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Unveiling Connections: Exploring Biology Beyond Your Walls

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PATRICK RÜHS
ETH ZÜRICH

SARA COLOMER-LAHIGUERA
UNIVERSITY OF LAUSANNE

DOMINIQUE SOLDATI-FAVRE
UNIVERSITY OF GENEVA

JOHN HOWL
BIRMINGHAM CITY UNIVERSITY

DEBORAH KRONENBERG-VERSTEEG
DZNE TÜBINGEN

MORE INFORMATION

12TH MAY 2025
MATTHIAS MAYOR CHUV
09H00 - 17H30

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DDAY'25

ADAS UNIL

Unveiling connections: exploring biology beyond your walls

PROGRAM

12 May 2025
Auditoire Mathias Mayor (CHUV)

8:30
REGISTRATION AND COFFEE

9:00
WELCOME

9:10
DEBORAH KRONENBERG-VERSTEEG
Human(ized) brain slice culture as novel tools to investigate microglia in neurodegeneration

9:40
MARGOT RENARD - Transcriptome dynamics in developing hypothalmic circuits in reproduction

9:55
Elevator Pitches

10:20
Coffee break + poster session 1
ODD NUMBERS

11:10
JOHN HOWL
Bioportide Technologies: New Biological Agents and a Platform for Drug Discovery

11:40
DANIELA DIANA - APRIL - proteoglycan interactions are important for correct plasma cell development

12:00
Lunch

13:00
PATRICK RÜHS
Shaping the future of food: transforming food processing for nutrition

13:30
INES LEPREUX - Joint Modeling for Trauma and Psychosis: Understanding Pathways to Remission

13:45
PAOLA GUERRERO ARUFFO - Investigating immunesuppression in breast-to-brain metasatasis

14:00
DOMINIQUE SOLDATI-FAVRE
Breaking Barriers: How the Conoid Drives and Regulates Motility and Invasion in Apicomplexa

14:30
RAPHAËL BAUDIN - Establishing a phage collection as a first step towards a new strategy for the management of non-typhoidal Salmonellosis

14:45
KEYUAN LIU - The association between nightmare and cardiometabolic disease

15:00
Coffee break + poster session 2
EVEN NUMBERS

15:50
Michele Zeverino - Bringing AI-based automation of breast cancer radiotherapy into clinical practice

16:05
SARA COLOMER-LAHIGUERA
Researching for whom? When science forgets its users

16:35
Break

16:50
Prizes and Closing remarks

17:00
Apero

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Key Note Speakers' Abstracts

Human(ized) brain slice culture as novel tools to investigate microglia in neurodegeneration

Deborah Kronenberg-Versteeg – DZNE Tübingen

Microglia, the primary myeloid cells of the brain, are crucial for maintaining brain homeostasis and are implicated in various neuropathological processes. Microglial identity and function are determined by their ontogeny and the brain microenvironment. Therefore, model systems that faithfully reproduce mature human microglial molecular and functional phenotypes are crucial for understanding their role in brain health and disease.

I will present data showing that microglial precursors derived from induced pluripotent stem cells can integrate and mature in murine organotypic brain slices achieving a near-complete replacement of murine with human microglia. Their maturation is driven solely by the tissue environment and allows to study microglia in the context of disease pathology, such as alpha-synuclein inclusions or tau pathology. I will conclude by giving an outlook at why these small ‘micro’ glia are nevertheless mighty cells with unexplored therapeutic opportunities.

Bioportide Technologies: New Biological Agents and a Platform for Drug Discovery

John Howl - Birmingham City University, UK

The directed structural modification of peptides has facilitated their continued advancement as innovative research tools. Within this context, Cell Penetrating Peptides (CPPs), usually short cationic sequences of 10-20 AA, can overcome the pharmacokinetic limitation of membrane permeability to deliver bioactive compounds to discrete intracellular loci. The rational design of CPPs, to include protein mimetic sequences, has progressed the CPP field from inert vectors towards a new biology of innovative chemical agents. Distinguished as bioportides, these bioactive CPPs enter cells to modulate intracellular protein-protein interactions (PPIs).

This presentation will focus upon two key targets for bioportide technologies: STOPSPERM bioportides, including the lead compound MSS1 (YRSVITFVAVRQIKIWFQNRRMKWKK), disrupt protein phosphatase 1 complexes to inhibit the motility of human sperm. Metabolically stable formulations of STOPSPERM bioportides may serve as a novel male contraceptive modality. The planarian *Schmidtea mediterranea* is a viable system to determine the influence of bioportides upon stem cell biology. Bioportides mimicking a highly conserved helical domain of the Eyes Absent proteins, e.g. [Aib^{13}]Djeya1; RKLAFRYRRIKE(Aib)YNSYR Aib = aminoisobutryric acid) prevent tissue regeneration and remodelling of planarian tissues driven by stem cell differentiation and proliferation. Thus, this technology offers unique access to the study and discrete manipulation of those intracellular processes which govern life.

Shaping the future of food: transforming food processing for nutrition

Patrick Rühs – ETH Zurich

We must transform our food system to improve our planet and human health. However, our current food processing approach often hinders our ability to produce sustainable and nutritious food products. In this talk, I will present processing solutions, such as fungal fermentation, that enable us to enhance the nutritional quality of food through processing. We combine biological and physical processes, such as solid-state fermentation and foaming, to improve food's texture, flavor, and nutrition. To achieve this, it is essential to understand the structure-property-process relationships among microbes, materials, and processes to predict the impact of processing on the nutritional quality of food. By establishing these relationships, we hope to provide a foundation for healthier diets and contribute to a more resilient global food system.

Breaking Barriers: How the Conoid Drives and Regulates Motility and Invasion in Apicomplexa

Dominique Soldati-Favre – University of Geneva

Members of the phylum Apicomplexa are unified by the presence of an apical complex specialized for motility and host cell invasion. This complex includes regulated secretory organelles and a conoid, which is anchored to the apical polar ring, the origin of the subpellicular microtubules. In motile parasites, the conoid extrudes through the apical polar ring. Advances in proteomics, along with nanoscale imaging techniques such as expansion microscopy and cryo-electron tomography, have provided a more comprehensive view of the spatial and temporal organization of conoid subcomponents. Combined with phenotyping of targeted mutants, these approaches are beginning to clarify the biogenesis, turnover, dynamics, and function of the conoid.

Researching for whom? When science forgets its users

Sara Colomer-Lahiguera – University of Lausanne

In health and biomedical sciences, research often claims to serve patients and society — yet those most affected by research are rarely involved in shaping the questions we ask, the methods we use, the outcomes we prioritize, or the priorities we set. Participatory Research offers an alternative: a research-to-action approach that directly engages the experiences, knowledge, and priorities of patients, caregivers, and communities to co-construct knowledge for meaningful change.

In this talk, I will share some of our research projects, which focus on co-designing care pathways with patients and caregivers, developing models for patient and public involvement in research, and advancing the use of patient-reported outcomes. I will discuss how meaningfully involving users strengthens not only the scientific and practical value of research but also why integrating the voices of those we aim to serve is not simply an ethical responsibility, but a scientific necessity for relevance, innovation, and sustainability.

Beyond presenting our research, this talk is an invitation to rethink the relationship between researchers and the “users of research”: not as distant subjects or passive beneficiaries, but as active partners. Reconnecting research with its users makes science more rigorous, more ethical, and ultimately, more meaningful. It challenges us to reflect on a fundamental question: Who are we researching for — and how can we build science that truly serves?

Student Abstracts

Mitochondrial fatty acid β-oxidation in astrocytes is important for postnatal brain development and brain lipid homeostasis.

Alicia Rey

The synthesis, degradation, storage and recycling of lipids within cells directly affect energy production, cell membrane turnover, signaling pathways, and lipotoxicity. Therefore, lipid homeostasis plays a crucial role in optimal cellular function across diverse tissues. In the brain, dysregulated lipid metabolism is linked to several neurodegenerative disorders, highlighting the significance of lipid homeostasis for normal brain function. Recent studies have emphasized the role of astrocytes in neutralizing toxic lipids from stressed neurons through lipid transfer and mitochondrial fatty acid beta-oxidation (FAO). However, the contribution of astrocytic FAO to lipid homeostasis and postnatal brain development remains poorly understood. To investigate this, we characterized the expression pattern of one of the key enzymes of FAO, carnitine palmitoyl-transferase 1a (Cpt1a), and evaluated the functional role of FAO in astrocytes by selectively deleting Cpt1a at both early and late stages of postnatal development. Our findings demonstrate that Cpt1a is predominantly expressed in glial progenitors and astrocytes throughout the entirety of postnatal development and into adulthood. Single-nucleus RNA sequencing, lipidomics, behavioral tests, and imaging revealed that the deletion of Cpt1a in astrocytes disrupts lipid homeostasis, adversely affecting both astrocyte maturation and normal brain development.

