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

# HABILITATION THESIS REVIEWER'S REPORT

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| **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** | JanMotlík, MVDr., DrSc., profesor |
| **Reviewer's home unit, institution** | Institute of Animal Physiology and Genetics, Czech Academy of Sciences, Liběchov |

Retinal organoids, generated from pluripotent stem cells. represent the unique model that mimic the complexity and functionality of the retina. The retinal organoids contain all cell types found in the retina, such as photoreceptors, ganglion cells, and bipolar cells. This morphology allows to study questions related to retinal development and function. Moreover, retinal organoids simulate mechanisms of retinal disorders and as well as their possible treatment. Tomáš Bárta's habilitation in a broad international cooperation, fulfilled all above mentioned aspects of this new experimental area.

Retinal organoids represent invaluable tools for studying retinal development, function, and diseases, providing a platform to investigate the underlying mechanisms of retinal disorders, test potential therapies, and develop personalized treatment strategies. This thesis explores their potential in understanding retinal development, function, and disease modelling, highlighting key contributions from his research group and collaborating researchers.

Important part of the Thesis is "Theoretical background". Author explains on 20 pages all essential aspects of the retina structure and development. I highly evaluate the precise explanation to the functional relationship between photoreceptors and the retina epithelial cells.

In spite of the fact that the emphasis is placed primarily on the human retina, the specific aspects of knowledge discovered on the animal models are discussed, too.

Chapter devoted to „Retinal organoids as a Tool to Study Function of the Human Retina" is written with the full understanding for this key organ of vision. It is evident that Discussion part of all three key author's publications have the same

impact. The most impressive part represents the role of key transcription factors such as PAX6, SOX2, RAX and VSX2 that play a pivotal role in the early stages of eye development and retinal cell fate determination. The elucidation of these developmental processes has been significantly advanced by the utilization of retinal organoid models.

As the retina progresses in its development, transcription factors like CRX and NRL become instrumental in the differentiation of photoreceptors. CRX is particularly crucial for the development of cones and rods, and its mutations are associated with several retinopathies. Thesis did not omit limitations of retinal organoid technology and rectify the absence of the RPE layer.

The variable maturity of photoreceptors within organoids and their lack of integration with the RPE layer limit their functionality in light sensitivity[53]. Current strategies involve co-culturing organoids with RPE cells to improve connectivity and function
However, challenges related to human PSC-derived retinal organoids, including their use in studying retinal development, disease modelling, and as a platform for drug screening, must be acknowledged.
This variability affects the efficiency of reprogramming somatic cells into iPSCs and their subsequent differentiation into retinal cells.

The utilization of retinal organoids has emerged as a transformative approach in advancing our understanding of the complex processes underlying the development, function, and diseases of the human retina. Experiments using the retinal organoid technology uncovered deep insights into the cellular and molecular dynamics underlying retinal biology. These findings shed light on the complexities of retinal development and function and offer promising potential for the development of novel therapeutic strategies for retinal diseases. Continued exploration and refinement of retinal organoid technologies have the potential to study and treat a wide variety of retinal disorders, ultimately improving outcomes for patients worldwide.

This thesis summarizes author's work and work from other research groups that use retinal organoid models to study the human retina. However, the essence of the work still lies in harnessing the power of retinal organoid models to understand the retinal development, function, and diseases. These models offer a unique opportunity to recapitulate human retinal biology *in vitro*, providing a platform for investigating disease mechanisms, testing potential therapeutics, and exploring personalized treatment approaches. Through

collaborative efforts and ongoing refinement of organoid technologies, we will enhance understanding and management of various retinal disorders.

Unique approach to disease modeling and drug discovery confirms the strong author's interest in biomedical research. Limitations or week points of organoids methodology are mentioned, too. All parts of this chapter is based on the most recent literature data which testifies to the author's orientation in the field.

Commentary to three key published papers is described very compactly, with the focus to the aspects of achieved experimental data.
All papers are attached in extenso so I fully agree with the limited but fully understandably formulated part of dissertation.
Tomáš mentioned in his thesis USHER1b eye disease. I am glad that Center PIGMOD disposes with the transgenic piglets with mutation in the gene MYO7A. It seems that both experimental ways, human retinal organoids and large animal models are essential on the way to the safe and efficient curing of this serious eye disease.

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

Several serious eye diseases are caused by interrupted communication between photoreceptors and the retinal epithelial cells. They are retinal organoids able to mimic this interaction?

Muller's cells represent the special type of the retinal interstitium. Their function in retina physiology was underestimated for a long time. They are able retinal organoids to mimic retinal function of Muller cells, too?

Connected cilium plays the essential role in the correct communication between the basal and apical part of photoreceptors. There were discovered in retinal organoids structures like caliceal processes?

**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: May 12, 2025 Signature: