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LIMNA
LAUSANNE INTEGRATIVE METABOLISM & NUTRITION ALLIANCE

METABOLISM IN AGING AND DISEASE

- POSTER ABSTRACTS -

POSTER NUMBERS (BY NAME OF ABSTRACT SUBMITTER)

1) **Joan Blanco I Fernández**
2) **Talayeh Sadat Brügger**
3) **Cristiana Centofanti**
4) **Simone Crivelli**
5) **Juliane Da Graça**
6) **Haissa de Castro Abrantes**
7) **Asya Dolgikh**
8) **Nadine Eliasson**
9) **Nadia Elshareif**
10) **Konstantina Kioseoglou**
11) **Gioele La Manno**
12) **Sylviane Lagarrigue**
13) **Benjamin Lair**
14) **Esther Landaluce Iturriria**
15) **Pauline Leal**
16) **Weilin Li**
17) **Miriam Lisci**
18) **Jaime Lopez-Alcala**
19) **Isabel Cristina Lopez Mejia**
20) **Julia Primavesi**
21) **Sruthi Raja**
22) **Alicia Rey**
23) **Amélie Sabine**
24) **Clarisse Simons**
25) **Cassandra Tabasso**
26) **Aart Adriaan Cornelis van der Graaf**

1) **Joan Blanco I Fernández**

Integrated profiling reveals distinct roles for mitochondria in shaping the IL-4/IL-13 macrophage response

Joan Blanco-Fernandez (1), Miriam Lisci (1), Mads M. Foged (1), Chloé Chapuis (1), Tim Pflästerer (2), Tatjana Kleele (2), Alexis A. Jourdain (1)*

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Mitochondria drive cellular reprogramming by integrating metabolism and signaling. In macrophages, mitochondria are central to the immunometabolic response to external cues, but the extent to which mitochondria are remodeled and participate to macrophage reprogramming remain unclear. Here, we integrate transcriptomics with whole-cell and purified mitochondrial proteomics to profile LPS/IFNγ- and IL-4/IL-13-stimulated macrophages. We reveal a striking disconnect between mitochondrial transcripts and protein levels following either stimulus, and a STAT6-dependent increase in mitochondrial DNA (mtDNA) expression and intramitochondrial translation in IL-4/IL-13 macrophages. We demonstrate that pharmacological inhibition of mitochondrial translation or individual respiratory chain complexes variably impairs reprogramming, and that ATP synthase inhibition uniquely triggers the integrated stress response (ISR) through mitochondrial hyperpolarization, thus preventing IL-4/IL-13 reprogramming. Mechanistically, we show that restoring mitochondrial membrane potential or inhibiting the ISR rescues IL-4/IL-13-mediated reprogramming. Together, we identify mtDNA expression, intramitochondrial translation, and mitochondrial membrane potential as critical, drug-sensitive determinants of the IL-4/IL-13 response.

2) Talayeh Sadat Brügger

Astrocytic Mitochondrial Responses to Blue Light: From Membrane Potential to Metabolic Shifts

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Blue light affects various aspects of physiology, including circadian rhythm, sleep, and learning. In recent decades, human exposure to blue light has significantly increased due to widespread use of screens and LED-lighting. Concurrently, blue light through the implementation of optogenetics has become a powerful experimental tool. Prior to the development of optogenetics, studies already reported that visible light, in particular blue light, impacts astrocytic mitochondria, leading to increased reactive oxygen species production and elevated intramitochondrial Ca2+ levels. Our recent findings show that blue light modulates mitochondrial membrane potential (ΔΨm) in astrocytes, acting similarly to a mitochondrial uncoupler. We used primary mouse astrocyte cultures incubated with or without all-trans retinal (a light-sensitive cofactor), and assessed ΔΨm in situ using tetramethylrhodamine methyl ester (TMRM). Cells were exposed to blue light (480nm) for different durations (1 s to 2 min) at an intensity of 2mW, and the effects of different light intensities (60μW to 2mW) were assessed. Our results show that, in astrocytes, blue light depolarizes ΔΨm in situ, proportionally to both light exposure duration and intensity. Notably, the response to blue light varied among individual astrocytes. We are currently investigating whether blue-light influences the energy metabolism by measuring the glycolytic lactate output.

These findings reveal that blue light may impact metabolic pathways of astrocytes, which should be further examined in other cell types, particularly in the retina, which is naturally exposed to ambient light. Finally, researchers running optogenetic experiments need to consider potential unintended effects of blue-light when using long-term exposure.

3) Cristiana Centofanti

Slc6a8Y389C knock-in rat model of creatine transporter deficiency exhibits changes in cardiac phenotype and motor dysfunction

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Creatine transporter deficiency (CTD) is a still untreatable debilitating IEM, X-linked and associated with loss-of-function mutations in the SLC6A8 gene encoding the creatine transporter responsible for cellular creatine uptake throughout body tissues. This is reflected in the clinical profile of patients characterized by intellectual disabilities, delayed speech development, seizures, movement disorders as well as distinct cardiac phenotypes.

