for 6-PP biosynthesis and plays a role in the antifungal activity of T. atroviride.

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Artificial Siderophores: A new tool for differentiating bacterial and fungal strains in infection imaging

Positron Emission Tomography (PET) holds potential as a non-invasive and rapid tool for imaging complex infectious sites in patients. Pathogen-specific molecules, which are exclusively taken up by infectious agents, offer a promising approach to advancing nuclear medicine for infection imaging.

An example of these special molecules are siderophores—iron-binding compounds used by fungal and bacterial cells. By incorporating radionuclides like Ga-68 or Zr-89 into siderophores instead of their naturally binding iron, we can achieve imaging capabilities.

Our research extends beyond natural siderophores, focusing on artificial variants designed in the laboratory to enhance specificity for distinct bacterial and fungal strains. Before using siderophores in PET imaging, it is crucial to determine which types are effectively recognized by specific pathogens. To address this, we conducted uptake assays to evaluate their potential.

By radiolabeling these siderophores with Ga-68 or Fe-59, we performed uptake assays to identify which bacterial or fungal species recognize natural and/or artificial variants. Our findings show that the artificial siderophore FOX 2-5 exhibits a distinct recognition pattern across species compared to the natural FOX E control. While no significant differences were observed in Acinetobacter baumannii and fungal species—both gallium-labeled variants behaved similarly—FOX 2-5 and FOX E differed notably in Pseudomonas aeruginosa and Klebsiella pneumoniae.

This differentiation could aid in distinguishing infectious diseases, laying the groundwork for targeted diagnostics and therapies. Further in vitro and in vivo imaging studies using PET are planned to confirm these findings

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Comparing dynamics of emerging and existing respiratory viral challenges within immune-competent lung models

DCs, which are prominent in sites of high pathogen risk such as the lungs, are key to studying lung-pathogen interactions. To study the interaction of DCs with pathogens in the lung we established a co-culture model with human DCs and normal human bronchial epithelial cells (NHBE) grown in an air-liquid interface (ALI) model on Transwells inserts, where we focused on tissue integrity, inflammation, cell maturation, and viral infection.

Our findings reveal that monocyte-derived DCs attach and migrate into the epithelial tissue, with the number of DCs on the Transwell approximating normal lung physiology. During the migration into the tissue, the integrity of the respiratory tissue is maintained as determined by trans-epithelial resistance. Upon viral infection, we observed approximately three times more DCs in the tissue. Using cytokines such as CCL19 and CCL21, which induce migration in activated DCs, two thirds of the DCs migrate out of the tissue, suggesting activation and retraction from the tissue. Depending on DC migration, the viral RNA in respiratory tissue is reduced when more DCs remain compared to samples where DCs are encouraged to migrate out post-activation. However, viral activity remains unaffected by the number of DCs, as shown via plaque assays.

These results highlight the importance of DCs in modulating viral infection and suggest potential therapeutic targets to enhance antiviral immunity and improve vaccine design.

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Matrix Metalloproteinases in Diabetic Retinopathy

Diabetic retinopathy (DR) is a late complication of diabetes, in which persistent high glucose levels damage the blood vessels and neurons of the retina. Retinal neurodegeneration has been hypothesised to contribute to the pathogenesis of DR either independently, or as a consequence of vascular damage. Tissue injury and regeneration are both associated with inflammatory responses regulated by matrix metalloproteinases (Mmps). Emerging evidence suggests that Mmps contribute to tissue damage in DR, and play a role in photoreceptor (PR) regeneration. Hyperglycemia in cell and animal models impacts vascular and neuronal cells, but the molecular mediators, and the role of Mmps, have not been well defined. In this project, Mmp expression and activity within the retina are being localized and correlated with disease using the lab's established zebrafish model of DR. Unlike humans, zebrafish can regenerate damaged organs including the retina, and PR restoration was observed in the background of disease progression in the zebrafish DR model. Moreover, mitochondrial changes have been associated with neurodegeneration in DR, and increased mitochondrial localization of Mmps was reported in retinal vessels. As this has not yet been examined in retinal neurons, Mmp expression will be localized relative to mitochondria and correlated with mitochondria status. Understanding the role of Mmps in DR will provide insights into the pathological mechanism and reveal potential targets for modulation of neurodegeneration in DR.

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Artificial ageing in neural cells through UVB irradiation and Progerin overexpression

Investigating neuronal ageing and senescence in vitro is limited by the incapability of induced pluripotent stem cell (iPSC)-derived models to retain age-related signatures.

To overcome this, our group developed an engineered line of small molecule neural progenitor cell (smNPC) line capable of Doxycycline (DOX)-inducible Progerin overexpression, which has been shown to induce key ageing hallmarks. However, the analysis of senescence-associated phenotypes has not been fully characterized. Therefore, in this study, we aimed to develop a UVB irradiation protocol for wildtype smNPCs to induce an artificial ageing phenotype in human smNPCs and to be combined with Progerin overexpression.

We tested different irradiation intensities (0.015, 0.02, and 0.025 J/cm^2), applied on four consecutive days. We observed a four-fold increase in p53BP1 foci, a three-fold increase in γH2AX foci and a two-fold increase in p16 and p21 mean fluorescence intensity at 0.02 J/cm^2 with 5 × 10^5 cells. 0.02 J/cm^2 with 5 × 10^5 cells being the most effective condition, we combined it with Progerin overexpression, which led to increased p53BP1 and γH2AX foci but did not enhance senescent markers.

Our findings suggest that UVB irradiation with 5 ×10^5 cells at 0.02 J/cm^2 can induce key ageing hallmarks in smNPCs, including an accumulation of DNA double-strand breaks and senescence, providing a valuable model for artificial neural ageing. We plan to further characterize the phenotype to investigate human-specific mediators of neuronal ageing and senescence and to use the UVB irradiation model to screen for rejuvenation factors.

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Engineering covalent small molecule–RNA complexes in living cells

Covalent labeling of RNA in living cells poses many challenges. Using a structure-guided approach, we have engineered covalent RNA aptamer-ligand complexes by chemical modification of the ligands. We show that highly specific covalent linkage is possible under the physiological conditions of living cells for two distinct aptamer-ligand systems, namely the preQ1 riboswitch and the fluorescent light-up aptamer Pepper. We present several examples for imaging as well as pull-down applications of the covalent Pepper system (coPepper) in living cells. In particular, we demonstrate the unique advantage of the covalent system for FRAP (fluorescence recovery after photobleaching) analyses allowing the monitoring of intracellular RNA dynamics. The ease with which the Pepper FLAP can be converted into a coFLAP bodes well for the rapid dissemination of this approach to in vivo RNA imaging.

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Identifying preQ1 riboswitches in Listeria monocytogenes

Riboswitches are RNA-based gene control elements mostly found in Bacteria and Archaea, but also to a lesser extent in Eukaryota. They are typically located in the 5' untranslated regions (5'UTR) of bacterial mRNAs where they form secondary and tertiary structures that bind to a specific ligand with a high affinity. This highly conserved aptamer domain may undergo structural alterations upon ligand binding which triggers changes in the folding pattern of the expression platform. Therefore, riboswitches can regulate gene expression using several different mechanisms, mostly premature transcription termination and inhibition of translation initiation. More than 55 riboswitch classes have been identified in the last twenty years. Nevertheless, it is estimated that more than 1000 riboswitch classes remain hidden so far. New riboswitches have generally been predicted based on bioinformatics analysis of bacterial genomes. In preliminary experiments, we established an in vitro approach to identify preQ1 riboswitches in Listeria monocytogenes using a chemically synthesized preQ1 ligand by the lab of Prof. R. Micura. We generated a long list of candidate genes that are under the control of a potential preQ1 riboswitch and established methods to test those candidate riboswitches for translational or transcriptional riboswitch activity.

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Nuclear lamina–dependent mechanisms in neuroplasticity

The nuclear lamina (NL) is a filamentous meshwork of A- and B-type lamins attached to the nuclear envelope via interactions with inner nuclear membrane (INM) proteins. While studies in non-neuronal cells have established the role of the NL in chromatin organization and gene regulation via lamina-associated domains (LADs), its function in neurons remains poorly understood. Specifically, it is unclear which proteins mediate chromatin-lamina tethering in neurons and how these interactions influence activity-dependent gene transcription.

In this project, we investigate the role of two INM proteins of the LAP2-Emerin-MAN1 (LEM) family, LEMD2 and LEMD3, in regulating gene expression upon neuronal activity. Using transcriptomics analysis from mouse primary cortical cultures (control versus Lemd2 cKO or Lemd3 KD pyramidal neurons) we identify significant transcriptional alterations affecting both activity-dependent and activity-independent processes.

We propose that these changes arise from the capacity of LEMD2 and LEMD3 to interact directly and indirectly with DNA, thereby influencing the radial organization of the genome within the nuclear space. To explore this hypothesis, we are currently mapping LEMD2 DNA-binding sites using CUT&TAG and identifying its interactors via co-Immunoprecipitation coupled with LC-MS proteomics.

This study will provide novel insights into the role of LEMD2 and LEMD3 in nuclear lamina-associated mechanisms in cortical neurons, shedding light on their involvement in neuronal plasticity processes critical for higher cognitive functions such as learning and memory.

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Antihistamine-Mediated Inhibition of GIRK 1/2 Channels

Antihistamines are widely used to treat allergic reactions, but first-generation antihistamines, in particular, are linked to severe neurological side effects, including seizures and worsening of epilepsy, especially at high doses. A proposed mechanism involves the inhibition of G protein-gated inwardly rectifying K^+ (GIRK) channels, which regulate neuronal excitability. While inhibition of GIRK channels by first- and second-generation antihistamines has already been demonstrated, the precise chemical structural requirements underlying GIRK interaction and selectivity remain to be elucidated.

In this study, we therefore investigated the inhibition of KIR3.1/3.2 (GIRK1/2) channels by first-generation antihistamines using whole-cell patch-clamp recordings. Subsequently, we investigated H1-receptor blockade by first-generation antihistamines to evaluate differences in their therapeutic window. To analyze the chemical moieties essential for GIRK inhibition further, we evaluated structurally related derivatives of diphenhydramine.

Our results demonstrate near-complete inhibition of GIRK1/2 channels by all tested antihistamines. Of those, diphenhydramine exhibited a more favorable therapeutic window than orphenadrine, carbinoxamine, and chlorpheniramine, indicating differential selectivity among first-generation compounds. The use of diphenhydramine derivatives enabled us to identify critical chemical properties responsible for GIRK inhibition.

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SATB2-dependent gene programs in human NGN2-excitatory neurons are linked to cognition and synaptic signaling

SATB2 encodes a DNA-binding nuclear protein genetically associated with human intelligence and schizophrenia. Individuals with SATB2 haploinsufficiency suffer from SATB2-associated syndrome defined by developmental delay, severe intellectual disability, and absent/limited speech. Previouslly, we have identified SATB2-dependent epigenetic profiles and higher-order chromatin interactions in primary cortical neurons derived from Satb2 conditional knockout (cKO) and floxed mice. Here, we study the effect of SATB2 in human glutamatergic neurons, differentiated from induced pluripotent stem cell (hiPSC)-derived neural progenitors by Neurogenin 2 (NGN2) overexpression. In our model, glutamatergic NGN2 neurons expressing recombinant SATB2 are compared to SATB2-negative control NGN2 neurons. Similar to mouse, transcriptome profiling of human neurons reveals enrichment for synapse, behavior and membrane potential-related GO categories among the differentially expressed genes between SATB2+ and SATB2- excitatory neurons. Currently, we are mapping SATB2 binding sites, SATB2-dependent chromatin accessibility and chromatin interaction changes in human neurons, which will be further compared to the corresponding data from mouse primary cortical neurons. The intergration of high-resolution, multidimensional datasets from the two species will uncover evolutionary conserved as well as human-specific SATB2 effects on 3D epigenome and provide novel insights into gene regulatory mechanisms associated with human intelligence and neuropsychiatric disease.

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Investigating salience processing during an oddball paradigm using dual color calcium imaging

Aberrant functional connectivity between the salience network and the default mode network is one of the most consistent anomalies reported in autism spectrum disorder (ASD) (Uddin et al., 2015). Our data suggest that vasoactive intestinal polypeptide (VIP)-expressing interneurons (VIP-INs) in the anterior insular cortex (aIC) play a crucial role in salience detection and gating sensory stimuli to adaptively shape behavior (Ramos-Prats et al., 2022). The aIC, along with the anterior cingulate cortex, forms the salience network, which filters the most relevant internal and external stimuli to guide behavior.

We hypothesize that impaired VIP-IN function in the aIC disrupts salience encoding, leading to altered sensory processing and contributing to ASD symptomatology. To test this, we generated a mouse model with selective deletion of an ASD-associated gene in VIP-INs. We employ a classical auditory oddball paradigm in head-fixed mice, where a low-probability oddball tone (10%) is embedded within a high-probability standard tone (90%). Using dual-color calcium imaging, we simultaneously monitor principal neuron and VIP-IN activity in the aIC while tracking arousal states via pupil size fluctuations.

We will present our experimental setup and preliminary findings at the meeting.

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Neuronal Activity Patterns Induced by CO2-elicited Anxiety: Impact of CO2 concentrations

Interoception, the subjective experience of internal sensation processing, is increasingly recognized as an important component of anxiety disorders. Interoception-induced anxiety can be activated by CO2 inhalation which causes mild hypercapnia and elicits anxiety across species. Our knowledge of the underlying neuronal circuits of CO2-induced anxiety is still limited. Here, we investigated the effects of varying concentrations of CO2 (10% and 20%) on neuronal activation patterns in anxiety- and stress-related regions including the paraventricular nucleus of hypothalamus (PVN), bed nucleus of the stria terminalis (BNST), and lateral septum.

We observed that CO_2 elicited concentration-dependent responses, from inhibition to escape jumps. Neuronal activation was assessed by quantifying the expression of the immediate early genes c-Fos and Zif268 after exposure to CO2 or air. Relative to air control, exposure to 20%, but not 10% CO2 increased the number of c-Fos-positive cells in the PVN and in the dorsolateral BNST. In contrast, c-Fos induction was lower in the lateral septum after inhalation of 20% CO2 than air. Furthermore, we obtained evidence of reduced neuronal activation of the anterior, but not posterior insular cortex in the CO2 as compared with air condition, with effects dependent on CO_2 concentration in some insular subregions.

Overall, our findings show that varying concentrations of CO_2 differentially activate anxiety- and stress-related brain regions. These findings suggest that CO_2-induced engagement of the interoceptive pathway modulates key components of the brain's acute stress and anxiety response system to drive specific defensive behaviours.

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miRNA-mediated regulation of neuronal regeneration following peripheral nerve injury

MicroRNAs (miRNAs) are small regulatory RNA molecules that modulate gene expression and protein synthesis, playing essential roles in cellular homeostasis, including neuronal regeneration and pain modulation following peripheral nerve injury (PNI). miRNA expression changes after PNI indicates their potential involvement in governing nerve repair mechanisms.

To investigate this, knock-out mouse models were utilized to examine the functional significance of specific miRNAs in neuronal regeneration. Dorsal root ganglia (DRG), containing the sensory neuron cell bodies, were subjected to mRNA sequencing and RT-qPCR to identify potential miRNA target genes. In parallel, inducible plasmid and viral vector systems were employed to overexpress selected miRNAs in human neuron-like cells, and their effects on neurite outgrowth were assessed in vitro. Neurons lacking a particular miRNA exhibited impaired outgrowth as well as increased expression of genes involved in reduced axonal regeneration, cytoskeletal dynamics, epigenetic modifications, and ion channel regulation processes. Suppression of these genes led to partial restoration of neurite outgrowth. Furthermore, SH-SY5Y cells transduced with inducible viral vectors successfully replicated the miRNA expression changes observed in injured sensory neurons. Future studies will extend this work to human induced pluripotent stem cell (iPSC)-derived nociceptors (iNocs) to further dissect the role of miRNAs in neuronal regeneration. This research provides new insights into the molecular regulation of nerve repair and could offer innovative therapeutic strategies targeting nerve injuries and neurodegenerative disorders.

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Changes in brain activity during learning of fictive arithmetic problems: Preliminary results of a pilot EEG study

Background: Arithmetic competence is essential for navigating our rapidly changing digital society. As fMRI studies demonstrate, intensive arithmetic training can lead to performance improvements that are accompanied by specific changes in the brain structures activated during arithmetic tasks after training. This study aims to investigate changes in brain activity as individuals undergo intensive arithmetic training using two different learning methods.

Methods: Eight participants trained simultaneously on two sets of new, invented arithmetic problems (n=6 each). One set had to be learned by memorising the associations between operands and solution (memory condition – MEM; e.g., 3#11=20), while the other set was learned by applying a newly invented algorithm (strategy condition – STR; e.g., 3§13="[(2ndop+1stop)-10]+2ndop"=19). The problems were practiced over five days, during which EEG measurements were taken. EEG data were preprocessed to correct for artifacts; subsequently, frequency band power was calculated.

Results: Participants showed performance improvements with both learning methods. Results of the EEG analysis indicated an increase in theta and alpha power over time for both learning conditions. However, compared to the MEM condition, the STR condition was associated with lower theta power across training days.

Conclusion: Increased theta power in midline and parietal regions suggests improved cognitive control and memory retrieval, while the rise in alpha power reflects more efficient processing with reduced cognitive effort. These results highlight the neuroplastic effects of cognitive training, promoting efficient and sustained cognitive performance

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Quantitative Analysis of Fluid Compartment Profiles Along the Human Cochlea Using 3D Segmentation

Cross-sectional area of the fluid compartments such as scala tympani is a key anatomical parameter influencing cochlear implant placement, round window drug spread and inner ear fluid dynamics. Understanding its morphological variations is essential for optimizing clinical interventions and enhancing computational models of cochlear mechanics and fluid dynamics. In this study, we conducted a quantitative analysis of fluid compartments geometry using 3D segmentation data from multiple human cochleae segmented previously. The segmentation was performed using Thermo Fisher's AMIRA software. We calculated the compartment's centrelines with AMIRA's "CenterlineTree" module, extracted centerline points via AMIRA'sPythonInterface, and applied the Savitzky-Golay filter for smoothing.

Tangent vectors along the centerline were computed using the 5-point central difference method, facilitating the creation of perpendicular planes at defined intervals along the cochlear spiral. Cross-sectional areas of the scala tympani were measured at these planes, enabling the assessment of area variations along the cochlea and across the tonotopic map.

Our results reveal significant anatomical variability, influencing drug diffusion efficiency, targeting precision, and the fit and stability of cochlear implant electrode arrays. Additionally, these morphological variations may affect ion homeostasis, fluid dynamics, acoustic pressure transmission, and electrical signal propagation within the cochlea. Clinically, this data supports surgical planning, implant design, and post-operative monitoring. From a computational neuroscience perspective, the detailed characterization provides critical parameters for refining models of cochlear mechanics and auditory signal processing. This study bridges real anatomical data with practical applications, offering insights that enhance both therapeutic strategies and theoretical models in auditory neuroscience and pharmacological design.

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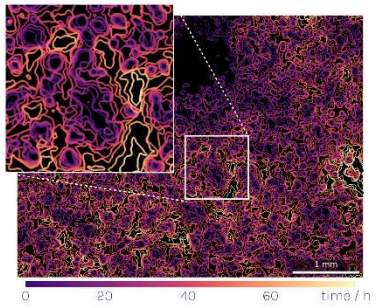
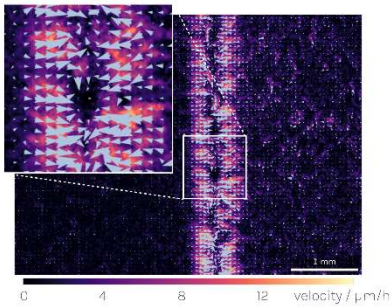
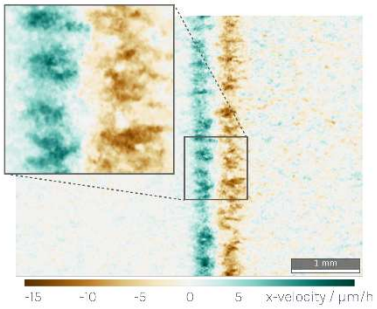


Cluster growth of stem cells



Spatially resolved cell motility of a scratch



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Frequency-Specific Mapping of Auditory Nerve Fibers: Investigating G-ratio in serial sections

The cochlea encodes sound via a precise tonotopic organization, where specific frequencies map to distinct locations along its length, ranging from 1kHz to 100kHz in mice. To achieve frequency-specific analysis on thin plastic sections, we generated a three-dimensional frequency map using high resolution microCT datasets and Greenwood function. Given the minimal anatomical variation in inbred mouse strains, this serves as a universal reference for a precise frequency localization.

Age-related auditory nerve degeneration impacts hearing, with frequency-specific patterns varying across mouse strains. Selective loss and preservation of distinct nerve fiber populations may influence hearing function. By integrating frequency-specific auditory brainstem response (ABR) audiometry with precise frequency mapping on histological sections , we correlate physiological data with nerve fiber morphometry. Manual segmentation of the basilar membrane at the inner hair cell (IHCs) level enabled spatial mapping of nerve fibers into an "atlas" dataset, allowing the registration of the thin sections within the microCT dataset for an exact frequency correlated morphological analysis. The software-based segmentation and automated evaluation of the g-ratio using deep learning algorithms will provide an objective assessment of nerve fiber morphometry across different frequency regions. By correlating ABR parameters, including hearing thresholds and latencies between young vs aged mice, we aim to refine our understanding of frequency-specific neural degeneration. This insights into cochlear pathology will inform strategies for optimizing cochlear implant electrode placement and stimulation paradigms, ultimately improving clinical outcomes by tailoring interventions to preserve and enhance neural function at critical frequency regions, ensuring better auditory performance for cochlear implant users.

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Therapeutic targeting of NLRP3 inflammasome with Dapansutrile in a transgenic mouse model of multiple system atrophy

Objective: Multiple system atrophy (MSA) is a rare neurodegenerative disease characterized by α-synuclein (α-syn) aggregation in oligodendrocytes and progressive autonomic and motor decline. Neuroinflammation in MSA involves NLRP3 inflammasome activation, which promotes pro-inflammatory signaling and may contribute to disease progression. Dapansutrile (OLT1177®) is a β-sulfonyl nitrile small molecule and a selective NLRP3 inflammasome inhibitor. This study assessed its disease-modifying potential in a transgenic MSA mouse model.

Methods: Six-month-old PLP-α-syn mice were fed dapansutrile at 0g, 3.75g, or 7.5g per kg food pellets for six months. Motor function was evaluated using the pole test, which assesses bradykinesia and motor coordination. Cytokine levels of IL-1β and IL-18 were quantified in plasma and brain tissue using a ProcartaPlex multiplex assay. Immunohistochemistry and stereology were used to determine the survival of dopaminergic neurons in the substantia nigra pars compacta (SNc) and DARPP-32-positive medium spiny neurons in the striatum. The density of phosphorylated α-syn (pS129)-positive glial cytoplasmic inclusions (GCIs) was analyzed across treatment groups.

Results: Dapansutrile treatment significantly reduced brain IL-1β and IL-18 levels, indicating suppression of NLRP3 inflammasome activity. Mice receiving dapansutrile showed improved motor performance, with significantly reduced time on the pole test. Higher doses of dapansutrile preserved dopaminergic and striatal neurons in a dose-dependent manner and reduced GCI density, suggesting neuroprotective effects.

Conclusions: These findings highlight the dose-dependent disease-modifying potential of dapansutrile in the PLP-α-syn transgenic mouse model, supporting its further clinical development for MSA.

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Structural Determinants of Dopamine Receptor Agonist Selectivity

Dopamine receptors (DRs) are G protein-coupled receptors (GPCRs) expressed in the central nervous system. When activated, DRs can trigger different downstream signal transduction cascades based on which they are divided into two major classes: D1-like, which includes excitatory D1 and D5 receptors, and D2-like, including inhibitory D2, D3 and D4 receptors. Drugs acting on DRs are used to treat several neurological disorders, like Parkinson´s disease (PD), schizophrenia, depression or bipolar disorders. PD, for example, is caused by the early death of dopaminergic neurons in substantia nigra pars compacta. Therapeutic options for PD acting on DRs include the D2-like selective agonists ropinirole and pramipexole. Despite their approval over two decades ago, a comprehensive investigation of the structural determinants responsible for their D2-like DR selectivity has not yet been conducted. In this work we therefore aim to elucidate the molecular determinants conferring (un)selective binding of DR agonists, including dopamine, pramipexole and ropinirole. For this purpose, we investigated DRs signaling cascades through 16 Galpha-proteins (collectively named the transducerome) using bioluminescence resonance energy transfer (BRET) biosensors and a luminescence based cAMP assay. Computational analyses allowed us to perform information driven site-directed mutagenesis. Selected mutations in D2 and D1 receptors modified the efficacy and/or potency of pramipexole and dopamine dependent activation in comparison to wild-type receptors. In this study, we were able to identify hotspot mutations within the binding pocket of D1 and D2, which are involved in D2-like pramipexole selectivity, efficacy and potency.

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Optic coherence tomography – A possible biomarker in early Huntington's disease.

Background: Huntington's disease (HD) is a neurodegenerative disorder characterised by motor, cognitive, and behavioural abnormalities. With the ongoing therapeutic trials, there is a constant need for sensitive and reproducible biomarkers to monitor neurodegeneration. Optical Coherence Tomography (OCT) offers a non-invasive method to measure retinal changes that reflect neurodegenerative processes.

Methods: This cross-sectional study compared spectral domain OCT data in HD patients and healthy controls (HC). HD patients were classified into Stage1 and Stage2 based on motor symptoms and functional capacity.

Results: We recruited a total of 68 participants including 39 HD patients (22 stage1, 17 stage2) and 29 age-matched HC. There were no significant differences in age and gender between the groups. Stage2 HD patients showed worse motor function (UHDRS-TMS 28.44±18.13 vs. 13.74±8.78, $p=0.002$), functional capacity (UHDRS-TFC 8.13±2.03 vs. 12.44±0.99, $p<0.001$), and lower scores on the MMSE (27.36±1.64 vs. 28.73±1.74, $p=0.005$ vs. 29.45±0.91, $p<0.001$) compared to stage1 HD patients and HC respectively. Both stage1 and stage2 HD groups displayed significantly reduced macular retinal nerve fibre layer thickness (mRNFL) (33.45±4.70, 31.90±3.47 vs. 38.45±5.00; $p<0.01$) and ganglion cell-inner plexiform layer thickness (GCIPL) (71.63±6.38, 60.42±4.67 vs. 77.03±8.40, $p<0.01$) as compared to HC.

Conclusion: HD patients exhibit significantly thinner retinal ganglia cell and macular retinal nerve fibre layer compared to healthy controls, even in early disease stages. These findings suggest that OCT may serve as a valuable biomarker, potentially suitable to track disease progression especially in the early stages of HD.

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Facial Emotion Processing in Relapsing-Remitting Multiple Sclerosis: An Eye-Tracking Study

Background: The ability to remember previously seen faces and interpret others' emotions is crucial for successful functioning in everyday social interactions. Previous studies have suggested that emotion processing may be impaired in people with multiple sclerosis. This study aimed to investigate facial emotion processing through explicit and implicit paradigms.

Methods: 30 individuals with relapsing-remitting multiple sclerosis (PwMS) with an Expanded Disability Status Scale (EDSS) score ≤4 and 35 healthy controls (HC) participated in this study. Both groups were comparable in terms of age and education level. Participants completed a neuropsychological evaluation as well as experimental tasks, including an eye-tracking age estimation task, a facial memory recognition task, and a facial emotion recognition task.

Results: PwMS showed only minor cognitive alterations (verbal attention span, verbal WM, and figural memory) and minimal-to-moderate disability (EDSS). While HC demonstrated emotional enhancement of memory by more accurately recognizing previously seen fearful faces compared to neutral faces ($P = .024$), PwMS lacked this memory advantage. Both groups performed comparably on facial emotion recognition. However, eye-tracking data revealed that PwMS displayed a more pronounced visual scanning predominance in the eye area relative to the mouth area, particularly during the early phase of visual exploration.

Conclusion: These findings suggest that subtle alterations in visual exploration and the absence of emotional memory enhancement are present in PwMS who have intact explicit facial emotion recognition abilities. The combined use of implicit and explicit face processing paradigms offers a promising approach to the understanding of social cognitive changes in PwMS.

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Language learning at the NICU – Auditory enrichment supports language discrimination in very preterm infants

Very preterm (VPT) birth is associated with a higher risk of language delays. The developing brain is shaped by early sensory experiences and the perception of speech differs between the intrauterine space and the outside world. In the womb the fetus can only perceive the prosodic regularities of language. After birth, an infant is exposed to the full-frequency range of speech, which enables also the learning of phonotactic regularities. Whether early intervention in the form of additional speech exposure supports language learning in VPT infants is unclear. To address this question, we exposed VPT born infants to additional speech stimuli during their time in the neonatal intensive care unit (NICU). 37 VPT born children were included in this study, 23 of whom received additional speech stimulation in the form of audiobooks (intervention group IG) and 14 received standard care (control group CG). We assessed the ability to discriminate between native (German) and non-native prosody (French) and phonotactics (Slovak) in the IG and CG at three months of corrected age using electroencephalography. Pseudowords differing in their phonotactic or prosodic regularities were presented via loudspeakers.

Preliminary results show that the IG but not the CG was able to discriminate between native and non-native prosodic and phonotactic regularities. Compared to familiar language stimuli, unfamiliar language stimuli elicited a more negative brain potential in the IG group. This effect was not observed in the control group. Our results suggest that additional exposure to speech supported language learning in our group of VPT infants.

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Is performance on the MoCA a good predictor for an elevated risk to develop Parkinson's disease?

Introduction: The diagnosis of Parkinson's disease (PD) is preceded by a 'prodromal phase', characterized by the presence of non-motor symptoms, such as hyposmia, dream representation or constipation. To a lesser extent, cognitive impairment has also been described. One of the aims of the longitudinal, multicenter Healthy Brain Aging (HeBA) project is to assess subjective and global cognitive performance (with the Montreal Cognitive Assessment -MoCA-) among low- and high-risk population cohorts.

Methods: At the Innsbruck's center, 240 participants without obvious neurological symptoms (mean age 60 years; 68, 75% female) performed standardized neuropsychological test including the MoCA. In addition, they underwent questionnaire based assessments of a variety of other non-motor symptoms, e.g. sleep, hyposmia, and memory. Based on a Movement Disorders Society (MDS) estimator of the likelihood of developing PD, participants were divided in low- (scores < 10%) and high-risk for PD (scores ≥ 10%).

Results: 203 participants (85%) were classified as low-risk and 37 (15%) as high-risk. The high-risk group reported a higher number of non-motor symptoms (Ps<.001). Thirty eight participants (14 in the high-risk group) reported subjective memory problems. Impairment in the MoCA (score<26) was a significant predictor of group classification in low and high risk (Nagelkerke R2=.13, P<.001). After adjusting for demographic variables (age, education, and sex), MoCA impairment and sex remained significant predictors (Nagelkerke Δ-R2=.118, P<.001).

Conclusions : High-risk group participants show changes in subjective memory and global cognition and, thus, strongly supports the notion that cognitive changes could be part of the clinical picture in prodromal PD.

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Advancing Two-Photon Immunofluorescence Microscopy in Human Brain Research: From Hippocampal Slices to the Fully Isolated Hippocampus

The use of experimental approaches in Neuroscience research has significantly improved our understanding of brain functions and dysfunctions. Imaging techniques are widely used to collect functional and structural data which in turn are essential to characterize brain activity. The aim of the present study was to obtain high-resolution images of murine and human hippocampus by means of two-photon microscopy and automated 3D analysis to reconstruct the neuronal placement of entire hippocampal regions. The preliminary study has been carried out on murine samples to standardize the experimental protocols before moving to human samples obtained from patients undergoing neurosurgical intervention. Briefly, an immunofluorescence (IF) protocol has been optimized to work on 300 um thick slices using a CoraLite 555-conjugated anti-neuron-specific nuclear protein (NeuN) antibody. The IF protocol was performed on isolated murine hippocampus which was extracted, separated from parahippocampal regions and located in a recording chamber specifically designed and manufactured for two-photon microscopy (2PM). As a proof of concept, z-stack images from isolated murine hippocampi have been generated through two-photon imaging. The combination of 2PM with fluorescent probes coupled with neuronal antibodies allowed to describe with submicrometer resolution the complex morphologies and distribution of neuronal soma within intact tissues. We generated high-resolution images of extended brain regions, which are analyzed through machine learning algorithms to compute the 3D reconstruction of neuronal soma coordinates. Our preliminary results open promising perspective for the investigation of human tissues through similar IF protocols thus allowing the generation of realistic models of the human hippocampus in silico. This work has received funding from the Italian National Recovery and Resilience Plan (NRRP), "M4C2, funded by the European Union – NextGenerationEU – Award Number: Project code IR0000011, adopted by the Italian Ministry of University and Research, CUP B51E22000150006, Project title 'EBRAINS-Italy)"

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A novel isoform of Skp2 generated by alternative translational initiation

Skp2 is an oncoprotein, which is often deregulated in cancer. In the human cell lines, the Skp2 protein has been detected as two bands in the Western Blots, with the size of 47kDa and 43kDa. The smaller, faster migrating band has been considered as a degradation product.

We have discovered that the second isoform is translated from an alternative translation codon, Methionine-36. We observed that the shorter isoform is more stable than the full-length isoform during the G1-phase, due to the lack of the "destruction box", by which Skp2 is targeted for ubiquitination. Using CRISPR-Cas9 edited cell lines, we showed that both Skp2 isoforms were able to downregulate the Skp2 substrates p27, p21 or p57. Also, we detected that cyclin D1 was accumulated in cells lacking Skp2 expression. Interestingly, the accumulation of CycD1 was also present in the cells, which express solely the shorter Skp2 isoform. Thus, we initially speculated that full-length Skp2 might be a part of E3 ubiquitin ligase for cyclin D1 degradation, while Methionine-36-initiated Skp2 might not be. However, in immunoprecipitation experiments, we observed that both Skp2 isoforms interacted with Cyclin D1. Lastly, re-expression of Skp2 isoforms in a CRISPR-Cas9 edited cell line that does not express Skp2 rescued p27 degradation but not the cyclin D1 accumulation. These experiments confirmed that both Skp2 isoforms could initiate the degradation of p27. The consequences of cyclin D1 binding to Skp2 and the molecular cause for the cyclin D1 accumulation in cells lacking full length Skp2 remain to be determined.

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Development of an ex-vivo model to study cancer cell invasion

Cancer remains a major health challenge, with metastases rather than primary tumors being the leading cause of death. While in vivo models (mainly mouse-based) are a powerful tool to study metastasis, their complexity and long duration limit routine use. Conversely, most in vitro models oversimplify the extracellular matrix, failing to capture the complexity of the whole process.
To fill the gap between in vivo and in vitro models, we set to establish an ex-vivo model based on decellularized mouse tissues. Briefly, we collect several mouse organs and incubate them in detergents to eliminate the cellular fraction. We then slice the organs with the help of a vibratome and include the slices into microscopy-compatible microchannels together with fluorescent cancer cells. Invasion is then tracked via epifluorescence microscopy.

To assess the impact of decellularization on tissue mechanics, we measured the stiffness of our slices using a nanoindenter. Our results aligned with published data on intact organs, suggesting that the process preserves the tissues' physical properties.

To validate our system, we tested three breast cancer cell lines (MCF7, CAL51, and MDA-MB-231) with standard in vitro assays (wound healing, single-cell migration, gelatin degradation, and transwell invasion). Our ex vivo results revealed organ-specific differences in invasion. Notably, MDA-MB-231 displayed greater aggressiveness than CAL51, challenging in vitro findings.

In conclusion, this ex vivo model aims to bridge the gap between in vitro and in vivo studies, providing a robust framework for understanding and ultimately targeting the metastatic behavior of cancer cells in physiologically relevant settings.

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Deciphering the role of the healthy tissue microenvironment in early-stage NSCLC

Non-small cell lung cancer (NSCLC) is one of the most lethal cancers worldwide with curative surgery being the first line treatment for early-stage NSCLC. Despite complete tumor resection, recurrence occurs in 30 to 55% of the patients. Differences in the immune response within the tumor microenvironment (TME) have been suggested as major factor explaining the differences in outcome for patients after surgery. Paradoxically, the TME is removed at surgery, raising the question of whether critical immune components that influence recurrence exist elsewhere, particularly in the adjacent lung tissue. To explore this, we analyzed the NSCLC single-cell atlas. Compared to healthy lung of non-cancer patients, we found a higher abundance of T cells in the adjacent lung tissue of cancer patients, suggesting that this environment is affected by the tumor before resection. To investigate further, we collected tumor tissue, adjacent lung tissue and blood from six early-stage NSCLC patients – three who relapsed and three who did not – matched for age, sex and cancer stage. Using single-cell targeted transcriptomics, TCR- and CITE-sequencing, we generated a dataset of 40.000 high-quality cells. Analysis of the CD8+ T cell compartment revealed differences in both abundance and clonal expansion between relapse and non-relapse patients in both tumor and adjacent lung tissue. These findings suggest that immunological changes within adjacent lung tissue may influence disease outcome after surgery. In the future, we will expand our multi-omics sequencing cohort and integrate public datasets to validate our findings, aiming to improve our understanding of NSCLC recurrence mechanisms.

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Intratumoral microorganisms and their effect on antitumor immunity

The discovery of intratumoral microbiota has led to research uncovering their diversity and impact on anticancer immunity. These findings can support diagnosis and therapeutic strategies, including cancer immunotherapy. The impact of intratumoral microorganisms on antitumor immunity are species-specific, with many relationships yet to be elucidated. To study these mechanisms, we investigated fungi, bacteria, and viruses in ovarian serous cystadenocarcinoma (OV) and pancreatic adenocarcinoma (PAAD).

Using raw RNA sequencing data from The Cancer Genome Atlas, we identified microbial species by removing human reads and taxonomically classifying the remaining sequences with kraken2. Final microbial abundance estimation was performed using bracken, and decontamination was performed by identifying an inverse relationship between relative abundance and initial RNA concentration (decontam package). Alpha and beta diversity revealed that bacterial species richness was highest in both cancers compared to fungal and viral richness. Furthermore, we found no significant differences between normal and tumor tissue in PAAD, suggesting microbial diversity depends on tissue of origin rather than tumor presence. To evaluate microbial impact on anti-tumor immunity, we correlated microbial presence with immune cell fractions and immune-related pathways. Several microorganisms were associated with tumor-promoting M2 macrophages and overall survival. Most interesting species were the fungus Verticillium dahliae in OV and the previously described Malessezia restricta in PAAD, which could play an important role in the respective cancer type.

In summary, this work has provided a basis for how intratumoral bacteria, fungi and viruses can be assessed based on RNA sequencing data, and has highlighted potential links to antitumor immunity.

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Investigating the interplay between cell death and senescence in polyploidy

Cytokinesis failure results in polyploidy and supernumerary centrosomes. The protein PIDD becomes primed at centrosomes triggering the activation of caspase-2 at the complex termed the "PIDDosome". Caspase-2-mediated BID cleavage then triggers BAX/BAK-dependent mitochondrial outer membrane permeabilisation (MOMP) and apoptosis. Cytokinesis failure also induces senescence, although the mechanisms remain unknown.

During apoptosis, all mitochondria in a cell undergo BAX/BAK-dependent MOMP. After sub-lethal stress, a small number of mitochondria permeabilise, causing limited caspase activation and DNA damage but not cell death ("minority MOMP"). This process is linked to senescence as the release of mitochondrial DNA activates cGAS-STING and the senescence-associated-secretory-phenotype (SASP), a state in which senescent cells release pro-inflammatory cytokines. Given the role of BAX/BAK-dependent MOMP in cytokinesis failure and minority MOMP in senescence, we aimed to determine if senescence observed in these cells could be due to minority MOMP.

