CHARLES UNIVERSITY
Faculty of Pharmacy
in Hradec Králové

ASSESSMENT OF DOCTORAL THESIS

Study of pharmacokinetic and pharmacodynamic mechanisms of drug resistance and their modulation in non-small cell lung cancer

by You Zhang, M.Sc.

Characteristics of the thesis

The subject of the submitted doctoral dissertation was an experimental in vitro, in silico and ex vivo study on characterization and potential modulation of multidrug resistance to an important group of anticancer drugs. The submitted thesis presents a relative broad complex study with several related aims. The main aim was to explore the roles of pharmacokinetic and pharmacodynamic mechanisms in anti-cancer drug resistance and their modulation in non-small cell lung cancer (NSCLC). The author focused on several novel epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKis) used for treatment of (NSCLC) and evaluated their interactions with efflux transporters and cytochrome P450. Moreover, drug resistance of several NSCLC cell lines to novel antineoplastics was characterized, pharmacodynamic and pharmacokinetic factors affecting EGFR-TKis drug resistance were evaluated and a bioinformatic analysis was performed. Several state-of-the-art methods and models were used to solve the issue, including genetically modified cellular models, molecular docking and cancer tissue samples ex vivo.

The thesis is divided into standard sections typical for the presented type of scientific report: abstracts, a brief theoretical background, aims of the studies, a commentary on published papers, conclusions and perspectives, list of publications and list of references. Given that the evaluated work represents an article-type dissertation, an appendix containing a set of seven published articles is attached as the second part of the thesis. All presented papers were published in scientific journals with higher impact factor. In the case of two published articles, the applicant is the first author. The focus and content of the attached publications is in accordance with the subject of the dissertation. All seven articles represent original experimental studies. In addition, one more experimental study with the candidate as the first author has been sent for publication in a scientific journal.

Evaluation of the dissertation

The area of scientific topics that the author dealt with in his work fully corresponds to the field focus. The topic of the dissertation aimed at pharmacological characterization and potential affection of drug resistance to selected antineoplastics can be considered highly topical, because it is associated with real clinical issue.

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In the theoretical part of the thesis, the author briefly characterize NSCLC and it therapy and described the main types of pharmacokinetic and pharmacodynamic mechanisms of drug resistance. The review is written in a comprehensive way, without serious content or formal shortcomings. The introductory part is relatively short, but it brings sufficient information to the understanding of the matter and interpretation of results provided further.

The following part of the dissertation "Description of the results" summarizing the obtained results is an extract of the found data across the individual publications. The part is divided exactly according to the aims of the thesis. Therefore, it is easy for reviewers to recognize that the goals of the dissertation were completely fulfilled. In particular, the complexity of the presented research should be appreciated. The achieved results led to the creation of a very complex set of knowledge about multidrug resistance to novel low-molecular antineoplastics for treatment of NSCLC. Furthermore, the identification of many ABC transporter inhibitors among the studied anti-EGFR drugs could be appreciated, as these findings may have not only clinical significance, but the tested compounds may be potentially used in further experimental studies as comparative agents. From a pharmacological point of view, the effort to reveal pharmacokinetic and pharmacodynamic mechanisms involved in multidrug resistance in NSCLC seems to be very contributing component of the work.

The level of achieved scientific results contained in the attached publications is high, as evidenced by the fact that the obtained experimental data were published in peer-reviewed scientific journals with an IF between 4.5 and 6.5. It is a bit of a shame that the copies of individual publications in the work are not numbered. It would make it much easier for readers to oriented them within the dissertation. The reviewer appreciates that precise definition of the candidate's contribution to the published papers is clearly presented in the section 4.

Comments and questions:

Taken together, the thesis reaches a very high level compared to other dissertations. The publication of all papers in quality scientific journals documents very good achievements of the candidate and supervisor's team. The results represent a significant advancement in scientific knowledge and, after further investigation, may become clinically interesting. All published papers were reviewed by experts in the appropriate area. Thus, the following questions shall contribute to general discussion and do not challenge the candidate's work:

1. Information on estimated number of mortality cases in tumour patients affected by drug resistance (p. 9) seems to be very high. Is the estimated number 90% realistic and confirmed by clinical trials?

2. Inter-species differences in properties of P-gp are mostly not considered. Is this approach acceptable or are there any inter-species differences in P-gp structure and function?

3. You describe several generations of ABC transporter inhibitors preclinically and clinically tested as modulators of pharmacokinetic multidrug resistance (section 2.2.1.3). Could you summarize the results found in the clinical trials carried out so far? Are there agents potentially employable in the clinical conditions?

4. You extensively described potential future perspectives in the given field of research in the part 6. However, for example, several critical points may limit the use of pharmacokinetic modulation of anti-tumour drug resistance. Which of them do you consider as the most important?

Conclusion:

Based on the above-mentioned facts, I state that the dissertation submitted by Yu Zhang "Study of pharmacokinetic and pharmacodynamic mechanisms of drug resistance and their modulation in non-small cell lung cancer" meets the requirements for a doctoral dissertation in the given scientific field and documents the author's ability to independently work scientifically at an appropriate level. The professional quality of the presented work can be assessed as very high overall. I therefore recommend the aforementioned dissertation for defense, on the basis of which the applicant would be awarded the scientific degree of Ph.D.

In Hradec Králové, 1st June 2023

Prof. PharmDr. František Trejtnar, Ph.D.