

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University

Applicant

RNDr. Jan Škoda, PhD

Habilitation thesis

Novel molecular approaches to overcome therapy resistance in pediatric solid tumors

Reviewer

MUDr. Aleš Vícha, PhD

Reviewer's home unit, institution

Klinika dětské hematologie a onkologie 2. LF UK

In his habilitation thesis, Dr. Jan Škoda addresses the issue of resistance in childhood tumors. The subject of tumor resistance is of great significance and contemporary relevance in the field of pediatric oncology. The thesis is structured as an annotated compilation of published articles, divided into two distinct sections. The initial section outlines the characterization of cancer stem cells and their function in the context of therapeutic resistance. The subsequent section is dedicated to the discussion of novel molecular targets for targeted therapy. In this context, the study of mitochondrial biogenesis and single-cell reconstruction of developmental trajectories are of particular significance.

In the course of this initial section, the author makes reference to his or her own published work. The aforementioned publications are presented in the form of appendices and constitute the second distinct section of the thesis.

In the initial section of the thesis, the author offers commentary on a total of 18 articles published in journals with impact factors (IF). These comprise 15 original research articles and three reviews. The author acted as the primary author on ten of these papers, with the majority (eight) published in Q1 journals.

A particularly noteworthy publication is "Mitoribosomal synthetic lethality overcomes multidrug resistance in MYC-driven neuroblastoma." *Cell Death & Disease*. 2023;14:747.

In summary, the scientific value of the submitted habilitation thesis is considerable. This is also demonstrated by the subject matter addressed in each publication. The individual articles have been published in high-quality journals. The high level of organization and ease of reading of the habilitation thesis itself should also be appreciated. Despite the difficulty of the subject matter, the author has explained it in a very clear way. The candidate demonstrated in his habilitation thesis a detailed knowledge of the problem of resistance to therapy in pediatric solid tumors. The thesis is original, and the topic is very topical. Overall, I evaluate the thesis as very important, as it brings new scientific knowledge to the field.

The habilitation thesis of the candidate thus corresponds in its scope and content to the requirements set for a habilitation thesis according to paragraf 72 odstavec 3 Zákona o vysokých školách č. 111/1998 sb

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

- 1) As you describe in your thesis, during the induction treatment period, there is a decrease in the expression of adrenergic markers (e.g. PHOX2B, TH) and an increase in the expression of mesenchymal markers (e.g. FMO3, POSTN, and PRRX1). However, adrenergic phenotypes are again detected at disease relapse. Have comparable phenotypic alterations been observed in your neuroblastoma experiments? Additionally, if you are discussing E/M T in sarcomas and its heterogeneity, have you observed a return to the original phenotype after previous exposure to cytostatics in the absence of cytostatics?

- 2) In the course of your examination of neuroblastoma, primary tumors, and recurrent disease, have you observed a notable alteration in the mitochondrial phenotype?

Conclusion

The habilitation thesis entitled "Novel molecular approaches to overcome therapy resistance in pediatric solid tumors" by Jan Škoda **fulfils** requirements expected of a habilitation thesis in the field of Molekulární biologie a genetika.

Date: 14.10.2024

Signature: