

## Reasoning of dissertation topic and competency of potential supervisor for admission onto joint LSU and TU doctoral studies in 2019

<b>Area of research (title and code)</b>	Biomedical Sciences
<b>Field of research (title and code)</b>	01B Biology
<b>Topic of research</b>	Ketoglutarate and succinate supplements in regulation of skeletal muscle mass and function in mouse and human
<b>Institution</b>	LSU

### Potential supervisor

<b>Pedagogical and scientific degree</b>	<b>Name, surname</b>	<b>Academic position</b>
Dr.	Aivaras Ratkevičius	Professor

### Short reasoning of proposed dissertation topic

<b>Title</b>
Ketoglutarate and succinate supplements in regulation of skeletal muscle mass and function in mouse and human
<b>Summary</b>
<p><b>Importance of research</b></p> <p>Diet plays important role in health (Sacks et al. 2017) and regulation of muscle mass (Phillips 2018). However, conclusions drawn from the epidemiological studies on nutrient intake have often raised doubts about the underlying assumptions (Ioannidis 2018). It appears that animal studies with strict control of experimental conditions are helpful in verification of the findings of the epidemiological studies.</p> <p>Dietary supplements that can be added to food and/or drink to promote health are of particular interest due to a potential for commercial applications. Our aim is to investigate if ketoglutarate and succinate as intermediates of mitochondrial Krebs cycle could be useful dietary supplements. A recent study shows that succinate supplements increase metabolic rate and reduce weight gain in mice fed high fat diet which resembles typical diet consumed by humans (Mills et al. 2018). There is also evidence that succinate and ketoglutarate stimulate protein synthesis in the muscle cells (Cai et al. 2016, Yuan et al. 2017). Ketoglutarate has been proposed as useful dietary supplement for improvement of metabolism (Zdzisinska et al. 2017). On the other hand, succinate accumulates in blood during exercise in humans, but the physiological significance of this change remains unclear (Hochachka and Dressendorfer 1976). It appears that there is sufficient ground to investigate effects of dietary ketoglutarate and succinate on the whole body metabolism and skeletal muscle function in mouse and human.</p> <p>One of the potential effects of dietary succinate and ketoglutarate supplementation is associated with regulation of muscle mass. There is evidence suggesting the that genes belonging to at least three signalling pathways are able to induce hypertrophy: (a) Igf1-Akt-mTOR pathway, (b) myostatin-Smad signaling, and (c) the angiotensin-bradykinin signalling pathway (Verbrugge et al. 2018, Wackerhage and Ratkevičius 2008). The majority of muscle hypertrophy studies have been limited to a few signalling pathways (Georges et al. 2018). However, skeletal muscle overloading modulates activity of the whole network of signalling pathways and relative contribution of these pathways might vary during the course of muscle adaptation to the overloading (Nader et al. 2014). Recent developments in proteomics allow for unbiased screening of all major proteins involved in regulation of muscle growth (Potts et al. 2017). Such approach combined with metabolomics which includes comprehensive analysis of metabolic profile of skeletal muscles can provide valuable insight into regulation of muscle mass under conditions of overloading and disuse (Cirulli et al. 2019).</p>

We have previously examined muscle hypertrophy in response to synergist ablation (Minderis et al. 2016). We have now acquired expertise in targeted denervation of skeletal muscles which allows for examination of muscle atrophy and hypertrophy in the same animal. The findings about involvement of some signalling pathways mediating muscle atrophy have been published in *Experimental Gerontology* (Hendrickse et al. 2018).

### **Research questions**

The current PhD project has the following aims:

- 1) Determine the effect of ketoglutarate and succinate supplements on regulation of body and muscle mass under conditions of overloading and denervation in mice;
- 2) Determine proteomic and metabolomics markers for muscle hypertrophy and atrophy in mice;
- 3) Determine effects of ketoglutarate and succinate supplements on physical fitness and muscle function in humans.

### **Feasibility of the project**

LSU is equipped with all the necessary equipment and facilities to carry out the proposed research project on both mice and humans. The project includes collaboration with prof. Henning Wackerhage, Department of Sport and Health Sciences, Technical University of Munich (TUM), Germany. TUM is one of the leading universities in Germany and is equipped with the state of the art facilities for proteomics and metabolomics that will be used in the proposed project. Prof. Henning Wackerhage will contribute to the costs (~5000 EUR) of the sample analysis in these facilities. Dr. Martin Schönfelder and Dr. Phillip Baumert who specializes in proteomics and metabolomics will provide help to Ph.D. student in this analysis. LSU and TUM have established ERASMUS+ agreement for exchange of staff and Ph.D. students. This agreement will serve as a basis for student and staff exchange in the framework of this project.

### **Collaboration with prof. Henning Wackerhage**

The collaboration between prof. Aivaras Ratkevicius and prof. Henning Wackerhage has already been supported by the grant from the Baltic-German University Liaison Office in 2018. The grant included the workshop “Fighting muscle weakness when we get old” which was organized at LSU on the 23rd November 2018. The workshop was attended by more than 80 students and members of staff from four universities in Lithuania. Both parties expressed the desire to make this workshop a regular event and will be applying for grant from the Baltic-German University Liaison Office to organize this workshop in November 2019.

Prof. Arvydas Stasiulis, Head of Department of Applied Biology and Rehabilitation will be visiting TUM to get acquainted with teaching labs and research facilities at this university. Prof. Henning Wackerhage has proposed to develop a joint course for MSc students about the role of exercise in prevention and treatment of chronic diseases in 2019-2020.

### **References**

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**Please indicate the links between the proposed topic for the doctoral thesis and health promotion / physical therapy / sports study programs.**

The proposed topic is linked to „Health promotion“ as the area of research

**Is the proposed topic for the doctoral thesis related to currently funded research projects?**

No

**Is the proposed topic for the doctoral thesis related to joint research with a foreign institution?**


**Yes.**

Research team includes:

Supervisors: prof. Aivaras Ratkevicius (1st supervisor, Lithuanian Sports University, LSU), prof. Henning Wackerhage (2nd Supervisor, Technical University of Munich, TUM); Consultants: Dr. Martin Schönfelder and Dr. Phillip Baumert (Technical University of Munich, TUM).

Currently I am supervisor of **3** doctoral students.

Supervisor



(signature)

Aivaras Ratkevicius

(Name, surname)

Date: 12.03.2019