To determine the PIDDosome's role in senescence post-cytokinesis failure, we utilized cells deficient for key components of the PIDDosome. To investigate the potential involvement of BAX/BAK in senescence and SASP regulation we exploited BAX/BAK-deleted cell lines. Cytokinesis failure was induced using dihydrocytochalasin-B, ZM447439 and etoposide followed by DNA content analysis by flow cytometry and senescence onset was assessed by β-Galactosidase staining. To further confirm the senescent state, we tested the expression of multiple SASP factors.

Our findings reveal that senescence and SASP induction following cytokinesis failure occur independently of the PIDDosome. Additionally, we ruled out minority MOMP as a contributing factor and characterized the unique SASP composition induced in this context.

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Metabolics features of cancer cells during contact guide

Cancer cells often reprogram their metabolism to meet increased energetic and biosynthetic demands, particularly during migration. The energy required for migration is influenced by microenvironmental factors such as substrate rigidity and topography. Notably, cancer cells can exploit the extracellular matrix's heterogeneous topography to facilitate movement in a process called contact guidance. Although observed already a century ago, contact guidance remains poorly understood at the molecular level.

Focal adhesions (FAs) link the actin cytoskeleton to the extracellular matrix, transmitting forces required for migration and are considered essential for contact guidance. However, using metastatic breast cancer MDA-MB-231 cells depleted of Talin1, a key FA component, we found that FAs are dispensable for this type of migration. Since FA maturation requires energy-intensive acto-myosin contractility, we hypothesized that FA-independent migration may be more energy-efficient. To test this, we cultured cells on polydimethylsiloxane (PDMS) substrates engineered with ridge-like topographies functionalized with collagen. Preliminary immunofluorescence analysis shows a significant increase in both the number and elongation of mitochondria in cells on ridges compared to those on flat surfaces. Interestingly, FA-deficient cells exhibited an increased number of mitochondria on ridges, but decreased ATP production.

Additionally, adhesion on ridges seemingly increases the proportion of mitochondria positive for pyrroline-5-carboxylate synthase (P5CS), a mitochondrial enzyme and marker for mitochondrial subpopulations specialized in amino acid production. This may reflect a metabolic shift favoring proline synthesis, which could be related to a reduced need for cells to produce ATP when on ridges. Collectively, these results could indicate a contact guidance-induced metabolic adaptation.

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A new approach to tackle ANKRD26-related thrombocytopenia

ANKRD26-related thrombocytopenia (ANKRD26-RT) is a common inherited platelet disorder characterized by mild to moderate thrombocytopenia and a predisposition to myeloid neoplasms. Most disease-causing mutations occur in the 5′ untranslated region (5′ UTR) of ANKRD26, preventing transcription factor (TF)-mediated downregulation during megakaryocyte (MK) differentiation. Notably, patient mutations disrupt RUNX1 binding, a key TF in blood cell formation, leading to abnormally high ANKRD26 expression. However, how dysregulated ANKRD26 impairs platelet formation remains unclear.

ANKRD26 plays an essential role in centrosome biology, particularly in polyploid MKs, which undergo multiple incomplete cell divisions. Excess centrosomes trigger ANKRD26-mediated activation of the PIDDosome-caspase-2-p53 pathway, blocking cell cycle progression. As MK polyploidy is crucial for effective platelet production, we hypothesize that sustained ANKRD26 expression in patients leads to aberrant p53 activation, impairing polyploidization and platelet formation, causing thrombocytopenia.

To investigate this, we are using the CHRF288 human megakaryocytic cell line, which differentiates into mature MKs. We are engineering these cells to mimic patient mutations by disrupting the ANKRD26 5′ UTR, generating mutant cell lines lacking pathway components or overexpressing ANKRD26. These models will allow us to characterize the molecular mechanisms of MK differentiation under deregulated ANKRD26 expression. Finally, we are testing whether blocking the ANKRD26-p53 axis using a caspase-2 inhibitor can restore MK polyploidy and proplatelet formation, offering a potential therapeutic approach for ANKRD26-RT patients.

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Migration and Contact Guidance in cancer cells

Metastases are the leading cause of cancer-related mortality, yet no therapies specifically target cancer cell dissemination. Metastatic tumors often exhibit aligned collagen fibers, which cancer cells use for invasion—a process known as contact guidance. In vitro, cells similarly align and migrate along structured topographies, but the underlying mechanism remains unclear.

To investigate contact guidance, we developed a soft lithography method to generate transparent nanocurvatures. We then optimized an automated workflow to track cell migration using phase contrast imaging. This allowed us to observe that metastatic breast cancer cells (MDA-MB-231) migrate along nanocurvatures, exhibiting strong contact guidance.

We reasoned that adhesion and force transmission are key for contact guidance. Focal adhesions (FAs) typically mediate adhesive migration by connecting the extracellular matrix to the cytoskeleton enabling force transmission. Talin1 is a key protein for FA assembly. To assess the role of FA in contact guidance, we generated cells Talin1-deficient clones (MDA dTLN1). Surprisingly, dTLN1 cells retained their ability to undergo contact guidance, suggesting an alternative mechanism for topographic sensing. We hypothesized that Endocytosis-Related Adhesions (ERAs), which form when endocytosis stalls on oversized cargo like collagen fibers, may mediate adhesion. Indeed, ERA markers accumulated on nanocurvatures. To explore force transmission in contact guidance, we performed a small-scale drug screen targeting the actin and microtubule cytoskeleton using topographical migration as readout. Preliminary results indicate a role for microtubules in contact guidance. Future studies will focus on defining ERA an microtubules function in topography sensing. Unraveling this mechanism enable to design new anti-metastatic therapies.

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CD8+HLA-DR+CD45RC- T cells: A novel human T cell population with regulatory potential

Regulatory T cells (Treg) are essential in immune homeostasis and medical conditions such as autoimmune diseases and cancer. While their phenotype and functions are extensively described for CD4+ Treg, CD8+ Treg are contradictorily discussed due to a lack of precise markers. In our laboratory, an HLA-DR-expressing CD8+ T cell population with regulatory capacities was described. Other groups proposed CD122+ or CD45RClow/- as CD8+ Treg markers, but none of those markers is widely accepted. The suppressive capacity of CD8+HLA-DR+ Treg amongst donors is variable. These results and the necessity to define bona fide CD8+ Treg markers prompted us to characterise these cells in more detail. We investigated the expression of inhibitory molecules and the production of various cytokines to identify potential markers for CD8+ Treg candidates. Therefore, we stimulated human PBMCs via anti-CD3/anti-CD28 and analysed T cells using flow cytometry. CD8+HLA-DR+CD45RC- T cells showed higher percentages of the inhibitory molecules CTLA-4 and PD-1 compared to CD8+HLA-DR+CD45RC+ T cells and CD8+HLA-DR-CD45RC- T cells. Additionally, IL-10 levels were higher in CD8+HLA-DR+CD45RC- T cells compared to CD8+HLA-DR+CD45RC+ T cells and CD8+HLA-DR-CD45RC- T cells, while pro-inflammatory cytokine levels were lower. Moreover, we found generally higher TGFβ levels in HLA-DR+CD8+ T cells. Our results propose CD8+HLA-DR+CD45RC- T cells as a potential Treg population based on their cytokine profile and their expression of inhibitory molecules. We will further investigate CD8+HLA-DR+CD45RC- T cells by RNA sequencing and in vitro experiments with sorted cells to analyse the impact of CD8+HLA-DR+CD45RC- T cells on T cell proliferation, survival, and migration.

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Investigating the interplay between mechanobiology and cell death

This research investigates how the mechanical properties of the extracellular matrix (ECM) influence cell death mechanisms, particularly in cancer cells. Cancer treatments often target tumor cells via the mitochondrial apoptosis pathway, where the mitochondrial outer membrane becomes permeabilized, releasing proteins that activate caspases to trigger cell death. In healthy cells, this process is tightly regulated by anti-apoptotic BCL-2 family proteins. However, recent findings suggest that under sub-lethal stress, a small subset of mitochondria can permeabilize, leading to partial caspase activation, a phenomenon known as "minority MOMP." This can initiate a DNA damage response, which may contribute to the transformation of normal cells into malignant ones.
The study focuses on how changes in the ECM stiffness might influence the occurrence of minority MOMP. Mechanotransduction, the process by which cells sense and respond to mechanical forces, is known to affect mitochondrial dynamics, including fusion and fission. Importantly, different anatomical cancer sites have wide degrees of different stiffnesses: for example, pancreatic cancer is known to thrive in very stiff environments, whereas breast cancer exists in a very soft environment.

In this project, I am testing the idea that altering extracellular stiffness leads to a greater or lesser tendency for cells to undergo minority MOMP in either physiological (untreated) conditions, or in response to sub-lethal stress. Better understanding of the interplay of cell death and mechanobiology may lead to more optimised cancer therapies in the future.

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ALTERED SPINDLE ASSEMBLY CHECKPOINT FUNCTION IMPAIRS B CELL SURVIVAL BUT DRIVES B CELL TRANSFORMATION

The mitotic spindle assembly checkpoint (SAC) is crucial to preventing chromosomal instability (CIN), which can result from mitotic errors and lead to aneuploidy - a hallmark of cancer. The SAC is active in the presence of unattached kinetochores, driving the inhibition of the anaphase-promoting complex (APC) and thereby halting mitotic progression. Paradoxically, SAC deficiencies in healthy tissue are associated with cell death and developmental defects, while they were shown to contribute to CIN, accelerated tumour progression and unfavourable clinical prognosis in a tumour setting. Analysing an early B-cell development mouse model, expressing a hypomorph of the key SAC component Mps1, we observed that loss of SAC fidelity leads to a significant block in B-cell development due to increased cell death. In an in vitro whole genome CRISPR screen, apoptosis, p53 signalling and mTOR signalling were identified as pathways promoting B-cell demise. Consistently, inhibition of apoptosis by transgenic BCL2 suffices in vivo to rescue the death of pre-B cells during development. However, an increase in spontaneous transformation or accumulation of aneuploidies was not observed. In contrast, when combined with oncogenic MYC or p53 deficiency, MPS1 impairment accelerates the formation of highly aneuploidy B cell lymphomas. Remarkably, arising aneuploidies were non-random, allowing cells to overcome a high degree of cell death in untransformed cells and ultimately enable malignant transformation. In conclusion, our findings suggest that apoptotic cell death drives the selection of karyotypes that adapt to SAC perturbation but fails to act as a barrier against CIN-driven lymphomagenesis.

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miR-142 levels regulate Wnt signaling in progenitor B cells.

B-cells are critical regulators of the adaptive immune system. These cells are generated via a complex multistep path, transitioning through the pro, pre-, and immature stages in the bone marrow, in particular. Proper developmental progression relies on various layers of regulation, like miRNA-mediated suppression of protein synthesis. Our observations indicate that mice with inactivated miR-142 locus in B-cells exhibit a reduced pre-B cellularity. However, the precise role of miR-142 remains unclear. Transcriptome analysis of mutant pre-B cells suggests aberrant Wnt signaling, consistent with several pathway components being possible targets of the miR-142s. Notably, β-Catenin expression is upregulated in these mutant cells. Additionally, mutant progenitor B-cells treated with Wnt3a in vitro display a reduced frequency of live cells and lower CD25 surface levels. These findings are reminiscent of the smaller CD25-positive pre-B cell population seen in the bone marrow of mutant mice. Thus, appropriate miR-142 levels appear essential for establishing the typical Wnt signaling required for normal B cell development.

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Automatic trajectory planning for stereotactic radiofrequency ablation in non-discrete search space]{Automatic trajectory planning for stereotactic radiofrequency ablation in non-discrete search space

Radiofrequency ablation is a well established minimally invasive procedure to treat tumors in solid organs. During the procedure applicators are inserted into the tumor and cells around their tips are destroyed by heat-induced denaturation. Manual trajectory planning requires a trained interventionalist, and its complexity and planning time rise significantly with an increasing number of trajectories.

We propose a trajectory planning method using a genetic algorithm to accelerate the planning process by automatically generating multiple safe plans. Our method uses a non-discrete search space to find the best entry and target points and does not need any prior calculation of such candidate's points sets. The method offers multiple plans, allowing the interventionalists to choose the most appropriate one. We tested on an open-source and in-house dataset, comparing with related work and retrospectively with the in-house clinical planning.

Our method, tested on 154 liver tumors across all segments using a 10 mm ablation radius, achieves a mean coverage of over 99% of the tumor and 5 mm safety margin. The method provides safe trajectories for all solutions and is on average 4x faster than related approaches.

To the best of our knowledge, we are the first to propose a fast and accurate planning technique using multiple applicators with 10 mm ablation radius. Our algorithm can deliver solutions optimizing more than ten trajectories, approaching the clinical practice at our institution, where large tumors are treated with multiple ablations rather than resection.

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Vascular Changes in the Human Inner Ear with Ageing

The stria vascularis, a highly vascularized structure in the scala media of the cochlea, is crucial for maintaining an electrochemical gradient fundamental for hair cell function . Structural and functional changes in this region are hypothesized to contribute to secondary sensorineuronal degeneration, particularly with aging. Understanding these alterations and influencing factors is essential for optimizing future therapeutic approaches. This study investigates vascular and sensorineuronal changes in the cochlea, cochlear nerve by combining 3D segmentation analysis and correlative histology.

Morphometric changes of the stria vascularis come along with functional deficits, hence 3D segmentation of the entire stria vascularis was performed using ThermoFisher Amira software. For the thorough description of the method, we refer to approach by Mahdi Fallahtaherpazir which involved Savitzky-Golay filtering and computation of tangent vectors to generate perpendicular planes. These planes allowed for cross-sectional area profiling, enabling the assessment of tonotopic changes along the cochlea.

Correlated histological analysis of structural changes with additional immunohistochemistry (IHC) on paraffin and cryo sections involved, targeting markers such as Beta-Amyloid (aging and neurodegeneration), CD45 (inflammation), CD31 (endothelial activation), α-SMA (vascular smooth muscle and pericytes transformation), and CD68 (inflammation and atherosclerosis). Thin-sections of epoxy-embedded cochleo-vestibular nerves served to assess neuronal degeneration. This integrative approach shall enhance our understanding of inner ear vascular deterioration and its role in hearing loss, providing critical insights for future therapeutic strategies.

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True twins? 68Ga and 18F labeled Glycopeptides for functional Liver Imaging

Objectives: [68Ga]Ga-NODAGA-NonaLysan (1) is a recently published PET liver imaging agent developed in Innsbruck. It targets the asialoglycoprotein receptor (ASGR) a c-type lectin, specifically expressed on functional hepatocytes. To enhance its clinical translatability [18F]F-SiFA-NonaLysan (2) was synthesized. Here we compare the properties of the two tracers.

Methods: The preparation of both compounds followed a fragment coupling approach. Both derivatives were glycosylated in solution using click-chemistry. For 68Ga-labeling NODAGA-NHS, for 18F-labeling SiFA-benzoic acid was attached to the N-terminus. Radiolabelling with 68Ga occurred by complex formation and 18F-labeling via isotopic exchange. In vitro evaluation included logD, protein binding, and metabolic stability studies in human blood serum. The pharmacokinetic profile was studied in healthy BALB/c mice.

Results: Radiolabelling with 68Ga occurred in high radiochemical yield. Fluorination yield ranged between 15-58 % d.c.. LogD values demonstrated high hydrophilicity of both compounds. The stabilities in serum and PBS were high. The amount of protein binding was moderate. Liver uptake of (1) reached its maximum 30 min p.i. with almost 80 % ID/g and stayed at a high level for up to 60 min p.i.. Compound (2) showed maximal initial liver uptake (101 % ID/g 10 min p.i.). However, it dropped rapidly to 5 % ID/g 60 min p.i.. Metabolite analysis revealed the excretion of a lipophilic species into the intestine upon binding to the ASGR.

Conclusion: Both radiotracers possess unique liver-targeting properties. However, the biodistribution profile of (1) is superior to its fluorinated sibling (2).

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Deep learning approach for improving prognastic value CT imaging of brain Ischemic stroke

Stroke is among the leading causes of mortality and disability worldwide. Neuroimaging plays a vital role in the diagnosis and treatment of strokes. Among the imaging techniques used in the diagnosis of brain-related disorders is brain dual-energy CT (DECT) images. Accurate segmentation of brain stroke lesions in medical images is essential for obtaining and predicting detailed quantitative and spatial information about the extent and location of stroke-related abnormalities in the brain.

Deep convolutional neural networks (DCNNs) have shown potential in segmenting stroke lesions and predicting changes in follow-up lesions based on initial imaging data. This study aims to evaluate whether low- and high-energy DECT acquisitions alone, the reconstructed form of low- and high-energy images displayed in the brain window, or a combination of low-, high-energy, and reconstructed form can enhance early infarct visibility for machine learning. Infarct segmentation maps were generated from the follow-up CT and co-registered to the DECT to serve as ground truth for segmentation. The multichannel input images were then trained using a self-configuring nnU-Net.

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Development of a patient-reported outcome measure for individuals at risk for hereditary cancer – Phase 1-3a of the EORTC QLQ-HCR31

Purpose:

The aim is the development of a multi-lingual questionnaire for the assessment of the quality of life (QOL) of individuals diagnosed with a hereditary cancer predisposition syndrome (HCPS) with or without a previous cancer diagnosis.

Methods:

Following the EORTC Module Development Guidelines, we conducted a literature review and interviews with health-care professionals and individuals at risk for or living with an HCPS to identify a list of relevant QOL issues (Phase 1). The issues were transformed into items (Phase 2) and the resulting questionnaire was then pre-tested in an international sample for comprehensiveness, understandability and linguistic validation (Phase 3a). Based on qualitative results and predefined decision rules we retained items.

Results:

From literature, 694 issues were identified and clustered to a list of 63 potentially relevant issues. The list was extended in interviews resulting in the preliminary EORTC QLQ-HCPS73, which was then tested in 119 counselees recruited in 12 centers across 9 countries. The sample included individuals with different HCPS (e.g. BRCA, Lynch-Syndrome, Li-Fraumeni), with or without cancer diagnosis and different testing status (positive, negative, no result). As qualitative results suggested irrelevance for individuals without or a negative result, the target group was limited to individuals who tested positive for a HCPS. We reduced the questionnaire to 31 relevant and linguistically valid items resulting in the new hereditary cancer risk questionnaire (EORTC QLQ-HCR31).

Conclusion:

The questionnaire was found suitable and relevant for individuals diagnosed with a HCPS and is ready for preliminary psychometric evaluation.

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Magnitude dependent QSM in the Static Dephasing Regime

INTRODUCTION: Quantitative MRI has significantly advanced the study of microstructural tissue components, particularly in quantifying iron-based structures, which plays a key role in the early diagnosis of neurodegenerative diseases. Accurate iron quantification requires determining concentration, oxidation state and molecular structure. While phase-dependent Quantitative Susceptibility Mapping (QSM) effectively maps iron distribution, R2* describes a semi-quantitative measure from raw signal decay. The exact impact of iron on magnitude decay remains unclear.

GOALS: To investigate, if it is possible to derive the magnetic susceptibility from magnitude data instead of phase data with our proposed model.
METHODS: Using static dephasing theory (SDT), we extracted susceptibility information from magnitude data in phantom experiments by fitting the numerically (Gauss-Kronod integration) evaluated signal decay to the magnitude decay data (L-BFGS-B algorithm). Phantoms included ferritin, ferric, and ferrous chloride at different concentrations in various backgrounds (agarose 2%, BSA 2%, gelatine 2%). The three iron samples were analyzed using multi-echo gradient-echo (GRE) measurements. We evaluated three approaches for iron susceptibility quantification: artificial dipole field fitting on background-removed phase maps (reference), classical QSM dipole inversion, and the new SDT signal decay method.

RESULTS: The SDT signal decay model reconstructed the measured decay more accurately than standard R2* mono- and bi-exponential decays. Susceptibility measurements from magnitude data coincided well to the gold standard phase derived super-paramagnetic ferritin, but varied for paramagnetic ferric and ferrous chloride.

CONCLUSION: The SDT signal decay model outperforms standard mono-exponential approaches. Magnitude signals for susceptibility mapping provides partial success in iron quantification, demanding an improved model.

