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Annex No. 10 to the MU Directive on Habilitation Procedures and Professor Appointment Procedures

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University

Applicant	RNDr. Jan Škoda, Ph.D.
Habilitation thesis	Novel molecular approaches to overcome therapy resistance in pediatric solid tumors
Reviewer	Mgr. Karel Souček, Ph.D.
Reviewer's home unit, institution	Institute of Biophysics of the Czech Academy of Sciences, Department of Cytokinetics/Faculty of Science, Masaryk University, Brno

Dr. Škoda's habilitation thesis focuses on an innovative molecular strategy to combat treatment resistance in pediatric solid tumors. His research career is focused on understanding and overcoming treatment resistance in pediatric solid tumors, particularly neuroblastoma. A key theme is the role of mitochondria and the integrated stress response in drug resistance and potential therapeutic targeting.

The text of the habilitation thesis is based on a selection of 18 peer-reviewed publications, including 15 original research articles and three reviews. Dr. Škoda was the first and/or corresponding author on 10 papers, 8 of which were published in journals with Q1. The publications are listed in the thesis and are categorized according to the author's contribution to experimental work, mentoring, manuscript preparation, and research guidance. The full texts of each publication are given in the appendices.

The thesis is structured in two parts and is written logically and clearly. The first part examines the molecular determinants of cancer stem cells (CSCs) and their role in treatment resistance in solid tumors, emphasizing pediatric sarcomas. This part highlights the critical role of the transcription factor SOX2 as a marker of CSCs in these tumors. It also presents evidence suggesting that mesenchymal tumors can modify their CSC characteristics by adopting a hybrid epithelial-mesenchymal phenotype, which may represent novel therapeutic targets. The second part discusses current approaches to overcome treatment resistance, including targeting mitochondria and exploiting vulnerabilities in the tumor microenvironment.

The final part of the habilitation summarizes the major challenges and future direction for targeting mitochondria and CSCs in resistant and pediatric cancers.

Overall, this is a very good thesis regarding both factual and formal aspects.

Reviewer's questions for the habilitation thesis defence (number of questions up to the reviewer)

- Are there any specific or unique molecular mechanisms that regulate the stemness of cancer stem-like cells, particularly in pediatric solid tumors?

- How can therapeutic approaches targeting mitochondria be used to overcome drug resistance and enhance the efficacy of cancer treatment in these tumors? What is the current state of clinical trials in this area? What is a measurable benefit for the patient?

- What are the limitations and perspectives of in vivo models for CSCs and pediatric solid tumor research?

Conclusion

The habilitation thesis entitled “Novel molecular approaches to overcome therapy resistance in pediatric solid tumors” by RNDr. Jan Škoda, Ph.D., **fulfils** the requirements expected of a habilitation thesis in the field of Molecular Biology and Genetics.

Date: 16.10.2024 Signature: