Quality assessment of myogenic stem cells in various patient populations with non-genetic skeletal muscle wasting.

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Muscle atrophy refers to the loss of muscle mass, which can have a variety of causes, including cancer (cachexia), and ageing (sarcopenia). Cachexia in lung cancer patients has a negative impact on quality of life, treatment outcome, and increases mortality rates (up to 22%) [1, 2]. In elderly, sarcopenia is a major contributor to frailty and causes an increase of the risk for hip fractures. In turn, frailty causes extended hospital stay and reduced chances of independency after a hip fracture [3, 4]. Often it cannot be counteracted with solely dietary intervention and/or exercise [5]. Sometimes, exercise is not an option within these patient groups due to the severity of the disease. No effective treatment is available for the regeneration of muscle tissue in these conditions. Therefore, we aim to develop a stem cell therapy with autologous muscle stem cells, called mesoangioblasts, for these patients.

Mesoangioblasts surround the blood vessels and can be characterized as pericyte-derived mesenchymal cells. Mesoangioblasts are capable of differentiating into the skeletal muscle lineage and can fuse with existing muscle fibres. They cross the endothelium of the blood vessel, which

allows systemic, intra-arterial delivery [6-8]. The first aim of the project is to assess the quality of mesoangioblasts isolated from biopsies of patients with cachexia and sarcopenia. Skeletal muscle biopsies will be obtained at MUMC and ZMC. Lung cancer patients with cachexia (50-60y, 60-70y, n=10/group) will undergo a needle puncture. Surplus muscle tissue will be obtained from frail elderly with sarcopenia (60-70y, 70-80y, n=10/group) and healthy elderly (age-matched, n=10/group) during total hip replacement surgery. Proliferation-, differentiation capacity (*i.e.* capability to form Myosin Heavy Chain+ myofibres) and mitochondrial morphofunction will be determined. Also, RNA sequencing for myogenesis-related genes, qPCR for mitochondrial DNA copy number and fluorescent dyes for mitochondrial membrane potential will be performed. Quality will be compared to healthy-donor mesoangioblasts to see whether these patient cells can be used for an autologous stem cell therapy in the future.

If of sufficient quality, we will test in mouse models, the efficacy of the treatment with healthy mesoangioblasts. These clinical- and animal studies will give insight in the potential of this novel therapeutic approach.

Keywords: sarcopenia, cachexia, stem cells

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