



**PPP final report**

PPPs that have been finalized need to deliver a factual and financial final report. For the financial report an overview of the project expenses on realisation and financing should be given in a separate format.

**Final reports will be published in their entirety on the TKI/top-sector websites. Please make sure there are no confidential matters in the report.**

PPP final reports have to be submitted - pooled for each research organisation - before 1 April 2019 to the TKIs at info@tkitu.nl, or at info@tki-agrifood.nl. For Wageningen Research the delivery of reports occurs centrally.

General data	
PPP number	AF-14502
Title	What moves wasting muscle?
Theme	Voeding en gezondheid
Research Institute(s) involved	WUR
Project leader research (name + email address)	Lisette de Groot (lisette.degroot@wur.nl)
Coordinator (on behalf of private parties)	
Contact person of government	
Total project budget (k€)	419
Project website address	<a href="http://www.tifn.nl">www.tifn.nl</a>
Starting date	01-01-2014
Final date	16-03-2019

**Approval coordinator/consortium**

The final report has to be discussed with the coordinator/consortium. The TKI(s) like to be informed regarding potential comments on the final report.

The annual report is ..... by the coordinator on behalf of the consortium	<input checked="" type="checkbox"/> approved <input type="checkbox"/> not approved
Potential comments regarding the final report	Because the TKI funding was only a small part of the PhD project, the project was divided in TIFN and TIFN informed parts. For the sake of completeness all output of the project has been reported.

**Brief description content/aim PPP**

What is the matter and what does the project contribute?

What does the project deliver and what are the effects of its delivery?

Cachexia is a common, serious and yet often under-recognised complication of cancer. Most obvious clinical manifestations of cachexia are loss of muscle mass, sometimes also including loss of fat mass and hence weight loss. This is driven by metabolic changes with or without a reduction in food intake, including elevated energy expenditure, excess catabolism and inflammation. Cachexia affects most patients with advanced stage cancer, with in some cancers more than 60% of all patients showing weight loss. Patients suffering from cachexia often also experience fatigue, muscle weakness and reduced response to cancer treatment. Conventional nutritional support is generally ineffective, the more so as anorexia often also develops in these patients. Together, these factors not only contribute to a reduced quality of life in these patients but are also assumed to be directly responsible for 20% of all cancer deaths.

Thereby, aim of the current project was to get more insight into the processes driving this complex cachexia syndrome.

Deliverables:

Substantiation of the relationship between low muscle mass and chemotherapy-induced toxicities

A metabolic profile of mouse models related to changes in physical outcome parameters of muscle wasting

A metabolic comparison between human and mouse

Identification which pathways are conserved between mouse and human and could be targets for future interventions

The effects of the deliverables is :

- more insight in the mechanism behind cachexia
- more insight in possible treatment targets and modalities

<b>Mutations with respect to the original project plan and follow-up</b>	
Have there been changes in the consortium/project partners? If so, which.	No
Have there been factual changes in the project?	No
Has a patent application been filed from this PPP (or a priority filing)?	No
Has a spin-off developed from this project (contract research, additional funding or spin-off activity)?	No
How many years will the private parties need in practice to use results from this project?	In a few years
How did the project contribute to the development of the research organisation involved (e.g. scientific track record, new technology, new collaboration)?	<p>The total project (inclusive the TKI part) resulted in: An improvement of the scientific track record:</p> <ul style="list-style-type: none"> <li>- a PhD thesis (to be submitted to the committee in April / May 2019)</li> <li>- 4 papers (3 submitted, 1 published)</li> <li>- published paper: <a href="https://icsm-clinical-reports.info/index.php/icsm-cr/article/view/46">https://icsm-clinical-reports.info/index.php/icsm-cr/article/view/46</a></li> </ul> <p>New collaborations on mitochondrial functioning (with prof Jaap Keijer), resulting in input in a paper from the project from VLAG : <a href="https://www.sciencedirect.com/science/article/pii/S0304419X18300726">https://www.sciencedirect.com/science/article/pii/S0304419X18300726</a></p> <p>Renewed collaborations with prof dr Josep Argiles and prof dr Alessandro Laviano, resulting in one of the papers mentioned above.</p>
Will there be a follow-up for the project such as a new project or a new collaboration? If so, please explain.	<p>Within this project a clinical study (COMUNEX) was set-up, for which inclusion of patient took longer than expected. The WUR will finish this clinical study on their own costs. It is a study concerning gain for mechanistic insight in the mechanism behind cachexia in colorectal cancer patients.</p>