Machine learning model identifies patients with ejection fraction improvement after Stereotactic Arrhythmia Radioablation (RAVENTA and CHUV registries)

Andrei Alexandru Mercea

Background: Stereotactic arrhythmia radioablation (STAR) treats refractory ventricular tachycardias (VT). Animal studies showed left ventricular ejection fraction (LVEF) improvements after STAR. Our previous work identified key features for predicting the need for redo catheter ablation (CA) after STAR using LIME explainable AI: planned target volume (PTV), LVEF, administered radiation dose, presence of hypertrophic or dilated cardiomyopathy and number of VT ablations before STAR.

Objective: We hypothesized that machine learning (ML) models can predict the improvement in LVEF after STAR.

Methods: 38 patients from the RAVENTA and CHUV registries were analyzed after excluding two for incomplete data. LVEF change after STAR was binarized (+1: increase, -1: decrease/no change). A logistic regression model was trained on 30 patients and validated on 8, with point biserial correlation assessing features' relationship to LVEF change.

Results: The model achieved 87.5% accuracy (Table). Out of the used features, PTV and number of prior VT ablation showed inverse correlations with LVEF improvement ($r = -0.32$, $p = 0.04$ and $r = -0.3$, $p = 0.06$). The STAR effect on LVEF is shown in Figure.

Conclusion: ML models can predict LVEF improvement after STAR in patients with VT. The more VT ablations performed before STAR and the higher the PTV was, the lower the likelihood of EF improvement was.

Nanomotion Technology for Rapid Antimicrobial Susceptibility Testing of Mycobacterium tuberculosis: Evaluating Novel Benzothiazinone Derivatives

Anthony Vocat

Background: *Mycobacterium tuberculosis* remains a major cause of morbidity and mortality worldwide, particularly in low- and middle-income countries. The emergence of multidrug-resistant and extensively drug-resistant strains presents significant challenges for treatment. Rapid and accurate antimicrobial susceptibility testing is essential for optimizing therapy and addressing antimicrobial resistance. This study investigates the use of nanomotion technology, a phenotypic AST method that measures bacterial viability, to evaluate the activity of benzothiazinone derivatives targeting MTB.

Methods: Nanomotion-based AST was performed using the Resistell Phenotech device in a BSL-3 laboratory. MTB H37Rv and a DprE1-resistant mutant were exposed to benzothiazinones, and nanoscale vibrations were monitored over seven hours. The variance in nanomotion signals was analyzed, and the rate of variance decrease (k) was calculated to assess bacterial viability. Minimum inhibitory concentrations (MICs) were determined using resazurin microtiter plate assays (REMA) for comparison.

Results: All benzothiazinone derivatives exhibited significant activity against H37Rv, with PBTZ169 showing the lowest MIC at 0.3 ng/mL. Nanomotion signals displayed substantial reductions in bacterial activity within seven hours for susceptible strains, with median k values ranging from -0.43 h^{-1} (PBTZ169) to -0.25 h^{-1} (BTZ043). Resistant mutants demonstrated minimal variance reduction (median k = -0.03 to 0.05 h^{-1}). The method achieved 100% differentiation for PBTZ169 and H2-PBTZ169. Time-to-result (TTR) was reduced to seven hours, nearing the performance of molecular diagnostics.

Conclusions: Nanomotion technology offers a rapid, reliable method for phenotypic AST of MTB, providing real-time viability assessments that distinguish between susceptible and resistant strains. This method bridges the gap between molecular and phenotypic diagnostics and could facilitate improved MDR and XDR tuberculosis management. Ongoing work focuses on adapting the technology for direct sputum testing to streamline diagnostic workflows. Additionally, we are working with *M. smegmatis* to establish phage production according to our GMP protocol accredited by SwissMedic, paving the way for standardized, high-quality phage therapies.

The role of lipid droplets during mouse and human brain development

Carla Marie Igelbüscher

Lipid droplets (LDs) are intracellular lipid storage organelles. Recently, we showed that adult mouse neural stem/progenitor cells (NSPCs) contain a large number of LDs, which directly influence NSPC proliferation and metabolism. To further study LDs in the brain, we have developed a novel endogenous fluorescent LD reporter mouse (tdTom-Plin2 mouse) to allow staining-free visualization of LDs. We have demonstrated that LDs are highly abundant in various cell types in the healthy adult brain, and we also found numerous LDs in the developing brain. Furthermore, adding lipids to the medium of ex vivo embryonic brain sections resulted in increased LDs. This suggests that the build-up, breakdown, and storage of lipids in LDs might play an important role in NSPC regulation during brain development. However, very little is known about how LDs influence mouse brain development and their role in human brain development is even less explored.

We here use the novel tdTom-Plin2 mouse to characterize the distribution and dynamics of LDs over a developmental time-course. Using genetic and pharmacological means, we will further perturb LD usage and numbers and assess the consequences for brain development. We also utilize human induced pluripotent stem cell (hiPSCs) derived NSPCs and cerebral organoids to characterize and dissect the role of LDs in human brain development. These different model systems allow us to better understand the importance of LDs during early mouse and human brain development.

T-cell Receptor Constant β 1 Clonality Score (TRBC1-CS) indicates T Helper Cell Clonality in Skin Tissues

Christoph Iselin

Background: Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin lymphoma characterized by the clonal proliferation of neoplastic T cells in the skin. Its early diagnosis is often challenging due to its overlapping clinical features with benign skin diseases, frequently leading to misdiagnosis or diagnostic delays.

Objectives: This study investigates the utility of T-cell receptor beta constant region 1 (TRBC1) as a marker for T-cell clonality in formalin-fixed paraffin-embedded (FFPE) skin biopsies.

Methods: We analysed single-cell RNA sequencing data from CTCL skin lesions to examine the expression of TRBC1 in T-helper cells (Th cells). To quantify the extent of TRBC1 polarization, we developed a TRBC1 Clonality Score (TRBC1-CS). Using patient-specific TRBV mRNA probes and TRBC1 antibodies, we demonstrated polarized TRBC1 expression in TRBV-defined clonal Th cells in FFPE skin samples. Next, we established a simplified immunofluorescence panel consisting of T-cell markers and TRBC1 to differentiate between CTCL and benign dermatoses. The findings were further validated in an independent cohort by comparing the TRBC1-CS to PCR-based BIOMED-2 T-cell clonality assays.

Results: We identified polarized TRBC1 expression in TRBV-positive clonal Th cells within FFPE skin samples. The TRBC1-CS demonstrated high specificity for CTCL, enabling delineation from benign dermatoses. Furthermore, when validated in an independent cohort, TRBC1-CS exhibited superior specificity and positive predictive value compared to PCR-based methods.

Conclusions: TRBC1 staining and the TRBC1-CS provide practical and highly specific tools for assessing T-cell clonality in FFPE skin biopsies.

Characterizing the mechanisms underlying the persistence of Chlamydia trachomatis

Daniel Rodriguez Rozo

The life cycle of Chlamydia trachomatis (CT) includes a biphasic developmental sequence. Additionally, in response to stressors such as IFN-γ, temperature changes or iron deprivation, the bacteria can survive in a reversible persistent state. However, the precise mechanisms leading to the transition from replicative, reticulate bodies (RBs) to aberrant bodies (ABs) have not been characterised. By comparing the transcriptomes of RBs and ABs, we have identified differentially expressed genes predicted to be part of a two-component regulatory system (TCS). TCSs are used by bacteria to sense and respond to their environment. AB formation was induced in CT infected cells by depleting iron using the chelator 2,2'-bipyridyl (BPDL). RT-qPCRs were performed to quantify RNA levels and to assess gene expression during normal growth and persistence. In parallel, immunofluorescence microscopy was carried out to compare gene expression with morphological changes associated with AB. Results indicated that TCS genes, were strongly downregulated in ABs compared to RBs. After 8 hours following BPDL removal, expression levels returned to those found in control infections. Downregulation in gene expression was specific to the stressor applied, indicating a relationship between different stress stimuli and TCS. We have also identified upregulated genes encoding some Inc proteins in ABs.. Incs are required for the biosynthesis and the establishment of the bacterial inclusion. Unexpectedly, preliminary results showed that Incs expression is depending on host cell line. Further knowledge of the biological mechanisms triggering the development of persistent bacteria can give insights into mechanisms at play during chronic chlamydial infections.

APRIL - proteoglycan interactions are important for correct plasma cell development

Daniela Diana

The TNF family ligands B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) support B cells and plasma cells, thereby contributing to humoral immunity and, when deregulated, autoimmunity. BAFF primarily mediates B cell survival through its receptor BAFFR. BAFF and APRIL also interact with TACI and BCMA in terminally differentiated plasma cells. Unlike BAFF, APRIL also binds to proteoglycans (PGs). PGs are rich in negatively-charged sulfated polysaccharide chains that interact with a variety of basic factors, including APRIL. A biological function of APRIL - PGs interaction was proposed as PGs and APRIL colocalized in tonsils where plasma cells thrive and secrete antibodies1. This interaction was further evidenced in arteries and was suggested to play a protective role in atherosclerotic plaque formation2 , indicating that the physiological activities of APRIL binding to immune receptors differ from those involving proteoglycans. We engineered mutations in APRIL to selectively disrupt its interaction with PGs while preserving its receptor binding site (PG-dead), and vice versa (REC-dead). Knock-in mice expressing these APRIL mutants were generated. Cohorts of wild-type (WT) and APRIL PGdead mice were treated with a function blocking anti-BAFF antibody to force plasma cells survive on the sole contribution of WT or PG-dead APRIL. Negative and positive controls received an isotype control or a combination of anti-BAFF and anti-APRIL antibodies, respectively. In the absence of BAFF, splenic B cells were similarly reduced in both groups. However, compared to WT, APRIL PG-dead mice also showed a significant decrease in bone marrow plasmablasts (CD138+/B220+) and plasma cells (CD138+/B220-), particularly of the IgA and IgM isotypes. Blocking BAFF also translated in deeper reductions of circulating IgA, IgG, and IgM in APRIL PG-dead mice compared to WT. In the specific case of IgA, levels could be further decreased with combined anti-APRIL and anti-BAFF treatment, indicating that APRIL PG-dead maintains a residual activity. Circulating APRIL levels were elevated 20-fold in APRIL PG-dead compared to WT mice, showing that PGs indeed restrict APRIL distribution in vivo and/or that feedback mechanisms attempt to compensate for diminished APRIL signaling. These findings establish the importance of APRIL-proteoglycan interactions in plasma cell homeostasis and survival in vivo. Combining these results with those from REC-dead mice will help dissect and identify the respective contributions of APRIL binding to receptors or proteoglycans in immunity and cardiovascular settings.

Deciphering the antibody-mediated neutralization of the BK virus

David Vinyals Sales

The BK polyomavirus, also known as BK virus (BKV) or BKPyV is a non-enveloped virus belonging to the Polyomaviridae family, whose infection is usually asymptomatic and could be considered ubiquitous in the general human population. Clinical complications occur in immunocompromised hosts, particularly during kidney or multi-organ transplantation, when the administration of immunosuppressants attenuates the immunity, allowing the virus to reactivate and spread. In this context, up to 10% of kidney transplant recipients develop polyomavirus-associated nephropathy (BKVAN), resulting in the loss of 50-70% of graft function and often leading to acute organ rejection. Management of BKVAN is currently mostly limited to tight regulation of the intensity of immunosuppression since there is no available specific therapeutic agent to control viral replication and reduce viral loads. Current investigations in the field focus on developing therapeutic agents based on the activity of neutralizing antibodies. However, the mechanism through which those antibodies neutralize the BK virus is poorly understood and leaves room for investigation. We have implemented a protocol to isolate antibodies from peripheral B cells that allows us to select, produce, and characterize antibodies that potently neutralize the BK virus. Among the identified antibodies, clone D23 neutralizes the BK virus at the picomolar range and stands out compared to most of the antibodies reported in the literature. Moreover, this antibody seems to compete with other antibodies for the binding of a same or proximal epitope, potentially implying the existence of a vulnerability site on the structure of the capsid of the BK virus. Performing a structural analysis of the interaction between selected antibodies and the virus will allow us to validate the epitopes that are crucial for a potent and mutant-resistant neutralization of the virus, which is a key step in understanding the mechanism of infection of BKV and a major contribution to the optimization and design of specific therapeutics.

Proteomic Biomarkers for Neurocognitive Disorders in People with HIV

Diego De Haro

Background: Despite effective antiretroviral therapy (ART), neurocognitive disorders (NCDs) affect up to 50% of people with HIV (PWH). HIV-associated neurocognitive disorder (HAND), in particular, remains difficult to diagnose due to confounding NCDs in this population such as depression, neurodegenerative disease, and age-related cognitive decline. Identifying reliable biomarkers in cerebrospinal fluid (CSF) and blood could not only improve diagnosis and enable earlier detection, but also reveal much needed therapeutic targets. We therefore aim to identify biomarkers for NCDs in PWH and distinguish HAND from other NCDs by analyzing inflammatory and neurological markers in CSF and blood using targeted proteomics.

Methods: In this pilot study, we investigated paired CSF and serum samples from 20 PWH on ART, with NCDs (n=13, of which 4 were characterized as HAND) and without (n=7 controls). We quantified 45 cytokines using Olink's Proximity Extension Assay and analyzed relationships between CSF and blood analyte levels, as well as global inflammatory profiles and differentially expressed proteins between clinical phenotypes.

Results: Some participants displayed visible neuroinflammation, even in the absence of detectable virus in the CSF. Levels of CCL4, linked to blood-brain barrier disruption, were strongly correlated between the CSF and serum compartments in the NCD group but not in controls. HGF correlated positively in the controls but negatively in NCD, suggesting a regulatory shift during neurocognitive impairment. Additionally, CSF3 levels were increased in HAND serum. However, inflammatory profiles did not clearly align with clinical diagnosis, underscoring diagnostic complexity.

Conclusion: Despite the observed heterogeneity of inflammatory signatures, this proof-of-concept pilot study highlights the potential of proteomics to improve NCD and HAND detection in PWH on ART. We are now analyzing a larger cohort of 200 participants, to refine these signatures and assess their clinical utility for more precise diagnostics as well as serve as therapeutic targets.

Machine Learning without Coding Experience: Introducing CRISP Framework to Translate Your Experimental Data into Biomedical Insights

Duy Cat Can

Despite the increasing availability of high-throughput experimental data, many biomedical researchers face a steep barrier when attempting to harness machine learning (ML) for their research due to limited coding expertise and lack of accessible tools. In this talk, I will introduce the CRISP framework – an open-source, user-friendly ML toolkit designed to empower researchers without programming experience to build robust, interpretable models from their own data. CRISP stands for Consistent, Reproducible, Interpretable, Sparse, and Predictive, reflecting the framework's guiding principles. It enables seamless integration of data pre-processing, feature selection, model training, validation, and clinical report generation through an intuitive graphical interface. Researchers can load datasets, fine-tune ML pipelines, and obtain patient-level predictions with clinical explanations in just a few clicks. I will demonstrate the application of CRISP on real-world biomedical datasets, including examples from cardiology, immunology, and neurology. This session aims to inspire early-career scientists to explore ML-driven discovery, without being limited by technical barriers, and to foster crossdisciplinary collaboration through transparent and reproducible AI tools.

Unravelling the molecular signature of persistent HIV-specific CD8 T cells dysfunction in people living with HIV (PWH)

Giulia De Bernardi

Although antiretroviral therapy improves HIV outcomes, it fails to eliminate latent reservoirs in people with HIV (PWH), leading to viral rebound upon treatment interruption. Elite controllers (ECs), who suppress the virus without treatment, have more functional HIV-specific $CD8^+$ T cells compared to chronic progressors (CPs), who exhibit $CD8^+$ T cell exhaustion due to chronic antigen exposure, impairing their ability to control HIV. Upon ART-induce suppression of the antigen this dysfunctional immune response is only partially reversed. We hypothesize that HIV-specific $CD8^+$ T cell dysfunction during ART is maintained by an imprinted transcriptional and epigenetic program.

We live-sorted 2,000 HIV-specific $CD8^+$ T cells from PBMCs using an activation induced marker assay based on co-upregulation of CD69 and 4-1BB after from a 15-hour in vitro stimulation with an HIV Gag peptide pool. We investigated three cohorts of PWH: 12 ECs, 12 ART-suppressed PWH, and 12 CPs. RNA-seq was performed on the HIV-specific $CD8^+$ T cells to identify differentially expressed genes (DEGs) between ECs, ARTs and CPs, followed by Gene Set Enrichment Analysis using Gene Ontology, KEGG, and Reactome databases.

We observed the highest number of DEGs in the EC vs CP comparison (208), followed by CP vs ART (75) and EC vs ART (23), indicating partial transcriptional restoration with ART. Notably, 39 DEGs linked to T cell activation and exhaustion remained persistently dysregulated in ART-treated CPs, including IFNG, IL2RA, TOX2 and BATF3. Pathway analysis revealed downregulation of ribosome biogenesis, translation, and mitochondrial metabolism in CPs and ART, and upregulation of antigen processing and NK-mediated cytotoxicity pathways.

Extensive differences exist between the transcriptional landscapes of CP and EC PWH, and ART alone fails to fully restore HIV-specific $CD8^+$ T cell function. This persistent transcriptional dysregulation suggests that targeted interventions are needed to reprogram these cells and restore an EC-like phenotype.

Rational step-by-step design of a two-phage cocktail against a contemporary A. baumannii strain recovered from a burned patient at CHUV

Hugues de Villiers de la Noue

Acinetobacter baumannii is a major threat to human health. With the spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, the development of complementary strategies is needed. A promising strategy could be phage therapy, which uses bacteriophages (phages), i.e viruses that specifically kill bacterial cells.

We designed a two-phage cocktail highly efficient against an XDR *A. baumannii* isolate collected from a patient with burn wound infection at CHUV (termed Ab125). A first *in vitro* screen of our collection of 36 different phages identified only phage vB_AbaM_3098 as capable of lysing Ab125. However, quick (ca. 6 h) selection of phage-resistant clones (termed Ab139) occurred. Comparative genomics between Ab125 and Ab139 revealed a Single Nucleotide Polymorphism (SNP) in an intergenic region, currently under investigation.

Very interestingly, we observed that Ab139 became susceptible to six different phages in the collection, otherwise inactive on Ab125. Phage-resistance was also selected when Ab139 was challenged with either of the six phages, with bacterial regrowth observed between 12 h and 16 h. However, combination of vB_AbaM_3098 and phage vB_AbaM_3014 led to a clinically usable two-phage cocktail capable of totally inhibiting the growth of Ab125. Treatment with the phage cocktail led to 86.67% survival after 5 days in the *in vivo Galleria Mellonella* model, compared to 0% in the non-treated group. Finally, the therapeutic potential of the assembled cocktail was tested in synergy with Standard-of-Care (SOC) antibiotics, and a synergy with colistin was detected.

We show that the combination of a phage that only slightly shifted the in vitro bacterial growth curve with an “inactive phage” led to the formulation of a highly bactericidal phage cocktail against an XDR *A. baumannii* clinical isolate. This work highlights the complexity involved in the assembly of phage cocktail, as well as their potential in difficult-to treat infections in combination with antibiotics.

Joint Modeling for Trauma & Psychosis : Understanding Pathways to Remission

Ines Lepreux

Background: Schizophrenia is a chronic psychiatric disorder with significant personal and societal burden. Despite existing treatments, approximately 25% of patients remain treatment-resistant. Childhood trauma is a major risk factor, associated with increased symptom severity, relapse, suicidality, and cognitive impairments. Prior research suggests that specific trauma types (e.g., abuse vs. neglect) differentially impact symptom profiles and are mediated by affective and biological mechanisms. However, traditional group-level analyses fail to support individualized clinical predictions.

Aims: This study aims to predict 36-month symptomatic remission in early psychosis patients using a dynamic, trauma-informed precision psychiatry model. We apply joint modeling to integrate longitudinal functioning trajectories with baseline trauma exposure and other clinical predictors.

Methods: Participants (N = 400) were recruited from the TIPP early psychosis program in Lausanne. Data included baseline assessments of childhood trauma (abuse, neglect, polyvictimization), functioning (GAF), symptoms (PANSS, MADRS, YMRS), cognition (MATRICS), peripheral biomarkers (GPX, GR, GSH), and polygenic risk scores (PRS-SCZ). Functioning was assessed at months 2, 6, 12, and 36; symptomatic remission at 36 months was defined per Andreasen criteria.

We constructed a joint model comprising a linear mixed-effects model for GAF trajectories and a Cox regression for remission status. Predictors included age, sex, SES, trauma type, functioning slope, and interaction terms.

Hypotheses :

1. Dynamic trajectories of functioning will significantly predict remission at 36 months.
2. Lower improvement in functioning during the first year will predict lower remission rates.
3. Among patients with poor functional improvement, those with childhood trauma will have lower chances of remission, particularly in the case of abuse.

Results (Preliminary): Initial findings indicate that reduced early functional improvement is associated with non-remission. Trauma exposure, especially childhood abuse, moderates this relationship. The joint model outperforms static models in predictive accuracy.

Conclusion: Joint modeling provides a promising framework for integrating temporal dynamics and trauma exposure into individualized remission predictions. This approach contributes to the development of precision tools in early psychosis, bridging research and clinical application.

Adaptation response to immunoproteasome inhibition in immune cells

Kalvin Nugraha

Proteasome activity is crucial for maintaining protein homeostasis and producing active degradation products that drive cellular processes, such as cytokine production, cell cycle, and cell death. Immune cells express an extra subset of proteasome called the immunoproteasome which possesses different proteolytic profile compared to standard proteasome. The transcription factor Nrf1 (NFE2L1) serves as a sensor of low proteasome activity. Impaired proteasome activity triggers the stabilization and activation of Nrf1 in the presence of DDI2, culminating in the induction of proteasome subunit genes. This adaptation response serves to restore general proteasome activity in cells and has been shown to mediate resistance to proteasome inhibition in multiple myeloma cells. In this study, we investigated whether similar adaptation response exists in the context of specific immunoproteasome inhibition in immune cells. We used a specific inhibitor for the β5i immuno-subunit to examine the induction of adaptation responses, including DDI2-mediated Nrf1 activation. Our study aimed to determine the mechanism by which immune cells adapt to immunoproteasome inhibition and the functional consequences this might have on immune function.

The association between nightmare and cardiometabolic disease

Keyuan Liu

Introduction: It has been suggested that nightmares alter the autonomic nervous system and lead to insufficient and poor-quality sleep. These pathways may be related to cardiometabolic disease (CMD) and its risk factors. However, research on the association between nightmares and CMD in the general population is limited.

Method: Cross-sectional study using the first, second, and third follow-up data from the CoLaus|PsyCoLaus study (Lausanne, Switzerland). The first nightmare follow-up was assessed by questionnaire, and the second and third nightmare follow-ups were assessed by questionnaire and Nightmare EMA(Ecological Momentary Assessment), which were categorized into "frequent nightmares" and "no frequent nightmares" groups. Cardiovascular disease (CVD), hypertension, obesity, and diabetes were collected. Analyses were conducted for all participants, then by gender, using multivariable logistic regression.

Results: For the results of the questionnaire survey, after multivariable analysis, the first follow- up data showed that nightmares were positively associated with obesity in overall participants and in men, and positively associated with hypertension in women; the second and third follow-up data both shows no association with nightmares. For the results of the Nightmare EMA survey, after multivariable analysis, the second follow-up data showed that nightmares were positively associated with hypertension in overall participants and in men, the third follow-up data showed that nightmares were positively associated with CVD in overall participants.

Conclusion: The results vary depending on the age of the follow-up participants and the accuracy of different nightmare collection methods, but overall, nightmare disorder is significantly and positively associated with hypertension in overall participants, men, and women; and positively associated with CVD in overall participants; and positively associated with Obesity in overall participants and men.

Neonatal lung dysbiosis models to investigate mucosal allergic priming

Kirby Frank

Background: Early microbial colonization plays a key role in immune maturation and respiratory health. Disruptions in the neonatal lung microbiota have been associated with asthma susceptibility, yet their effects on immune priming and barrier function remain unclear. We hypothesized that microbial perturbations in neonatal lungs create an immune environment that predisposes to exaggerated allergic airway inflammation.

Methods: BALB/c mice at 14 days, 21 days, and 8 weeks of age were exposed nasally to S. pneumoniae (10^3–10^5 CFU) or vancomycin/colistin over 5 days, followed by house dust mite extract instillations every 48h for 14 days. 16S gene amplicon sequencing confirmed microbiota alterations, while flow cytometry characterized immune and structural cell subsets.

Results: Both bacterial and antibiotic exposure induced lung dysbiosis. Neonatal mice exposed to S. pneumoniae exhibited an expansion of ILC2/ILC3 populations, eosinophilia, and increased memory T-cell frequencies, with stronger effects at 14 days compared to 21 days. Adult mice showed fewer innate immune alterations, exhibiting stronger Th2 cytokine responses following allergen exposure; weanlings displayed intermediate effects. Females demonstrated greater eosinophilia and dendritic cell activation (CD80). Antibiotic-exposed mice showed a distinct immune shift, characterized by reduced dendritic cell activation (CD80) and increased ILC3 frequencies.

Conclusions: We established and validated two neonatal lung dysbiosis models, offering new frameworks to study early-life immune programming. Neonates are highly susceptible to dysbiosis, underscoring the need for targeted interventions to maintain microbial equilibrium and reduce asthma risk.

How Gut Derived Metabolites Improve Peripheral Neuropathy In Dysbiotic Models

Laetitia Raux

Introduction: The widespread Western diet, rich in fast and processed foods, leads to high prevalence of metabolic diseases such as obesity and type 2 diabetes (T2D)[1,2,3]. Many complications are associated with these disorders, and intriguingly, evidence indicates that one of the most frequent complications is peripheral neuropathic pain[4]. Peripheral neuropathic pain is a condition characterized by the loss of sensory functions, leading to symptoms like itching or pain due to damage or dysfunction of peripheral nerves[4], affecting patients' quality of life. Unfortunately, besides addictive drugs acting on pain symptoms, there are still no treatments targeting the underlying causes of pain.

Lately, it has been highlighted that modifying the gut microbiota through fecal microbiota transplantation (FMT) in rodents or patients improves the function of sensory neurons and leads to neurogenesis[2,5]. Beneficial commensal bacteria present in our gut produce metabolites from dietary fiber, the short-chain-fatty-acids (SCFAs)[6]. Building on this, we investigated whether fiber supplementation could improve peripheral neuropathy in mice.

Methods: Previous work in our lab demonstrated that mice fed different diets — standard chow, Western diet, or Western diet supplemented with inulin, a prebiotic fiber — respond differently to mechanical and thermal sensitivity tests. Inulin supplementation, whether used preventively or as a treatment, positively impacted peripheral sensitivity.

Results: Mice on Western diet displayed increased hypersensitivity compared to those on standard chow. Inulin supplementation alleviated these effects, indicating its potential to restore sensory function.

Conclusion: While FMT has shown efficacy in restoring gut balance and improving sensory function in both mice and humans, it relies on donor availability, complex manipulation, and infrastructure, limiting its accessibility and scalability. Our findings suggest that inulin supplementation could serve as a practical and accessible alternative to FMT, directly supporting gut microbiota balance and SCFA production and providing a convenient solution for patients.

Development of an in vitro vaginal epithelium model for studying microbial interactions and bacteriophage-probiotic therapy

Laetitia Bernard

Introduction: The composition of the vaginal microbiota plays a fundamental role in women's reproductive health, influencing conditions such as bacterial vaginosis and preterm birth. However, antibiotic treatments often disrupt microbial balance. Our study addresses this challenge by developing an *in vitro* vaginal epithelium model that mimics the *in vivo* environment. This model enables the study of vaginal epithelial-bacteria interactions and the evaluation of phages and probiotics as alternatives to antibiotics, offering innovative approaches for managing vaginal dysbiosis and improving reproductive health globally.

Methods: Primary vaginal cells are isolated from colporrhaphy biopsies, enzymatically digested to obtain the epithelial fraction, and cultured at an air-liquid interface (ALI) to replicate the vaginal environment. Additionally, the VK2/E6E7 vaginal cell line is used as a parallel model. Specific bacterial species from vaginal samples are introduced to colonize the ALI, and the colonization's impact is assessed. Phages are isolated from wastewater using double-layer plaque assays, targeting bacteria of interest within the vaginal microbiota.

Results: We successfully established a vaginal epithelium model using the ALI method, which histologically resembles the natural vaginal epithelium. By optimizing hormone concentrations, we enhanced epithelial integrity, providing a robust foundation for bacterial colonization studies. Initial experiments showed successful bacterial adhesion to the epithelium, as confirmed through confocal microscopy. We also initiated the isolation of vaginal epithelial cells from patient samples, aiming to integrate them into future ALI models. Future work will focus on analyzing epithelial responses to bacteria, including assessments of integrity, cytokine secretion, and apoptosis markers. Phage therapy will target specific bacterial populations, and probiotics will be introduced to promote a balanced vaginal microbiota.

Discussion & Conclusion: Our in vitro vaginal epithelium model offers a powerful platform for studying bacterial colonization and the therapeutic potential of phages and probiotics. This approach could lead to targeted treatments that eliminate harmful bacteria while preserving beneficial ones, presenting promising alternatives to antibiotics for managing vaginal dysbiosis and enhancing women's reproductive health.

An updated inventory of genes essential for oxidative phosphorylation identifies a mitochondrial origin in familial Ménière's disease

Marcell Harhai

Mitochondrial disorders (MDs) are among the most common inborn errors of metabolism, and dysfunction in oxidative phosphorylation (OXPHOS) is a hallmark. Their complex mode of inheritance and diverse clinical presentations render the diagnosis of MDs challenging and, to date, most lack a cure. Here, we build on previous efforts to discover genes necessary for OXPHOS and report a highly complementary galactose-sensitized CRISPR Cas9 "growth" screen, presenting an updated inventory now with 481 OXPHOS genes, including 157 linked to MDs. We further focus on FAM136A, a gene associated with Ménière's disease, and show that it supports mitochondrial intermembrane space protein homeostasis and OXPHOS in cell lines, mice, and patients. Our study identifies a mitochondrial basis in a familial form of Ménière's disease (fMD), provides a comprehensive resource of OXPHOS-related genes, and sheds light on the pathways involved in mitochondrial disorders, with the potential to guide future diagnostics and treatments for MDs.

Transcriptome dynamics in the developing hypothalamic circuits of reproduction

Margot Renard

GnRH neurons are a small cell population essential to mammalian reproduction. They migrate from nose to brain tissue during embryonic development, where they mature within the hypothalamus. There, they integrate signals from their surrounding network, shaping activity patterns that regulate puberty onset and adult fertility. However, the precise molecular mechanisms governing these processes remain largely unknown.

Our study aims to characterize the transcriptomic landscape of the migrating and maturing GnRH neurons and identify critical gene expression trajectories necessary to their proper development and to reproductive function.

To investigate gene expression across different cell types within these regions while ensuring sufficient representation of our population of interest, we perform single-cell RNA sequencing on mouse embryonic and hypothalamic samples enriched for GnRH neurons using fluorescence-activated cell sorting (FACS).

Cell identity classification in our dataset aligns with previous research on mouse embryonic development. Our analysis reveals dynamic changes in gene expression within GnRH neurons throughout these developmental stages, consistent with prior findings on bulk data from our lab. Furthermore, we identified heterogeneity within GnRH populations, with distinct subpopulations emerging during embryonic development, as well as sexually dimorphic gene expression.

Future analyses will incorporate a larger dataset currently under acquisition. We will apply spatial inference methods, leveraging published spatial transcriptomics studies, to better understand the spatial organization of GnRH neurons migratory route and hypothalamic network. We also plan to evaluate their cell-to-cell communication networks and validate novel markers as potential therapeutic targets for infertility-related pathologies, including hypogonadism.

Innovation and Digital Solutions in Switzerland for Cancer Patients: A Scoping Review

Maria Paraskevi Moschofidou

Introduction: Switzerland, despite its reputation for innovation, has been slower to adopt digital health solutions compared to countries like Denmark and Estonia. This lag is largely due to its complex federal structure, fragmented stakeholders, and intricate legal frameworks. The health policy strategy for 2020-2030 highlights technological and digital transformation as a key challenge. Currently, there is a lack of studies synthesizing digital solutions for cancer patients in Switzerland. This scoping review aims to explore the state of digitalization in Swiss healthcare.

Methods: This scoping review followed the Arksey and O'Malley framework and adhered to the PRISMA-ScR 2025 guidelines. The review aimed to identify available or developing digital health solutions for cancer patients in Switzerland. A systematic search was performed across three databases (PubMed, MEDLINE, Embase) and Google Scholar for grey literature, including organizational websites like Digital Health Zurich and Swiss Cancer Research. Search terms included "digital health," "cancer," "Switzerland," "ePRO," "mobile app," and "remote monitoring," using Boolean operators to refine results. Titles and abstracts were screened for relevance, and full-text articles or project descriptions were retrieved for those meeting inclusion criteria. A single researcher conducted the search strategy and data synthesis. Data extraction utilized a standardized form to capture study/project title, population characteristics, intervention type, key features, main outcomes, and relevance to Switzerland. The synthesized data were organized into a table to provide an overview of digital health solutions in Swiss oncology, incorporating both peer-reviewed studies and organizational initiatives. Studies or initiatives were excluded if they did not focus on cancer patients in Switzerland; did not involve digital health interventions; were purely theoretical or lacked empirical data (for peer-reviewed studies).

Results: This scoping review reveals the limited digital health solutions for Swiss cancer patients, focusing on patient-centered care and remote monitoring. A total of 204 records were screened, with 17 initially eligible studies; ultimately, 9 were included in the final analysis, main reasons of exclusions related to population and geographic criteria. Key findings include the five different aspects: **National Initiatives** (n=1): The DigiSanté Program aims to modernize Swiss healthcare infrastructure (Federal Office of Public Health). **Mindfulness Apps** (n=4): Apps like the *STREAM Program* effectively reduces distress and improves quality of life through cognitive-behavioral techniques, *CanRelax and Focus Me App* offer mindfulness exercises and symptom tracking, reducing stress symptoms[1, 2]; Similarly the *Mika app*, supports breast cancer patients in Switzerland by providing personalized symptom management, psychological coaching, and AI-driven recommendations, enhancing their quality of life during treatment [3]. A study in Switzerland indicate that mindfulness and relaxation apps can be a feasible and effective method for delivering self-care interventions to cancer patients, particularly benefiting those experiencing high levels of distress[4]. **ePRO Systems** (n=2): The Medidux ePRO app (or consilium care ePRO app) enhances

communication between cancer patients and treatment teams at See-Spital Horgen and other Swiss clinics, improving the communication between patients and treatment teams, regarding the personalization care therapy in clinic practice [5, 6]. The lePRQ Model of care study is designed as a bicentric longitudinal randomized controlled phase II trial [7], aims to test a model of care that uses electronic patient-reported outcome (ePRO) questionnaires to enhances symptom management for immune checkpoint inhibitor (ICI) therapy by detecting adverse events early and improving patient [8]. **Care Coordination Platforms** (n=1): The Swiss Post Cuore Platform facilitates integrated care delivery by securely connecting patients, providers, insurers, and pharmacies within a centralized ecosystem including cancer [9]. **Personalized medicine in clinical practice** (n=1): The SwissMTB (Swiss Molecular Tumor Board) is a comprehensive molecular diagnostics workflow designed to improve personalized cancer treatment in Swiss clinics [10]. These findings highlight Switzerland's commitment to improving cancer care through digital health solutions.

Conclusion: The limited evidence suggests that digital health, can provide significant benefits to cancer patients in Switzerland. However, the digital solutions in Switzerland's healthcare sector, highlight the need for continued efforts to embrace digitalization. Fostering innovation, and educating stakeholders are crucial for realizing their full potential in Swiss oncology practice.

Unraveling the relationship between physical activity and unhealthy alcohol use in the general population: A cross-sectional study

Marianthi Lousiana Deligianni

Background: Numerous studies documented an unexpected association between physical activity (PA) and alcohol use suggesting that higher rates of PA may be linked to increased alcohol use. Evidence is lacking on factors explaining this relation. This study investigated cross-sectional associations between time devoted to different domains of PA and unhealthy alcohol use and tested whether these associations differed by age and sex.

Methods: Data were drawn from the 2017 Swiss Health Survey. Participants (N=17,328) are representative of the Swiss population and provided information on 3 PA-domains (hours/day of sport/exercise, leisure, commuting) and unhealthy alcohol use (chronic risky drinking [≥20g mean daily ethanol for women; ≥40g for men], heavy episodic drinking [≥1occasion/month with ≥40g for women/≥50g for men]). Logistic regression models were used to estimate associations between hours/day spent on the 3 PA-domains and unhealthy alcohol use, and to test interactions between PA-domains and sex and age separately. All models were adjusted for tobacco use, BMI and demographics.

Results: Hours/day of leisure PA was positively associated with chronic risky drinking (OR=1.06, p=0.030). Hours/day of sport/exercise PA was positively associated with heavy episodic drinking (OR=1.12, p=0.007). No significant association was found for commuting PA. There was a significant interaction between sport/exercise PA and age on heavy episodic drinking (p<0.001). Age-stratified analyses revealed positive associations for participants aged 18-<25 (OR=1.44, p<0.001), 25-<35 (OR=1.23, p=0.019), and ≥75 (OR=1.74, p=0.003), negative for participants aged 35-<45 (OR=0.73, p=0.019), and non-significant associations for participants aged 45-<55 (OR=0.96, p=0.720), 55-<65 (OR=0.99, p=0.909), and 65-<75 (OR=1.05, p=0.713).

Conclusions: Our results highlight the importance to account for PA-domains and alcohol use patterns when studying the PA-alcohol relationship. Associations between sport/exercise and heavy episodic drinking differed by age, possibly reflecting the socio-environmental context's impact across the lifespan. Findings may have implications for alcohol screening and interventions among physically active people.

Bringing AI-based automation of breast cancer radiotherapy into clinical practice

Michele Zeverino

Aim: To fully automate and optimize the treatment planning process for early-stage breast cancer radiotherapy by developing a deep learning (DL) model capable of predicting the 3D dose distribution, and implementing this approach into daily clinical practice.

Materials and Methods: The research followed four key milestones:

a) Development of a DL-based auto-planning model for left-sided breast cancer, including data collection and model training.

b) Evaluation of model performance against conventional manual planning under patient-related uncertainties.

c) Adaptation of the left-sided model for right-sided breast cases using scripting tools to generalize dose prediction.

d) Optimization of dose exposure to organs-at-risk (OARs) through an automated, anatomy-specific approach.

Results: a) Eighty high-quality manual treatment plans were curated and used to train a U-Net-based DL model. Validation on 15 additional cases showed comparable or superior plan quality versus manual plans, enabling clinical implementation for left-sided patients.

b) The DL model demonstrated robustness in the presence of anatomical and contouring variations, maintaining similar performance to manual planning under uncertainty conditions.

c) A custom scripting technique was developed to adapt left-sided dose predictions for right-sided patients. The adapted model was validated against 20 manually planned right-sided cases and introduced into clinical use.

d) A fluence-based thresholding technique was incorporated to further reduce OAR doses based on patient-specific anatomy, enhancing plan quality without compromising target coverage.

Conclusions: DL methods were successfully integrated into the clinical treatment planning workflow for early-stage breast cancer on both sides. The automated plans not only reduced planning time but also consistently outperformed conventional manual plans in terms of overall quality, supporting a shift toward AI-driven planning in routine practice.

Triangulating evidence to detect signatures of stabilizing selection acting on molecular traits in humans

Mihaela Diana Zanoaga

Background: Evidence suggests that stabilizing selection shapes molecular trait evolution in primates, maintaining transcript and protein levels within optimal range. However, quantifying stabilizing selection remains challenging. Here, we propose a comprehensive approach that triangulates evidence from non-linear Mendelian Randomization (MR) and selection-aware GWAS models.

Material and Methods: We leveraged UK Biobank data from 337,386 unrelated whiteBritish individuals, alongside association summary statistics for protein QTLs (~3,000 proteins). First, we applied state-of-the-art methods, including GRM-MAF-LD and LDpred2, to infer stabilizing selection on protein levels. Second, we developed a robust non-linear Mendelian Randomization (MR) approach, using linear and squared Polygenic Risk Scores (PRS) as instruments, to investigate the presence of an inverted U-shaped causal relationship between molecular traits and fitness proxies (e.g., number of offspring), which would indicate stabilizing selection.

Results: Applying GRM-MAF-LD to ~2,000 proteins, we identified significant selection estimates ($p \leq 0.01$) for 858 proteins, 94% of which were negative and therefore indicative of stabilizing selection. Non-linear MR identified 14 hits ($p \leq 0.01$), 71% of which showed evidence of stabilizing selection. Among these, 7 proteins were also confirmed by the GRMMAF-LD approach and were primarily linked to immune function and lipid metabolism. PLA2G4A, a highly conserved gene across species and involved in inflammation signaling was identified to be under the strongest selection.

Conclusion: While selection-aware GWAS methods appear to be more powerful than MR, they provide orthogonal lines of evidence for stabilizing selection enabling robust prioritization of proteins most shaped by this evolutionary mechanism.

Gut-Brain Axis: Molecular mechanisms underlying the beneficial effect of prebiotics on metabolic health

Nadine Eliasson

The Western diet (WD), rich in fat and sugar but low in dietary fiber, contributes to obesity by disrupting energy homeostasis and impairing gut-brain communication. Supplementation with dietary fiber has been shown to mitigate these effects, yet the mechanisms remain unexplored. In mice, adding 10% dietary fiber to a WD reduced food intake, increased satiety, and elevated energy expenditure. These benefits are likely mediated by short-chain fatty acids (SCFAs), produced through microbial fermentation of fiber. SCFAs are known to activate the brainstem—particularly the nucleus tractus solitarius (NTS)—and are associated with increased production of glucagon-like peptide-1 (GLP-1). Given that exogenous SCFA administration also alters feeding behavior, we hypothesize that the neuronal sensing of SCFAs, which relays signals to the hypothalamus via gut-brain pathways, underlies the protective effects of dietary fiber against WD-induced obesity.

To explore the role of GLP-1 signaling in this process, we selectively ablated Glp1r-expressing vagal afferent fibers by injecting a Cre-dependent diphtheria toxin A (DTA) virus into the nodose ganglion of Glp1r-ires-Cre mice. Preliminary results revealed a reduction in body weight across all dietary conditions, indicating a possible role for Glp1r-expressing vagal afferents in regulating energy balance. These findings support a model in which SCFA-driven activation of gut-brain signaling—potentially through GLP-1 sensing pathways—contributes to the metabolic benefits of dietary fiber. Ongoing studies will further dissect the neural circuits involved and determine whether SCFA sensing is a key mechanism linking fiber intake to protection against diet-induced obesity.

Exploring the etiology and immune microenvironment of Cutaneous T-Cell Lymphoma

Pacome Prompsy

Cutaneous T-cell lymphoma (CTCL) is a complex and heterogeneous cancer of the T cells, characterized by the clonal proliferation of malignant T cells in the skin. Despite advances in treatment, the etiology of CTCL remains poorly understood, and improved diagnostic and prognostic tools are urgently needed. This PhD aims to address these challenges by exploring spatial multi-omics, viral integration analysis, and T-cell receptor (TCR) clonality studies.

First, we focus on understanding the spatial immune microenvironment of CTCL using spatial multi-omics techniques, integrating both RNA and protein data. Building on the lab previous proteomics analysis of a 50-patient cohort, which identified that this impairement of malignant T cells, we are now expanding our study to a larger cohort of 80 patients. We aim to understand what drives proliferation of malignant T cells in the skin and what distinguishes patients progressing to an aggressive stage of the disease from those that remain controlled.

Second, given the unknown etiology of CTCL and based on previous evidence of onco-virus in closely related cancer, ATL/L, we are investigating the potential role of viral DNA integration in the disease. Using large genomic databases of CTCL patients, we will search for evidence of viral integration events that may contribute to tumorigenesis.

Finally, we are exploring the clonality of TCRs in CTCL patients. Malignant T cells in CTCL often share a dominant clone, suggesting a common antigenic trigger. By analyzing TCR sequences across patients, we aim to identify common pathogens or self-peptides that may drive tumorigenesis.

With this PhD, we hope to shed light on the origin and development of CTCL. Better understanding of these origins might help us finding therapeutic targets for the disease and treat it more efficiently in patients at risk of disease progression.

Investigating immunesuppression in breast-to-brain metasatasis

Paola Guerrero Aruffo

Introduction: Metastatic dissemination to the brain occurs in approximately one-third of patients with breast cancer (BC) and can lead to life-threatening neurological damage. Stereotactic radiosurgery (SRS), a standard-of-care treatment for brain metastasis (BrM), controls over 80% of targeted lesions. However, the emergence of new BrM lesions outside the irradiation field and the progression of extracranial disease limit median overall survival to just over one year. Therefore, there is an urgent need to develop more efficient therapies. To achieve this, it is crucial to understand how the local tumor microenvironment (TME) responds to treatment.

Material and Methods: To study the changes in the BC-BrM TME, we used various in vivo studies, transcriptional analyses, and functional assays to directly compare orthotopic BC tumors with their BC-BrM counterparts.

Results and discussion: Here, we show that while CD8+ T cells can infiltrate breast cancer-brain metastases, their anti-tumor cytotoxicity is locally suppressed in the brain. Conversely, CD8+ T cells exhibited tumoricidal activity in extracranial mammary lesions originating from the same cancer cells. Consequently, combined high-dose irradiation and anti-PD1 therapy was effective only in extracranial tumors, but not intracranial lesions. Transcriptional analyses and functional studies identified neutrophils and Trem2-expressing macrophages as key sources for local T cell suppression within the brain, providing rational targets for future therapeutic strategies.

Conclusion: In this study, we show that while CD8+ T cells infiltrate BC-BrM, they lack anti-tumor cytotoxicity even under T cell-stimulating conditions. Single-cell profiling and ex-vivo functional assays identified BrM-infiltrating neutrophils and Trem2+ monocyte-derived macrophages and microglia (collectively termed tumor-associated macrophages, TAMs) as key sources of local T cell suppression.

Establishing a phage collection as a first step towards a new strategy for the management of non-typhoidal Salmonellosis

Raphaël Baudin

Background: Acute non-typhoidal salmonellosis is the second most common cause of gastroenteritis in Switzerland. Antibiotics are not recommended due to limited efficacy and the perturbation they cause to the gut microbiota, a natural barrier to the infection. Thus, untreated carriers represent an important reservoir for transmission to vulnerable people, in whom the infection can become life-threatening. Using bacteriophages, specific bacterial viruses, is proposed as a decolonization strategy for carriers.

Methods: A collection of Salmonella clinical isolates was assembled in collaboration with NENT, UZH. Bacteriophages were isolated from local wastewaters. Their host ranges were characterized through efficiency of plating (EOP) assays. *In silico* analyses of the phage genomes allowed evaluation of their suitability for clinical intervention.

Results: We retrieved eight genetically distinct lytic phages. None carried genes coding for known virulence or antimicrobial resistance determinants. The collection efficiently infected and lysed 99% of 104 *Salmonella* clinical isolates from the six most dominant serovars (Enteritidis, Typhimurium, Monophasic Typhimurium, Napoli, Infantis, and Derby). However, *S*. Infantis and *S*. Derby displayed high resistance to individual phages, suggesting presence of specific and highly effective anti-phage mechanisms in these serovars. First phage training experiments suggested possibility to increase virulence of some phages.

Conclusions and perspectives: Genetically different Salmonella phages with clinical potential were isolated from Swiss wastewaters. These phages cover a broad spectrum of dominant serovars, *S*. Infantis and *S*. Derby being the exceptions. Next steps towards clinical application are i) to evaluate their *in vitro* efficacy, ii) to produce few promising candidates through the Swissmedic authorized CHUV phage manufacturing pipeline and to iii) evaluate their efficacy *in vivo* in a preclinical model of *Salmonella* infection.

Sleep assessment using accelerometry : not all algorithms are equal

Ruyan Zhou

Background: accelerometry devices are increasingly being used to assess sleep metrics. Whether different algorithms lead to similar findings has seldom been studied.

Objective: compare the results of two accelerometry-based algorithms and one self-reported sleep journal.

Methods: data from the second (2014-17, 2724 participants, 53.3% women, 62.0±10.0 years) and the third (2018-21, 2087 participants, 53.5% women, 65.1±9.6 years) follow-ups of the CoLaus|PsyCoLaus study. Seven-day accelerometry data was processed by two algorithms: GGIR running on R (GGIR), and an Excel macro-command (MACRO). A subset of participants also completed an ecological momentary assessment (EMA) tool for one week. Results for sleep onset (categorized into <22:00, 22:00-23:59 and 24:00+), average sleep duration, and average sleep efficiency were compared.

Results: in both surveys, GGIR provided higher sleep duration than MACRO: 406±103 vs. 378±79 and 397±60 vs. 366±84 minutes for the second and the third surveys, respectively, both $p<0.001$. Sleep duration assessed by GGIR and MACRO showed a Spearman $r=0.592$ in both surveys, and a Lin's concordance correlation (95% confidence interval) was 0.269 (0.236-0.301) and 0.513 (0.486-0.540) for the second and the third surveys, respectively. GGIR results were closer to EMA than MACRO. For sleep onset, GGIR categorized over 80% of participants in the <22:00 category, vs. 38%-64% for MACRO and 8%-12% for EMA. GGIR provided higher sleep efficiencies than MACRO, 72±17 vs. 70±14 and 70±7 vs. 67±15% for the second and the third surveys, respectively, both $p<0.001$, with Spearman $r=0.383$.

Conclusion: when assessing sleep using accelerometery data, different algorithms might lead to significantly different results.

