# Late abstracts

## Posters

## LP1

### The effect of the myosin inhibitor BDM and calcium desensitizer W7 on actin-myosin interaction in the presence of the R90P-mutant Tpm3.12

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It is known that point mutations in tropomyosin can lead to skeletal muscle diseases such as congenital fiber-type disproportion (CFTD), nemaline myopathy, and cap myopathy. The molecular mechanisms underlying the deregulation of muscle contraction by mutant forms of tropomyosin are not well understood. There is no effective treatment for congenital myopathies associated with tropomyosin or any other proteins mutations. The present study was devoted to the search for adequate ways for correcting disturbances in the regulation mechanisms of actin-myosin interaction caused by mutant tropomyosin leading to muscle weakness and hypotension in CFTD. We have shown that a mutation in the *TPM3* gene, leading to the amino acid substitution R90P in Tpm3.12, changes the ratio of myosin heads that are strongly and weakly bind with actin in the ATP hydrolysis cycle. The mutant tropomyosin is displaced into an open position on actin, which allows a strong interaction of myosin with actin even under conditions of low $Ca^{2+}$ concentration and when simulating the relaxation state of the actin-myosin system of the muscle fiber. This may be the main reason for the abnormally high sensitivity of thin filaments to $Ca^{2+}$ and the appearance of muscle weakness and hypotension. It was found that the abnormal number of actomyosin cross-bridges in strong-binding state could be reduced in the presence of the myosin ATPase activity inhibitor BDM and the calcium desensitizer W7. In this way, it is possible to weaken the worsening effect of the R90P substitution in tropomyosin on contractile function.

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## LP2

### Phosphorylation and calcineurin regulate myotilin function in the Z-disc

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Myotilin is one of the many proteins which form the Z-disc in vertebrate striated muscle. Its remarkable ability to interact with main Z-disc constituents (e.g. actin, α-actinin, filamin C, FATZ, etc.) suggested its importance in the maintenance and organization of the Z-disc. A clear understanding of not only these interactions, but also the ways how they are regulated is important for unraveling mechanism(s) by which mutations in myotilin may cause muscular diseases such as limb-girdle muscular dystrophy and myofibrillar myopathy. Z-disc has been recently recognized as "hot spot" for protein phosphorylation with myotilin being one of the targets. This motivated us to investigate effects of phosphorylation on myotilin function. We created phosphomimetic mutants of residues found in the close proximity of recently characterized actin binding region of myotilin [1]. Interestingly we found that phosphorylation does not modulate binding of myotilin to F-actin, however, it affects its degradation and turnover mediated by calpain. In addition, we found that calcineurin binds to myotilin. We characterized this interaction by peptide mapping, ITC and were able to solve the structure of calcineurin-myotilin peptide complex. We found calcineurin binding site to lay in the vicinity of the investigated myotilin phosphosites (residues), and showed that these residues can be dephosphorylated by calcineurin. Thus myotilin function is regulated by phosphorylation and dephosphorylation, the latter being mediated *via* calcineurin. Both, calcineurin and calpain are activated by calcium suggesting that turnover and thus function of myotilin could be modulated in response to various calcium levels.

**References:**

1. Kostan *et al.* (2021) *PLoS Biol* **19**(4): e3001148.

# LP3

## (-)-Epicatechin inhibits development of dilated cardiomyopathy in δ sarcoglycan null mouse

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**Background and aims**: Several studies propose that (-)-epicatechin, a flavonol present in high concentration in the Theobroma cacao seed, has cardioprotective effects. This study aimed to evaluate the impact of (-)-epicatechin on the development of dilated cardiomyopathy in a δ sarcoglycan null mouse model (Sgcd null).

**Methods and results***:* Sgcd null mice were treated for 15 days with (-)-epicatechin. Histological and morphometric analysis of the hearts treated mutant mice showed significant reduction of the vasoconstrictions in the coronary arteries as well as fewer areas with fibrosis and a reduction in the loss of the ventricular wall. On the contrary, it was observed a thickening of this region. By Western blot analysis, it was shown, and increment in the phosphorylation level of eNOS and PI3K/AKT/mTOR/p70S6K proteins in the heart of the (-)-epicatechin treated animals. On the other hand, we observed a significantly decreased level of the atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) heart failure markers.

**Conclusion***:* All the results indicate that (-)-epicatechin has the potential to prevent the development of dilated cardiomyopathy of genetic origin and encourages the use of this flavonol as a pharmacological therapy for dilated cardiomyopathy and heart failure diseases.

# LP4

## Oxidised microRNAs as novel players in muscle wasting

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There is currently a disproportionate increase in age-related health issues, with one of the major problems being the age-related loss of muscle mass and function - sarcopenia. Redox and epigenetic factors are key regulatory pathways associated with ageing. MicroRNAs, stable RNAs with half-life >24 h, regulate muscle homeostasis posttranscriptionally. Oxidative modification of microRNAs could result in the regulation of non-native targets. Redox balance is disrupted during ageing and the accumulation of oxidised, most likely pathogenic, microRNAs in muscle leads to their disrupted specificity for regulating protein content. We have validated microRNAs/mRNAs/proteins networks affected by ageing in muscle and have shown that modifying microRNA expression improves muscle function, but there is currently no research into the function of oxidised microRNAs in ageing. Integrating omics and functional approaches, we have shown that miR-378 is oxidised in muscle of mice and humans during ageing and disease. Oxidised miR-378 regulates different genes to miR-378 and leads to myotube atrophy *in vitro*. Moreover, our data show that inhibiting oxidised miR-378 in old mice positively affects myofibre size and muscle strength.