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Adherence to (daily) electronic symptom screening in pediatric cancer: impact of time, location, and pain

Purpose: Regularly collected patient-reported outcome measures (PROMs) can facilitate early symptom detection and improve health outcomes. This explorative analysis aimed to investigate PROM aderence and factors associated with daily PROM completion among pediatric cancer patients.

Methods: We analyzed data from a prospective study at the Medical University of Innsbruck in which pediatric patients with cancer treated with chemotherapy completed daily PROMs via a web-based portal (ePROtect). We analyzed the PROM adherence during their first year of treatment descriptively and using a linear mixed model to evaluate factors associated with PROM adherence.

Results: Fifty patients (42% female) with a median age of 10.7 years (IQR 7.1 - 15.4) were included in this analysis (analysis period 05/2020 to 05/2023). The mean adherence was 48.7% (SD 27.2), with the highest adherence during the first 30 days (77.1 %). Significant predictive factors for lower adherence included time in the program (logarithmic; $\beta = -0.093$, $p < 0.001$) and admission to the intensive care unit ($\beta = -0.270$, $p < 0.001$). In contrast, inpatient stays ($\beta = 0.035$, $p = 0.014$) and self-reported pain ($\beta = 0.087$, $p = 0.002$) were significant predictors for higher PROM adherence. Occurrences of adverse events were not significantly associated with adherence.

Discussion: Our findings suggest that continuous daily symptom monitoring is feasible over extended periods. Adherence stabilized over time despite an initial drop, with higher participation observed during inpatient stays and in weeks with self-reported pain. Future research should explore and evaluate strategies to improve adherence.

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Introducing FAPI-DyeMER: the „Swiss Army Knife" for cancer guided surgical resection

Introduction

The complete and minimally invasive resection of solid tumours remains challenging. As a Swiss Army Knife, dual-modality probes combine several functionalities in one single tool and have the potential to enhance surgical outcomes through the integration of preoperative imaging and intraoperative fluorescence real-time guidance. Here, we investigated the potential of FAPI-DyeMER, the first dimeric candidate targeting the fibroblast activation protein (FAP).

Methods

The precursor was successfully labelled with Gallium-67/68 and Zirconium-89. In vitro, we investigated the binding and retention with HT1080hFAP cells. Tumour targeting and biodistribution of the 67Ga-labelled compounds were evaluated in xenografted mice up to 1 day p.i. In the same model, the in vivo imaging potential was evaluated at early time points via PET and up to 2 days p.i via SPECT and FI.

Results/Discussion

Cell binding assays revealed that 68Ga-FAPI-DyeMER exhibited higher cellular uptake (28.01±2.54 % after 1h of incubation) than the control compound (18.91±2.53 %) demonstrating the advantageous impact of the fluorophore. The efflux study showed a significant enhancement in cellular retention for this candidate (with 97% internalised 2h after incubation) when compared to the established 68Ga-FAPI-46 (22%). Ex vivo experiments and in vivo PET, SPECT and FI studies in HT1080hFAP xenografted mice demonstrated sustained tumour uptake (7.57±1.06 and 5.44±0.23 % ID/g at 1 h and 1 day p.i. respectively).

Conclusions

This study introduced FAPI-DyeMER, a novel dual-modality imaging agent, with significant potential for preoperative lesion detection and intraoperative margin delineation in malignancies exhibiting positive FAP expression such as prostate, ovarian and head and neck cancer.

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Modelling cardiac complications in LCHADD/VLCADD-patients using Induced Pluripotent Stem Cells (iPSCs)

Background:

Long-chain-3-hydroxy-acyl-CoA-dehydrogenase-deficiency (LCHADD) and Very-long-chain-acyl-CoA-dehydrogenase-deficiency (VLCADD) are rare disorders of the oxidation of long-chain fatty acids (LC-FA). Cardiac complications are the leading cause of early and sudden death in LCHADD/VLCADD-patients. Approximately 80% of patients diagnosed with LCHADD/VLCADD will develop severe cardiomyopathy or arrhythmia during their lifetime.

Methods:

To model cardiac complications in patients with LCHADD/VLCADD, patient-derived defective fibroblasts were reprogrammed into iPSCs and differentiated into cardiomyocytes to examine potential patient-related differences. Differentiated cardiomyocytes were analyzed for cardiac markers using immunochemistry. In addition the reprogrammed iPSCs were differentiated into mesenchymal-like stem cells and functionally characterized by trilineage differentiation (adipogenesis, osteogenesis, and chondrogenesis).

Findings:

Functional characterization of the reprogrammed patient-derived iPSCs indicated a profibrotic phenotype with osteogenic and chondrogenic, but not adipogenic differentiation and increased levels of stress fibers. Cardiomyocyte differentiation revealed morphological differences between healthy and patient-derived cells. Additionally, we observed differences in the beating activity of the differentiated cardiomyocytes.

Interpretation:

Our findings will improve the understanding and therapy of LCHADD/VLCADD, as there is no existing model of cardiac complications in LCHADD/VLCADD-patients using human iPSC technology. This model will be used to study patient-related differences and the effect of different treatment modalities.

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Computational prediction of activating kinase mutations

Erroneous kinase signalling is a major cause of cancer and these proteins are thus an important drug target in cancer therapy. During the transition from inactive to active state, kinases undergo significant conformational changes. Amino acid mutations, such as the epidermal growth factor receptor L858R mutation, lead to the constitutive activation of kinases, and are therefore classified as oncogenic mutations. Likewise, mutations which shift the equilibrium from a drug-bound - and thus inhibited – kinase conformation towards an active state confer resistance to drug treatment. However, such mutations are often only identified and characterized once they have emerged in patients, leading to a lack of effective therapies until new drugs have been discovered.

We have developed an in-silico workflow to identify these activating/resistance mutations, which is based on the stability changes of different protein conformations upon mutation. In addition, with the help of mutational signatures, we are able to predict which mutations are most likely to occur in patients. We have retrospectively validated our workflow using patient data and confirmed that a large number of mutations occurring in the clinic were identified by our workflow. To further validate our workflow, newly identified and previously uncharacterized patient mutations are tested in vitro.

This allows us to identify novel clinically relevant kinase mutations and, ultimately, to design new anticancer drugs in a prospective manner.

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Central amygdala VIP signaling as a modulator of stress and anxiety responses in mice

Vasoactive-intestinal-polypeptide (VIP) is a neuropeptide that is localized together with its receptors (VPAC1 and VPAC2) in brain areas of the stress and anxiety circuit, such as central amygdala (CeA). However, the exact role of the CeA-VIP system in stress and anxiety function is not fully known. By using a pharmacological and chemogenetic approach we investigated the role of VIP in the CeA on anxiety and stress responses of mice. First, we administered specific VIP/VPAC receptor agonists/antagonists bilaterally into the CeA to evaluate effects on anxiety- and stress-related behaviors as well as neuroendocrine stress response. We found that intra-CeA infusions of VIP cause anxiogenic-like behavioral effects, reduced risk-assessment in behavioral tasks for the assessment of anxiety-related behavior such as elevated plus-maze and a more passive coping style in the forced swim test, compared to vehicle-injected controls. Conversely, intra-CeA administration of VPAC1/2 receptor antagonists induced opposite behavioral changes suggesting anxiolytic-like efficacy and improved stress coping ability. Moreover, in a subsequent experiment we chemogenetically activated VIP+-neurons within the ventral periaqueductal grey (vPAG) the main source of VIP innervation of the CeA through cre-dependent designer-receptors-exclusively-activated-by-designer-drugs (DREADDs) to reveal the impact of a PAG-VIP-CeA circuit in stress- and anxiety function. Our data show that CNO-induced activation of VIP+-neurons of the vPAG resulted in an increase of anxiogenic-like behavior and reduced risk-assessment in the elevated plus-maze and light-dark test. Thus, our findings identify a VIP-mediated circuit in the brain that plays a critical role in the regulation of stress- and anxiety-related behaviors indicating translational potential. (FWF-P33534-B)

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Detecting Aneuploidy and Chromosomal Instability and their transcriptional consequences in tumor and tumor-immune interactions using single-cell RNA sequencing data

Aneuploidy and Chromosomal Instability (CIN) are both hallmarks of cancer. Aneuploid cells harbor an abnormal number of chromosome or chromosome arms in approximately 90% of solid tumors. CIN is the propensity of cells to mis-segregate chromosomes during mitosis, giving rise to an aneuploid karyotype. This dynamic instability creates tumor heterogeneity, allowing for rapid adaptation to selective pressures, such as therapy or immune surveillance. The incidence of CIN has been quantified to between 60 and 80% of tumors, yet this number is often derived from observing aneuploidy rather than the ongoing nature of mis-segregations. CIN has been studied experimentally by manipulating the mitotic spindle checkpoint, or in observational cohorts by using karyotype heterogeneity as a surrogate measure. The availability of the latter has recently increased massively due to single-cell DNA and RNA sequencing. Yet, there has been no comprehensive study to confirm whether the lessons learned from spindle manipulation hold true in large patient cohorts.

In this study, we analyze previously published single-cell RNA sequencing data across multiple cancer types, disentangling aneuploidy levels from karyotype heterogeneity and linking them to downstream gene expression programs. Our preliminary findings in breast and lung cancer indicate that samples with high aneuploidy but low heterogeneity downregulate inflammatory pathways, whereas those with low aneuploidy and high heterogeneity show elevated inflammation. However, divergent patterns emerge in other lineages, such as colorectal cancers. Using this approach, we plan to provide a comprehensive overview of intrinsic and extrinsic responses across cancer types.

Cancer - scRNA - CIN vs aneuploidy

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Automated liquid handling extraction and rapid quantification of underivatized amino acids and tryptophan metabolites from human serum and plasma using dual-column U(H)PLC-MRM-MS and its application to patient samples

Amino acids (AA) represent the building blocks of proteins and other biomolecules. AA and their metabolites, in particular the ones of tryptophan (TRP), exhibit an important role as neurotransmitters and in inflammatory response. Dysregulation of AA metabolism is associated with pathological phenotypes and metabolic disorders. Measurements of AA and their metabolites in serum and plasma provide information about the metabolic status of an individuum and may serve as diagnostic readouts to monitor disease progression. Quantitative analysis of AA and TRP metabolites in patient cohorts, requires reproducible and sensitive high-throughput workflows covering extraction, sample preparation and measurement. Although LC-MS is a powerful tool for absolute quantification of small molecules, separation of free amino acids is still challenging due to their physical-chemical properties.

For the derivatization-free absolute quantification of 20 AA and 6 TRP metabolites from serum and plasma, we developed an automatized protocol for sample extraction and preparation using an Andrew+ Pipetting Robot and (mixed mode-) reversed phase-chromatography coupled to triple quadrupole mass spectrometry. Fast analysis (under 10 min/sample) represented excellent reproducibility (CV < 15%), linearity (R2 ≥ 0.98) and sensitivity (LLOQ ≤ 0.6 µM). Optimized extraction protocols revealed high recovery (≥ 85%) and good reproducibility (CV < 15%). Extracted serum samples exhibited values consistent with the literature, the plasma protocol was successfully verified against certified reference values. Extraction workflow and dual-column LC-MS method was applied to a human prostate cancer study, where we were able to discriminate between treatment regimens based on the differences in measured metabolite level.

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Single-cell profiling of striatal organoids derived from Leigh syndrome patients reveals dysregulated gene network during neurodevelopment

Leigh syndrome (LS), a severe neurodevelopmental disease, is caused by mutations in mitochondrial genes leading to dysregulated ATP production. The nuclear DNA-encoded gene NDUFS4 encoding a subunit of mitochondrial complex I is frequently mutated in patients causing alterations in various brain regions including the striatum. The underlying pathophysiological mechanisms driving this rare disease remain elusive. Here, we aimed to investigate transcriptomic alterations in early development of striatal organoids derived from LS patient induced pluripotent stem cells carrying a NDUFS4 mutation. Single cell RNA sequencing (scRNA seq) revealed a slight dorsalisation of LS patient-derived organoids. In particular, the fraction of dorsal telencephalic glutamatergic neurons expanded at the expense of ventral telencephalic GABAergic neurons. Differential expression analysis confirmed downregulation of genes involved in mitochondrial complex I and OXPHOS with ventral telencephalic GABAergic neurons being highly susceptible to these changes. Across the vast majority of cell types, 7 upregulated and 16 downregulated genes were found to be shared. Lastly, leveraging tools for network construction allowed us to further narrow the list of candidates to the genes NR2F1, FOXP2, and ETV1 interacting during neurodevelopment apart from genes involved in mitochondria function. In conclusion, our study revealed genes candidates involved in the neuronal phenotype paving a way for further understanding of LS and establishing novel intervention paradigms.

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Developing 3D-bioprinted vascularized neuroblastoma-on-chip model to study metastasis

The progression and metastatic potential of neuroblastoma, the most common extra-cranial pediatric malignancy, relies on shaping tumor microenvironment (TME) and stimulating vascularization. The mammalian forkhead box O3 (FOXO3) transcription factor plays a key role in cell death and oncogenesis. Under molecular or genotypic stress (chemotherapy, hypoxia), FOXO3 relocates from the cytoplasm to the nucleus, which contributes cancer cell protection and chemo-resistance. Previously developed FOXO3 modulator, compound S9, prevents FOXO3 binding to its target promoters and thus affects the associated signaling.

We have developed a 3D-bioprinting method recapitulating neuroblastoma TME by combining tumor cells with fibroblasts, perfusable channels, and vessel-containing tissue in fluidic chips. This model will allow for investigating how immune cells affect vessel barriers and migration during metastasis, a vital clinical question challenging to answer using conventional 2D cell culture. To study the effects of S9 on FOXO3 and its effect on tumor cell migration and survival, we employ neuroblastoma cell lines with diverse molecular characteristics. In cells expressing FOXO3(A3)ERtm transgene, FOXO3 can be activated by 4-hydroxy-tamoxifen, allowing the study of FOXO3 modulation.

Aiming for the tumor-on-chip to resemble the real-life situation, the model will be enhanced by immune cells. We will investigate the impact of dendritic cells and cytokines on vessel permeability, and cell migration. Neuroblastoma-on-chip will be connected to liver and kidney-on-chip tissue surrogates to study drug activation, metabolism, clearance, and metastasis. This model will ultimately serve as a platform for personalized therapeutic testing, including FOXO3 modulators and metastasis inhibitors, and their metastasis-mitigation potential.

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Comprehensive analysis of the regionalisation and differentiation capacity of early neural stem cells derived from human embryonic brain tissue

Understanding early human neurodevelopment is essential to uncover fundamental biological processes and improving strategies to address neurodevelopmental disorders. With the aim to provide a suitable model system for that, previous studies described tissue-derived rosette-like progenitors and PSC-derived neuroepithelial cells. However, the establishment of a stable human neural progenitor cell line from embryonic tissue has remained an unreached goal. Here, we present a long-term in vitro maintained embryonic neuroepithelial stem/progenitor cell (eNSPC) line, stabilized using a chemically defined medium. These cells exhibit a naïve, non-polarized, pre-rosette phenotype and were confirmed by scRNA-seq as a homogeneous population of multipotent stem cells. They therefore not only address the need of a model system for early human neurodevelopment but may also be a valuable tool in the development of cell replacement therapy approaches. They demonstrate broad differentiation potential into forebrain, midbrain, and hindbrain identities, sensory neurons, and commit into neural crest lineages, highlighting their capacity to generate diverse central and peripheral nervous system derivatives. Different monoclones derived from distinct tissue preparations show limited clone-to-clone variation but consistently exhibit robust differentiation and regionalization capacities. This novel cell line not only addresses the need for an advanced in vitro model of early human neurodevelopment but also represents a valuable tool to explore cell-based therapies for neurodegenerative and developmental disorders.

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Semantic processing in the young and aging brain: electrophysiological signatures

Insights into the neural processing of semantics may help to better understand speech intelligibility in people with hearing loss and provide clues for improving hearing rehabilitation. Since semantic processing changes with age, we investigated the underlying brain mechanisms in a sample of younger (< 30 years) and older (> 50 years) healthy subjects without hearing impairment.

In order to study neural correlates of semantic processing we recorded neural activity using electroencephalography while participants listened to acoustically presented semantically correct and incorrect sentences. We then performed event-related potential (ERP) analyses to investigate the fast dynamic mechanisms involved in language processing and compared the ERPs of younger and older participants.

Consistent with previous research, our preliminary analysis show an N400. This centro-parietally distributed ERP component after about 400 ms is an electrophysiological marker that reflects the integration of semantic information. We found larger N400 amplitudes for semantically incorrect compared to correct sentences in both age groups, indicating increased difficulty of processing semantic information. Preliminary data suggests that the elderly participants elicit slightly delayed N400 latencies accompanied with a broader, thus less focused, scalp distribution compared to the younger participants, which could indicate that semantic processing alters with age.

In an ongoing project, we are investigating the same electrophysiological signatures in older patients with hearing loss (cochlear implant users). The results of the current study, using the same stimulus material as in the large-scale project, will allow an even more accurate interpretation of the neural processing of semantics in people with hearing loss.

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Adaptive growth control of human brain development in brain organoids

Brain development consists of an initial expansion of neural stem cells, followed by a gradual switch to the generation of differentiating, non-cycling functional cells, such as neurons. Neurogenesis occurs mainly during embryonic stages, while it becomes limited in later life. Throughout these stages, the developing brain is susceptible to environmental impacts, with various stressors potentially causing abnormalities in volume, microstructure, and connectivity of certain brain regions. Since human brain development differs from that of rodents and relies on scarce tissue samples, its study is challenging. Human brain organoids have emerged as a valuable in vitro model for neurodevelopment, as they recapitulate early stages of brain development, including neurogenesis. However, lineage growth control and plasticity of developing human brain tissue remain poorly understood. Previous work has shown human brain organoids to exhibit compensatory growth after tissue insults, mitigating developmental deficiencies when up to 80% of neural progenitor cells are perturbed. To address these processes in more detail, we use chimeric organoids containing 80% WT and 20% puromycin-resistant ESCs. Puromycin treatment allows for selective depletion of subsets of cells within organoids and thereby enables exploring compensatory processes of unaffected cells. Image-based and FACS analyses show how cerebral organoids treated with puromycin from day 16 compensate for the loss of 80% of their tissue, focusing on alterations in the cell-type composition and cell cycle dynamics. Additionally, bulk RNA and single-cell sequencing analyses uncover compensatory growth on a molecular level. Altogether, our experiments will shed light on adaptive tissue growth in human brain development.

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Accuracy of CBCT-based impressions compared to intraoral scanning - New technologies in dental research

This study aims to develop a hybrid imaging system for dental restorations by combining threedimensional cone beam computed tomography (CBCT) and intraoral scanning (IOS). Real tooth models representing the dentate maxilla were fabricated, scanned using IOS, X-rayed with CBCT, and measured via an industrial 3D scanner to establish a ground truth. A key focus is to evaluate stitching errors in IOS compared to CBCT models by repeatedly removing and reinserting individual teeth. The hybrid approach leverages the superior spatial accuracy of CBCT and the high-resolution details of IOS, aiming to enhance both imaging precision and clinical applicability. Additionally, the study investigates the potential of CBCT to capture subgingival preparations in three dimensions. The advantage of CBCT imaging is that the gingiva does not need to be removed, making the clinical process more efficient. Calibration techniques using reference objects and reverse engineering software are employed to compare STL files from both modalities, quantify deviations, and assess the impact of restorative materials on imaging accuracy. Anticipated outcomes include determining whether CBCT and IOS data can complement each other to achieve clinically acceptable results, even if standalone CBCT accuracy is insufficient. Challenges include managing artifacts in CBCT images and ensuring reliable segmentation. This project aims to create a novel system that integrates the strengths of both modalities to improve the accuracy and efficiency of dental restorations.

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MRI QuantificatioMRI Quantification of Magnetic Nanoparticles for Hyperthermia Applicationsn of High-Concentration Magnetic Nanoparticles for Hyperthermia Monitoring

Introduction - Quantitative spatial in vivo magnetic nanoparticles (MNP) distribution is crucial for advancing bio-magnetic hyperthermia as a therapeutic modality.

