

Pitch ANABOLIC RESISTANCE AND MUSCLE LOSS WITH AGING, Lex Verdijk / Luc van Loon

The challenge

The aging process negatively impacts on various organ systems. For skeletal muscle tissue, this entails both qualitative and quantitative changes that ultimately result in an overall decline in muscle mass and function. Independent of whether this is related to aging per se or to any other age-associated condition, the loss of muscle mass and function has become a key topic in the realm of 'successful, healthy aging'. This is not surprising as muscle loss is strongly associated with reduced independence and quality of life, as well as increased healthcare costs and even mortality. The challenge is to further unravel the underlying mechanisms of age-associated muscular impairments (or 'sarcopenia'), and use this information to further develop effective intervention strategies to counteract the negative aging consequences. We propose that the 'anabolic resistance' of skeletal muscle tissue plays a central role in this respect.

The opportunity.

Our lab specializes in *in vivo* human metabolic research with a strong focus on skeletal muscle protein metabolism. We strive to increase knowledge on the factors that drive (skeletal muscle) protein turnover, which will enable us to define more effective interventions to improve health and functional performance in both healthy and more clinically compromised (older) individuals. We do this using state-of-the-art approaches including the application of stable isotope tracer methodology to study *in vivo* protein metabolism, as well as extensive phenotyping to assess whole body and regional muscle mass, muscle function, and muscle health in response to long-term exercise, nutritional, and pharmacological interventions. We have shown that physical inactivity with aging and as a result of trauma, sickness, or (major) surgery is associated with a *reduced responsiveness of skeletal muscle to anabolic stimuli* (e.g. protein intake). This so-called 'anabolic resistance' may reside at various different levels, and plays a key role in the age-associated decline in muscle mass and function. In future projects, we will further expand our knowledge on the mechanisms underlying anabolic resistance in skeletal muscle, and use this information to further develop and study exercise, nutritional and pharmacological interventions to support more active, healthy aging.

Apart from this 'muscle' focus, we have recently extended our work using stable isotope tracers to study protein metabolism in various other tissues that are interconnected with skeletal muscle tissue, including bone, collagen, and even various organs where we have been able to assess protein turnover rates of both healthy and diseased tissue. This leaves ample opportunities to study e.g. age-related physiological changes in these tissues, including the potential existence of 'anabolic resistance', as well as the ability of specific interventions to alleviate such changes, and support healthy aging.

The offer

In developing future grant proposals, we would seek collaboration with other partners to further study the mechanisms underlying anabolic resistance in muscle and other organ systems, using either a human or (in setting a mechanistic base) animal approach. Further collaboration to unravel the potential for pharmacological treatment of anabolic resistance and/or muscle loss (e.g. selective activation/inhibition of anabolic/catabolic pathways, senolytics, etc.) would also be of much added value. Finally, we strive to span the broad range from understanding the mechanistic base for age-associated deterioration, to showing proof-of-principle for certain interventional strategies to counteract such deterioration, to ultimately implementing such interventions in large-scale studies to establish the actual benefits in terms of muscle mass, strength, function, and overall health. As such, we envision that collaboration with other partners for large-scale multicenter intervention studies (as we continue to successfully do with e.g. Wageningen University) would be part of future grant proposals.