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A4L Virtual Research Center

Mini-Conference - Webinar

Integrative (Patho)physiology of Skeletal Muscle and Metabolic Disorders: from Cellular Mechanisms to Interventions

Book of Abstracts

7 January 2026

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Foreword

The creation of the A4L Virtual Research Center (Virtual Research Center by A4L) initially seemed almost as its name suggests – virtual, a pie in the sky – when we first began to envision it. There were several challenges along the way, not least the need to secure the necessary funding. However, once the A4L_BRIDGE project, funded by the European Union, was obtained, the path to achieving our objective became clear.

Since its establishment in February 2025, the A4L Virtual Research Center has expanded from three foundational virtual departments – Cardiovascular Diseases, Metabolism and Endocrinology of Skeletal Muscle, and Neurobiology – to seven departments, now also including Cancer Biology and Targeted Therapy, History of Medicine and Medical Humanities, Membrane Biochemistry, and Translational Education and Training in Biomedical Sciences (TETra-BioMed). Importantly, with more than 100 members – a severalfold increase since February 2025—the VRC has clearly attracted significant attention within our community.

To promote scientific discussion, the exchange of ideas, international collaboration, and the dissemination of knowledge both within and beyond our consortium, the A4L Virtual Research Center is committed to organising regular virtual Journal Clubs and Mini-conferences in a webinar format.

Integrative (Patho)physiology of Skeletal Muscle and Metabolic Disorders: From Cellular Mechanisms to Interventions is the first mini-conference in what I hope will be a long series of such international events covering a wide range of topics. This mini-conference is organised by the A4L virtual department of Metabolism and Endocrinology of Skeletal Muscle, in collaboration with the Mitochondrial Physiology Society (Mitochondrial Physiology Society - Bioblast) and the European Society for Muscle Research Early Careers Association (ESMR-ECA) (ESMR - Early Careers). I would especially like to acknowledge the advice and support provided by Erich Gnaiger and Verena Laner (Mitochondrial Physiology Society) and Maicon Landim-Vieira (ESMR-ECA). My thanks also go to A4L colleagues who have supported the Virtual Research Center from the very beginning: Ester Jarour, Jernej Jorgačevski, Ivana Kugler, Anežka Malčíková, and Filip Sedlić. Without their support, the Virtual Research Center and its activities would have remained a pie in the sky.

As a symbol of transforming our ideas about the Virtual Research Center into reality with a mini-conference focused on muscles, I find René Magritte's 1927 painting *Les muscles célestes – The Muscles of the Sky*, which can be seen at the Musée Magritte in Brussels, particularly appropriate, although our muscles have now come down to earth.

Sergej Pirkmajer

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Abstracts

Neural Adaptation to Physical Activity after Spinal Cord Injury

Lenka Ihnátová, Karolína Kuchárová, Martina Magurová, Alexandra Kisucka, Mária Ileninová, Tomáš Kuruc, Ján Gálik, Nadežda Lukáčová

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Traumatic spinal cord injury (SCI) causes extensive changes in motor and sensory circuits that significantly limit spontaneous recovery of locomotion. After SCI, neuronal centers below the lesion exhibit plasticity that can be enhanced by appropriate therapeutic interventions. Physical activity is one of the most effective non-pharmacological strategies to promote spinal cord function and improves motor recovery.

The aim of this study was to analyze the effects of body-supported treadmill training on spinal plasticity in rats after experimental SCI. Following injury induction, animals were enrolled in a rehabilitation protocol consisting of repetitive treadmill locomotion, while the control group received no motor intervention. During the experiment, recovery of locomotion was regularly assessed using behavioural tests. After completion of the study, immunohistological analyses of the spinal cord were performed, focusing on the integrity of neural tissue, the activity of excitatory and inhibitory neuronal populations, and the expression of neuroplasticity markers.

Our results indicate that treadmill training promotes the reorganization of sensorimotor circuits, modulates the excitatory/inhibitory balance, and contributes to a partial improvement in motor function. Repetitive rhythmic movement provides substantial sensory and motor input that stimulates adaptive processes in the spinal cord, including the stabilization of remaining connections and the facilitation of functional reorganization of neural networks.

