

**PROF. DR. VLADIMÍR KŘEN, FRSC**

*Head of department*

Vídeňská 1083  
CZ 142 20 Prague 4  
Czech Republic

Tel.:(420)-296442510; 296442569

Fax:(420)-296442347; 296442509

e-mail: kren@biomed.cas.cz

<http://www.biomed.cas.cz/mbu/biotrans>

February 2, 2010

Review

on the PhD Thesis

by: Hillary Elizabeth Hoffmann

Title: Characterization of recombinant human serine racemase

Presented PhD thesis deals with a serine racemase, an enzyme synthesizing D-serine. Human recombinant enzyme was expressed in *E. coli* and compared with its mouse orthologue. Kinetic parameters of the recombinant enzyme were investigated in detail. Series of small molecule (potential) inhibitors was tested and one compound, e.g., L-aspartate  $\beta$ -hydroxamate has been identified to be one of the best selective inhibitors. To overcome problems of (so far unsuccessful) crystallization series of mutants has been prepared to identify structurally and catalytically important AA residues.

Major part of this thesis has been published in renowned, high-impact journals with thorough peer-review procedures and, therefore, it is not easy to find any questionable points. Papers are multi-authored and the candidate clearly describes her rôle in performing the experiments and in the paper preparation.

I have some general questions:

Do you know something about glycosylation (if any??) of human SR?

You tested series of inhibitors of SR, is there something known about their toxicity?

It is known that D-serine disturbs the citric acid cycle through inhibition of citrate synthase activity in rat cortex (Brain Res. 1298, 186, 2009)- is it possible that intervention into the SR activity with inhibitors can misbalance neuronal energetic metabolism; did you tested some successful inhibitors in this respect, please?

In conclusion, Ms. Hillary Elizabeth Hoffmann demonstrates in her PhD-thesis solid and profound scientific expertise, which is impressively documented by three original

research publications published in very good journals. Ms. Hoffmann has, thereby significantly contributed to the structural knowledge of the serine racemase and demonstrated her capacity of the scientific worker.

Therefore, I recommend the PhD-thesis without reservation to the Charles University in Prague for further processing leading to award the diploma of „Philosophy Doctor“.

Prof. Vladimír Křen