CHARLES UNIVERSITY

FACULTY OF PHARMACY IN HRADEC KRALOVE

Department: of Pharmacology and Toxicology Master´s degree program in Pharmacy

Opponent´s review of Master´s thesis

Student´s name: Aigul Sagandykova

Mentor of the thesis: PharmDr. Martina Čečková, Ph.D.

Opponent of the thesis: RNDr. Eva Novotná, Ph.D.

Year of the thesis defense: 2017

Title of the thesis:

The effect of lipid signalling pathway interference on sorafenib cytotoxic efficacy and function of efflux transporters in mouse hepatocellular carcinoma cells.

Formal comments: number of pages: 53, number of figures: 6, number of tables: 1, number of references: 134.

Type of work: Experimental work

a) The aim of the thesis is: Fulfilled

b) Language and graphic level: Excellent

c) Processing of the theory: Excellent

d) Methods description: Very good

e) Results description: Very good

f) Discussion and conclusions: Excellent

I recommend Diploma thesis for the recognition as Rigorous thesis ☒.

Opponent´s comments: Multidrug resistance is one of the major limitations of successful cancer treatment.The idea of the research was to create a situation in which cells are unable to support both the inflammatory microenvironment and the chemoresistance mediated by the ABC transporters. To investigate this, two experimental compounds JJKK-048 and LBG-10119, which are known to influence the lipid signaling pathway, were used in the research. It was investigated whether these compounds could increase intracellular accumulation of efflux probes and increase the antiproliferative efficacy of sorafenib. Although the results are not perfectly fitting the research hypothesis (e.g. the transporters are inhibited at a much higher concentration of JJKK-048 than monoacylglycerol lipase and the compounds do not potentiate the antiproliferative effect of sorafenib) everything is clearly discussed and compared with other unpublished data. The overall results of the study have shown that inhibition of NMDA receptor and monoacylglycerol lipase (MAGL) affects ABC transporters. Further experiments that should confirm and explain this fact are mentioned and discussed in the conclusion of the thesis.
It can be concluded, that the idea of the diploma thesis is innovative. The work is written carefully. The author demonstrated the ability to work independently in the laboratory as well

as a good orientation in scientific literature as evidenced by a large number of literary sources.

Questions:
1) It is described that NMDA receptors have been found on the surface of various tumor cell lines and tumors. What is the natural role of these receptors? Can you name some drugs that interact with NMDA receptors?
2) One of the objectives of the study was to evaluate the effect of JJKK-048 and LBG-10119 on the antiproliferative activity of sorafenib. However, sorafenib has not been reported in the theoretical part. Why did you choose sorafenib for your research? What is the role of sorafenib in hepatocellular carcinoma and MDR cancer?
3) In the discussion, there is mentioned that MAGL expression in mouse hepatocellular carcinoma cells Nras driven p19ARF - /- is not sufficiently high. Did you measure or have any information regarding the expression of MAGL in the test cells?

Evaluation of Master´s thesis: Excellent

Recommendations for the thesis defense: Recommended

In Hradec Kralove 11. 9. 2017 ……

Opponent´s signature