Overall, the findings confirm that treadmill-based physical activity represents an effective tool to influence spinal plasticity after SCI. These results contribute to a better understanding of the mechanisms underlying locomotor recovery and may support the optimization of rehabilitation strategies aimed at improving motor skills following spinal cord injury.

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From Mitochondria to Mind: Bioenergetic Architectures of Neurodevelopmental and Neurodegenerative Disorders in the Era of Metabolic Psychiatry

Fontanini Walter

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The traditional neurocentric model of psychiatric and neurological disorders, which focuses predominantly on neurotransmitter dysregulation and protein aggregation (e.g. amyloid-beta), has produced few therapeutic breakthroughs for complex phenotypes ranging from autism spectrum disorder (ASD) to Alzheimer's disease (AD). This presentation, therefore, proposes a paradigm shift towards **metabolic psychiatry**, identifying systemic metabolic dysfunction as a common driver of pathology throughout the lifespan of the nervous system.

Drawing upon systems biology and recent clinical data, we will explore the hypothesis that, as the body's most energy-demanding organ, the brain is uniquely vulnerable to bioenergetic failure. We will examine the molecular pathways that link neurodevelopmental conditions (such as ADHD and ASD) and neurodegenerative states (such as dementia and Alzheimer's disease), with a particular focus on:

1. **Cerebral Insulin Resistance:** The impact of impaired glucose utilisation on synaptic plasticity and cognitive decline (often conceptualised as "Type 3 Diabetes" in AD).
2. **Mitochondrial Dysfunction & Oxidative Stress:** How compromised ATP production and elevated Reactive Oxygen Species (ROS) contribute to the "noisy brain" phenotype in ADHD and proteostatic failure in dementia.
3. **The Neuro-Immune Axis:** The role of systemic inflammation (via the gut-brain axis) in driving microglial activation and excitotoxicity.

We will present evidence suggesting that targeting these metabolic drivers upstream through metabolic therapies, including ketogenic interventions, targeted micronutrient protocols and optimisation of mitochondrial cofactors, offers a viable pathway for neural repair. In neurodevelopmental disorders, restoring metabolic competence can alleviate core symptoms such as inattention and sensory dysregulation. In neurodegenerative contexts, providing alternative cerebral fuels (e.g. ketone bodies) has the potential to bypass glycolytic blockages and preserve cognitive function and quality of life.

Keywords: Metabolic Psychiatry, Bioenergetics, Mitochondrial Dysfunction, Cerebral Insulin Resistance, Neuroinflammation

Mapping Necrosis, Regeneration, and Border-Zone Transcriptional Signatures in Cocaine-Induced Myopathy with Xenium Spatial Transcriptomics Platform

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Background: Skeletal muscle is highly spatially heterogeneous. In toxic myopathies, including cocaine-induced necrotising myopathy, the transcriptional signatures of necrotic, regenerative, and neighbouring fibres remain poorly characterised, and it is unclear how far pathological signals spread beyond morphologically affected regions. We therefore aimed to define fibre-type–resolved and spatially organised transcriptional signatures in cocaine myopathy.

Methods: A diagnostic biopsy of the left lumbar paraspinal muscle was obtained from a young adult cocaine user presenting with acute paraspinal pain and MRI-confirmed oedema. Individual fibres were manually segmented, yielding transcript counts normalised to fibre area and global transcript density. Fibres were examined on HE, MyHC and neonatal myosine stained sections, allowing comparison of necrotic, regenerative, neighbouring, and remote normal type 1 and type 2 fibres. Differential expression analysis was performed with Mann–Whitney tests and FDR correction.