The Causes and Consequences of Early Life Malnutrition

Sarah McHugh

Recent years have seen a global surge in deaths linked to diet-related noncommunicable diseases. Evidence suggests that both early life under- and overnutrition contribute to an increased risk of metabolic disease in later life. Both forms of malnutrition share common pathophysiological hallmarks and their prevalence is of particular concern in low- and middleincome countries, where both forms of malnutrition can exist within individuals concomitantly or at different stages during their lifetime ("double burden of malnutrition" - DBM). Many aspects of health are driven by the gut microbiota and dysbiosis due to early life malnutrition may contribute to the physiological responses to nutrition-related disorders. The factors linking early life malnutrition to metabolic syndrome development in later-life however, remain unclear. We investigate a causal role of the early-life gut microbiota in the trajectory from early life over- and undernutrition to metabolic syndrome. We aim to elucidate the mechanisms underlying DBM through a neonatal mouse model of in utero dietary growth restriction or macrosomia followed by an exposure to a western-style or chow diet at weaning. Our findings show that offspring born to undernourished dams displayed a sex-dependent increased weight gain compared to overnourished or control mice post-wean. Additionally, offspring born to undernourished mothers demonstrated a trending increase of serum biomarkers of metabolic disease, including resting glucose. Analysis of 16S rRNA sequencing data revealed characteristic faecal microbial compositions between groups. Differential abundances of specific taxa from mice born to malnourished mothers, despite exposure to a chow diet at weaning, reflected imprinting of dysbiotic maternal microbial inheritance, early-life succession and dietary shifts. We anticipate that our findings highlight the role of maternal nutrition in shaping the early-life gut microbiota and downstream metabolic health. It is essential to understand these mechanisms to design targeted preventable strategies and treatments.

Single-Cell Dissection of Evolved Malnutrition Adaptation in Drosophila Fat Body

Shrinath Narayanan

Chronic nutrient limitation drives profound physiological and developmental adaptations, yet the cellular basis of these changes remains poorly understood. We have leveraged a *Drosophila melanogaster* experimental evolution model in which ten populations—five "Selected" lines reared for >300 generations on a nutrition limiting poor diet and five "Control" lines maintained on standard nutrient levels—exhibit heritable differences in growth rate, adult body size, fat storage, and amino-acid assimilation. Bulk transcriptomic profiling of whole larvae identified metabolic pathways associated with these adaptive traits, but lacked the resolution to assign changes to specific cell types.

To bridge this gap, we have undertaken single-cell RNA sequencing of the larval fat body, the primary organ for energy storage, nutrient sensing, and inter-organ signaling during development. By profiling tens of thousands of nuclei from third-instar fat bodies of Selected and Control populations under the same nutritional regime, we aim to chart the full repertoire of fat-body cell states at a critical developmental checkpoint and to determine how long-term selection reconfigures their proportions and gene-regulatory programs.

We compare fat-body cell compositions to identify subpopulations that expand, contract, or emerge uniquely in Selected versus Control lines. Next, we will examine single-cell transcriptional profiles to see how metabolic modules—lipid handling, amino-acid transport, energy sensing, and signaling—are remodeled by long-term selection. Finally, we are looking for evidence of adaptive trade-offs, that may accompany enhanced growth under nutrient limitations.

By integrating cell-type maps with different evolutionary regimes, we identify candidate genes and pathways mediating the evolved nutritional phenotypes. This single-cell atlas offers novel insights into how selection pressure on whole-animal performance translates into re-wiring of specific cellular architectures and networks. Our findings will illuminate the cellular logic of quantitative metabolic adaptation and establish a generalizable framework for linking organismal evolution to cell-type–specific transcriptomic shifts under environmental stress.

Impact of exercise training intensity on endurance capacity and skeletal muscle metabolic transcriptional adaptations in a mouse model of peripheral artery disease

Slobodan Kojic

Introduction: Lower extremity peripheral artery disease (PAD), caused by the buildup of atherosclerotic plaques that narrow the arteries supplying the legs, is a global health issue. Exercise training is a cornerstone therapy for PAD, yet the effects of different training intensities on skeletal muscle adaptations remain unexplored.

This study examined the effects of moderate-intensity continuous training (MICT) versus high-intensity interval training (HIIT) on endurance performance and skeletal muscle metabolic gene expression in a mouse model of PAD.

Methods: Male C57BL/6 mice underwent right common iliac artery ligation and were randomized into three groups: sedentary (SED), MICT (40 minutes of running at 70% of maximal aerobic speed), and HIIT (8x 2.5 minutes running at 90% of maximal aerobic speed, interspersed with 2.5 minutes running at 50% of maximal aerobic speed). PAD mice run on a treadmill 3 times/per week for 8 weeks. Endurance capacity was assessed by determining maximal running distance (MRD). Quantitative PCR (qPCR) was performed to determine metabolic gene expression in both ischemic and non-ischemic gastrocnemius (fast-twitch fibers), and soleus (slow twitch) muscles.

Results: Both MICT and HIIT significantly improved MRD, with no significant difference between them. In the ischemic gastrocnemius, HIIT upregulated PFK, CD36, HSL and CS mRNA expression, while in the non-ischemic muscle only CS gene expression was upregulated. MICT did not significantly alter metabolic gene expression in gastrocnemius muscle. In the ischemic soleus, HIIT upregulated mtND6 and CYTB, while in the non-ischemic soleus HIIT upregulated PGC-1a and CYTB, and lead to downregulation of CD36 and HK2. MICT upregulated GLUT-4, LDHA and TFAM expression only in the ischemic soleus muscle.

Conclusion: MICT and HIIT are equally effective in improving endurance capacity, whereas HIIT induces greater transcriptional adaptations in skeletal muscle compared to MICT in our experimental model of PAD.

Brain dysconnectivity and cognitive impairment in early psychosis: interplay between nature and nurture

Teya Petrova

Processing speed (PS) impairment is one of the most common and severe cognitive deficits in schizophrenia, related to poor clinical outcome and impacting other cognitive domains. Previous research has reported correlations between PS and white matter diffusion properties, particularly generalized fractional anisotropy (gFA), suggesting that white matter alterations could underlie decreased PS.

Schizophrenia is known to arise from a complex interaction of genetic and environmental factors. Among environmental factors, childhood adversities, including subtypes of abuse (sexual/physical/emotional) and neglect (physical/emotional), have been linked to a higher risk for psychosis, increased symptom severity and greater functional impairment. Genetically, schizophrenia is highly heritable and has a polygenic basis. Genome-wide association studies have provided novel insights into the etiology of schizophrenia capturing the combined effects of many genetic variants through polygenic risk score (PRS) calculation. More recently, pathway-specific PRSs, related to the pathophysiology of psychosis, have improved predictive accuracy in distinguishing patient status.

Participants included early psychosis patients from the Treatment and Early Intervention in Psychosis (TIPP) program in CHUV (n = 168) and healthy controls from the general population (n = 179). All participants underwent a comprehensive set of clinical, cognitive, genetic and neuroimaging evaluations. Logistic regression analyses were conducted to study the predictive power of pathway-specific PRS and of the presence of childhood adversities. Voxel-based analysis was used to examine correlations between gFA and processing speed performance.

Pathway-specific PRS related to neuroinflammation (OR = 1.33; p = 0.006) and GABAergic interneurons (OR = 1.17; p = 0.009) significantly predicted patient status. Childhood trauma was associated with psychosis, especially neglect (OR = 1.31; p > 0.001) along with its subtypes. Patients showed reduced gFA compared to controls (t = -4.13; p > 0.001); however, no significant correlation was found between gFA and processing speed.

Stimulation of astrocytes in the neurogenic niche of the dentate gyrus

Thibault Sprenger

Adult neurogenesis is a process by which hippocampal neural stem cells (NSCs) proliferate and produce new and functional neurons. This process is observed in two regions of the mammalian brain, the subventricular zone and the dentate gyrus of the hippocampus. In the hippocampus, adult neurogenesis is involved in learning and memory.

Interestingly, the direct cellular environment of NSCs, the neurogenic niche, provides major neurogenic cues. In particular, astrocytes play a crucial role in several steps of adult neurogenesis including NSC proliferation, new neurons' survival, and synaptic integration.

In order to further investigate the role of astrocytes on the regulation of adult neurogenesis, we used a novel viral approach to target the expression of activating Designer Receptor Exclusively Activated by Designer Drugs (DREADD) specifically in astrocytes. Using calcium imaging, we verified the appropriate targeting of astrocytes and DREADD functional expression in these cells. We then used this approach in vivo to control the activity of astrocytes in the dentate gyrus and examine their role in the regulation of adult hippocampal neurogenesis. The goal of this study is to test the possibility that artificially activating astrocytes may increase adult neurogenesis and hippocampal function.

These investigations will enable a better understanding of the regulation mechanisms of adult neurogenesis in the hippocampus by the neurogenic niche. These mechanisms are relevant to hippocampal function and diseases, such as Alzheimer's disease and mood disorders.

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