Purpose - This study aims to investigate the effectiveness of MR imaging to quantitatively assess high concentrations of MNPs, which are required for effective hyperthermia applications.

Approach - We conducted MR imaging on phantoms containing various iron concentrations (from 0 to 1.7 mg/mL) of MNP-capsules. A multi-echo (6TE) GRE pulse sequence was used for both R2* and phase. Then we applied different categorical quantification methods to assess the concentrations and limitations of MRI-based MNP quantification. Where the change of effective transverse relaxation rate $\Delta R2$, susceptibilities $\Delta\chi$, the local magnetic field inhomogeneities were determined for the capsules.

Findings - The relaxometry method enables mapping of R2* with sensitivity up to 0.08 mg, while susceptibility mapping extends the quantification range to 0.425 mg. Meanwhile, the model-based method allows the quantification of iron concentrations as high as 0.85 mg. Findings indicate that MRI quantification of high concentrations of MNPs is challenging and only possible up to a certain concentration regime, which is still not sufficient for hyperthermia monitoring.

Value - This limitation underscores the need for a multimodal approach, to improve clinical feasibility in hyperthermia treatment planning and monitoring. The insights from this study support ongoing development in image-guided hyperthermia monitoring and enhance the potential for clinical translation.

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Development of a 3D-bioprinted Mesothelium-on-Chip system to study Ovarian Cancer and Novel Treatments

Ovarian cancer (OvCa) is the most lethal gynecological malignancy and the fourth-common cause of cancer death in the western world. Reasons for its high mortality are nonspecific symptoms, the lack of useful biomarkers and therapeutic limitations. Furthermore, in more than 50% of OvCa patients the ascites contains multicellular aggregates, which are likely to cause metastasis and relapse of the cancer. However, currently used models lack the ability to directly investigate the OvCa-spheroid invasion into the peritoneal mesothelium. Therefore, we are in need of a more complex, animal-free model that mimics the peritoneal mesothelium, to get a better understanding of the invasion of OvCa in mesothelium and to identify the role of mesothelium and tumor spheroids for OvCa disease progression. Using 3D-bioprinting, we developed a unique in vitro system for studying OvCa-spheroid mesothelium interaction. The tissue equivalent is 3D-bioprinted using micro-valve jetting into a custom-made small laser-cut acryl chip. The artificial mesothelium consists of three layers of fibroblasts covered by a monolayer of peritoneal mesothelium cells.

Using this newly developed Mesothelium-on-Chip system, we investigated the invasion process of two ovarian cancer cell lines, HTB77 and SKOV6. Furthermore, we were able to show blockage of the invasion process of the OvCa-spheroids using various treatments including Fibronectin binding peptide, anti-TGF-beta antibody, Resveratrol and Metformin.

This model allows us to study OvCa-spheroid adhesion, invasion and drug resistance in a 3D bioprinted, animal free model. Furthermore, it will give us the opportunity to predict patient's therapy response using ascites-derived multicellular aggregates to improve patient-tailored therapy.

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Sustainable use of electronic patient-reported outcome assessment in routine cancer care: Results from a systematic scoping review and follow-up survey

Background

Routine electronic assessment of patient-reported outcomes (ePRO) can improve cancer care, yet its implementation in routine practice and long-term sustainability remain unclear. Understanding these aspects is critical to advancing the field.

Methods

We conducted a systematic review of publications on ePRO use in oncology care up to December 31, 2023, extracting data on clinical ePRO applications. A follow-up survey was sent to authors of published ePRO applications to assess their current use. Data were analyzed using descriptive statistics and regression models to evaluate time trends, with year of publication as the predictor.

Results

Of 2,933 references screened, 303 met inclusion criteria. Publications increased significantly over time (2003–2023, $P < .001$). Trends showed a rise in mobile application use (OR = 1.211, $P < .001$), remote assessments (OR = 1.094, $P = .002$), and feedback provided to patients (OR = 1.060, $P = .036$). The survey had a 35.3% response rate (78/221), with 61.1% of ePRO applications still in use, lasting a median of 5 years. The most common reason for discontinuation was a lack of funding and resources (42.9%, 12/28).

Conclusion

The field of ePRO assessment in oncology is growing, and shifting towards remote and app-based assessment, as well as increasingly providing feedback to patients. We present, for the first time, data on sustainability of ePRO use in routine care and show that financial and resource barriers remain a key challenge to sustainable implementations.

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Influences of the anti-diabetic treatment dipeptidyl peptidase-4 (DPP4) inhibitor on radiation response of breast carcinoma cells with different metastatic capacities

Diabetes mellitus and cancer are major global health concerns. Breast cancer patients with diabetes often face worse outcomes than non-diabetic patients. Dipeptidyl peptidase-4 (DPP4) inhibitors, such as sitagliptin, are widely used for diabetes treatment, but their impact on radiation therapy in breast cancer is unclear.

This study aimed to investigate how sitagliptin influences radiation responses in breast carcinoma cells with varying metastatic potentials. Carcinoma cells with enhanced invasive capabilities (INV cells) were derived from triple-negative (TNBC, MDA-MB-231) and hormone-dependent (T47D) breast carcinoma cell lines. These cells, compared to parental, were treated with sitagliptin (4 µM), radiation (2 or 8 Gy), and a combination of both. The study examined cell cycle distribution, cell death, and underlying molecular mechanisms.

Both INV cell types showed increased DPP4/CD26 expression. Sitagliptin did not induce cell death or cell cycle arrest in either parental or INV cells. However, it promoted senescence in parental MDA-MB-231 cells and autophagy in INV MDA-MB-231 cells, especially at higher radiation doses. T47D cells did not exhibit senescence under any treatment, though INV T47D cells showed notable downregulation. Parental T47D cells increased autophagy marker expression with higher radiation doses, further amplified by sitagliptin. INV T47D cells showed a marked rise in autophagy markers with combined sitagliptin and radiation treatment.

These results indicate, sitagliptin has minimal impact on radiation-induced cell cycle arrest or death in breast carcinoma cells but promotes senescence and autophagy in TNBC cells, potentially protecting them from radiation damage. Hormone-dependent breast cancer cells are less responsive to these protective effects.

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The Fatty Acylizer webserver enables modeling of fatty acyl patterns through combinatorial deconvolution of complex lipid compositions

Lipid metabolism forms a densely interconnected metabolic network that reacts sensitively to disease states and/or changes in nutritional availability, especially of essential precursors. Metabolic alterations not only affect the overall abundance of lipids on a class level but can also substantially impact respective fatty acid substitution patterns. However, accurately resolving such changes on the molecular species level in LC-MS experiments is challenging due to the potential for high isobaric overlap and similar chromatography behaviors, especially for more complex phospholipids such as cardiolipins. During database-guided annotation of experimental data, usually entire chromatography peaks are assigned to the most prominent fragment spectra, leading to an under-estimation of the actual lipid diversity of the sample.

We developed Fatty Acylizer, a webserver that enables users to reconstruct this missing fatty acid information from user-derived lipid profiles, without requiring prior MS2-based fatty acid annotations. Furthermore, Fatty Acylizer provides helpful visualizations of the results, enabling users to validate the accuracy and reliability of the modeled fatty acid profiles. At the core of the deconvolution algorithm lies a combinatorial lipid side chain substitution model that links fatty acid profiles with their corresponding predicted lipid profiles. The algorithm reconstructs fatty acid profiles by fitting the model to quantified lipid profiles.

We scrutinized the algorithms performance using three biological validation data sets, covering various cell culture models, tissue samples and model organisms. The results align closely with experimental data across a wide range of lipid environments, exhibiting only a few well-defined, metabolically explainable limitations in brain tissue and bacterial samples.

Fatty Acylizer provides researchers with a practical tool for resolving fatty acid compositions of complex lipid profiles, improving our understanding of lipid metabolic pathways and their side chain remodeling processes in response to genetic, biochemical and environmental perturbations.

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Reactivation of human endogenous retroviruses (HERVs) as a driver of calcific aortic valve disease (CAVD)

Background

Human endogenous retroviruses (HERVs) constitute approximately 8% of the human genome, representing remnants of ancient retroviral infections. Although largely silenced through epigenetic mechanisms, recent studies suggest that external stressors, such as ionizing radiation, can induce HERV re-expression, leading to dsRNA accumulation and potentially contributing to pathological processes like ageing and tissue calcification.

Methods

Human valvular interstitial cells (VICs) were exposed to 10 Gray radiation using a Linear Accelerator (LINAC). Radiation-induced molecular changes were analyzed via quantitative RT-PCR and RNA sequencing. The presence of dsRNA was quantified using ELISA, while calcification in vitro was assessed using Alizarin Red S staining. HERV-K knockdown and overexpression experiments were performed via plasmid transfection and presence of retrovirus-like particles was assessed via electron microscopy. Inhibition experiments were performed with the anti-retroviral drug Abacavir.

Results

Radiation exposure led to the upregulation of inflammatory and pro-calcific genes. Functionally, VICs exhibited enhanced calcification following irradiation and dsRNA levels were markedly increased post-radiation. RNA sequencing revealed a significant upregulation of endogenous retroviral elements, which was further validated by qPCR. HERV-K knockdown effectively prevented the inflammatory and calcific responses to radiation. Increased expression of the HERV-K envelope protein was observed post-radiation, and electron microscopy revealed the presence of retrovirus-like particles in irradiated cells. Functionally inhibiting retroviral replication using the antiretroviral drug Abacavir successfully blocked radiation-induced VIC calcification.

Outlook

To further elucidate the underlying mechanisms, we are aiming to produce GFP-tagged HERVs to track their mechanism of action and investigate their role in cellular processes like inflammation, senescence, and calcification.

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Wavefront corrections over large fields fo view via beam conce tomography

Imaging objects in scattering media requires the correction of complex wave distortions. Adaptive optics and wavefront shaping can correct these distortions, but aberrations are rarely isoplanatic and vary spatially over the field of view. We propose a tomographic approach to reconstruct the local refractive index distribution of a scatterer, allowing the calculation of aberration maps for larger fields of view. The approach is guided by wavefront measurements at test points around the target area. We demonstrate the ability of our tomographic approach to provide spatial aberration maps through numerical simulations and proof-of-concept experiments.

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Machine learning models including patient-reported outcome data in oncology: a systematic literature review and analysis of their reporting quality

Purpose: To critically examine the current state of machine learning (ML) models including patient-reported outcome measure (PROM) scores in cancer research, by investigating the reporting quality of currently available studies and proposing areas of improvement for future use of ML in the field.

Methods: PubMed and Web of Science were systematically searched for publications of studies on cancer patients applying ML models with PROM scores as either predictors or outcomes. The reporting quality of applied ML models was assessed utilizing an adapted version of the MI-CLAIM (Minimum Information about CLinical Artificial Intelligence Modelling) checklist. The key variables of the checklist are study design, data preparation, model development, and reproducibility.

Results: The literature search yielded 1634 hits, of which 52 (3.2%) were eligible. Thirty-six (69.2%) publications included PROM scores as a predictor and 32 (61.5%) as an outcome. Results of the reporting quality appraisal indicate a potential for improvement, especially in the areas of model examination. According to the standards of the MI-CLAIM checklist, the reporting quality of ML models in included studies proved to be low. Only nine (17.3%) publications present a discussion about the clinical applicability of the developed model and reproducibility and only three (5.8%) provide a code to reproduce the model and the results.

Conclusion: The herein performed critical examination of the status quo of the application of ML models including PROM scores in published oncological studies allowed the identification of areas of improvement for reporting and future use of ML in the field.

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Gabapentin alters murine pancreatic islet excitability and insulin release in a glucose-dependent manner

Pancreatic β-cell electrical activity and insulin vesicle exocytosis is controlled by the activation of High Voltage-gated calcium channels (HVCC). Previously, we demonstrated that genetic ablation of α2δ-1 HVCC subunit reduced β-cell calcium influx by ~60% leading to severely impaired insulin release. The antiepileptic and analgesic gabapentinoid drugs bind to the $\alpha_2\delta$-1 subunit, also reducing HVCC calcium currents in heterologous expression systems, smooth muscle cells, and neurons. Contradictory, several case reports showed that chronic gabapentinoid use causes hyperinsulinism and hypoglycemia. To identify the potential mechanism, here we investigate if chronic gapapentin (GBP) treatment can alter murine islet calcium dynamics, insulin release and islet cell glucose-dependent electrical activity. Isolated islets incubated for 36-40 hours with gabapentin showed spontaneous calcium transients when bathed in 5 mM extracellular glucose whereas untreated islets remain silent. While untreated islets respond with calcium waves in 10 mM glucose, most GBP-treated islets show a continuous calcium transient. Consistent with increased excitability, GBP-treated β-cell display a higher resting membrane potential and plateau potential. However, these changes in excitability are not caused by alterations in β-cell HVCC calcium current amplitude. Furthermore, preliminary experiments demonstrate that GBP-treatment impairs maximum insulin release. Therefore, our experiments suggest that GBP treatment increases β-cell excitability and insulin release at lower glucose levels but decreases insulin in higher glucose concentrations in an HVCC-independent manner.

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Investigating the Mechanism of Action of Novel Platinum Complexes as Potential Anticancer Agents

Cisplatin and oxaliplatin are widely used anticancer drugs known for their DNA-binding properties. However, their efficacy is limited by dose-limiting side effects and the development of resistances. This highlights the need of new chemotherapeutics with enhanced selectivity and less important side-effects. To achieve this goal, we focused on molecular targets, which are present selectively in cancer cells. With this aim, two novel platinum complexes, [Pt(Butene-ASA)Cl3]- and [Pt(L-Ala)(Butene-ASA)Cl] were recently synthesized, initially designed as cyclooxygenase inhibitors, to investigate their potential as anticancer agents. Our research aimed to determine whether these new complexes share the same mechanism of action as cisplatin and oxaliplatin.

We employed high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) along with MS2 fragmentation, to compare the DNA-binding properties of our novel complexes with those of established platinum-based drugs. Results revealed that particularly [Pt(L-Ala)(Butene-ASA)Cl] forms fewer adducts with the model oligonucleotide compared to cisplatin. The same complexes were also tested for their ability to bind to model peptides and proteins using HR-ESI-MS. Moreover, a competitive LC-MS assay for model proteins was established to highlight the different binding preferences depending on the donor atom on the protein. The findings suggest a different mode of action for these complexes compared to cisplatin and oxaliplatin, opening new avenues for anticancer drugs. Further investigations into the specific mechanisms and potential therapeutic applications of these novel platinum complexes may lead to the development of more effective and better-tolerated anticancer treatments.

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Cytotoxic carboplatin-siderophore conjugates for image-guided therapy of fungal infections

Introduction:

Carboplatin-based Platinum(IV) complexes conjugated with the siderophore deferoxamine (DFO) were developed for pharmaceutical use. Due to the metal-binding capabilities of DFO, we evaluated these compounds for potential antifungal use, utilising this structure to bind the radioisotope Gallium-68 for positron emission tomography (PET) application, and to enable specific uptake in microorganisms like Aspergillus fumigatus (AFU) via dedicated siderophore transporters (SITs). Here, we present data of two carboplatin-DFO conjugates for potential application in targeted image-guided antifungal therapy.

Methods:

Two carboplatin derivatives featuring a DFO moiety at an axial position were radiolabelled with Gallium-68, tested for protein binding and stability in serum. In vitro uptake assays in AFU and AFU mutants lacking the siderophore transporter SIT1 were performed. Cold-labelled Gallium-complexes were tested in MIC assays for antifungal activity in comparison with natGa-DFO. Additionally, PET/CT imaging of a rat pulmonary aspergillosis model was performed as well as biodistribution and in vivo stability tests.

Results:

Compounds showed high radiolabelling yields with sufficient purity, low protein binding and high stability in serum. Uptake assays resulted in high uptake in AFU. MIC assays showed moderate antifungal activity, but with limited SIT1 dependence. PET/CT imaging revealed favourable pharmacokinetics with rapid distribution and exclusive renal excretion pattern with high and pronounced accumulation in AFU infected lung tissue. Rapid metabolism releasing the carboplatin core from DFO was observed in vivo.

Conclusion:

Our work demonstrates the potential of carboplatin-DFO conjugates for image-guided therapeutic applications in fungal infections. Future work on these molecules aims to provide wider application towards antibacterial use.

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Ca^{2+} channelopathy-associated CACNA1D (Cav1.3) missense variants exert a C-terminal-mediated dominant effect on channel gating

Background: Ca2+-influx through Cav1.3 voltage-gated Ca2+ channels (encoded by CACNA1D) contributes to several physiological processes. Complete channel loss-of-function (LOF) leads to bradycardia and deafness, while gating-modifying de novo variants cause a neurodevelopmental disorder (NDD). In contrast to previous studies, we herein mimic the heterozygous patient background and functionally characterise co-expressed mutant and wild-type (WT) channels.

Methods: Whole-cell voltage-clamp recordings were performed on tsA201 cells transfected with C-terminally long/short wild-type (WTL/WTS) or mutant human Cav1.3 α1-subunit, β3, α2δ-1 and EGFP.

Results: Cells expressing the V1447L variant (alone/co-expressed with WTL) showed typical NDD-associated hyperpolarising shifts in the voltage dependence, revealing a dominant effect on co-expressed WTL. A376V, associated with clinical LOF, surprisingly showed robust Ca2+ currents with NDD-linked gating features, that were again preserved when co-expressed with WTL. Similarly, A749G, alone or co-expressed with WTL, showed comparable hyperpolarising shifts in the voltage dependence and faster inactivation kinetics. Interestingly, F747S displayed a dominant effect (hyperpolarized voltage-operation range, slower inactivation kinetics) when co-expressed with WTL, but not WTS. Finally, a C-terminally truncated variant, C1436X, gave no measurable currents. However, when co-expressed with WTL, but not WTS, it caused NDD-associated gating changes.

Discussion: Our data revealed a dominant effect on WTL channels for all tested pathogenic variants when present in full-length channel constructs (not the case for WTS). These results show that the CACNA1D variant-induced gating changes can be transferred to WTL channels in vitro, a mechanism that could contribute to the complexity of the associated phenotype(s) depending on the expression of C-terminal splice variants.

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Quantitative proteomics enables the detection of varying severity levels of congenital stationary night blindness type 2 mouse models

Pathogenic variants in the CACNA1F gene, which encodes Cav1.4 L-type calcium channels in the retina, alter visual signal transmission from photoreceptors to bipolar cells, leading to congenital stationary night blindness type 2 in humans. This study examines the impact of the Cav1.4 C-terminal truncation variant R1827X (RX) and compares its effects with the gain-of-function variant I756T (IT). Human electroretinograms (ERGs) indicate that the IT variant leads to a notably severe phenotype. In contrast, patients with the R1816X mutation experience photophobia that resolves over time, and they do not develop night blindness. Furthermore, their ERG results display typical electronegative responses. Our mouse studies confirmed that the IT variant causes a severe phenotype marked by retinal degeneration and impairments in both photopic and scotopic pathways. In contrast, the RX variant results in a milder phenotype that predominantly affects the rod pathway, with corresponding morphological and functional changes. As an additional investigation, we examined how the impact of different Cav1.4 variants on retinal function and structure is mirrored in the retinal proteome. To do so, we integrated advanced techniques as such as label-free quantitative proteomics. Our findings revealed that the variation in dysregulated proteins might play a significant role in determining the differences in disease severity, Although both variants impacted similar pathways, the IT variant uniquely altered pathways critical for the synaptic vesicle cycle and retinal degeneration, effects not observed in the RX variant. This discovery provides a potential mechanism for predicting the intensity of the disease in individual cases.

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Sustained hypo- and hyper-glycemia induces a shift in beta cell glycemic set point

Pancreatic islets, functioning as a 'micro-organ,' comprise diverse endocrine cell types that coordinate to regulate glucose homeostasis. The glycemic set point, representing the range of blood glucose levels maintained for optimal metabolic function, is critically regulated by β-cell activity. β-cells couple glucose metabolism to insulin secretion to facilitate glucose uptake and storage under hyperglycemic conditions. However, in chronic hyperglycemia, as seen in diabetes, β-cells fail to restore normoglycemia.

In this study, we utilized transgenic zebrafish expressing the genetically encoded calcium indicator, GCaMP6s under the control of a pan-endocrine promoter to investigate the effects of sustained exposure to low or high glucose on the β-cell glycemic set point. By perfusing a gradient of glucose concentrations ex vivo, we identified the threshold at which β-cells exhibit synchronous calcium activity, reflecting insulin secretion. Chronic glucose exposure induces a significant shift in this threshold - with prolonged hyperglycemia or hypoglycemia leading to disruptions in β-cell responses, impairing their ability to appropriately sense and regulate glucose levels. These findings highlight key features of metabolic disorders such as diabetes.

Our findings reveal that β-cell glycemic set point is dynamically regulated and susceptible to chronic metabolic stress, providing valuable insights into the mechanisms driving β-cell dysfunction in diabetes. Additionally, these results highlight the use of transgenic zebrafish as a model for investigating β-cell physiology and identify potential therapeutic targets for restoring glucose regulation in metabolic disorders.

Keywords: beta cells, insulin, glycemic set point, ex vivo calcium imaging

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Role of Stac2 adaptor protein on membrane excitability and hormone secretion of endocrine cells

Stac adaptor proteins (Stac1-Stac3) have recently been identified as novel regulators of L-type calcium channel (LTCC) expression and biophysical properties. While Stac3 isoform is almost exclusively expressed in skeletal muscle, Stac1 and Stac2 show a broad tissue distribution including neurons and endocrine cells. In heterologous expression systems and cultured hippocampal neurons Stac2 overexpression abolished LTCCs calcium dependent inactivation.
Here we set to investigate if genetic ablation of the endogenous Stac2 protein alters mouse chromaffin cells (MCCs) or pancreatic β-cells excitability and hormone release. In MCCs, constitutive deletion of Stac2 does not affect resting membrane potential or spontaneous firing frequency. However, the AP depolarization threshold was significantly reduced in Stac2-KO cells compared to WT. Additionally, step current injection elicited an electrical activity with higher initial AP firing frequency in Stac2-KO compared to WT that led to earlier depolarization block. Stac2 deletion did not alter whole-cell calcium currents amplitude or inactivation kinetics but significantly shifted the voltage-dependence of activation to more hyperpolarized potential. Surprisingly, despite the similar calcium current amplitude the cathecholamin vesicle exocytosis was significantly reduced. Similarly, in pancreatic β-cells, Stac2 deletion seems to cause a reduced glucose-induced insulin release without alterations of β-cell whole cell calcium influx or spontaneous glucose-induced electrical activity.

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Effect of FAHD1 knock out on the development of mouse embryonal fibroblast and cardiomyocytes

Impairments in the TCA cycle or electron transport chain (ETC) disrupt metabolism, affecting energy production and regulation. FAHD1, a key TCA cycle enzyme, regulates oxaloacetate levels. Its loss leads to oxaloacetate buildup, inhibiting succinate dehydrogenase and causing metabolic disruptions. Despite this, FAHD1 knockout (KO) mice survive by increasing mitochondria and shifting to glycolysis. My previous work showed FAHD1 KO MEFs adapting by redirecting oxaloacetate through alternative pathways when asparagine and glutamine were restricted.

Cardiomyocyte (CM) development involves a metabolic shift from glycolysis to fatty acid oxidation postnatally, linked with MYH7-to-MYH6 transition and structural maturation. Disruptions in this process contribute to cardiovascular diseases (CVDs), which revert to glycolysis and reduce oxidative phosphorylation. FAHD1 may be crucial in maintaining TCA cycle flux and supporting CM maturation.

Future research will investigate FAHD1's role in CM development and metabolic transitions. Metabolome analysis of FAHD1 KO CMs will assess whether they revert to glycolysis or remain immature. Additionally, myocardial infarction models in FAHD1 KO mice will determine if altered metabolism affects cardiac repair. A CM-specific FAHD1 KO model (MYH6-Cre-FAHD1) will help clarify whether observed phenotypes are cell-autonomous or systemically influenced.

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Elevated ROS and extracellular acidification rate in a human neural model of brain ageing

Ageing is a complex process causing functional decline and increased risk of age-related diseases, such as Alzheimer's (AD). However, studying human brain ageing in vitro remains challenging due to the inability of induced pluripotent stem cells (iPSCs) to retain age-related signatures. To overcome this, we previously developed GFP-T2A-PROG, an iPSC line enabling inducible and robust Progerin overexpression across different lineages. Progerin-overexpressing neural progenitor cells (NPCs) and neurons exhibit key ageing hallmarks, including significantly increased DNA damage, loss of heterochromatin (H3K9me3, HP1γ), and elevated p21+ senescent cells.

Here, we focus on mitochondrial dysfunction in this brain ageing model. Progerin overexpression induced a two-fold increase of reactive oxygen species (ROS) in aged NPCs. Notably, metabolic analysis revealed increased extracellular acidification rate (ECAR), suggesting a metabolic switch towards glycolysis in artificially aged NPCs. Similarly, in cortical organoids, besides a 40% reduction in heterochromatin and two-fold increase in DNA breaks (γH2Ax, p53BP1), Progerin induced a significant 1.5-fold increase in ROS. Transcriptome-wide analysis identified 1,366 differentially expressed genes, including downregulation of mitochondrial (OPA1, TOMM20) and synaptic genes (SYN1, CAMK4). These results align with data from post-mortem brain tissue of aged individuals and AD cases. Additionally, prolonged artificial ageing in organoids led to reduced mitochondrial respiration. Our findings highlight the critical role of mitochondrial dysfunction in human brain aging, revealing increased ROS, mitochondrial gene downregulation, and a metabolic shift toward glycolysis in artificially aged NPCs. Overall, our model provides a powerful tool for further investigating age-related brain metabolic alterations in vitro and developing novel therapeutic strategies.

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THE SCAFFOLD PROTEIN ERC1 MODULATES CAV1.1 CURRENTS AND SKELETAL MUSCLE EC COUPLING

ERC1 is a scaffold protein essential for active zone assembly and known to interact with the CaVβ subunit of voltage-gated Ca2+ channels (VGCCs). This interaction facilitates VGCC activity, as ERC1 deletion has been shown to reduce calcium influx in inhibitory synapses of the hippocampus, the calyx of Held, rod photoreceptors, and pancreatic β-cells. Given its endogenous expression in skeletal muscle, we hypothesized that ERC1 modulates the membrane and functional expression of CaV1.1, and voltage-induced Ca2+ release from the sarcoplasmic reticulum. Our findings confirm the presence of two ERC1 isoforms in skeletal muscle at the cDNA level: ERC1-long (1120 aa, isoform 201) and ERC1-short (368 aa, isoform 202). Patch-clamp recordings in HEK cells demonstrated that both ERC1 isoforms significantly enhance CaV1.1 current density by upregulating its functional expression. To investigate the physiological role of ERC1 in skeletal muscle, we overexpressed each isoform in myotubes and analyzed calcium currents alongside depolarization-induced cytoplasmic Ca2+ transients. Interestingly, overexpression of ERC1-long resulted in a significant reduction of CaV1.1 currents without affecting excitation-contraction (EC) coupling. In contrast, ERC1-short overexpression enhanced EC coupling without altering CaV1.1 currents.

To further investigate the isoform-specific contributions of ERC1 to EC coupling, we generated two novel CRISPR/Cas9-engineered skeletal muscle cell lines: one with selective deletion of ERC1-long and another lacking both isoforms. ERC1-long deletion significantly impaired EC coupling, an effect that could be rescued by reintroducing ERC1-long or overexpressing ERC1-short. Ongoing studies aim to characterize the consequences of total ERC1 knockout and determine its overall importance in skeletal muscle ECC.

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Deciphering Ca-channel interactomes using sequence covariations

Calcium channels are essential cellular components that regulate numerous physiological processes, yet a comprehensive understanding of their protein-protein interactions remains elusive. This research presents an innovative approach to identifying precise interaction points at the residue level between Ca-channel subunits by analyzing sequence co-variation patterns, leveraging the vast amount of genomic data now available through modern sequencing technologies. By examining evolutionary correlations across protein sequences, we can identify meaningful couplings between residues that indicate potential interaction points between proteins.

Our methodology employs advanced computational and statistical techniques to enhance coupling calculations, using well-characterized interactions between the main pore-forming subunit (α1) and auxiliary subunits α2δ and β as validation benchmarks. Through analysis of sequence data spanning billions of years of evolution, this computational approach complements traditional experimental methods by revealing both individual residue mutation probabilities and significant co-variations between proteins.

The research aims to resolve experimental inconsistencies and uncover novel interaction partners by going beyond static structural analysis to incorporate different protein states and competing binding interactions at the residue level. This comprehensive understanding of the Ca-channel interactome has important implications for both basic research and therapeutic development, particularly for channelopathies and calcium channel-related disorders.

This interdisciplinary approach promises to advance our understanding of calcium channel regulation and potentially identify new therapeutic targets for calcium channel-related pathologies.

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Developing Novel Approaches for Population-wide Fiber Tracing of Spiral Ganglion Neurons in the Auditory Periphery

Hearing relies on the transmission of sound pressure waves from the outer to the inner ear, where they are transformed to neuronal code. Here, spiral ganglion neurons (SGNs) in the cochlear periphery transmit this information from the primary afferent synapses with inner hair cells of the organ of Corti to the cochlear nucleus in the brainstem. However, holistic population-wide and subtype-specific morphological as well as molecular analyses of SGNs – from their peripheral inputs to their central projections – are lacking to date. This is mainly due to the extremely tight packing density of SGN fiber tracts, which renders conventional fiber tracing and analysis approaches largely inapplicable in the cochlea.

To address this issue, we evaluated two conceptually different methodologies: (i) a Brainbow approach for stochastic multicolor-labeling – and hence facilitated identification – of individual SGN fibers, and (ii) an expansion microscopy (ExM) protocol to physically expand the inner ear tissue and thus overcome the resolution problem.

First, in a proof-of-concept in vitro study, a single adeno-associated virus (AAV) of a Cre-dependent Brainbow-system was successfully used to express EYFP and TagBFP in organotypic organ of Corti explant cultures of Cre-expressing mice. Moreover, to expand the applicability of this approach, we tested simultaneous dual-AAV transduction with a second Cre-encoding AAV to allow directed multicolor labeling of wild-type SGNs.

Second, in a parallel stream of experiments, we evaluated and optimized previously established ExM protocols to achieve fourfold physical expansion of the intact SGN innervation and visualized these preparations using lightsheet fluorescence microscopy.

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From Sound to Movement: The Neural Backbone of the Acoustic Startle Reflex

The acoustic startle reflex (ASR) is a fast reactive body movement in response to a loud and unexpected auditory stimulus that has been observed in all mammalian species. In rats, large cochlear root neurons (CRNs) – located between auditory periphery and cochlear nucleus – have been identified as the first neural substrate of the underlying reflex circuit. CRNs receive auditory input from primary afferent spiral ganglion neurons (SGNs) and are subject to modulatory pathways descending from higher brain areas. Their axons mainly target neurons of the contralateral pontine reticular nucleus (PnC) formation, which project onto cranial and spinal motor neurons and are in turn subject to extensive modulatory inputs from various cell types located in higher brain areas. Despite their central role in a reflex circuit directly implicated with individual survival, CRNs are still remarkably poorly characterized in regard to their cellular excitability and activity patterns as well as their molecular composition and morphology in situ. In an attempt to spatially map the entire population of CRNs, we combine immunofluorescent labeling with whole cochlea tissue clearing and 3D reconstructions. Furthermore, we employ various genetic reporter and knockout mouse models alongside neuronal tracer dyes to characterize the afferent input pattern of SGNs and assess their cellular morphology as well as connectivity. Finally, we seek to complement these histological datasets with functional analyses. In this way, we hope to further the understanding of the primary neural base of the ASR, building the base for further investigations in different mammalian species, including humans.

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Analysing SARS-CoV-2 cross-neutralizing antibodies after different history of exposure to SARS-CoV-2

Since the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, the diversity of virus variants steadily increases. Many of these have a large number of mutations, particularly in the spike protein, some of which exhibit an increased immune evasion. Previous exposure histories influence neutralization patterns after exposure to distant variants via immune imprinting. As breadth of neutralization may be influenced by the nature of the exposed variants, we compared neutralization patterns in samples after exactly two exposures: two similar (twice vaccinated or pre-Omicron infected and vaccinated) or two antigenically distinct SARS-CoV-2 variants (pre-Omicron + Omicron or two different Omicron variants). We determined IC50 titers via neutralization assays against different variants, including a range from pre-Omicron to recent Omicron variants and generated antibody landscapes. Using antibody depletion experiments we analyzed whether the second exposure predominantly expanded cross-reactive antibodies or whether a de novo response against the second variant was generated. Exposure to two antigenic distant variants increased the neutralization breadth and flattened antibody landscapes. However, no significant cross-neutralization against the genetically closely related human coronavirus SARS-CoV was induced. Moreover, we revealed that there is only a limited de novo production of antibodies against the later exposed variant and the second exposure rather back boosts previous variants and expands existing cross-neutralizing antibodies. Overall, our results indicate that multiple exposures to SARS-CoV-2 broadens the induced neutralization pattern, but does not significantly induce cross-neutralization to other human coronaviruses and that the first exposed variant strongly influenced the specificity of antibodies.

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Oxford Nanopore sequencing to identify tissue-specific AAV vectors in normothermic organ perfusion models

Oxford Nanopore sequencing has revolutionized contemporary modern molecular virology by enabling unbiased direct, real-time sequencing of native DNA or RNA molecules. This long read sequencing devices allow the capture of the full-length genomes and epigenetic modifications, thereby advancing our understanding of viral diversity, evolution, and pathogenesis. Moreover, in optimization and development of viral vectors, such as adeno-associated viruses (AAV) and lentiviruses, this technology represents a highly valuable molecular tool.

Viral vector systems, often engineered from adenoviruses, adeno-associated viruses, herpes simplex viruses and lentiviruses represent highly efficient tools for gene delivery. Their efficacy is largely attributed to their natural ability to infect cells, facilitate the transfer of genetic material, and enables the precise manipulation of genomes. The non-pathogenic AAV belongs to the Parvoviridae family and has a single stranded DNA-genome enclosed in a protein capsid. Engineered rAAV vectors are ideal for gene therapy due to their low immunogenicity, high tolerance, stringent safety standards, and ability to ensure long-term expression of the gene-of-interest (GOI). Normothermic machine perfusion (NMP) enables ex situ organ preservation for prolonged periods of time under close-to physiological conditions. Further to detailed evaluation of the organ quality and function, it facilitates organ treatment and reconditioning.

Thus, this system offers a unique opportunity to conduct AAV vector evolution directly within the human system, circumventing and avoiding biases obtained by using animal models. Highly efficient rAAV clones specific for organ tissues, identified by nanopore sequencing and bioinformatic pipelines out of larger rAAV vector libraries.

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The Role of Complement in Dendritic Cell Activation during SARS CoV 2 Infection

Background: Early detection of SARS-CoV-2 by the innate immune system is crucial for host defense. Dendritic cells (DCs) and the complement system are key components of this response.

Methods: We investigated the complement opsonization of SARS-CoV-2 wild type (WT), Delta, and Omicron variants and their interactions with DCs. Following stimulation with complement-opsonized virus, we analyzed viral binding, internalization, and post-entry mechanisms using confocal microscopy, mass spectrometry, examining DC maturation and cytokine secretion.

Results: SARS-CoV-2 opsonized with human sera showed C3 deposition, unlike virus exposed to saliva or mucus. Complement-opsonized virus demonstrated significantly higher DC binding and internalization compared to non- or immunoglobulin-opsonized forms. Immunofluorescence confirmed enhanced uptake via co-localization of viral particles with C3 fragments and complement receptor 4 (CR4). Complement-opsonized WT virus induced DC activation, while Delta and Omicron variants did not elicit a similar response.

Conclusion: Complement opsonization significantly enhances DC uptake and processing of SARS-CoV-2, particularly the WT virus, facilitating better antigen presentation. In contrast, variants of concern diminish or evade this interaction, potentially compromising immune activation. These findings underscore the complement system's critical role in shaping innate and adaptive immune responses to SARS-CoV-2.

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Analysis of Cross-Neutralizing Antibodies Induced by HPV Single-Genotype Immunization of BALB/c Mice

Human papilloma virus (HPV) persistent infections with high-risk genotypes such as 16 or 18 can eventually cause cancer. In the past years, preventive vaccines were approved including up to 7 oncogenic types (16, 18, 31, 33, 45, 52, 58). The vaccines induce high titers of neutralizing antibodies against the included genotypes, efficiently preventing infections and consequent tumor development. However, little is known about cross-neutralization of genotypes not included in the vaccines. HPV infections start at young ages and its high prevalence make analysis of cross-neutralization intricate. To overcome this limitation, we immunized BALB/c mice with single HPV genotype pseudoviruses.

BALB/c mice were immunized with a single HPV genotype pseudovirus for 9 genotypes in total. Neutralizing antibody titers against the immunized types were induced already after prime immunization and reached very high titers after boosting. Cross-neutralizing titers were induced only for a few genotypes and were generally a few orders of magnitude lower than against the immunized type.

The implemented HPV vaccines provide a robust protection against infection with included genotypes already with antibody titers close to the detection limit, impeding the estimation of a protective titer. Cross-neutralization titers of other genotypes could only be observed with titers that exceed those achieved in natural infections and a multivalent vaccine will always yield lower titers compared to immunization with a single-type. Nevertheless, a considerate choice of genotypes holding into account the cross-neutralization at high titers could ameliorate the general antibody response and protect against oncogenic genotypes not yet covered by the vaccines.

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Bone Quality in Focus: Cement Augmentation in Degenerative Thoracolumbar Spondylodesis

Introduction: Instrumentation of the thoracolumbar spine remains a cornerstone in treating degenerative spinal diseases. With an aging patient population and associated comorbidities, low bone quality is becoming increasingly significant. Cement augmentation is routinely used to improve screw fixation, but it also carries risks and potential complications with severe consequences for patients.

Methods: This retrospective study included patients who underwent thoracolumbar spondylodesis at our center between 2015-2022. Demographic data, medication use, comorbidities, CT bone density, and intraoperative data were recorded. Patients with incomplete data were excluded.

Results: A total of 195 patients (111 female, 84 male) with an average age of 60 years (interquartile range [IQR] 50–71) were included in the study. During surgery, 14 patients (7.2%) received cement augmentation. Significant factors associated with an increased likelihood of cement augmentation included pre-diagnosed osteoporosis ($p=0.001$), Parkinson's disease ($p=0.05$), prior vertebral fracture ($p=0.001$), known use of osteoporosis-inducing medications ($p=0.024$), and known anti-osteoporotic therapy ($p<0.001$). The average CT-measured bone quality for patients with augmentation was 94 ± 30 Hounsfield units compared to 125 ± 45 for patients without augmentation ($p=0.014$). No intraoperative complications occurred during cement augmentations.

Conclusion: Our retrospective study identifies several significant factors associated with the use of cement augmentation in thoracolumbar spinal fusions. Patients with lower CT bone quality and/or pre-diagnosed osteoporosis, Parkinson's disease, and prior vertebral fractures may have an increased risk of screw loosening, supporting the indication for cement augmentation. Clearer guidelines based on these factors could help optimize clinical outcomes and minimize potential complications.

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Soluble Neprilysin in ST-Elevation Myocardial Infarction: a sex-based analysis

Objective:

In patients with heart failure and reduced ejection fraction (HFrEF), neprilysin has shown to be able to independently predict the occurence of future cardiovascular events. Furthermore, angiotensin-receptor-neprilysin inhibitors have become an integral part of the pharmacological treatment regimen in patients with HFrEF. However, little is known about the role of neprilysin in patients with myocardial infarction. This study was aimed at analysing sex-based differences regarding plasma levels of soluble neprilysin and clinical characteristics in patients with ST-Elevation Myocardial Infarction (STEMI).