Our recently described Slc6a8Y389C knock-in(KI) rat model carries a patient-derived missense mutation that completely abolish creatine transporter activity. Our previous results on 4-months-old KI male rats exhibits deficits in muscles development with no sign of muscle atrophy and altered neuronal connectivity in the cerebellum. These findings, together with altered behavioural outcomes in motor tests, indicate that our model recapitulates the main phenotypes of the disease. Our group newly aimed to explore the cardiac phenotype of our CTD model. Our results indicate a trend towards an increase in cardiomyocyte width in the KI group. This observation may suggest a compensatory structural adaptation to the disruption of the creatine–phosphocreatine system. At the same time, we measured the expression levels of specific calcium and potassium channels (Cav1.2 and KV11.1), which are involved in the regulation of cardiac excitation–contraction coupling. Our findings suggest an overexpression of both proteins in the KI group compared with the WT one. This ion channel remodelling could be associated with alterations in the ECG profile that have been previously reported in other murine models and in a recent clinical study.

4) **Simone Crivelli**

Overexpression of UCP4 in astrocytes induces fatty acid oxidation for mitochondria respiration fuelling

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A growing body of evidence recognizes astrocytes' ability to oxidize fatty acids as an energy substrate, a process that appears critical for higher-order cerebral functions. However, the signals that reprogram astrocytes from primarily glycolytic metabolism to fatty acid utilization remain unclear. Here, we provide the first evidence that increased expression of mitochondrial uncoupling protein 4 (UCP4) in primary astrocytes induces a metabolic shift favoring β-oxidation. UCP4 overexpression upregulate genes associated with fatty acid uptake, synthesis, transport, and metabolism, enabling fatty acids to fuel mitochondrial respiration while redirecting glucose-derived pyruvate toward lactate production. This astrocytic metabolic shift prevented neurodegeneration in the familial Alzheimer's disease mouse model 5xFAD. Mice treated with an adeno-associated virus (AAV) overexpressing UCP4 did not develop memory impairments at 6 months of age. Moreover, brain levels of Aβ1-42 as well as synaptic markers such as PSD95 were rescued. Our data suggest that inducing a metabolic shift toward β-oxidation could provide a biological framework for developing treatments for neurodegenerative diseases such as AD.

Keywords: β-oxidation, mitochondria, mitochondrial uncoupling protein 4, astrocytes, Alzheimer's disease

5) **Juliane Da Graça**

Lysosome–mitochondria contact sites and lipid flux as drivers of α-synuclein aggregation initiation in parkinson's disease models.

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Parkinson's disease (PD) is characterized by prion-like aggregation of α-synuclein (aSyn) into Lewy bodies within vulnerable neuronal populations. This process coincides with mitochondrial and lysosomal dysfunction, yet the mechanisms linking organelle integrity and aSyn propagation remain unclear. Lipid imbalances are increasingly implicated in PD, and mutations in lipid metabolic genes are risk factors. We hypothesize that neuronal lipid profiles and organelle contact sites coordinate membrane integrity and lipid flux, thereby modulating aSyn aggregation and driving PD pathogenesis. Here, we investigate how lysosome–mitochondria interactions shape lipid exchange and contribute to aSyn pathology. We use primary mouse hippocampal neurons and patient-derived induced dopaminergic neurons exposed to preformed aSyn fibrils (PFFs). To monitor lysosome-mitochondria dynamics during PFF seeding, we apply super-resolution imaging and correlative light electron microscopy. We are also mapping the proteome of these contact sites using split-TurboID proximity labeling coupled with mass spectrometry. By combining lipidomics with advanced imaging, we aim to identify lipid distributions linked to neuronal susceptibility and dissect lipid flux at lysosome-mitochondria contact sites.

6) Haissade Castro Abrantes

Brain ASIC1a regulates systemic energy balance and thermogenesis

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The integration of central nervous system signals with peripheral metabolism is essential for maintaining energy homeostasis. The acid-sensing ion channel 1a (ASIC1a), a proton-gated ion channel widely expressed in the brain, has been implicated in neuronal excitability and behaviour, but its role in metabolic control remains unclear. Notably, previous work from our group demonstrated that ASIC1a-deficient mice exhibit reduced core body temperature, suggesting a role in thermoregulation [a]. Here, we investigated the metabolic consequences of ASIC1a deficiency using knockout (KO) mice. We found that ASIC1a KO males exhibit reduced core body temperature, confirming and extending prior findings, alongside a shift in substrate utilization toward increased lipid oxidation. No differences were observed in ASCI1a KO females. At the systemic level, ASIC1a KO males display reduced body weight and fat mass, accompanied by smaller white adipocytes and elevated circulating free fatty acid blood levels, consistent with enhanced lipid mobilization. Despite this, brown adipose tissue (BAT) shows reduced levels of uncoupling protein 1 (UCP1), a key thermogenic mediator. Proteomic profiling of BAT reveals a coordinated downregulation of pathways related to fatty acid oxidation, mitochondrial function, and thermogenesis, suggesting impaired thermogenic capacity despite increased systemic lipid utilization. Importantly, these effects occur without changes in circulating corticosterone, indicating that the phenotype is not driven by altered stress axis activity. In contrast, ASIC1a KO males exhibit elevated testosterone levels, pointing to a potential neuroendocrine mechanism underlying these adaptations. Together, our findings identify ASIC1a as a regulator of whole-body energy balance and thermogenesis in a sex-dependent manner.

7) Asya Dolgikh

Precision Nutrition in ALS: A Multi-Omics Approach to Identifying Metabolic Therapeutic Targets

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor neuron degeneration and profound metabolic dysregulation. Despite mounting evidence that nutritional status directly influences disease progression and survival, clinical nutritional care in ALS remains generic and non-personalized — a critical gap that precision medicine approaches are uniquely positioned to address.