Results: Necrotic and regenerative fibres displayed the most contrasting transcriptional signatures. Necrotic fibres showed strong up-regulation of immune and proliferative genes (*SLAMF7, MS4A6A, CENPF*), whereas regenerative fibres preferentially expressed contractile and calcium-handling transcripts (*S100A1, MYLK, PVALB*). Compared to normal type 1 and type 2 fibres, necrotic regions were enriched for stromal–immune cues (*SFRP2, SPIB, APOLD1*), while regenerative fibres upregulated cell-cycle and innate immune markers (*CDK1, CENPF, CD14*). Neighbouring fibres exhibited intermediate, microenvironment-dependent shifts: immune checkpoint genes near necrosis, and extracellular matrix genes near regeneration. These transitional signatures positioned neighbouring fibres between pathological and normal clusters.

Conclusions: Cocaine myopathy features sharply divergent necrotic and regenerative transcriptional signatures, accompanied by a distinct "border-zone" signature in neighbouring fibres. Pathological signals extend beyond histologically damaged regions, reshaping transcriptional states across fibre types.

Biological Mechanisms of Muscular Ageing

Justina Kilaitė[1], Valentina Ginevičienė[2], Erinija Pranckevičienė[3], Alina Urnikytė[4], Rūta Dadelienė[5], Asta Mastavičiūtė[6], Ieva Eglė Jamontaitė[7], Vidmantas Alekna[8], Ildus I. Ahmetov[9]

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Sarcopenia is the age-related loss of skeletal muscle mass, strength, and quality. **Aim:** This case-control study investigated the phenotype, genomic determinants, and telomere length in older adults with sarcopenia. **Materials and methods:** Eligibility criteria included age ≥65 years, unrestricted mobility, and a Mini-Mental State Examination score ≥21. The control group comprised 82 healthy individuals (17 men and 65 women; mean age 80.2 ± 7.5 years), whereas 93 participants (25 men and 68 women; mean age 85.3 ± 6.7 years) had sarcopenia, diagnosed according to EWGSOP2 (European Working Group on Sarcopenia in Older People 2018–2019) criteria. Lean mass index (LMI) and psychomotor speed were assessed. Muscle oxygenation (SmO2) was measured at rest, during a 6 min cycle ergometer test, and throughout recovery using near-infrared spectroscopy. Genomic DNA was extracted from peripheral blood leukocytes for genome-wide association studies (GWAS) and relative telomere length (RTL) measurement. **Results:** SmO2 after exercise differed significantly between control and sarcopenia groups (68.06% ± 19.75% vs. 26.00% ± 11.14%) and after 5 min recovery (77.55% ± 16.18% vs. 46.09% ± 11.21%) ($p < 0.001$). Psychomotor speed was significantly lower in the sarcopenia group. GWAS: 2 SNPs (rs75652203 and rs17102732) were identified as significantly associated with handgrip strength, and 12 SNPs previously linked to sarcopenia were confirmed in association with LMI. **Conclusion:** Muscle decline phenotypes (handgrip strength and lean mass index), together with genetic determinants (14 SNPs, and relative telomere length) show significant associations with sarcopenia, underscoring the combined role of phenotypic and genomic factors in its pathogenesis.

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Disclosure: All authors state that they have no conflicts of interests.

Effects of Type 2 Diabetes on Postural, Locomotor and Respiratory Muscles Assessed by Histomorphometry and 3D Microvascular Analysis

Nataša Pollak[1], Jiří Janáček[2], František Saudek[3], Erika Cvetko[1], Barbora Radochová[2], Armin Alibegović[4], Chiedozie Kenneth Ugwoke[1], Davide Basello[2], Žiga Šink[1], Luka Pušnik[1], Rok Tit Tomazin[1], Nejc Umek[1]

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Background: Type 2 diabetes mellitus (T2DM) disrupts skeletal-muscle metabolism and microvascular function, yet postural and respiratory muscles remain understudied relative to locomotor muscles. We examined whether T2DM alters fibre morphology, intramyocellular lipid (IMCL) storage and 3D capillary architecture across functionally distinct muscles.