Methods:

This study included STEMI patients which were treated with primary percutaneous coronary intervention (pPCI) at the University Hospital Innsbruck between 2012-2023. Infarct size (IS) and left ventricular ejection fraction (LVEF) where measured by cardiac magnetic resonance (CMR) imaging within a week after the event, using a standardized protocol. Neprilysin levels were measured 48 hours after the index event using a validated immunoassay.

Results:

A total of 559 patients (19% female) with a median age of 58 (IQR 52-67) years were analyzed. Plasma levels of soluble neprilysin showed no significant difference between male and female patients (p= 0,465). IS and LVEF after the event did also not show any sex-related differences (p=0,800; p=0,768). Female patients were shown to be significantly older (p=0,001), and suffered significantly more often from diabetes and hypertension (p=0,027; p=0,001)

Conclusion:

In this population no sex-related difference in plasma levels of soluble neprilysin could be observed. Despite differences in baseline patient characteristics, no sex-related differences in myocardial damage, measured by CMR, could be demonstrated.

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The Role of the Immune System and Trained Immunity in Calcific Aortic Valve Disease

Calcific aortic stenosis (AS) is a leading cause of valvular heart disease, with risk factors including age, sex, hypercholesterolemia, diabetes, and hypertension. Calcific aortic valve disease (CAVD) leads to progressive thickening and calcification of the aortic valve, impairing blood flow. Once considered passive degeneration, CAVD is now recognized as an active inflammatory process with no pharmacological treatment available.

Chronic inflammation is a key driver of CAVD. Endothelial injury activates valve interstitial cells (VICs) and macrophages, leading to fibrosis and calcification. Damage-associated molecular patterns (DAMPs), such as oxidized low-density lipoprotein (oxLDL) and biglycan, activate Toll-like receptors (TLRs), promoting pro-inflammatory cytokine release and osteogenic pathway activation.

Recent research highlights the involvement of trained immunity in atherosclerosis, a closely related vascular pathology. Trained immunity refers to the epigenetic and metabolic reprogramming of innate immune cells, particularly monocytes and macrophages, following exposure to inflammatory stimuli such as oxLDL. This results in an exaggerated immune response upon subsequent challenges, contributing to chronic inflammation and tissue remodelling. Given the similarities between atherosclerosis and CAVD, trained immunity may play a critical role in the pathogenesis of aortic valve calcification

This PhD project aims to investigate the immune system's role in CAVD, focusing on trained immunity as a potential contributor. Understanding these mechanisms may lead to novel biomarkers for early detection and therapeutic targets to prevent or slow disease progression.

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Der Einfluss von HSD17B13-, PNPLA3- und TM6SF2- Spender- und Empfänger:innen-Genotyp auf Fibrose, Steatose und Überleben nach Lebertransplantation

Hintergrund:
Der Zusammenhang zwischen bestimmten genetischen Varianten und der Schwere einer Metabolischen Fettlebererkrankung (MASLD) ist gut etabliert. Ziel unserer Studie war es, den Einfluss dieser genetischen Varianten auf das Outcome nach Lebertransplantation zu untersuchen.

Methodik:
In dieser monozentrischen retrospektiven Studie wurden erwachsene Patient:innen, die zwischen 2000 und 2019 eine Lebertransplantation erhalten hatten, sowie ihre jeweiligen Spender:innen auf bestimmte Risikovarianten von PNPLA3, HSD17B13 und TM6SF2 untersucht.

Ergbenisse:
In unserer Kohorte von 435 transplantierten Patient:innen entwickelten 34% nach der Transplantation eine Steatose (mittlere Nachbeobachtungszeit: 8 Jahre). Die Risikovarianten von PNPLA3 und TM6SF2 waren unter den Lebertransplantationsempfänger:innen häufiger als bei ihren jeweiligen Spender:innen (62% vs. 43% für PNPLA3, $p < 0.001$; 19% vs. 10% für TM6SF2, $p < 0.001$). Im Gegensatz dazu war das protektive G-Allel an Position rs6834314 des HSD17B13-Gens häufiger bei den Spender:innen als bei den Empfänger:innen zu finden (47% vs. 37%, $p = 0.006$). In einer Subgruppe von 392 Individuen, die zusätzlich für rs72613567 in HSD17B13 genotypisiert wurden, zeigte sich eine starke Kopplungsungleichgewicht zwischen beiden HSD17B13-Varianten ($D' = 0.94$, $r^2 = 0.87$, $p < 0.001$). Ein kombinierter Risikoscore aus PNPLA3, TM6SF2 und HSD17B13 zeigte höhere Raten von Posttransplant-Steatose mit höheren Scores, jedoch ohne statistische Signifikanz (27,5% mit 0–1 Punkten, 31,7% mit 2 Punkten, 36,8% mit 3 Punkten und 39,2% mit 4–6 Punkten, $p = 0.470$). Über den Langzeitverlauf waren die FIB-4-Scores signifikant niedriger bei Patienten, die homozygot für die protektive Variante von HSD17B13 waren.

Conclusion:
Bestimmte Varianten von PNPLA3, TM6SF2 und HSD17B13 beeinflussen spezifische Risiken nach einer Lebertransplantation.

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Biomechanical Analysis of Gender Differences in Subaxial Cervical Spine Fixation

Introduction: Anatomical differences between male and female cervical spines, such as vertebral body size and bone density, could potentially influence the stability of subaxial cervical instrumentation. This study evaluates whether gender impacts the biomechanical performance of lateral mass screws (LMS) and pars interarticularis screws (PIS) in cervical spine fixation.

Materials and Methods: Fourteen human cervical spine specimens (equal male/female distribution) underwent baseline biomechanical analysis before a two-level corpectomy (C5–C6). Ventrodorsal instrumentation was performed using either LMS or PIS from C4 to C6, with pedicle screws in C7. Flexibility testing was performed using a 3D motion analysis system, followed by pullout tests to assess screw anchorage.

Results: Both techniques provided comparable stability across all tested motion planes. Pullout testing showed no significant differences in screw anchorage between male and female specimens, indicating that fixation strength was independent of gender (ranging from $p=0.09$ to $p=0.9$).

Conclusion: The biomechanical stability of subaxial cervical instrumentation is not influenced by gender. Both LMS and PIS offer reliable fixation regardless of anatomical differences, supporting their use in a wide patient population. Further research may explore additional factors influencing screw performance in clinical settings.

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CT or MRI Before Thrombectomy - Predicting Infarct Progression, Recanalization Success, and Functional Outcome

Stroke is the second leading cause of death and the third leading cause of disability worldwide. Over 80% of strokes are ischemic, and prognosis depends strongly on the timing of intervention. With approximately 1.8 million neurons lost per minute, the principle of "time is brain" underscores the urgency of rapid diagnosis and treatment. Stroke imaging plays a critical role in assessing brain tissue damage and guiding treatment decisions.

This study hypothesizes that patients who undergo MR-based imaging prior to thrombectomy will experience better clinical outcomes (mRS after three months) and minimal stroke progression on imaging compared to patients who receive CT-based imaging.

A retrospective cohort study will be conducted, dividing patients into two groups: CT prior to thrombectomy and MR prior to thrombectomy. The primary outcomes will include stroke progression assessed via imaging (volumetric analysis and ASPECTS score), recanalization rate (TICI score) and functional outcomes measured by the mRS score three months post-thrombectomy. Secondary outcomes include mortality rate and symptomatic intracranial bleeding.

Inclusion criteria will encompass adults over 18 years old who suffer ischemic stroke, have imaging (CT or MRI) available, and follow-up data for mRS at three months. Pair-matching will be performed based on baseline characteristics such as age, sex, comorbidities, stroke risk factors, stroke location, and admission scores (NIHSS/mRS).

Subanalysis will focus on the impact of the 2015 thrombectomy guideline changes on imaging modality and outcomes, as well as the effect of imaging choice on “door-to-groin” time. This aims to evaluate the relationship between imaging and thrombectomy efficiency.

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Bone health in chronic liver disease: The impact of polygenic risk scores

Introduction:

Hepatic osteodystrophy is a metabolic bone condition associated with advanced chronic liver disease, characterized by reduced bone mineral density (BMD). Since BMD is determined by genetic factors, several polygenic scores (PGS) have been developed and validated.

Aim:

This study aimed to determine how BMD is affected by sex, age, severity of cirrhosis and PGS, in a cohort of patients listed for liver transplantation.

Methods:

In this retrospective analysis, dual-energy X-ray absorptiometry (DEXA) measurements of lumbar spine (L1-L4) were reviewed for patients listed for liver transplantation between 2005 and 2021. DNA from patients was analyzed using the Global-Screening-Array version 3.0 (Illumina), and PGS for low BMD were computed.

Results:

The study included 231 patients (24% females) with a median age of 59 (52; 64) years. The mean T-score was -0.76 (-4.7; 4.5) and the prevalence of T-score of less than -2.5 was 11% (26/231). BMD was significantly higher in man (57,57 vs. 53,64, $p<0.001$). No association between liver disease severity or etiology with T-score was found. Patients in the low BMD group of T-score less than -2.5 did not differ in age, markers of mineral metabolism or in any of the PGS predictive of osteoporosis. In patients with hepatocellular cancer, a significantly higher T-score was found.

Conclusion:

Established PGS did not effectively predict low BMD in this patient population. Higher T-score in patient with HCC may be attributed to less severe liver disease in HCC patients compared to those with decompensated cirrhosis.

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Gender Specific Differences in Early Stage Non-Small-Cell Lung Cancer

Introduction: The aim of this study is to evaluate gender specific differences in early stage of NSCLC in our cohort in Innsbruck.

Methods: 90 patients (53.3% women, 46.6 % men) who were diagnosed with NSCLC (UICC stadium IA – IIIA) and underwent surgery in Innsbruck between 2015 and 2019 were included. Samples of patients (plasma, serum, tumor tissue) where stored at baseline before surgery. Cox regression, spearman correlation and Mann-Whitney U tests were used for the statistical analysis.

Results: Women were diagnosed with cancer at a significantly younger age than were men (median age at diagnosis: 65.0 (range: 51.0 – 84.0) vs. 70.5 (55.0 – 88.0) p=0.030). Although more women were heavy smokers (69.8 % vs. 59.5 %), men presented with higher pack year rates (mean: 35.1 (95% Kofindenzintervall (CI): 26.5-43.6) vs. 45.2 (95% CI: 36.8-53.7), p= 0.020). Furthermore, men presented with a higher T score (tumor size) (p=0. 021). No differences between recurrence free survival or overall survival were observed. No other clinical or pathological differences between women and men were observed.

Discussion: Analysis of our early stage NSCLC cohort shows that women get diagnosed at a younger age. One possible conclusion is the higher rate of driver mutations described in the literature in women. A second conclusion is that as women in our cohort present with smaller tumor sizes and thereby representing the earlier detection of lung cancer in women.

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SEX DIFFERENCES IN THE DYNAMICS OF LIPOPROTEIN(A) FOLLOWING HIGH-RISK TRANSIENT ISCHEMIC ATTACK (TIA) OR ISCHEMIC STROKE: INSIGHTS FROM STROKECARD REGISTRY STUDY

Background and Aim: Lipoprotein(a) [Lp(a)] is an inherited, independent driver for cardiovascular disease. Sex-specific differences in the dynamics of Lp(a) levels post-stroke remain poorly understood. This study aimed to investigate changes in Lp(a) over time in female and male patients with high-risk transient ischemic attack (TIA, ABCD2-score≥4) or ischemic stroke.

Methods: Data were collected from 1,485 patients (515 females, 909 males) enrolled in the STROKE - CARD Registry (2020–2024). Lp(a) levels were measured at baseline (<24 hours post-indexevent, a1), 3 months (a2) and 12 months (a3) after stroke using a particle-enhanced immunoturbidimetric assay. In 833 (291 females, 542 males) patients, the Lp(a) concentration was determined at all three time points (a1, a2 and a3). Sex differences in Lp(a) dynamics were analyzed using a mixed-effects model to account for repeated measurements, and differences in changes (Δ1: a2-a1, Δ2: a3-a2, Δ3: a3-a1) were tested using Wilcoxon rank-sum tests.

Results: Over the 12-month follow-up males had significantly lower Lp(a) levels compared to females (β=-13.37, p=0.027), accounting for the effect of time. Temporal changes in Lp(a) differed between sex with Δ3(a3-a1) showing a significant difference (p=0.019). Females demonstrated a larger overall increase in Lp(a) levels over the study period compared to males while no significant differences were observed for Δ1 (p=0.15) or Δ2 (p=0.50).

Conclusions: Women are known to have higher Lp(a) levels than men. This study demonstrates that not only are Lp(a) concentrations higher in women, but they also experience greater changes in Lp(a) levels over time after a stroke.

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Unraveling Adipocyte Differentiation in Ether Lipid Deficiency Models

Ether lipids are glycerophospholipids where the hydrocarbon chain at sn-1 position of glycerol backbone is attached by an ether bond. They comprise two subclasses: the plasmanyl lipids with saturated ether bonds and the plasmenyl lipids, also known as plasmalogens, which are characterized by a vinyl ether double bond. Ether lipids play an important cellular role in membrane structure and architecture. The glyceronephosphate O-acyltransferase (GNPAT) enzyme starts the biosynthesis of ether lipids in peroxisomes, and it is completed in the endoplasmic reticulum where plasmanylethanolamine desaturase (PEDS1) introduces the characteristic vinyl ether double bond in plasmalogens. Recently, the gene coding for PEDS1 was described in our lab. Mutations in the initial enzymes involved in ether lipid metabolism lead to rare inherited disorders such as Rhizomelic Chondrodysplasia Punctata (RCDP) and Zellweger spectrum disorders. Affected patients suffer from severe clinical manifestations, including growth retardation. A similar phenotype was observed also in mice with impaired ether lipid metabolism.
To assess the body fat and water distribution both knockout mouse models were subjected to Dixon-MRI and differences in water content were found. Current work focuses on implementing an adipocyte differentiation protocol of primary preadipocytes with PEDS1 and GNPAT deficiency, to uncover whether ether lipids are necessary for this process and whether selective plasmalogen deficiency similarly affects it to the same extent as total ether lipid deficiency. We will investigate gene and protein expression, and evaluate lipid droplet formation. Together, these findings will contribute to a better understanding of whether ether lipid metabolism affects adipocyte function.

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KIDZ PAZ-NOWn_über die Kunst Jugend, Forschung und Gesellschaft zusammenbringen

Hintergrund: Im Rahmen eines innovativen Schulprojekts arbeiten rund 70 Schüler*innen während eines Schuljahres an der kreativen und wissenschaftlichen Auseinandersetzung mit Resilienz und deren Stärkung in Bezug auf Klimawandel und nachhaltige Entwicklung.

Ziel: Durch eine Kombination aus Exkursionen ins westalpine Hochgebirge, Workshops zu Themen wie Hydroklimatologie und mentaler Gesundheit sowie einem kreativen Schaffensprozess wird die Selbstwirksamkeit der Jugendlichen gefördert. Ziel ist es, gesellschaftlich relevante Exponate für eine Ausstellung zu gestalten, die abstrakte Konzepte wie Flexibilität, Widerstandsfähigkeit und Anpassungsfähigkeit anschaulich und interaktiv vermitteln.

Methoden: Die Exponate basieren auf Arbeiten der Schüler*Innen, die in den Workshops entstanden sind, sowie auf wissenschaftlichen Modellen und Daten, die vom Projektteam KIDZ PAZ-NOWn berechnet und ausgewertet wurden. Die fünf thematischen Wände – „Flexibilität & Kreativität", „Widerstandsfähigkeit & Gesundheit", „Anpassungsfähigkeit & Klima", „Unverwüstlichkeit & Wasser" sowie „Standhaftigkeit & Wald" – präsentieren die Ergebnisse in einem innovativen Ausstellungsdesign.

Ergebnisse: Die Ausstellung im Alpinarium Galtür verbindet Geschichte, Gegenwart und Zukunft des alpinen Lebens im Kontext Klimawandel mit den Erkenntnissen der Schüler*innen und bietet ihnen eine Plattform, ihre Stimme in die gesellschaftliche Diskussion um Resilienz und Klimawandel einzubringen. Mit der finanziellen Unterstützung der ÖAW zeigt dieses Projekt, wie Bildung, Wissenschaft und Kunst für eine nachhaltige Zukunft zusammenwirken können. Die Ausstellung ist noch bis 21.04.25 im Alpinarium in Galtür für die Öffentlichkeit zugänglich.

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Age-Dependent Inflammatory Response During Normothermic Machine Perfusion of the Liver: Potential Implications for an Aging Donor Pool

Background: As populations age, the mean age of liver donors increases. While age impacts transplantation outcomes, its influence on inflammatory responses during normothermic machine perfusion (NMP) remains unclear.

Methods: Blood samples from 30 donor livers undergoing NMP were collected at perfusion start and after 6 hours. Pro-inflammatory (IL-1β, IL-6, IL-8, TNF-α) and anti-inflammatory (IL-10) cytokine levels were measured by ELISA and correlated with donor age.

Results: Significant correlations emerged between donor age and pro-inflammatory cytokine levels (IL-1β, IL-6, IL-8, TNF-α) after 6 hours of NMP, while IL-10 showed no age-dependent correlation. These findings suggest enhanced susceptibility to ischemia-reperfusion injury in older donor livers, potentially reflecting a dysregulated senescent immune response.

Conclusions: Our study demonstrates age-dependent increases in pro-inflammatory cytokine expression during NMP. Given demographic trends toward older donor populations, these findings highlight opportunities for NMP-based anti-inflammatory interventions to modulate age-associated inflammatory responses and potentially improve outcomes in recipients of older donor livers.

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Preliminary results from ex-vivo application of von Willebrand factor concentrate on complement system and contact pathway in critically ill patients under extracorporeal support devices with or without sepsis

Critically ill patients, particularly those requiring extracorporeal membrane oxygenation (ECMO) or other mechanical circulatory support (MCS) devices, face a heightened risk of bleeding & thrombosis.

This study investigates the effects of ex-vivo application of von Willebrand factor (vWF) concentrate on clot stability, complement system activation, and contact pathway activation in critically ill patients with and without sepsis under ECMO support. The research aims to address the acquired vWF deficiency caused by mechanical and enzymatic proteolysis of high-molecular-weight (HMW) vWF multimers due to shear stress within centrifugal pumps, which contributes to coagulopathies in these patients.

Blood samples were collected from ECMO patients at three time points (pre-, during, and post-ECMO) and analyzed for coagulation parameters, platelet function, HMW vWF multimers, and clot structure. The study includes three cohorts: healthy controls (n=20), ECMO patients without sepsis (n=16), and ECMO patients with sepsis or COVID-19 sepsis (n=16). Preliminary results from a small subset of patients (n=3 ECMO, n=5 healthy) indicate reduced platelet counts and aggregation in ECMO patients, with a trend toward improved clot formation after vWF supplementation. Viscoelastic testing revealed increased clot firmness in septic patients, consistent with a procoagulant response to infection.

Despite limitations due to budget constraints and recruitment challenges, early findings suggest that vWF supplementation may mitigate coagulation dysfunction in ECMO patients. Further analysis of complement system and contact pathway interactions is pending. This study highlights the complex interplay of coagulation, inflammation, and mechanical stress in critically ill patients and underscores the need for targeted therapeutic strategies to improve outcomes.

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Gender Differences in Weather Sensitivity regarding Severe Device-Detected Sleep Apnea in Cardiac Pacemaker Patients

Sleep apnea (SA) is a prevalent condition associated with increased cardiovascular risk and neurological disorders. Weather factors like temperature or humidity significantly influence the occurrence of severe device-detected SA (DDSA) in cardiac pacemaker patients.

The ACaSA trial is a prospective cohort study that monitored 233 patients with MicroPort® pacemakers, recording DDSA events via transthoracic impedance. DDSA was defined as a respiratory disturbance index (RDI) ≥ 20 events per hour. Meteorological data were linked to the patients' residences. A generalized linear mixed-effects model was employed to analyze the relationship between weather variables and DDSA incidence.