We present NourishAI, a precision nutrition platform leveraging large-scale multi-omics data to identify metabolic therapeutic targets in ALS. Using population-scale cohort data integrating NMR-based metabolomics, genome-wide nutrigenetic variants, and longitudinal clinical phenotypes, we characterize the metabolic landscape of ALS across the disease continuum — distinguishing pre-diagnostic signatures from disease-consequence markers through temporal stratification.

Our analysis reveals that nutrigenetic effects — the interaction between nutritional genetic variants and circulating metabolite levels — are robustly preserved in ALS patients relative to healthy controls, providing a compelling biological rationale for applying precision nutrition frameworks developed in healthy populations directly to neurodegenerative disease contexts. Pathway-informed integration of genomic and metabolomic signals highlights specific nutrient domains, including folate metabolism, lipid homeostasis, and B-vitamin pathways, as candidates for targeted nutritional intervention.

These findings form the foundation of a clinical decision-support prototype currently being validated in an observational study at Swiss ALS centers, integrating AI-driven dietary tracking with metabolomic profiling to generate individualized nutritional recommendations. NourishAI represents a translational bridge between large-scale population biology and actionable clinical nutrition — with a roadmap to expand from ALS to broader neurodegenerative and aging-related conditions.

8) Nadine Eliasson

Gut-Brain Axis: The Role of GLP1R-Vagal Afferents in the Effect of Dietary Fiber on Energy Balance

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The global prevalence of obesity continues to rise, with evidence suggesting that this trend is driven more strongly by dietary intake than by sedentary lifestyle1. In parallel, consumption of ultra-processed foods (UPFs) has increased in the same countries experiencing rising obesity rates2. UPFs are typically high in sugar and fat but notably low in dietary fiber3, which is fermented by the gut microbiota to produce short-chain fatty acids (SCFAs) with key roles in metabolic regulation4. Consequently, many UPFs are now reformulated with added fiber, making it essential to understand how this supplementation, and the resulting SCFA production, influences metabolic regulation and feeding behavior.

Since SCFAs can directly stimulate glucagon-like peptide 1 (GLP1) production5, we hypothesized the fiber-induced SCFA production engages GLP1-dependent gut-brain signaling to promote satiety. To test this, GLP1R-expressing vagal afferents were selectively depleted in mice exposed to a Western-style diet (high fat, high sugar and low fiber) and subsequently supplemented with soluble fiber. Fiber supplementation rapidly increased satiety in control animals without affecting satiation. In contrast, mice lacking GLP1R+ vagal afferents failed to exhibit fiber-induced satiety and instead displayed altered meal termination.

These findings identify a critical role for GLP1R-dependent vagal signaling in mediating feeding adaptations to dietary fiber under obesogenic conditions. Ongoing work aims to define the central circuits integrating these gut-brain signals upon fiber nutrition. Overall, the goal is to understand how fiber supplementation in UPFs influences gut-brain signaling to inform obesity prevention strategies and potentially identify new therapeutic targets.

9) Nadia Elshareif

Maternal programming: How maternal diet imprints lifelong metabolic health outcomes

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Why does maternal diet powerfully shape offspring metabolic health, long before lifestyle choices have an effect? Evidence suggests that vulnerability to metabolic disease is programmed in utero and during critical early life windows, yet signals linking maternal nutrition to the development of offspring metabolic regulation remains poorly defined. Western-style diets are largely composed of ultra-processed foods, characterized by high fat, sugar, and low fiber, that disrupt the maternal gut microbiota and reduce fermentable substrates, thus impairing gut-brain signaling pathways vital for metabolic regulation. Consequently, bacterial production of short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, is reduced. These metabolites regulate glucose homeostasis, energy expenditure, and autonomic function via the gut-brain axis. However, their role in programming the gut-brain axis during early life remains unclear and a comprehensive characterization of this regulation is needed.

Here, we investigated whether maternal nutrition and gut-derived metabolites program offspring brown adipose tissue (BAT) thermogenesis through alterations in adipose tissue morphology and autonomic regulation. Using maternal dietary interventions, we performed metabolic phenotyping of offspring alongside analyses of BAT structure, and autonomic regulation across offspring lifespan. We show that maternal fiber intake and SCFA production during offspring development may protect against metabolic dysfunction, accompanied by preserved BAT morphology and thermogenic capacity. In contrast, disruption of the maternal gut microbiota by western diet increased susceptibility to impaired BAT thermogenesis and metabolic dysfunction. These findings highlight the importance of nutrition and gut-derived metabolites for neuro-metabolic programming as early as in the womb.

10) Konstantina Kioseoglou

Reinvigorating the Aged Immune System by Targeting the Immune, Hematopoietic, and Stromal Compartments

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Aging is a multifaceted biological process characterized by progressive cellular and molecular dysfunction, resulting in the progressive decline of cellular and systemic functions, increasing susceptibility to diseases and reducing overall resilience. This immune decline, known as immunosenescence, manifests through reduced innate and adaptive responses, chronic low-grade inflammation and impaired immune homeostasis. While the Hallmarks of Aging have been extensively studied, their integrated effects on the immune system during infection remain unclear. In addition, growing evidence suggests that immune dysfunction in aging does not occur in isolation, but rather arises from the intricate interplay between immune cells, the hematopoietic system that sustains them, and the stromal microenvironment that regulates their function, localization, and maintenance. Disruption across this immune–hematopoietic–stromal complex may underlie key aspects of age-related immune impairment. We have generated a high-resolution single-cell atlas of immune aging by analyzing key organs: lungs, spleen, and bone marrow, in young and old wild-type mice during a respiratory viral infection with Vaccinia virus strain Western Reserve (VACV-WR). By capturing transcriptional dynamics across age groups and infection time points, we aim to identify age-associated changes in immune composition, molecular pathways, and intercellular communication networks. Notably, our analysis has identified a distinct endothelial cell subset with immune-associated features, suggesting that the vascular compartment may actively contribute to infection-induced immune regulation and represent an additional layer of age-related immune remodeling. Our initial findings confirm impaired infection control in aged mice, motivating a deeper investigation into immune-stromal interactions and the potential for intervention. We aim to unravel possible intervention strategies that target these dysregulated pathways. Insights from this work will inform the design of these targeted strategies to reinvigorate aged immune dysfunction, enhance infection recovery, and promote immune resilience in aging populations. Ultimately, this work seeks to provide critical insights into the aging immune system and uncover potential targets to enhance immune resilience.

11) Gioele La Manno

Revealing the Lipidomic Architecture of the Brain

Gioele La Manno, EPFL

Lipids constitute a substantial fraction of the brain's dry weight, and their molecular diversity is vast. Yet, despite the potential impact on physiology and development recently highlighted by the lipotype hypothesis, the spatial heterogeneity of the brain lipidome in adulthood and during development remains largely uncharted. Mapping lipid metabolism spatially requires analytical tools capable of integrating large mass spectrometry imaging (MSI) datasets across acquisitions and developmental stages. We developed uMAIA, a computational framework for joint analysis of MSI data that enables the construction of multidimensional metabolomic atlases at micrometric resolution. Applying uMAIA to Danio rerio embryos, we mapped the four-dimensional distribution of over a hundred lipids, revealing metabolic trajectories that unfold in concert with morphogenesis and uncovering spatially organized biochemical coordination invisible to bulk measurements. Building on this framework, we mapped the membrane lipid architecture of the adult mouse brain across sexes and during pregnancy. This Lipid Brain Atlas reveals that lipids define a fine-grained biochemical structure aligned with functional anatomy, organized into spatial domains we termed lipizones. Lipizones expose organizing principles of gray matter related to connectivity and cytoarchitecture, a new axis of oligodendrocyte heterogeneity in white matter, and biochemical zonation in the choroid plexus. We further show that this architecture adapts to physiological demands: in pregnant females, white matter becomes metabolically activated and the outer cortex is reorganized.

12) Sylviane Lagarrigue

LACTB Regulates Skeletal Muscle Homeostasis Through Fiber Type–Specific Mitochondrial and Lipid Remodeling

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Mitochondrial dysfunction is a hallmark of many muscular diseases, including myopathies and sarcopenia. Lactamase B (LACTB), a mitochondrial protein derived from the bacterial penicillin-binding/β-lactamase family, is an intriguing candidate regulator of muscle metabolism. Although its ancestral bacterial role was linked to peptidoglycan synthesis, mitochondria lack this pathway, suggesting LACTB has evolved novel functions in eukaryotic cells.

To investigate its role in muscle physiology, we generated a zebrafish LACTB knockout (KO) using CRISPR-Cas9. KO fish exhibited normal body weight and length but showed increased body surface area and altered locomotor activity, characterized by reduced low-speed swimming and longer pause times. During incremental swimming tests, KO fish consumed more oxygen than controls at the same speed, consistent with impaired mitochondrial efficiency or altered energy substrate utilization. At the tissue level, fast-twitch fibers of KO fish displayed increased mitochondrial circularity and reduced respiratory capacity, whereas slow-twitch fibers maintained normal mitochondrial respiration but accumulated lipid droplets alongside elevated expression of lipid synthesis genes. The KO phenotype was even more pronounced with age. KO fish consistently consumed more oxygen than controls at the same swimming speed and began to show signs of fatigue compared to CTRL. Cross-sectional area of slow-twitch fibers was decreased with no accumulation of lipid droplets in KO, whereas fast-twitch fibers had reduced subsarcolemmal mitochondrial number.

These findings reveal that LACTB contributes to muscle homeostasis through fiber type–specific regulation of mitochondrial structure, respiratory function, and lipid metabolism. By linking altered mitochondrial dynamics and metabolic inefficiency to muscle performance, our study positions LACTB as a potential player in pathways underlying muscular pathologies. Understanding how LACTB shapes muscle bioenergetics may provide new insights into mechanisms driving mitochondrial myopathies, lipid accumulation disorders, and age-related sarcopenia.

13) Benjamin Lair

Sphingolipid Metabolism Emerges as a Complex Regulator of Skeletal Muscle Mass Across Aging

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As life expectancy increases in Western countries, healthy aging remains a major challenge. Preserving skeletal muscle mass and function is essential to maintain autonomy. To date, no pharmacological treatment has been approved to prevent or reverse muscle wasting. Previous studies have suggested that sphingolipids and more specifically ceramides, accumulate in skeletal muscle with aging and obesity. We investigated the relationship between muscle ceramide content and muscle mass *in vivo* and *in vitro*, and tested whether inhibition of *de novo* sphingolipid synthesis could improve muscle mass and strength in aged mice. Contrary to recent reports, this treatment did not improve muscle mass or strength in old animals. However, it promoted muscle fiber hypertrophy in young healthy mice. Similar effects were observed in C2C12 and human primary myotubes, supporting a muscle cell-autonomous mechanism. Because skeletal muscle targeting of ceramide synthase (CerS1), the most highly expressed ceramide synthase isoform in muscle, has previously been shown to induce muscle fiber atrophy, we next examined whether CerS2-derived very-long-chain ceramides might mediate the deleterious effects of sphingolipids. We found that intramuscular very-long-chain ceramide levels were increased in aged mice and negatively correlated with skeletal muscle mass in humans. Unexpectedly, AAV-mediated skeletal muscle-specific knockdown of CerS2 induced muscle fiber atrophy in both young and old mice, recapitulating the phenotype previously observed with CerS1 targeting. Altogether, these findings suggest that inhibition of *de novo* sphingolipid synthesis may represent a potential avenue to limit muscle wasting, while also highlighting a more complex role of sphingolipids in the regulation of skeletal muscle mass across aging.