Methods: Splenius capitis (postural), diaphragm and external intercostal (respiratory), and vastus lateralis (locomotor) muscles from adult male subjects with and without T2DM (n=24/group) were sampled <24 h post-mortem and analysed using MyHC-based fibre typing, Sudan Black B IMCL quantification and 3D capillary network morphometry (length, tortuosity, anisotropy, branching density).

Results: Groups were age-matched (T2DM 70.8±7.4 vs 69.7±11.8 years, p=0.684), but BMI was higher in T2DM (31.9±4.7 vs 24.8±2.7 kg/m^2, p<0.0001). Fibre-type composition and diameters did not differ between groups. Global IMCL was higher in T2DM in splenius capitis (p=0.013) and external intercostal muscle (p=0.020), but with no fibre-type specific effect; BMI strongly predicted higher IMCL, while age showed modest negative associations. Capillary length per fibre volume was selectively reduced in the diaphragm in T2DM (p=0.0005), while other capillary parameters showed minimal between-group differences, except for a modest increase in anisotropy in the external intercostal muscle (p=0.040).

Conclusions: Across functionally diverse skeletal muscles in older men with T2DM, findings point to discrete alterations in lipid handling and capillary architecture, particularly in postural and respiratory muscles, while overall fibre architecture appears preserved. This pattern is consistent with muscle-specific rather than generalised structural adaptation and suggests that local functional and metabolic demands, rather than systemic metabolic status alone, influence muscle architecture.

PDK1: One Abbreviation, Two Kinases, Relentless Confusion

Blaž Kociper[1], Katarina Miš[1], Pablo M Garcia-Roves[2, 3], Alexander V Chibalin[4], Arild C Rustan[5], Erich Gnaiger[6], Sergej Pirkmajer[1]

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Preprint: PDK1: one abbreviation, two kinases, relentless confusion Blaž Kociper, Katarina Miš, Pablo M Garcia-Roves, Alexander V Chibalin, Arild C Rustan, Erich Gnaiger, Sergej Pirkmajer bioRxiv 2025.12.01.691077; doi: https://doi.org/10.64898/2025.12.01.691077

The abbreviation PDK1 is used to denote two distinct proteins: pyruvate dehydrogenase kinase 1 and 3-phosphoinositide-dependent protein kinase 1. This nomenclatural overlap creates ambiguity and makes it difficult to determine which protein is being referenced. In this work, we present a widespread confusion associated with the use of "PDK1," including articles that specify incorrect antibodies, present inappropriate sequences for PCR, gene silencing, or plasmid construction, conflate the properties of the two proteins, or mistakenly reference the other protein. Notably, 19% of PubMed-indexed articles containing the term "PDK1" and published between 2019 and mid-2025 include at least one such error. This ambiguity is not confined to the scientific literature but also extends to biotechnology company and vendor websites, where antibodies or recombinant proteins are frequently misattributed. Mitigating this problem will require strict adoption of unique protein abbreviations, clear identification of antibodies and sequences, and more rigorous peer-review practices.

Funding: This work was supported by Slovenian Research and Innovation Agency grants P3-0043, J7-3153, J7-60125, and BI-NO/25-27-004.

Lipidomic Profiling Reveals Obesity-Linked Genotype-Diet Interactions Remodelling the Skeletal Muscle Lipidome

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Background: Genetic susceptibility to obesity, type of diet, and sex strongly influence skeletal muscle lipid organization. We performed a lipidomic analysis of gluteus maximus muscle from polygenically obese Fat-line (n=18) and Lean-line (n=16) mice of both sexes, maintained on either a high-fat diet (HFD) or a low-fat carbohydrate diet (LFD).

Methods: Untargeted lipidomic profiling was performed using ultra-high-performance liquid chromatography coupled with high-resolution mass spectrometry. QC-based peak filtering ensured retention-time stability and reproducible feature detection. Lipids were annotated using curated spectral libraries and classified into major functional groups. For each sample, we quantified total lipid abundance, class-specific lipid pools (TAG, DAG, PC, PE, CL, Cer), unsaturation and chain-length indices, putative lyso- and oxidized lipids, and mitochondrial lipid markers including cardiolipins and acylcarnitines. Biological effects of genotype, diet, and sex were evaluated using three-way ANOVA.

Results: Fat-line mice displayed markedly higher total lipid content, driven largely by increases in TAG and DAG species ($q<0.00021$), with HFD further intensifying lipid accumulation across genotypes. Cardiolipin abundance was strongly elevated in Fat-line animals ($q=0.00039$), accompanied by altered saturation indices indicating mitochondrial membrane remodelling. Ceramides also showed a significant genotype effect ($q=0.0052$). Lipotoxic markers, DAG/TAG and Cer/SM ratios, were consistently higher in Fat-line and HFD groups, with a sex effect observed for DAG/TAG ($q=0.043$). Lean-line mice maintained higher PUFA fractions within phospholipids, whereas females showed lower ceramide levels and a more unsaturated PC/PE profile. A significant genotype-sex interaction was observed for CL/PL ($q=0.0056$), suggesting sex-specific mitochondrial membrane adaptation.

Conclusions: Genotype, diet, and sex jointly remodel the skeletal muscle lipidome. Fat-line mice show broad lipidomic shifts, greater storage lipids, higher lipotoxic species, and altered phospholipid composition, exacerbated by HFD. Females retain a more PUFA-rich and less lipotoxic profile. These findings highlight key lipid pathways linking genetic obesity and dietary environment to muscle metabolic function.

Identifying Chronotype for the Preservation of Muscle Mass, Quality and Strength

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Chronotype, an individual´s preferred timing of sleep and activity within a 24-hour cycle, significantly influences metabolic health, muscle function, and body composition. This review explores the interplay between circadian rhythms, hormonal fluctuations, and behavioral patterns—such as nutrition timing, physical activity and sleep quality —and their impact on muscle mass, strength, and quality. Evening chronotypes (ETs) are consistently associated with poorer sleep, irregular eating habits, reduced physical activity, and increased risk of obesity, sarcopenia and metabolic disorders compared to morning types (MTs). At the molecular level, disruptions in circadian clock gene expression (e.g., BMAL1, PER2, CRY1) affect protein synthesis, insulin sensitivity, and energy metabolism, contributing to muscle degradation and impaired recovery. The review proposes integrative strategies—targeting chrono-nutrition, sleep quality, and exercise timing—to align lifestyle behaviors with circadian biology, thereby preserving muscle health and improving overall metabolic outcomes.

Targeting the redox-sensing properties of TCA cycle enzyme alpha-ketoglutarate dehydrogenase for the treatment of fatty liver disease

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Metabolic dysfunction-associated steatotic liver disease (***MASLD***) is surging across the world because of high fat/high sugar diets and poor life-style choices. Oxidative stress induced by fat overload is an early event in the manifestation of MASLD, which is due to the hyper generation of mitochondrial reactive oxygen species (mtROS). However, there is still a lack of consensus on the exact source of this mtROS and how its hyper generation can be prevented. Complex I and III of the electron transport chain (***ETC***) are conventionally credited as being the most potent mtROS sources in the liver. But we recently generated compelling evidence showing tricarboxylic acid (TCA) cycle enzyme α-ketoglutarate dehydrogenase (***KGDH***) is a highly potent mtROS producer in hepatocytes. Here, I will discuss this evidence and elaborate on how dietary fat overload in mice triggers the hyper-production of mtROS by KGDH causing MASLD. Furthermore, I will discuss our findings showing that targeting the redox-sensing properties of KGDH could be used as a means of abrogating MASLD manifestation through inhibition of mtROS hyper-production and the induction of hepatic oxidative stress. Finally, I will discuss how use of our cell line and mouse models to define the role of KGDH-mediated mtROS hyper-production in MASLD pathogenesis led to the promising discovery that elevated plasma succinate is a sex-dependent biomarker for MASLD pathogenesis and that it could be used to diagnose and track the progression of the disease. Overarchingly, our discoveries have identified KGDH as a potential target for the treatment of MASLD.


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