Data from 210 patients (36.7% female) over 74,031 patient-nights were analyzed. Males experienced DDSA in 32.0% of nights, while females experienced DDSA in 7.5% of nights (aOR: 0.18; 95%-CI: 0.09-0.39; $p<0.001$). Whereas higher maximum diurnal temperatures were associated with increased risk of suffering from severe DDSA in the overall patient cohort, subgroup-analysis showed a more pronounced effect of temperature in women ($p=0.006$) and patients under 75 years of age ($p=0.041$). As with temperature, associations with humidity were numerically more pronounced in patients below the age of 75 years ($p=0.058$) or in women ($p=0.112$).

Subgroup-analysis of the ACaSA-study identified gender-specific effects, with women under 75 showing a greater propensity for severe DDSA under warmer conditions. This observation aligns with existing evidence suggesting that women may be more susceptible to environmental exposures.

Further research is warranted to explore these associations and inform preventive strategies in vulnerable populations.

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Structured pelvic MRI assessment using the #ENZIAN score as a tool to minimize the gender health gap: how to optimize diagnosis and pre-surgical planning of endometriosis

The gender health gap relates to the lack of healthcare equity for women and men and can take shape in many ways, from access to medical care to research. Endometriosis, referred to as the "missed disease", is an underdiagnosed, still poorly understood condition that often leads to a major diagnostic delay (up to 10.4 years in Austria) and clearly highlights the gender health gap.

Defined as the presence of endometrium-like tissue outside the uterine cavity, Endometriosis is a common cause of chronic pain and infertility that affects 190 million people worldwide and 10-15% of women of reproductive age. Despite of its high prevalence, its etiology remains controversial and its lesions can manifest at several locations. This leads to a highly heterogeneous clinical presentation, with poor association between symptoms and disease-severity .

Surgical visualization with histopathological correlation is still considered the diagnostic gold standard of endometriosis. In an attempt to improve diagnosis, several non-invasive tests have been suggested, including laboratory markers and pelvic imaging. Currently, the most frequently employed diagnostic imaging modalities in endometriosis are TVUS (as a first-line imaging technique) and MRI. MRI is increasingly performed as a second-line investigation in suspected complex cases of endometriosis and to optimize surgical planning.

In an attempt to evaluate the diagnostic accuracy of pelvic endometriosis MRI, we retrospectively evaluated the results of structured and unstructured MRI analysis vs. surgical/histopathological findings (as a gold standard) using the #ENZIAN score in 83 patients with histopathologically confirmed endometriosis who received a preoperative pelvic MRI between 2018-2022.

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Delayed orthostatic hypotension in Parkinson's disease: Sex and gender differences

Background: Delayed orthostatic hypotension (DOH) may represent a specific cause of orthostatic intolerance in individuals with Parkinson's disease (PD). Nonetheless sex and gender differences in the frequency and clinical impact of dOH in PD have not been directly addressed yet.

Objective: Here we aim at assessing the differences in dOH prevalence and its associated features in men and women with PD.

Methods: We retrospectively studied 213 individuals with PD and history of syncope or orthostatic intolerance referred for tilt-table testing to the Innsbruck dysautonomia center and explored whether dOH is associated with any specific clinical-demographic characteristic, including recent history of falls and syncope. Results: Seventy-five women [72 (69; 76) years of age; 6 (3; 10) years of disease duration] and 118 men [73 (69; 76) years of age; 6 (3; 10) years of disease duration] with PD were included. DOH occurred with the same frequency in men and women (18%; p=0.950). Nonetheless upon prolonged head-up tilt, men showed a more pronounced fall in systolic (p=0.037) and diastolic blood pressure (BP; p=0.027) when compared to women. We found no association between dOH and a history of falls or syncope in either men or women.

Conclusions: Men and women with PD have the same risk of developing dOH, which is mainly driven by the BP fall. However, such progressive fall in BP appears to be more pronounced and severe in men than in women.

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Simulation-Based Training as a Tool for Bridging Gender Gaps in Endovascular Surgical Education

Introduction:

Gender disparities in surgical education persist, impacting trainee experiences and career trajectories. While female representation in surgery has increased, women often face challenges such as reduced operative autonomy and limited mentorship opportunities. Simulation-based training may help mitigate these disparities. This study aimed to examine gender differences in preferences and validity ratings for endovascular training models, including flexible and stiff 3D-printed models and a digital simulator.

Methods:

This study included 32 participants (16 females, 16 males) with varying levels of experience in endovascular interventions. Each participant performed standardized tasks in all three models. Participants assessed face validity (anatomical fidelity and realism), construct validity (usefulness and satisfaction), and concurrent validity (model preferences) through a structured questionnaire. Statistical analyses included Mann-Whitney U tests, Kruskal-Wallis tests, and Chi-Square tests to evaluate gender differences.

Results:

No significant gender differences were found in face validity or concurrent validity preferences. However, females consistently rated construct validity higher across all models (Flexible 3D: $p=0.039$, Stiff 3D: $p<0.001$, Digital: $p=0.01$). Male participants were more frequently represented in higher procedural exposure categories (50–100 and >100 interventions), while females were predominantly in the 20–50 range ($p=0.015$). Both genders expressed strong support for regular training, typically once per quarter.

Conclusion:

This study highlights significant gender disparities in procedural exposure and construct validity ratings, Addressing these disparities requires equitable access to training, simulation-based training programs, and mentorship initiatives to support an inclusive learning environment for all trainees.

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Sex and age-specific expression of inflammatory markers in the pediatric emergency department: a retrospective analysis

Background: Inflammatory biomarkers such as interleukin-6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP) are widely used for clinical diagnostics in the pediatric emergency setting. However, the impact of age, biological sex and pubertal development on these markers remains insufficiently studied.

Objective: This study aimed to describe age- and sex-specific differences in IL-6, PCT, and CRP levels in pre- and postpubertal children presenting to a pediatric emergency department.

Methods: We conducted a retrospective, monocentric study at the Innsbruck University Hospital, analyzing data from 13,397 patients (17,662 visits) between 2015 and 2023. Patients were stratified into a prepubertal (<8 years) and postpubertal (>14 years) group to indirectly assess the influence of pubertal developement. Inflammatory markers were correlated with clinical parameters including triage categories and admission data.

Results: Significant differences in inflammatory markers were observed between different age groups. Prepubertal children exhibited higher IL-6 levels than postpubertal patients ($p<0.001$). Sex differences were notable in postpubertal patients, with males showing higher IL-6 ($p=0.022$), PCT ($p<0.001$), and CRP ($p=0.015$) levels compared to females. Prepubertal sex differences were limited to CRP levels. Hospital admission rates were higher among postpubertal females, though other clinical outcome parameters showed no sex-specific differences.

Conclusion: Age-related differences in inflammatory markers were more pronounced than sex-specific variations. Further research is required to understand the clinical significance of these findings, particularly the role of sex hormones in the postpubertal inflammatory response.

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Age-Related Outcomes in CMR Versus CT-Guided TAVR: A Secondary Analysis of a Randomized Clinical Trial

Background and Aim: Transcatheter aortic valve replacement (TAVR) is the treatment of choice for older patients with severe aortic stenosis and is expanding into younger age groups. Computed tomography (CT) is the gold standard for TAVR planning. Cardiac magnetic resonance (CMR) is an alternative imaging modality for TAVR guidance. The aim of this study was to evaluate the impact of age on implantation success in patients undergoing CT- or CMR-guided TAVR.

Methods: This was a secondary analysis of the randomized TAVR-CMR clinical trial comparing TAVR planning by CT or CMR (NCT03831087). For this analysis, patients were categorized according to the median age (82 years). Implantation success, defined according to the Valve Academic Research Consortium-2 definition (absence of procedural mortality, correct positioning of a single prosthetic valve, and proper prosthetic valve performance), was compared at hospital discharge between age groups for each imaging strategy.

Results: A total of 267 patients (median age 82 [IQR 80-85] years, 50% female) underwent TAVR at two hospitals in Austria between September 2017 and December 2022. Implantation success was not significantly different between imaging strategies for patients ≤82 years (92% (CT group) vs. 95% (CMR group), p=0.524) and patients >82 years (89.4% (CT group) vs. 91.9% (CMR group), p=0.622). All-cause mortality at 6 months was not significantly different between imaging strategies for patients ≤82 years (4.8% (CT) vs. 5.3% (CMR), p=0.839) and >82 years (9.1% (CT) vs. 12.9% (CMR), p=0.490).

Conclusions: CMR-guided TAVR was associated with similar TAVR outcomes compared with CT-guided TAVR irrespective of age.

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Link Between Ovarian Ageing and Multiple Sclerosis: Anti-Müllerian Hormone as a Predictor of Disease Activity and Disability Worsening

Background: Ovarian aging as assessed by Anti-Müllerian Hormone (AMH) has been implicated in various health outcomes in women. In multiple sclerosis (MS) the effect of aging on the disease course is well known. However, the role of ovarian aging on MS disease activity has not yet been studied.

Methods: This prospective longitudinal study including women with MS was conducted at the Medical University of Innsbruck and. Cox regression analysis was used to investigate the impact of AMH on time to relapse and time to disability progression.

Results: A total of 104 women at the median age of 50 years, a median EDSS of 2.0 and a follow-up time of 48 month (IQR 43-50) were included. Univariate analyses revealed that women with relapses were younger (39 vs 52 years), but also showed higher AMH levels (median 0.5 vs 0 µg/l). Multivariable Cox regression analysis revealed that both age (HR 0.95, p=0.039) and AMH levels (HR 1.40, p=0.022) independent predicted time to relapse. With regard to disability progression, in univariate analysis women were older (53 vs 48) and had lower AMH levels (0 vs 0.1 µg/l). Multivariable Cox regression analysis showed that the AMH level (HR 0.54, p=0.0038) independent of age predicted shorter time to disability progression.

Conclusion: In this study, we showed that ovarian aging, as reflected by AMH, is a risk factor for future progression. These findings suggest that AMH may serve as an additional biomarker for predicting relapses and progression in women with MS.

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Quantitative magnetic resonance imaging in carotid artery stenosis

Magnetic resonance imaging (MRI) enables the acquisition of quantitative parameters through diverse sequences to measure and visualize physiological and pathological processes in the brain.

This study centers on advanced quantitative MRI methods, including voxel-based morphometry, diffusion-weighted imaging, arterial spin labeling perfusion, T1 and T2 mapping, multi-echo T2*, functional resting-state MRI and phosphorus-based MR spectroscopy to investigate smallest cerebral changes in patients with carotid artery stenosis.

Carotid artery stenosis is implicated in up to 20% of ischemic strokes. An invasive treatment is recommended for symptomatic patients with a ≥50% stenosis and asymptomatic patients with a ≥70% stenosis. We want to recruit 100 patients with asymptomatic severe (≥70%) stenosis undergoing therapeutic interventions as carotid endarterectomy or carotid artery stenting.

The participants undergo a study-specific MRI protocol, neurocognitive tests, and electroencephalography recordings (EEG) at three time points: immediately before and after the therapeutic interventions, as well as during the 90-day follow-up examination.

Preliminary study findings suggests that quantitative MRI can reveal perfusion deficits, microstructural damages, and metabolic changes in stenosis affected brain regions. This study wants to validate these findings, assess changes over time and evaluate their correlation with treatment options, and cognitive and clinical recovery. We anticipate the results will provide insights and more detailed information into the pathophysiology of carotid artery stenosis and its response to invasive treatment, potentially improving prognostic accuracy and guiding more individualized therapeutic strategies.

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Investigation of gender-specific physicians adherence with guideline-directed medical therapy in a disease management program for heart failure patients

Guideline-directed medical therapy (GDMT) is very effective in the early, vulnerable phase after discharge from an acute heart failure (HF) event. In addition to the limited implementation in everyday clinical practice, recent studys show that women are less likely to receive GDMT.

In a prospective, multicentre-open randomized study including a total of 260 patients, The AMPEL-service, a digital decision tool for physicians to improve adherence with GDMT, will be investigated. Striking features of the AMPEL study are that it is conducted as part of the well established disease management program (DMP) for heart failure, HerzMobil, and that participating physicians are given random access to the AMPEL module. The primary endpoint includes an implementation endpoint that will assess the quality of indication- and dose-adjusted GDMT at 90 days. A subgroup analysis regarding gender-specific differences in the frequency of prescribed GDMT will be performed with statistical group comparison. The second part of the primary endpoint is a hierarchical composite of death from any cause, number and time to first HF event at 180 days, changes in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TTS), and changes in NTproBNP at 90 days. The clinical endpoint will be assessed by a stratified win ratio. Stratification will be conducted at the level of the ejection fraction and at the level of gender.

Gender-specific investigations in the setting of an established disease management program may provide valuable insights into gender-specific prescription and benefits of heart failure related GDMT.

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Sex differences in intraocular inflammation after cataract surgery

Purpose:

Microincision phacoemulsification surgery is the standard of care for the treatment of the cataractous lens. Anterior chamber instability remains the most important risk factors for complications like posterior capsular. This study aims to compare anterior chamber flare (ACF) and central corneal thickness (CCT) as indicators of surgical trauma between male and female patients before and after cataract surgery.

Methods:

This was a retrospective study involving 134 patients with advanced or mature cataract. All patients were operated using an identical technique and received the same postoperative treatment. Primary endpoint was defined as the difference between pre- and postoperative ACF and CCT on days 1 and 7. The secondary endpoints included central macular thickness (CMT) and best spectacle corrected visual acuity (BCVA).

Results:

We analyzed 64 male- and 63 female patients with comparable demographic parameters. The average age of the women was 73, while that of the men was 72 ($p = 0.333$). Change in flare on day 1 was not significant between the two groups (7.9 vs 8.1 ph/ms; $p = 0.979$), as was CCT (55.1 versus 59.4 µm; $p = 0.568$) and MCT (5.6 versus 3.0 µm; $p < 0.708$). Furthermore we found no significant differences after seven days. There was no difference in BCVA between the groups.

Conclusions:

This study demonstrates that cataract surgery is associated with an increase in anterior chamber flare and central corneal thickness on the first postoperative day in both groups. However, no significant gender-specific differences were observed at any point during the postoperative examinations.

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Diversity Aspects in Patients with Head and Neck Cancer

Head and neck cancer is the sixth most common cancer worldwide, with approximately 90% of cases being squamous cell carcinoma.

In Austria, around 1,200 individuals are diagnosed each year with a head and neck tumor. Men are affected more frequently than women, which aligns with established risk factors such as smoking, particularly when combined with alcohol consumption. However, other diversity aspects also play a significant role in the risk factors and prevalence of head and neck cancer across different populations. Factors such as ethnicity, socioeconomic status, age, and sexual behavior influence not only the likelihood of developing the disease but also its distribution worldwide.

Beyond its physical impact, head and neck cancer has a profound effect on patients' quality of life, as it disrupts essential daily functions like swallowing, eating, and speaking. It also affects psychological well-being and social interactions, leading to a significant burden on overall quality of life.

To explore and address these challenges, the Department of Oral and Maxillofacial Surgery in Innsbruck is conducting a questionnaire-based study to examine quality of life among affected individuals. This research also delves into how gender and other diversity aspects influence quality of life outcomes, with the aim of improving patient care.

This poster focuses on diversity aspects associated with head and neck cancer, focusing on variations in risk factors and their impact on quality of life.

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Sex Differences in AI-Estimated ECG Age as a Predictor of All-Cause Mortality in Cardiovascular Patients

Background

Artificial intelligence (AI) algorithms applied to standard 12-lead ECGs enable age prediction, providing insights into biological aging beyond chronological age. Previous studies have shown ECG age to be associated with mortality, but sex differences in this relationship remain unexplored. This study investigates whether the predictive value of ECG age differs between male and female patients with cardiovascular disease.

Methods

We applied a validated open-source AI algorithm to calculate ECG age in 189,433 ECGs from patients treated between 2000 and 2021. Patients were classified into three groups based on the difference between ECG age and chronological age. Associations with all-cause mortality were analyzed separately for men and women using Cox proportional hazards models.

Results

The cohort included 59% men, with mean chronological ages of 63 years for men and 62 years for women. ECG age was younger than chronological age for both sexes (men: 54 years; women: 50 years). Patients with ECG age ≥8 years older had significantly higher mortality risk (HR: 2.37 in women, 2.08 in men), while younger ECG age was associated with lower mortality risk (HR: 0.38 in women, 0.55 in men).

Conclusion

AI-estimated ECG age predicts all-cause mortality in both sexes, with potential sex-specific differences. Women exhibited stronger associations between ECG age and mortality. Further research is needed to explore sex differences when applying ECG age as a biomarker in clinical practice.

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Ex Vivo Lung Perfusion: Model for Prolonged Ex Vivo Lung Perfusion and Oncological Testing Platform

Introduction:

Ex vivo lung perfusion (EVLP) is an already accepted technique in specialized centres to evaluate borderline donor lungs for organ transplantation. With prolonged perfusion time also the implementation of oncological research platforms is possible. In this feasibility study we aim to proof that stable EVLP for at least six hours is routinely possible at our department.

Methods:

A XVIVO XPS system was used to perfuse 5 porcine lungs. Performance parameters were analyzed to assess oxygenation capability and edema formation. Hygiene samples were taken to assess for bacterial and fungal colonization.

Results:

Perfused lungs showed stable lung perfusion and oxygenation capability for up to six hours. Some lungs even showed a tendency towards improvement of oxygenation and stable metabolism. All lungs accumulated significant edema over the course of EVLP. Even if the first microbiological sample was positive, extensive anti-biotic / fungal therapy lead to sterile samples after 6 hours of perfusion.

Cocnlusions:

This study delivers the basis for prolonged EVLP to promote and enable an oncological and transplant research model and shows that stable perfusion, with the preservation of oxygenation capability, is feasible.

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Sex and size disparities in access to deceased donor liver transplantation - Insights from a large Eurotransplant liver transplant center

BACKGROUND

Women on the liver transplant (LT) waiting list are less likely to undergo LT than men. Recent efforts to address this disparity have involved adjustments to the MELD score. This study evaluates the association between female sex, candidate size, and access to liver transplant among wait-listed patients at a large Eurotransplant LT center.

METHODS

This retrospective cohort study included all adult (≥18 years) LT candidates wait-listed between February 2012 and January 2024. The exposure of interest was candidate sex. Main outcomes were (1) receiving a deceased-donor liver transplant (DDLT) and (2) death or waitlist removal due to health deterioration. Analyses were adjusted for candidate size and other confounders.

RESULTS

Among 870 waitlisted patients, women waited longer for a DDLT than men (63 vs. 35 days, $p < 0.001$). Unadjusted Cox regression showed a lower likelihood of DDLT for women (HR 0.71, 95% CI 0.63 – 0.88). The risk of death or waitlist-removal was similar between sexes. After adjusting for age, size, weight, blood group, and match-MELD, candidate sex was not independently associated with DDLT (aHR 0.92, 95% CI 0.75 – 1.13). However, waitlist candidate size remained a strong independent predictor of receiving a DDLT (aHR 4.56, 95% CI 1.54 – 13.54).

CONCLUSION

Women were less likely to receive a DDLT, but this disparity was primarily due to differences in candidate size. Strategies to improve access to size-matched donor livers for smaller candidates are needed.

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Sex differences in AHA Life's Essential 8 among Tyrolean adolescents

Background: In 2022, the American Heart Association (AHA) introduced an updated cardiovascular health (CVH) assessment tool: the Life's Essential 8 (LE8). However, there are only few studies analysing it in the adolescent population.

Objectives: The aim of the study is to evaluate sex differences in the individual cardiovascular health metrics and the overall AHA LE8 score among Tyrolean adolescents.

Methods: Baseline data from the YOUhealTH study were used to analyse the individual score for each health metric and the overall LE8 score (0 - 100 points) according to sex among Tyrolean adolescents aged 14-17 years.

Results: Among the 83 adolescents included in this analysis, 43 % were male. The mean overall score was 72.5 (95 % CI: 68.2 – 76.8) for males and 74.6 (95 % CI: 71.2 – 77.9) for females. There was no significant sex difference in the overall score ($p = 0.410$), but sex differences existed in the individual CVH metrics of physical activity ($p = 0.012$) and blood pressure ($p = 0.038$).

Discussion: Sex differences exist in individual CVH metrics among Tyrolean adolescents. These findings are crucial for developing effective prevention strategies in adolescents for males and females.

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