

28.11. 2015

RE: Evaluation of PhD Thesis – Jan Dobes

Dear Committee Members,

The PhD thesis by Jan Dobes is outstanding in all perspectives. First of all it is structured, written and presented in a very clear and logical way. The introduction is very comprehensive, balanced and accurate. Second of all, the goals of the thesis are of a great scientific importance and are addressed in a very elegant way. Specifically, the thesis includes three separate but interconnected goals, whose resolution provides a broader and more comprehensive understanding of how self-tolerance to intestinal antigens is established and how intestinal homeostasis is maintained. The importance and quality of this work is probably best illustrated by the fact that a large fraction of the thesis was already published as an article in a prestigious peer-reviewed journal *Gastroenterology* (IF ~16), on which the student is the first author.

Specifically, these published data provide convincing evidence that a loss of function of the *Autoimmune regulator* gene is associated with the loss of self-tolerance to enteric α -defensins, which are produced by intestinal Paneth cells, as natural antimicrobial peptides. This subsequently results in autoimmune Paneth cell destruction, which is then manifested by various gastrointestinal symptoms. Moreover, the autoimmune destruction of Paneth cells subsequently impacts on the composition of intestinal microbiota, affecting the polarization of T-cells in the gut towards Th17 phenotype, which further aggravates perturbations in intestinal homeostasis.

The other parts of the thesis highlight the importance of several members of Wnt signaling cascade in the regulation of intestinal homeostasis and their impact on immune-mediated dysfunction of intestinal epithelia. These data were published as research articles in peer-reviewed journals, co-authored by the student.

Overall, these are very impressive achievements for a single PhD project. I strongly advise these outstanding achievements will be recognized by some kind of award for excellence by the University (e.g. Dean's prize) to the student.

Sincerely,

Dr. Jakub Abramson

