Review of doctoral dissertation

"Study on interactions of new anticancer drugs and their utilization for modulation of multi-drug resistance in solid tumors. "

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Formal requirements

The assessed dissertation fulfills all the prescribed requirements and is submitted in the form of an annotated set of publications. Submission of this format is permitted at the Faculty of Pharmacy only for works with significant publication achievements of the applicant in the role of first author. The thesis is clear and readable, based on citations of recent literature, which demonstrates the topicality of the topic. The results of the work are embedded in seven attached publications with an explicit declaration of the author's contributions, which proves the author's long-term diligent work during his postgraduate studies**.**

The author's publication activity meets the criteria for the defense of a dissertation

The applicant is the first author of two (IF = 6.2 (Q1) and 5.8 (Q1)) and co-author of another five original papers in impact factor journals. These works have already found 40 citations according in the Scopus database, and the *h*-index of the author is 4. This signifies the author's excellent publication activity.

Research focus

The content of the dissertation was the study of the highly actual scientific problem of multiple drug resistance modulation in cancer. The text shows the continuation of the supervisor's long-term research activities. The research core of the thesis is the influence of the evaluated drugs on the activity and expression of transport proteins and enzymes, which play a fundamental role in the resistance of tumor cells to the cytostatics used. These are primarily ABCB1, ABCC1, and ABCG2 transporters and enzymes from the first to third families of cytochrome P450. Since these molecules also have an essential role in the pharmacokinetics of the majority of drugs, the presented data are interesting not only concerning the modulation of drug resistance in tumors but, above all, for the evaluation of the interaction potential of the studied substances, which will logically concern mainly cytostatics administered in combination. In this context, several highly modern drugs from the category of tyrosine kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors, isocitrate dehydrogenase 2 inhibitors and others were studied. Specifically, these were: tepotinib, alisertib, sonidegib, enasidenib, talazoparib, encorafenib, tazemetostat, and capmatinib.

Many original results were achieved within these studies, and it is worth mentioning, in particular, a unique triple inhibition towards all tested ABC transporters by enasidenib, tazemetostat and capmatinib, inhibition of ABCC1 and ABCG2 by tepotinib and sonidegib, and significant inhibition of CYP3A4 and CYP2C9 by tepotinib .

Methodologies used

Subcellular and cellular models were used mainly to evaluate drug interactions with transporters and enzymes, which are currently recognized as the gold standard in the given type of studies. I appreciate the efforts of the author and the team to gradually expand the scope, which is demonstrated, for example, on the range of cytochrome P450 enzymes, but above all, on *ex vivo* models of 2D and 3D explanted primary human tumor cells and efforts on *in vivo* evaluation. All this proves the applicant had to master the top methodological equipment.

Opponent Questions

- What is the current status of the use of multi-drug resistance modulators in clinical oncology? Are modulators without their own antitumor effect also used?
- Does the documented inhibitory activity correspond to any drug-drug interactions observed with the investigational drugs in clinical practice?

Conclusion

The submitted dissertation meets all the formal and professional requirements for a qualification file of this category. The author participated in the creation of seven original scientific works published in high-impact journals, including two first-author publications, which more than fulfill the requirements for the defense of a dissertation at the Faculty of Pharmacy of Charles University in Hradec Králové. M.Sc. Budagaga thus demonstrated the ability to implement all aspects of high-end scientific work.

I therefore recommend the positive acceptance of the dissertation and its submission to the further procedure, the conclusion of which will be the awarding of the Ph.D.

Hradec Králové, May 5th, 2024

Prof. MUDr. Stanislav Mičuda, PhD.