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Annex No. 10 to the MU Directive on Habilitation Procedures and Professor Appointment Procedures

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University	
Applicant	Mgr. Tomáš Bárta, Ph.D.
Habilitation thesis	Utilizing Retinal Organoids to Understand the Development, Function, and Diseases of the Human Retina
Reviewer	Dr. rer. nat. Marius Ader, Professor
Reviewer's home unit, institution	Center for Regenerative Therapies Dresden (CRTD), Technische Universität Dresden

In the retina light is detected and transformed into a biological signal allowing vision. While insights into the structure, development and diseases of the retina have been assessed over decades of research, extensive studies on the human retina is severely restricted due to limitations in available primary tissue. This has significantly changed in the last decade with implementation of organoid technology, where 3D retinal tissue can be generated from pluripotent stem cells allowing the generation of, in principle, unlimited amount of human retinal tissue for research purposes. With his excellent work presented in this habilitation thesis, Dr. Tomáš Bárta provides detailed insights into his significant contribution to this research field by providing results in regard to developmental and light-responsive miRNAs as well as a model of inherited ciliopathy using human retinal organoids.

The habilitation thesis is based on three manuscripts published during the last four years in peer-reviewed, international science journals with high reputation. The publication record shows constant output at the forefront of this research field.

The habilitation thesis starts with a clear and compact written, highly informative introduction into the main topics essential for the presented studies. Accompanied by very informative and clear cartoons and figures, the development, structure and function of the retina is described with specific focus on the light-sensing photoreceptors. It follows highly interesting information into the history, generation and usage of pluripotent stem cell-derived retinal organoids as the main study object of the thesis. General information about studies on human retinal development, disease and function using retinal organoids is nicely combined with Dr. Bárta's own contributions. Finally, limitations in the use of retinal organoids for research is discussed and main findings of the three manuscripts are summarized. The original papers are then attached.

Using state-of-the art methods and technologies, Dr. Bárta provides important results to the influence of miRNAs in human retina development, identifying the miR-183/96/182 cluster as an important regulator of PAX6 expression, a key transcription faction in neural and retinal development, playing an important role in retina morphogenesis. By developing a sophisticated light-stimulation device, he continued his exciting work to look for light-responsive microRNAs in human retinal organoids. Indeed, distinct microRNAs were shown to be regulated by different wavelengths with rapid turnover, adding novel insights into the adaptation of the human retina to changing visual inputs. In the third manuscript, Dr. Bárta was involved in a study regarding the consequences of the ciliopathy protein TMEM107 on retinal tissue

development. By generating TMEM107$^{-/-}$ hESCs using CRISPR/Cas9 and knock-down of TMEM107 by shRNAs in hiPSCs, the development of retinal organoids was studied. Interestingly, loss-of-function of TMEM107 resulted in loss of the primary cilium and massively interupted neural retina formation in the generated organoids.

Overall, the presented habilitation thesis and publications demonstrate the excellent work of Dr. Bárta. His innovative approaches and use of state-of-art technologies to receive insights into the development and function of the human retina is of very high quality, while the habilitation is also clearly written, allowing the reader to follow this interesting topic.

Reviewer's questions for the habilitation thesis defence (number of questions up to the reviewer)

1. What are advantages and limitations of retinal organoids to model retinal diseases?
2. What are the consequences of light-induced changes in microRNA expression?
3. How can retinal organoids further improved to reflect physiological conditions?

Conclusion

The habilitation thesis entitled Utilizing Retinal Organoids to Understand the Development, Function, and Diseases of the Human Retina by Mgr. Tomáš Bárta, Ph.D. **fulfils** requirements expected of a habilitation thesis in the field of Anatomy, histology and embryology.

Date: 30.04.2025 Signature: