

To:

The Chairman of the Scientific Jury,

determined by Order No R-109- 469/09.11.2023

of the Rector of Medical University "Prof. Paraskev Stoyanov"

Varna

REVIEW REPORT

By: George N. Chaldakov, MD, PhD, FIACS

For: The dissertation for the award of the educational and scientific degree (ESD) "Doctor" of **Martin Nikolaev Ivanov, MD** at the Department of Anatomy and Cell Biology, Medical University, Varna.

Dissertation topic: "Proliferation and differentiation of progenitor cells in the subventricular zone from the brain of adult primates"

Scientific Supervisor: Assoc. Prof. Dr. Stoyan Pavlov, MD

Procedure and CV of the applicant

By Protocol #1/21 November 2023 of the first meeting of the Scientific Jury, I was appointed to prepare a review of the scientific work prepared by the candidate Dr. Martin Nikolaev Ivanov under the procedure for obtaining an educational and scientific degree “Doctor” at the Medical University - Varna. After I reviewed the the materials presented by the applicant, including the Dissertation and the Autoreferate are in accordance with the requirements of ZRASRB and the Rules for the conditions and procedure for obtaining academic degrees and holding academic positions at the Medical University “Prof. Paraskev Stoyanov” - Varna.

Martin Ivanov was born in 1994 in Sofia and he graduated “Medicine” in 2018 at the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna. He has held the following positions: honorary Assistant Professor at the Department of Anatomy and Cell Biology at MU-Varna, Assistant Professor at the Department of Anatomy and Cell Biology at the Medical University “Prof. Paraskev Stoyanov” – Varna, Junior researcher (R1) neural stem cells, TRANSTEM project, Medical University “Prof. Paraskev Stoyanov” - Varna.

Evaluation of the Dissertation

The dissertation is presented on 147 pages, the autoreferat - on 72 pages. The Introduction clearly motivates the need for research in the field of dissertation work. The literature review is well-presented with text

and 5 figures. The Materials and Methods are described in a way that allows the experiments to be repeated by other researchers. The Results are clearly described and illustrated with 46 very well presented - informatively and aesthetically - figures. The References comprise of 179 contemporary articles published in reputable scientific journals. The purpose and tasks of the study are clearly formulated. Statistical methods are described in detail. There is information about a positive ethical assessment preceding the collection of brain tissues.

Evaluation of the contributions of the dissertation and the applicant's contribution

The dissertation of Dr. Martin N. Ivanov is the first detailed study demonstrating the increased expression of the genes *TNC* (Tenascin-C), *APLNR* (Apelin receptor), *GJA1* (Gap Junction Alpha-1 protein) and *CD38* (Cluster of differentiation 38) after global ischemia in the largest neurogenic niche in the monkey brain, the subventricular zone (SVZ). Immunohistochemical characterization of apelin- and APLNR-expressing cells in the SVZ of elderly individuals without the presence of neurological and psychiatric diseases was also performed.

Altogether, the results obtained give reason for Dr. Martin N. Ivanov to draw the following conclusions:

1. Increased expression of the genes *TNC*, *APLNR*, *GJA1* and *CD38* was documented for the first time in a primate model of global cerebral ischemia.
2. The rostro-caudal expression of these genes in a healthy (normal) monkey is described for the first time.

3. Differences in rostro-caudal expression of *TNC*, *APLNR*, *GJA1* and *CD38* genes in three different mammals are demonstrated for the first time.
4. The SVZ phenotypic characterization of these genes in a normal monkey is documented in detail for the first time.
5. For the first time, the detailed phenotypic characterization of the *APLNR* gene in the SVZ of humans without pathology is elucidated.
6. Future studies may explore the possible application of apelin and/or *APLNR* agonists for the therapy of neurodegenerative diseases.

In summary, I conclude that the discoveries of the dissertation are original and complies with the Rules for the acquisition of the degree “Doctor”.

Evaluation of the publications

The list of publications attached to the procedure for acquiring a PhD degree includes 2 publications in Bulgarian and international journals. One of Dr. Martin Ivanov’s publications is in a magazine with an impact factor.

1. Stoyanov, D.S.; Ivanov, M.N.; Yamashima, T.; Tonchev, A.B. Expression of transcription factor ZBTB20 in the Dultp rimate neurogenic niche under physiological conditions or after Ischemia. *Genes* 2022, 13, 1559. <https://doi.org/10.3390/genes13091559>
2. Ivanov, M.N.; Pavlov, S.S. Distribution and expression of Apelin system in the mammalian body- a review. *Biomed Rev* 2023, 34, xx-xx

Based on the publications provided, I assert that the work performed was carried out through the personal participation of the applicant, whose role is leading in the generation of the scientific data.

The autoreferate reflects the main results achieved in the dissertation and meets the requirements for the acquisition of the EDS "Doctor".

Conclusion

The discovery of different genes with the potential to mark brain progenitor cells is a very valuable contribution of the dissertation work. Hence, I accept that the dissertation of Dr. Martin N. Ivanov has all the qualities to acquire the ESD "Doctor". In effect, I will vote **positively** and allow myself to recommend the same to the other members of the esteemed Scientific Jury as defined by Order No R-109-469/09.11.2023 of the *Rector* of the Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

With respect and 2024 best wishes to you, families, and friends,



George N. Chaldakov, MD, PhD, FIACS

31 December 2023
Varna