14) Esther Landaluce Iturriria

Adipose splicing plasticity in response to nutrient and inflammatory inputs

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The increasing worldwide prevalence of obesity has become a major public health concern. Obesity elevates the risk of metabolic disorders, including type II diabetes and cardiovascular disease. Given its high prevalence, healthcare burden and contribution to global morbidity, a deeper understanding of the molecular mechanisms underlying obesity and IR is essential for developing effective therapies.

To understand how dysfunction-associated changes emerge in vivo, we first analyzed differentially expressed genes in perigonadal white adipose tissue (pgWAT) from C57BL/6 mice fed for 6- or 12-week high-fat diet, where pathway analysis revealed an enrichment of the spliceosome pathway—particularly after longer dietary interventions. RNA splicing is a fundamental mechanism regulating gene expression in eukaryotic cells, yet its modulation by macronutrients in pgWAT remains poorly understood.

To investigate mechanistically alternative splicing (AS) in adipocyte dysfunction, we established an in vitro model of chronic obesity using 3T3-L1 adipocytes exposed to stimuli mimicking obese and IR patients conditions, including inflammation, hyperglycaemaia and hyperinsulinemia. Splice-switching oligonucleoRdes were used to probe the funcRonal impact of six TNFa-induced AS events, incuding Spag9 exon 30, Ralgapa1 exon 14 and Mink1 exon 19. ASO-mediated skipping of Ralgapa1 exon 14 impaired insulin-stimulated glucose uptake in 3T3-L1 adipocytes. ASO-mediated skipping of Spag9 exon 30 increased JNK activation, while ASO-mediated skipping of Mink1 exon 19 decreased it. Moreover, downregulation of Rbfox2, Srsf3 and Mbnl1 identified several of their splicing targets.

Together, our data identify AS events and their upstream regulators as potential RNA-based therapeutic targets in obesity-associated metabolic disease.

15) Pauline Leal

Assessment Of Metabolism And Viability In Live-3d Brain Organoids Within A Custom Bioreactor For Ultra-High-Field MRI/MRS

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The development of three-dimensional organoid cultures over the past decade has enabled researchers to outreach the possibility to study cellular and molecular mechanisms in cells within their complex environment. Indeed, its accurate reproduction of the organization of brain cells makes it a relevant model for studying the development, physiology and maturation of the brain. However, we still lack methods to non-invasively follow metabolism longitudinally. To tackle this, we developed an in-house-designed bioreactor adapted to preclinical horizontal-bore MR scanner to maintain organoids under controlled environmental conditions throughout the scan. The aims of this project are first to maintain the cellular integrity and viability of the organoids over a 6-hours MR-imaging period in the bioreactor, and then to study the metabolism of the organoids using proton magnetic resonance spectroscopy (1H-MRS). Organoids were obtained as described (Braissant et al. 2002, JNeurosci) by dissociation of 15-fetal-day-old rat brains. Organoids were maintained alive during the MR-scan by circulating culture medium at 1 mL/min through the bioreactor. We were able to characterize the stereotypical developmental profiles of these brain cell organoids using 1H-MRS spectra. We confirmed these metabolic data with 1H-NMR and mass spectrometry and assessed organoids viability using cleaved caspase 3 labeling to ensure that we maintained the organoids alive during the MR scan. Next steps will be to study the metabolism and the microstructure of these organoids along their development both using MRS and diffusion-weighted MRI/MRS techniques and histological analysis, including in the context of neurodevelopmental diseases.

16) Weilin Li

Tumour stiffening via cholesterol depletion potentiates cytotoxic CD4+ T cells-mediated cancer immunotherapy

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Current cancer immunotherapies predominantly enhance $CD8^+$ T cell responses but show limited efficacy in solid tumours. $CD4^+$ T cells, which can acquire direct cytotoxic activity, represent an underexploited therapeutic avenue, particularly for major histocompatibility complex class I (MHC-I)–deficient cancers. As T cell activation is highly sensitive to mechanical cues, we investigated whether engineering tumour cell mechanics could potentiate $CD4^+$ T cell cytotoxicity. We show that tumour cell softening—a common feature of malignant progression—impairs $CD4^+$ T cell–mediated cytotoxicity. Increasing tumour cell cortical stiffness through plasma membrane cholesterol depletion via acetyl-CoA acetyltransferase 1 (ACAT1) overexpression enhances $CD4^+$ T cell–mediated cytotoxicity in murine and patient-derived tumour models. Mechanistically, increased target cell stiffness stabilizes immunological synapse assembly and promotes activation of a phosphorylated signal transducer and activator of transcription 1 (pSTAT1)–interferon-γ (IFNγ) signalling axis in $CD4^+$ T cells. These findings establish tumour mechanics as a tunable therapeutic target and highlight mechanical engineering of cancer cells as a broadly applicable strategy to enhance $CD4^+$ T cell–based immunotherapy in solid tumours.

