



May 6, 2015

To whome it may concern:  
*Evaluation of PhD Thesis of Mgr. Kateřina Váňová*

Sir/Madam,

Please, find below (attached overleaf) my evaluation of the PhD Thesis of Mgr. Kateřina Váňová. I would also like to thank you for giving me the opportunity and honour to be involved in this matter. Kindly, contact me should you require any additional details.

Yours sincerely, \_\_\_\_\_

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Mgr. Kateřina Váňová, a PhD candidate, has presented her PhD thesis titled 'Heme Catabolic Pathway in Pathogenesis of Liver Diseases. First, I would like to congratulate the candidate on the high number of papers which she co-authored in the span of her PhD stage, five of which are the essence of the thesis. This is an excellent achievement of the candidate and documents that her PhD stage has been very prolific and that she is set to engage in further research career. On the side, I would like to thank her that by presenting her PhD Thesis in this way, she makes the life of the opponent much easier.

Liver diseases are a serious complication that requires better understanding of its genesis and progress on molecular level, in order to curb its spread in the society. Therefore, the topic of the candidate is of high importance and relevance. One of the key function of liver function is detoxification of various substances, including heme breakdown. The PhD thesis focuses in particular on this important process.

The thesis consists of several parts. It is the Introduction, where the candidate gives literature background of heme catabolism, transport of bile acids and pigments and pathogenesis of several liver pathologies, and finally links heme breakdown to liver diseases. This is a nice, short overview of aspects pertinent to the publications that the candidate co-authored and that make up part 3. It would be good to include a bit about the formation of heme, which is generated in mitochondria. Further, there should be a short chapter of a paragraph or two about the function of heme as a carrier of oxygen and as a redox-active group of enzymatic systems and important processes in the cell, such as the mitochondrial redox chain. I would also welcome some statements on the toxicity of the products of heme catabolism, such as that of bilirubin. It is not, in my opinion, absolutely clear that bilirubin has a physiologically relevant antioxidant function. Even if this is the case, the level of bilirubin is important. The candidate may have referred to studies linking bilirubin to lower incidence of atherosclerosis [Kang SJ et al (2013) Elevated serum bilirubin levels are inversely associated with coronary artery atherosclerosis. *Atherosclerosis* 230, 242-248. Oda E (2014) A decrease in total bilirubin predicted hyper-LDL cholesterolemia in a health screening population. *Atherosclerosis* 235, 334-338.], as well as the protective function of the bile pigment in peroxidation of low-density lipoprotein [Neuzil J, Stocker R (1994) Free and albumin-bound bilirubin are effective co-antioxidants for  $\alpha$ -tocopherol, inhibiting plasma and low density lipoprotein lipid peroxidation. *J Biol Chem* 269, 16712-16719], a hallmark of atherogenesis, to name only a few. Concerning the catabolism of heme, the issues of compartmentalisation of the process should be included. Given that heme is synthesised in mitochondria, are there any systems in mitochondria that result in heme catabolism? And if so, what is the fate of the products of heme catabolism in mitochondria – in case this is known? Concerning the illustrations, the figures taken from referenced papers are rather fuzzy, which may be due to the way the candidate cut them out from the original paper and pasted her into the thesis. A different way of moving them would be better, or the candidate could have re-drawn them, since they are not too complex.

Second part comprises the Aims of the study. They are all well thought through and flow in a logical sequence. They are then addressed in the individual publications, which are contained in the third part. There are five papers the candidate co-authored, of which she is first author on one paper. This achievement is highly commendable and gives an impression of high quality of the candidate.

The Discussion is well written and touches on the important points addressed in the five publications. The following chapter is Summary, which neatly puts together the most salient findings of the candidate. What I miss here is a (sub-)chapter or a separate paragraph at the end of the Discussion, addressing future directions. The candidate should indicate not only what was found



but give a clear statement what these findings may mean for future research and what may be done next, as a logical follow-up of the current very nice project of the candidate.

References are plentiful and seem to have been well chosen. To me, the style is rather unusual, however given the notion that it is consistent throughout, I have no problem with it. Perhaps reference 107 could be better the original chapter or book, rather than its Czech translation.

There is one issue with the Abbreviations part. CO is not an abbreviation of carbon monoxide but it is a chemical formula, so it should not be included as an abbreviation.

Finally, the style used in the List of Publications (part 8) is different than that used in the References part, but this is only a minor issue.

The criticism above is mild and should only indicate where some improvement should/could be made. However, this, in no way lessens the high quality of the thesis, on which I applaud the candidate.

To conclude, I am convinced that this PhD Thesis, supported by excellent work, without any doubt documents the creative and hard-working nature of the candidate and that it meets all requirements for the candidate to be awarded the PhD title.