



General data	
PPP number	AF-15502
Title	Mitochondrial Health
Theme	Gezond en Veilig
Executing research organisation(s)	Universiteit Maastricht, UMC Groningen, Wageningen Universiteit
Project leader research (name + email address)	Patrick Schrauwen p.schrauwen@maastrichtuniversity.nl
Coordinator (on behalf of private parties)	Chair Project Council – Marjolijn Bragt - Van Wijngaarden (FrieslandCampina)
Contact person of government	
Total project budget (k€)	2 162 k€
Project website address	n.a.
Starting date	1 juli 2016
Final date	30 juni 2020

Approval coordinator/consortium	
The annual report has to be discussed with the coordinator/consortium. The TKI(s) like to be informed regarding potential comments on the annual report.	
The annual report is by the coordinator on behalf of the consortium	<input type="checkbox"/> approved <input type="checkbox"/> not approved
Potential comments regarding the final report	

Description content/aim PPP	
Description of problem	<p>Mitochondria, the cell's powerhouses, are essential organelles in all cells relying on aerobic metabolism to maintain cellular energy levels necessary for all vital processes in the cell and human body. It has been known for decades that aging is associated with a decline in skeletal muscle mitochondrial function. Despite this fact, it is only recently that the therapeutic importance of mitochondria has become fully appreciated. Improving mitochondrial activity cannot only potentially delay the general aging process, but more importantly also retard the onset of diseases linked with aging, such as loss of muscle mass and physical function. This not only has led to an intense interest to identify molecular pathways that govern mitochondrial number and function, but also spurred an intense search to identify new nutrients and drugs that can be used to improve mitochondrial function. Relevant to TI Food and Nutrition, mitochondria are very sensitive to nutritional signals, which is not surprising given the role of these organelles in nutrient handling. This opens the way to explore the potential of food components and specific nutrients to boost muscle mitochondrial function, thereby improving muscle health and help in the prevention and improvement of age-related disturbances.</p>
Goals of the project	<p>The project Mitochondrial Health within TIFN will focus on evaluating novel food components on mitochondrial metabolism and its relation to muscle health. It is expected that basic science in in vitro muscle cell models can reveal novel food components that affect mitochondrial metabolism, and can unravel the underlying mechanisms. Using short-term human intervention studies, the translational aspect of the potential of such food components to boost mitochondrial function will be tested in the elderly population, with a focus on those with compromised physical function. Cross-sectional studies will be used to</p>

	<p>investigate the relationship between muscle mitochondrial function and muscle health in elderly, whereas we will use large cohort studies to investigate the relationship between habitual food consumption and markers of muscle health and physical function. Finally, we aim to identify novel biomarkers of mitochondrial function that can be applied in observational and intervention studies. It is anticipated that the project Mitochondrial Health will provide the industrial partners with novel insights in the potential of food components and specific nutrients to prevent, delay or improve aging associated decline and disturbances in muscle health and physical function, by targeting mitochondrial function.</p>
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Results	
Expected results 2019	<p>WP1: It was expected to finalize 3 out of the 4 groups of the cross-sectional human study. Furthermore, young and old human primary myotubes were cultured and extensive phenotyping performed.</p> <p>WP2: The study on mitochondrial capacity in endurance trained and untrained young males was expected to finish subject inclusion and the on Near-InfraRed Spectroscopy (NIRS) data to be analysed and the first draft of the manuscript to be written. CHIP analyses studying the effect of acyl-donors on histone modification in C2C12 myotubes was to be finished. The first manuscript of the in vitro paper on protein acylation and mitochondrial function is ready.</p> <p>WP3: The goal was to complete inclusion of the 14 subjects for the dietary intervention study, and to submit the METC protocol for fish-oil intervention study and start inclusion.</p> <p>WP4: Optimization and validation of a lipidomics assay was planned, next to measurements of organic acids in renal transplant recipients cohort and investigate associations between urinary excretion of organic acids and physical function. Furthermore, it was expected to perform the biomarker study in MitoHealth samples .</p> <p>Furthermore, the writing of the manuscript on the association between dietary intake and physical function in elderly was planned.</p>
Achieved results 2019	<p>WP1: Currently the majority of subjects of the cross-sectional human study are included, apart from the pre-frail group elderly. It was decided not to complete the pre-frail group completely and to add a few more active subjects. Primary muscle cells have been cultured from the obtained muscle biopsies for <i>in vitro</i> studies and performed extensive metabolic characterization of cells derived from young vs. elderly donors using fluxomics and also mitochondrial function using seahorse analysis. No difference was found in phenotype between the old and the young donors. Furthermore, these muscle cells have been subjected to propionylation while studying its subsequent effects on mitochondrial function (WP1 – WP2 collaboration).</p> <p>WP2: The manuscript from the first study “Mitochondrial capacity in endurance trained and untrained young males (MCAP)” was accepted for publication in European Journal of Applied physiology. The second human study on study “Mitochondrial Capacity and Acylation in Young and Elderly Males (MCAGE)” was finalised in March 2019. The results of the mitochondrial capacity were analysed and the manuscript was accepted for publication on the Journal of Geroscience. ChIP-PCR measurements showed significant results, yet ChIP-seq measurements were inconclusive due to difficulties with sequencing depth or antibodies. New leads were discovered in primary cell lines of old and young adults.</p>

	<p>WP3: The dietary intervention study with a focus on the NAD-pathway and a study on a combination of fish oil and complex lipids have started. The recruitment of the fish oil multi-center study between Wageningen and Maastricht started and personnel is trained with regard to the oxygraphy (mitochondrial function measurements) via the Maastricht site, such that the measurements are executed with exactly the same protocols and training.</p> <p>WP4: The manuscripts on biomarkers in a prospective cohort of renal transplant recipients and healthy kidney donors are published and submitted in Journal of Clinical Medicine. The lipidomics assays are up and running and measurements of urinary organic acids in the cohort are finished.</p> <p>Observational data from the Nu-Age study were analysed, evaluating how habitual food intake, plasma homocysteine and urinary biomarkers of niacin status relate to measures of muscle health and physical function in an elderly population. It was found that intake of vitamin B3 and B6 are related to higher handgrip strength in those with low physical activity levels, while intake of vitamin B6 is related to improved chair rise test performance. The associations were not mediated by homocysteine levels or niacin status. This concludes that intake of vitamin B3 and B6 might rescue physical functioning in absence of physical activity, but we need more information on the possible underlying mechanism(s), causality and intake thresholds.</p>
Expected results 2020	<p>WP1: The final subjects of the cross-sectional human study will be included early 2020 and the study will be finalized. The data will be analysed to study the relationship between mitochondrial function, age and physical activity and manuscript will be submitted. Also, via collaboration with Prof. Houtkooper (AMC), lipidomics and metabolomics in muscle biopsies of these volunteers will be performed and also goal to submit the manuscript. The thesis of Lotte Grevendonk is expected to be finalized. As it is not expected that the results of the <i>in vitro</i> human primary myotube work can be further explored <i>in vivo</i> in this project, it was decided to focus resources on the finalization of the human studies and the collaboration with WP2.</p> <p>WP2: RNAseq measurement and mitochondrial biomarker analysis in urine is currently ongoing and results are expected shortly. The draft <i>in vitro</i> manuscript on a specific type of acylation (propionylation) is completed and will be finalized for submission. <i>In vitro</i> manuscripts on the effects of acylation of muscle are in process. ChIP-PCR measurements showed significant results, yet ChIP-seq measurements were inconclusive due to difficulties with sequencing depth or antibodies. New leads were discovered in primary cell lines of old and young adults which call for subsequent, detailed analyses. Also, the goal is to finalize the inclusion and testing of the human study with WP1.</p> <p>WP3: The inclusion of subjects of the dietary supplementation study has gone relatively smooth and the study is expected to be finalized in Q1 2020. Planning of the analysis of the blood and muscle biopsies for the study has started. For the multi-centre study with Wageningen and Maastricht personnel to execute the study at Wageningen has been hired and all is ready to start the execution of the experiment early 2020. The thesis of Niels Connell is expected to be finalized.</p> <p>WP4: It is expected to finalize the lipidomics assays and processing of urinary organic acids in the cohort of renal transplants recipients and healthy kidney donors. The biomarker studies in mitochondrial health WPs will be planned upon the availability in other WPs. The thesis of Carolien Deen is expected to be finalized.</p>

	<p>Observational data from the Nu-Age study were analysed, evaluating how habitual food intake, plasma homocysteine and urinary biomarkers of niacin status relate to measures of muscle health and physical function in an elderly population. A manuscript is written and will be sent around for clearance early 2020. The thesis of Pol Grootwagers is expected to be finalized.</p>
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Delivered products in 2019 (give titles and/or description of products, or a link to the products on the project website, or other public websites).

Scientific articles:

Deen CPJ, van der Veen A, van Faassen M, Minović I, Gomes-Neto AW, Geleijnse JM, Borgonjen-van den Berg KJ, Kema IP, Bakker SJL. Urinary Excretion of N(1)-Methylnicotinamide, as a Biomarker of Niacin Status, and Mortality in Renal Transplant Recipients. *J Clin Med*. 2019 Nov 12;8(11). pii: E1948. doi: 10.3390/jcm8111948. PubMed PMID: 31726722.

Lagerwaard B, Keijer J, McCully KK, de Boer VCJ, Nieuwenhuizen AG. In vivo assessment of muscle mitochondrial function in healthy, young males in relation to parameters of aerobic fitness. *Eur J Appl Physiol*. 2019 Aug;119(8):1799-1808. doi: 10.1007/s00421-019-04169-8. Epub 2019 Jun 8. PubMed PMID: 31177324; PubMed Central PMCID: PMC6647177.

External reports:

Not applicable

Professional articles in journals:

Not applicable

Lectures/posters during workshops, conferences and symposia:

Patrick Schrauwen, invited speaker at the 55th annual meeting of the European Association for the Study of Diabetes (EASD), Barcelona, Spain. September 16-20, 2019. "Skeletal muscle insulin resistance: role of mitochondria".

Patrick Schrauwen: Invited Keynote speaker at the 2018 NUGO week – mitochondria, nutrition and health, New Castle, UK. September 3-6, 2018. "Mitochondrial dysfunction in skeletal muscle and type 2 diabetes".

Patrick Schrauwen, invited speaker at Keystone Symposium on Mitochondrial Biology in Heart and Skeletal Muscle/ Mitochondria in Aging and Age-Related Disease, Keystone, Colorado, USA, January 13-18, 2019. "Human Skeletal Muscle Mitochondrial function and Insulin Sensitivity".

Lotte Gevendronk, Annual TiFN retreat 11-09-2019. 'Cross-sectional analysis of mitochondrial function and muscle health in elderly'

Pol Grootwagers, Annual TiFN retreat 11-09-2019. 'Dietary intake of vitamin B3, B6, B12, folate in relation to physical functioning in healthy older European adults'

Bart Lagerwaard, Annual TiFN retreat 11-09-2019. 'In vivo assessment of muscle mitochondrial function in ageing research using near-infrared spectroscopy'

Bart Lagerwaard, FASEB 07-08-2019. 'Protein hyperpropionylation contributes to mitochondrial dysfunction and impairs C2C12 myoblast differentiation'. FASEB Reversible Protein Acetylation in Health and Disease Conference (2019), Lisboa, Portugal (poster presentation).

Niels Connell, Maastricht-Düsseldorf-Lille meeting 04-06-2019. 'Mitochondria and muscle health in elderly'. Annual Maastricht – Düsseldorf – Lille meeting, Lille, France (oral presentation).

TV/radio/social media/newspaper:

Not applicable

Others (techniques, machines, methods, etc.):

Not applicable