17) Miriam Lisci

Functional nutrient-genetic profiling reveals biotin and FBXW7 are essential to bypass glutamine addiction.

Miriam Lisci, Fanny Vericel, Yifan Liu, Hector Gallart-Ayala, Julijana Ivanisevic, Owen S. Skinner, Alexis A. Jourdain.

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Metabolic flexibility is key to survival and growth in all living organisms. In mammals, the pathways supporting cell proliferation in nutrient-limiting conditions have not been fully elucidated, although certain tumors display metabolic dependencies that can be targeted for therapy. Here, we combine metabolic tracers, nutrient supplementation, and genome-wide CRISPR-Cas9 screening to investigate the pathways mediating glutamine addiction, a hallmark of several cancers. We report that the vitamin biotin allows bypassing of glutamine dependence by activating pyruvate carboxylase (PC), and we discover a mechanism by which the tumor suppressor FBXW7 promotes pyruvate anaplerosis. Mechanistically, we show that FBXW7 prevents c-MYC accumulation and recruitment of a cluster of transcriptional repressors, including MAX, MNT and SIN3A, to the PC promoter, thereby maintaining PC expression and avoiding glutamine addiction. Our work sheds light on the molecular mechanisms that support metabolic flexibility and prevent glutamine addiction in cancer, with high relevance for FBXW7-associated cancer mutations.

18) Jaime Lopez-Alcala

CDK4 modulates the integrated stress response to impaired amino acid uptake, in triple-negative breast cancer

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During triple-negative breast cancer (TNBC) the epithelial cells that line the ducts or lobules of the breast increase their ability to resist death, sometimes even after chemotherapy treatment with inhibitors of cyclin dependent kinases (CDKs). The integrated stress response (ISR) is one of several conserved reprogramming mechanisms that allows cells to adapt to hostile conditions, through eIF2α phosphorylation, stress granules (SGs) assembly, and activating transcription factor 4 (ATF4) increase, which could restore homeostasis. However, if the stress cannot be alleviated, the ISR triggers apoptosis. An RNA-Seq analysis of MDA-MB-231 CDK4-knockout (KO) cells showed a strong decrease in the ISR process compared to wild type (WT) cells, demonstrated by suppression of ATF4 and its targets. Intriguingly, the amount or activation of the regulator eIF2α protein, was not altered. Cells were then challenged with sodium arsenite or amino acid (AA) deprivation, forming SGs. Furthermore, KO cells exposed to stressors showed a lower amount of SGs than WT cells upon such stimuli, as well as higher survival. In addition, phosphoproteomics data unveil that eukaryotic translation initiation factor 2B subunit 5 (eIF2B5) of the eIF2B complex is devoid of phosphorylation at S610 when CDK4 is missing, manifesting a steric hindrance that favors the general translation. This also prevented induction of AA Response Element-containing genes and ATF4 targets in mouse xenograft models. Altogether, our results suggest that the ISR pathway flux of TNBC CDK4-ablated cells enhances their resistance to cell death induced by stress insults, and that this harmful phenotypic advantage deserves to be unraveled.

19) **Isabel Cristina Lopez Mejia**

Srsf2 is required for white adipocyte homeostasis and β-adrenergic lipolysis

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Using RNA-sequencing of white adipose tissue (WAT) from mice fed a high-fat diet (HFD) for either 8 or 20 weeks, we identified RNA-binding proteins (RBPs) potentially involved in obesity and insulin resistance. This analysis revealed that the splicing factor Srsf2 is selectively upregulated in visceral WAT after prolonged HFD, coinciding with the onset of insulin resistance. Notably, Srsf2 levels increased in the mature adipocyte fraction after 12 weeks– but not after 6 weeks–of HFD, suggesting a role specifically associated with metabolic dysfunction rather than early obesity.

Adipose-specific Srsf2 knockout mice (Adiponectin-CRE; Srsf2ATKO) showed impaired lipolysis in vivo, failing to release glycerol upon β-adrenergic stimulation and exhibiting elevated respiratory exchange ratio during the light phase, consistent with defective lipid utilization. To dissect adipocyte-autonomous mechanisms, we deleted Srsf2 in differentiated primary adipocytes using TAT-CRE. Srsf2-deficient adipocytes displayed reduced fasting-induced and CL-316,243–stimulated lipolysis, accompanied by decreased HSL protein abundance and diminished PKA-mediated HSL phosphorylation, despite increased Lipe mRNA levels.

RNA-seq analysis using Srsf2ATKO isolated mature adipocytes identified 13 splicing events consistent across adipose depots, including decreased inclusion of exon 12 of translational regulator Fmr1. This alteration was validated in primary adipocytes and 3T3-L1 cells depleted of Srsf2.

Our findings indicate that Srsf2 regulates lipolysis through post-transcriptional mechanisms, potentially involving Fmr1-mediated translation of Lipe mRNA, supporting a role for Srsf2 as a critical regulator of white adipocyte homeostasis and lipid utilization.

20) Julia Primavesi

Plasma lipidome variability avross 10 repeated measurements in healthy houng adults

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Background: Plasma lipidomics is a rapidly advancing field with clinical applications in defining the physiology of aging, disease prognosis, and monitoring responses to interventions. However, quantitative data on lipid variability at the species level, essential for the clinical interpretation of lipidomics data and study design, remain limited.

