

## Jury Member Report – Doctor of Philosophy thesis.

**Name of Candidate:** Smirnov Dmitrii

**PhD Program:** Life Sciences

**Title of Thesis:** Investigation of the role of SIRT6 in molecular mechanisms of the gene expression regulation, metabolism and aging

**Supervisors:**

Assistant Professor Ekaterina Khrameeva, Skoltech

Associate Professor Deborah Toiber, Ben-Gurion University

**Name of the Reviewer: Carlos Sebastián**

I confirm the absence of any conflict of interest  (Alternatively, Reviewer can formulate a possible conflict)	<b>Date: 06-11-2023</b>
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*The purpose of this report is to obtain an independent review from the members of PhD defense Jury before the thesis defense. The members of PhD defense Jury are asked to submit signed copy of the report at least 30 days prior the thesis defense. The Reviewers are asked to bring a copy of the completed report to the thesis defense and to discuss the contents of each report with each other before the thesis defense.*

*If the reviewers have any queries about the thesis which they wish to raise in advance, please contact the Chair of the Jury.*

### Reviewer's Report

Reviewers report should contain the following items:

- Brief evaluation of the thesis quality and overall structure of the dissertation.
- The relevance of the topic of dissertation work to its actual content
- The relevance of the methods used in the dissertation
- The scientific significance of the results obtained and their compliance with the international level and current state of the art
- The relevance of the obtained results to applications (if applicable)
- The quality of publications

The summary of issues to be addressed before/during the thesis defense

The overall aim of this thesis is to characterize the role of SIRT6 on mammalian brain aging and age-associated diseases by focusing on the transcriptome and metabolome changes in SIRT6-KO mice and cells. The rationale and hypotheses of the thesis are based on previous work from the laboratory of Dr. Toiber (one of the PhD supervisors) and, overall, the experimental approach matches the proposed objectives. The thesis is very well written and structured, with different chapters covering the three main research lines carried on during this thesis. I miss though a “Objectives” section where the main objectives of the thesis are highlighted and contextualized.

The studies presented in this thesis are very relevant for human health, as they provide valuable information on the molecular mechanisms underlying brain aging and age-associated diseases, such as AD and PD. Moreover, although very preliminary, they also suggest a potential role of age-associated increase in TP73-AS1 on brain tumors. Importantly, some of the results presented are backed up by publications in top-tier journals where the PhD applicant is main author, an excellent outcome for a PhD student.

I have few comments that, in my opinion, could improve the quality of this thesis, as follows:

- Bibliography: the format of this section makes very difficult to find the references cited in the text as they are not numbered and the citation in the bibliography section does not start with the last name of the first author (as it appears in the main text).
- The role of SIRT6 as a regulator of mitochondrial metabolism (and glucose metabolism, which is intimately linked to mitochondrial metabolism) has been extensively studied in a variety of cell types and tissues. It is very surprising that any of these studies is mentioned and discussed in the current thesis, neither in the introduction nor in the results/discussion sections, despite being very relevant to interpret some of the results obtained in this thesis.
- One full chapter of this thesis is devoted to the set up and description of a new experimental strategy to analyze, quantify and visualize lipidomics data. However, I couldn't find any experiment in the other two chapters (and specially in the metabolomics experiments on SIRT6-KO cells) where this methodology has been employed, thus making difficult to contextualize this chapter in the overall thesis project.
- While mice brains have been used for the transcriptomic experiments, only cells with SIRT6-KO have been used for the metabolomics. It would have been better to use the same biological material to integrate both omics experiments to obtain a real multiomic approach.

In conclusion, although some of the experimental approaches could be improved, this is a thesis with very solid results that are very relevant for the fields of sirtuins biology and brain aging and associated diseases, with relevant implications for human health. I recommend though to change the format of the bibliography section and include the mentioned missing information about SIRT6 and metabolism.

#### **Provisional Recommendation**

*I recommend that the candidate should defend the thesis by means of a formal thesis defense*

*I recommend that the candidate should defend the thesis by means of a formal thesis defense only after appropriate changes would be introduced in candidate's thesis according to the recommendations of the present report*

*The thesis is not acceptable and I recommend that the candidate be exempt from the formal thesis defense*