## Results

### What tangible results the project has yielded?

- 1) Our findings suggest that in our study population (Dutch colorectal cancer patients), not muscle quantity, but muscle functional quality is associated with side-effects of chemotherapy treatment.
- 2) On in-vivo cachexia outcomes, we found that the vibration training was not able to reduce body weight loss or muscle loss. Despite that no major visible effects on body composition were found, the shift in muscle transcriptome were that promising that more studies into whole body vibration training as treatment component for cachexia seem warranted.
- 3) Fish-oil, and specifically DHA, could be an important treatment component for reducing tumour-induced hypercalcemia. (Nutricia Research sponsored part of the project)

### What are the effects of these results and for whom?

**Ad 1: medical and social relevance:** For colorectal cancer patients it seems worthwhile to measure intramuscular fat in the muscle by using CT-scans routinely taken in this patient group to better predict chemotherapy-induced toxicity

**Ad 2: medical and social relevance:** Cancer patients are often fatigued. If they could start with vibration training before real exercise training this might help to break the viscous circle of fatigue (fatigued, therefore no motivation to perform daily activities, resulting in muscle loss and more fatigue).

**Ad 3: medical, social and commercial relevance:** This part of the project was incorporated later and payed for by Nutricia. It resulted in support for a product feature previously hypothesized and patented by Nutricia

### What has not been delivered according to the original project plan and for what reason(s)?

All deliverables have been delivered. For sake of completeness it is good to mention that within this project a clinical study (COMUNEX) was set-up, for which inclusion of patient took longer than expected. The WUR will finish this clinical study on their own costs. It is a study concerning gain for mechanistic insight in the mechanism behind cachexia in colorectal cancer patients.

## Deliverables (give a short description per project deliverable)

Deliverables:

1. Substantiation of the relationship between low muscle mass and chemotherapy-induced toxicities

The possible consequences of cancer cachexia were studied in a retrospective cohort of colon cancer patients receiving a chemotherapy regime with capecitabine and oxaliplatin (CAPOX). Main finding was that patients with more intramuscular adipose tissue had more dose-limiting toxicities while there was no association with the absolute or relative amounts of muscle, visceral or subcutaneous adipose tissue (D1).

Paper: <https://jcsn-clinical-reports.info/index.php/jcsn-cr/article/view/46>

2. A metabolic profile of mouse models related to changes in physical outcome parameters of muscle wasting
3. A metabolic comparison between human and mouse

Different models are in use to evaluate possible therapeutic strategies in cachexia, like those based on nutritional, exercise and pharmacological intervention. We aimed to determine the relevance of mouse models used to mimic human cachexia, by comparing their effects on muscle

gene expression between models. Therefore, a comparative analysis was performed on muscle transcriptome data of different cachexia studies. In this comparison transcriptional data from many different labs were compared.

Overall, our analysis revealed similarities between animal models and, to lesser extent, to human datasets, in particular with respect to biological process level.

4. Identification which pathways are conserved between mouse and human and could be targets for future interventions

On gene level, analysis indicated only little similarity between the data from animal models and those from human datasets, while more similarities were found between the animal models. In our analysis, we identified an upregulated RNA transport pathway where human datasets cluster together with some well-known animal models. In this pathway, Eukaryotic translation initiation factor 4E binding protein 1 [EIF4EBP1] seems to be an important factor being highly downregulated. These findings need to be confirmed, because the human datasets were small and lacked some proper controls. The study currently running at the WUR should provide more clearance on this matter.

<b>Number of delivered products in 2018</b> (give titles and/or descriptions of products, or a link to the products on the project website, or other public websites).			
Scientific articles  4 papers (1 published and 3 submitted)  1 PhD thesis (to be submitted)	Reports	Articles in professional journals	Lectures/workshops  Part of the array analysis has been used in a Master course on cancer cachexia, for 5 years in a row.  4 poster presentations at the world cachexia and cancer cachexia conference  1 oral presentations at the cancer cachexia conference
<b>Titles/descriptions of prominent products in 2018 (max. 5) and their target groups</b>			
- Intramuscular fat mass analysis for risk analysis on chemotoxicity in cancer patients			

**Annex: Titles of deliverables or a link to products on the project website or other public websites**