Methods: We quantified the intra- and inter-individual variability of the plasma lipidome in healthy young adults (n =16, age: 24.3±6.8 years; BMI: 21.8±3.0 kg/m²) using fasting plasma samples (n = 160) collected at ~10-day intervals over ~88 days. Targeted HILIC-LC-MS/MS quantified 673 lipid species across 16 classes. Intra- and inter-participant coefficients of variation (CV) were calculated for each lipid species across the 10 measurement timepoints and summarized as mean ± SD within each lipid class. Intraclass correlation coefficients (ICC) were estimated for each lipid species using linear mixed-effects models to assess lipid temporal stability (TS).
Results: Intra-participant CVs were lower than inter-participant CVs for most lipid classes, although the magnitude of this difference varied by class. At the lipid class level, 13 of 16 classes showed moderate-to-strong TS (median ICC > 0.50), with SM and Hex1Cer being the only classes showing strong TS (median ICC ≥ 0.75). Cer, Hex2Cer, most phospholipids, glycerolipids, and FFA exhibited moderate TS (median ICC 0.51–0.74), whereas lysophospholipids (LPE, LPG, and LPI) showed poor TS (median ICC ≤ 0.50). At the species level, the proportion of species with ICC ≥ 0.75 varied across classes. Among moderately stable classes, this proportion ranged from 50% to 0%, with the highest values observed for PG and DG (50%), followed by Cer, CE, PC, LPC, and PI (41–25%). Among poorly stable classes (LPE, LPG, and LPI), no highly stable species were observed.

Conclusions: The plasma lipidome is highly individualized (i.e. intra-participant variability < inter-participant variability), with most classes showing moderate-to-strong TS. Importantly, the observed stability is species-specific rather than class-defined, highlighting the importance of species-level resolution in lipidomic profiling for clinical research applications.

21) Sruthi Raja

Early weaning impacts skeletal muscle metabolic & lipid homeostasis and impairs muscle stem cells and post-natal muscle growth

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Muscle stem cell–driven muscle growth dominates the early postnatal muscle development, but how nutrition shapes these myogenic programs during the weaning window is still not well understood. In the presented study, we use a preclinical model of early weaning to investigate how premature cessation of breast milk affects MuSC mediated postnatal muscle growth. Characterisation of early weaning phenotypes at the cellular and tissue levels using single nucleus RNA sequencing, bulk transcriptomics and phenotypic assays revealed a delay in muscle growth with elevated differentiation of myogenic progenitors and impaired acquisition of quiescence of muscle stem cells. We then profiled plasma and skeletal muscle metabolomes and lipidomes to map systemic and tissue specific metabolic changes associated with early weaning. Metabolomic profiling points to an energy depleted state in early weaned muscle and revealed lipids and metabolites specifically altered by early weaning. Together, this multi omic analysis connects premature weaning to disrupted MuSC function and impaired muscle growth, and identifies nutrient candidates that could regulate myogenesis and muscle growth during dietary transitions at weaning.

22) Alicia Rey

Astrocytic fatty acid b -oxidation regulates postnatal brain development by orchestrating neuronal lipid turnover

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Neurons and astrocytes are metabolically coupled, and growing evidence suggests that this interaction extends to lipid handling. However, during brain development, neurons are generated before astrocytes, which expand and mature predominantly postnatally. How coordinated lipid metabolism between neurons and astrocytes is established during this early postnatal period remains poorly understood.

Here we identify astrocytic fatty acid b-oxidation (FAO) as a critical regulator of coordinated lipid metabolism during this key period for brain maturation. We find abundant lipid droplets (LDs) in neurons early postnatally, which progressively decline as LDs increase in astrocytes, indicating the emergence of metabolic coupling. Early postnatal astrocyte-specific ablation of the FAO enzyme carnitine palmitoyltransferase 1a (Cpt1a) results in anxiety-like behavior and impaired learning. Mechanistically, loss of astrocytic Cpt1a causes widespread lipid dysregulation, leading to massive neuronal LD accumulation and activation of a metabolic stress response that predominantly affects excitatory neurons. Furthermore, FAO is also required cell-autonomously for postnatal astrocyte maturation. Together, these findings identify astrocytic FAO as a critical regulator of postnatal brain development through the coordination of cellular lipid metabolism.

23) Amélie Sabine

Staying slim while growing old: the new vascular trick

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As aging populations face rising metabolic dysfunction, understanding the mechanisms governing systemic energy partitioning is paramount. Traditionally, obesity research has focused on adipocytes or appetite regulation. Here, we describe a novel "vascular trick" involving the pan-endothelial protein MYCT1 as a critical metabolic gatekeeper. We identify a conserved MYCT1–IFITM2/3 complex that regulates endolysosomal trafficking in blood vessel-lining cells. MYCT1 normally restrains IFITM2/3 accumulation in RAB5+ early endosomes. In its absence, IFITM2/3 are "unleashed," driving enlarged endosomal compartments, enhanced endocytic uptake, and excessive lysosomal degradation of plasma nutrients. This intracellular nutrient overload hyperactivates endothelial mTORC1 signaling, inducing a state of "futile energy expenditure" at the vascular barrier. Consequently, endothelial-specific deletion of MYCT1 in mice results in striking restricted white adipose tissue expansion during aging. This phenotype is independent of changes in food intake, physical activity, or angiogenesis. Instead, the vasculature acts as an active rheostat, diverting nutrients toward internal consumption rather than systemic storage. Targeting this endosomal checkpoint offers a radical therapeutic frontier for metabolic health in aging, shifting the focus from the adipose tissue to the vasculature.

24) Clarisse Simons

FGF21 Drives the Protective Effects of Time-Restricted Feeding Against Elastase-Induced Abdominal Aortic Aneurysm in Male Mice

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Background: Abdominal aortic aneurysm (AAA) is an age associated vascular degenerative disease lacking pharmacological treatments. Metabolic dysfunction, chronic inflammation, and impaired mitochondrial activity accelerate AAA progression during aging. Time restricted feeding (TRF) is a dietary intervention known to improve systemic metabolism, but its impact on AAA and metabolic remodeling in vascular disease remains unknown.

Methods: We investigated how an early active phase TRF regimen affects elastase induced AAA development in young and aged male mice. We combined vascular morphometry, immunohistochemistry, mRNAseq, targeted liver metabolomics and lipidomics, and genetic loss of function approaches using Fgf21$^{-/-}$ mice to define metabolic pathways underlying TRF mediated protection.

Results: TRF reduced AAA growth by about 50% in both young and aged mice. Transcriptomic profiling revealed that TRF profoundly reprograms AAA tissue toward a metabolically active, mitochondria enriched, and lipid utilizing state, while suppressing inflammatory programs. TRF upregulated pathways involved in fatty acid metabolism, oxidative phosphorylation, PPAR signalling, and vascular smooth muscle cell contractile identity, and reduced immune and stromal activation signatures. In the liver, TRF remodelled systemic metabolism by enhancing fatty acid β oxidation and phospholipid fluxes toward mitochondrial membrane supportive lipid species. TRF increased circulating FGF21 during fasting, and genetic deletion of FGF21 abolished all vascular protective effects of TRF, including suppression of neutrophil infiltration, preservation of VSMC phenotype, and reduction of aneurysm size. TRF also increased circulating adiponectin, suggesting involvement of the FGF21–adiponectin endocrine axis in mediating metabolic remodelling of AAA tissue.

Conclusions: TRF induces a coordinated metabolic rewiring across the liver–endocrine–vascular axis that protects against AAA progression. Its benefits are mediated through FGF21 dependent enhancement of lipid utilization, mitochondrial function, and anti inflammatory remodeling of the diseased aortic wall. These findings identify TRF as a metabolism targeting, non pharmacological intervention that counters age associated vascular degeneration and highlight FGF21 as a potential therapeutic tool in AAA.

25) Cassandra Tabasso

Is plasma lipidome a hallmark of age-related insulin resistance?

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Insulin resistance, related to obesity and type 2 diabetes, is an age-related metabolic burden, exarcebated by sedentary lifestyle. Further, older people suffer of muscle mass loss, known as sarcopenia, worsening glucose homeostasis. Increasing physical activity in elderly volunteers can moderate muscle decay. Lipids are potent biomarkers and play a key role of age-related metabolic pathologies. However, plasma lipids as biomarkers to monitor exercise benefits, especially in older people, remains poorly characterized. Here, we hypothesized 1) that exercise would induce metabolic improvements in aging volunteers, and 2) that those effects would be marked by alterations in plasma lipidome.

Sedentary volunteers (60-80 years old), with or without obesity, underwent a 4-month supervised moderate-intensity exercise intervention. Subjects were compared to regular exercisers practicing >3 structured aerobic exercise sessions/week. Metabolic phenotyping assessed body composition, insulin sensitivity and exercise efficiency. Plasma was sampled before and after intervention for untargeted lipidomics.

Exercise intervention improved insulin sensitivity in sedentary volunteers independently of body morphotype. The intervention decreased bodyweight, BMI, and increased lean/fat mass percentage. Untargeted lipidomics showed that plasma glyceroplipids were higher with obesity, but unaffected by exercise. Plasma glycerophospholipids showed body morphotype- and exercise-dependent alterations. Classes like phosphatidylcholine and ether-phospholipids were higher in athletes, whereas phosphatidylethanolamine were higher with obesity. Exercise consistently increased glycerophospholipids in volunteers without obesity, but not in those with obesity.

In summary, exercise improved metabolic health of older adults, independently of body morphotype. Plasma lipids appear as valuable biomarkers of this therapeutic approach against insulin resistance.

26) Aart Adriaan Cornelis van der Graaf

Comprehensive metabolite ratio QTL mapping reveals disease relevant enzyme biology

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Metabolite ratios are valuable proxies for enzyme and pathway activity. However, systematic study of their genetic basis is computationally burdensome due to the quadratic search space. We present an efficient method to identify ratio quantitative trait loci (rQTLs) using only metabolite summary statistics. Validation showed strong correlation with classically estimated ratios (median R^2=0.94).
We identified 5,095 metabolite pairs with significant rQTLs exhibiting stronger associations than their constituent metabolites. Mapped genes were enriched for enzymes (OR 4.3–20). Metabolite pairs with rQTLs showed shorter reaction distances (median=4) than random pairs (P=8.0·10^−13). We identified 1,249 novel rQTLs across 53 loci where individual metabolites lacked significance, increasing QTL yield by 21%. These rQTLs captured activities including fatty acid desaturation (FADS2) and elongation (ELOVL2/5).
Notably, 72% of mapped genes were absent from pQTL studies. Tissue-specific eQTLs confirmed blood rQTLs can capture processes in other tissues (e.g., ETFDH in muscle). We also identified likely causal biomarkers for bladder cancer and ischaemic heart disease. Finally, a novel rQTL for the cAMP/PFOS ratio mapped to an ABCG2 missense variant, implicating the transporter in PFOS excretion. Our method systematically maps rQTLs serving as disease biomarkers, protein proxies, and biological insights.