**Pitch Patrick Schrauwen/Joris Hoeks- Sarcopenia**

**The challenge**

One of the distinctive features of aging is the progressive loss of muscle mass and physical function, collectively known as sarcopenia. The loss of skeletal muscle mass and tissue function has been related to mobility impairments, such as difficulties walking short distances or standing up from a chair, an increased risk of falls, physical frailty, and metabolic impairments, ultimately leading to a loss of physical independence and increased care need. In parallel with the progressive loss of muscle function, mitochondrial respiratory activity in human skeletal muscle has been shown to decrease with advancing age and some (preclinical) studies suggest that the reduction in muscle mitochondrial function may (partly) underlie the decline in muscle health during aging.

**The opportunity**

Over the past years, we have studied the relationship between age-associated decline in mitochondrial function and its effect on skeletal muscle physiology in humans. For this purpose, we performed a large, cross-sectional study in which we compared mitochondrial function in young and older adults, with similar habitual physical activity levels. We also studied older adults with a range of habitual physical activity levels and function, i.e. trained older adults, older adults with normal physical activity levels and physically impaired older adults. Older adults displayed lower mitochondrial capacity, maximal aerobic capacity, exercise efficiency, muscle strength, insulin sensitivity, gait stability following a perturbation, and walking performance compared to young adults, despite similar habitual physical activity levels and comparable muscle volume. In comparison to older adults with normal physical activity levels, endurance-trained older adults had a higher mitochondrial function, maximal aerobic capacity, exercise efficiency, muscle strength, and insulin sensitivity. From these findings we conclude that aging is associated with a decline in mitochondrial capacity, exercise capacity and efficiency, gait stability, muscle function, and insulin sensitivity, even when maintaining an adequate daily physical activity level. Nevertheless, a further increase in physical activity level, achieved through regular exercise training, can partially negate effects of aging. The observed correlations between mitochondrial capacity and muscle strength, exercise efficiency, and insulin sensitivity, support a link between mitochondrial function and age-associated deterioration of skeletal muscle health. Finally, we also performed untargeted metabolomics in the skeletal muscle biopsies from our cross-sectional study to investigate the muscle metabolome in young vs. groups of older adults that represent both healthy (trained older adults) and poor (pre-frail older adults) aging. This analysis identified that NAD is one of the main metabolites that is reduced upon aging. This reduction appeared even more severe in prefrail older individuals, but was (partially) rescued in trained older adults.

**The offer**

Taken together, we identified mitochondrial (dys)function as a contributor to muscle (metabolic) health in aging and showed that modulating metabolic flexibility and mitochondrial function, e.g. through exercise training, contributes to improved health related parameters. In addition, we have previously shown a 24-hour rhythm in mitochondrial oxidative capacity and that this rhythmicity is severely blunted in older individuals with pre-diabetes. **Our main research focus is to study if we can modulate (rhythmicity of) mitochondrial function and if this translates in improved muscle function and metabolic health in the face of aging and aging-related metabolic disturbances.** For our human interventions studies, we have created unique infrastructure and developed novel technology which permits a non-invasive approach to metabolism; extended by studies in tissues sampled and cells grown from participants in our studies, that allow a molecule-to-man approach. Using these translational approaches we aim to answer the following questions: 1) Does a reduction in mitochondrial function underly reduced muscle health in ageing? 2) What is the role of lifestyle (physical activity, diet, circadian)? 3) Can we boost NAD+ metabolism to prevent age-related decline

in muscle function? 4) Which molecular changes underly muscle ageing? and welcome collaborations to achieve these goals.