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DI PADOVA

SMA-RT - Mechanisms of Skeletal Muscle Adaptation to Resistance Training in Spinal Muscular Atrophy

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Spinal Muscular Atrophy (SMA) is a debilitating neuromuscular disorder characterised by progressive motoneuron degeneration, which causes muscle atrophy and weakness. By combining pre-clinical studies and a clinical trial, this 36-month Global Fellowship aims to explore the beneficial role of exercise as a therapeutic strategy to support SMA treatment and improve clinical outcomes. During my outgoing phase at Harvard University, I will employ two transgenic SMA mouse models to investigate the skeletal muscle adaptations to overloading, achieved via synergistic ablation, a model historically used to study muscle hypertrophy and mimic human resistance training. In WP1, I will investigate the muscle morphological, functional, and transcriptomic responses to overloading in SMNΔ7 mutant mice, which, similarly to patients, present ubiquitous SMN deficiency and lifespan extension via pharmacological treatment. In WP2, I will perform the same overloading protocol and similar analyses on a mouse model presenting SMN knockout restricted to muscle satellite cells (Pax7:SMN-KO). While ubiquitous SMN deficiency triggers motoneuron degeneration, this model enables to focus on the role of satellite cells in SMA by deleting SMN selectively in these cells. During my incoming phase at the University of Padova, I will assess whether the molecular mechanisms underlying muscle adaptation identified in mice are translatable to humans, examining the response of SMA type III/IV patients, presenting the milder form of SMA, to a resistance training intervention (WP3). I will employ musculoskeletal imaging techniques, advanced EMG methods, and muscle biopsy and blood sample analysis to perform a comprehensive analysis, which is lacking to date. This project aims to propose exercise as a novel strategy to improve the quality of life in patients affected by SMA and other devastating neuromuscular disorders, also reducing the heavy socioeconomic burden associated with these diseases.

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