

PEER REVIEW

by Professor Bistra Tsaneva Kalcheva, PhD in Pharmacology, Professor of Biochemistry
at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

Re: a competition for acquiring the academic position "PROFESSOR: in the area of higher education **4. Natural Sciences, Mathematics and Informatics**, professional field **4.3. "Physiology"**, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, for the needs of the Department "Physiology and Pathophysiology", Teaching Unit "Physiology", for a competition announced in the State Gazette No. 102/23.12.2022.

1. Brief information about the competition

On the basis of the decision of the Faculty Council of the Faculty of Medicine by Protocol №80/23.01.2023 and by Order № P-109-131/22.02.2023 of the Rector of Medical University - Varna, I have been elected as a member of the Scientific Jury, and by Protocol №1/06.03.2023, I have been appointed to prepare a peer review in relation to a procedure for tenure the academic position "PROFESSOR" in the area of higher education **4. Natural Sciences, Mathematics and Informatics**, professional field **4.3. "Physiology"** for the needs of the Department "Physiology and Pathophysiology", Teaching Unit "Physiology".

The only candidate in the competition is Margarita Stefanova Velikova, MD, PhD, Associate Professor in the same Department. The review of the documents showed that they were prepared accurately and fully comply with the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its implementation, and the Regulations for the Development of Academic Staff of MU – Varna. No procedural violations were found.

The set of materials submitted by the applicant in electronic form includes the following documents:

1. Application to the Rector for admission to the competition with signature of the candidate;
2. Creative curriculum vitae with signature of the candidate;
3. Data Protection Notice to employees, applicants for employment of Prof. Dr. Paraskev Iv. Stoyanov" - Varna with signature of the candidate;
4. Declaration of the authenticity of the data in the submitted documents with the signature of the applicant;
5. A certified true copy of the Master's degree with its annex;
6. A certified true copy of the diploma of the PhD degree;
7. A certified true copy of the diploma for the academic position of "Associate Professor";
8. Certified true copy of the document for the acquired specialty "Physiology";

7. Certificate of professional experience in the relevant specialty;
8. Certificate of teaching experience;
9. Certificate of supervision of successfully defended PhD students;
10. Reference teaching workload;
11. Medical certificate;
12. Criminal record;
13. Academic transcript of publications, citations and scientific profiles of the candidate, issued by the Library of MU-Varna, including:
 - Publications and citations meeting minimum national requirements;
 - Supervision of successfully defended PhD students;
 - Participation in a national scientific or educational project;
 - Published university textbooks;
 - Full-text publications and citations, beyond the minimum scientific requirements;
 - List of scientific works and citations used for obtaining the PhD degree and for holding a previous academic position "Associate Professor", including:
 - o Supplement for active profiles in Google Scholar, ORCID, Research Gate, SCOPUS ID;
 - o Supplement for Impact Factor;
16. Extended habilitation reference for scientific contributions;
17. Summaries of scientific works;
18. Reference of original scientific contributions with the signature of the candidate;
19. List of participation in scientific forums and copies of published abstracts;
20. Copies of full-text publications equivalent to a monograph/habilitation thesis;
21. Copies of full-text publications in journals referenced and indexed in worldwide databases of scientific information (Web of Science and Scopus);
22. Copies of full-text publications beyond the minimum scientific requirements;
23. Certification of participation in scientific projects;
24. Summary data on the scientific, teaching, administrative and expert activities with the signature of the candidate;
25. Declaration of identity of a person with different names with signature of the applicant.

2. Career profile of the applicant

Associate Professor Margarita Stefanova Velikova was born on 06.05.1963 in Varna. In 1988 she graduated from Varna High Medical Institute, specialty "Medicine" and acquired the qualification "medical doctor" (MD). In 1991 she was appointed assistant professor of physiology at the Department of Physiology of MU-Varna.

In 1995 she acquired a specialty in Physiology at the Medical University - Sofia, and from 2006 to 2009 he was a PhD student in independent training at the Department of Physiology and Pathophysiology, Teaching Unit „Physiology” at MU-Varna in the scientific specialty “Animal and Human Physiology”. In 2010 the Higher Attestation Commission at the Council of Ministers of the

Republic of Bulgaria awarded her PhD "Doctor" in the scientific specialty 01.06.17. "Animal and Human Physiology" on the basis of a successfully defended PhD thesis on "Behavioral responses induced by vasoactive interstitial peptide introduced into the hippocampus of rats with an experimental model of depression".

From 1996 to 2012, she was promoted as senior and head assistant professor, respectively, and in 2012 she was awarded the academic position "associate professor" in the scientific specialty 01.06.17. "Animal and Human Physiology".

From 2010 to 2023, she has held administrative positions as Administrative Assistant at the Teaching Unit of Physiology (2010-2012), Coordinator of the Master of Public Health program implemented by MU-Varna and Casa college, Cyprus (2012-2015), Head of the Teaching Unit of Physiology (2012-2019) and Head of the Department of Physiology and Pathophysiology at MU-Varna (2018-present).

As a member of a research team, she has participated in 3 research projects (2 joint projects with INB at BAS and one with MU-Pleven). She is a leading researcher of a scientific project funded by the Science Fund at MU-Varna.

Associate professor Margarita Velikova is a member of 5 national and one international scientific organizations: Bulgarian Medical Association, Bulgarian Society of Physiological Sciences, Union of Scientists - Varna, Board of IMAB, section "Medicine", Federation of European physiological societies (FEPS).

She is an elected member of the Program Council of the Faculty of Medicine at MU Varna, of the Examination Committee for conducting colloquia of graduate students in physiology at MU-Varna and of the State Examination Committee in Physiology.

She has completed one teaching mobility by Erasmus+ programme at the University of Messina, Italy (2019).

3. Teaching activities

Associate professor Velikova has over 30 years of teaching experience. Due to her excellent proficiency in English language, she gives lectures, seminars and practicals in the discipline of "Physiology" to students of "Medicine" and "Dental Medicine" in English language. Since 2016 she has been a course supervisor of the 3rd year medical students English-speaking programme. Associate professor Velikova also gives lecture courses on physiology to students studying in Bulgarian language in the specialties of "Dental Medicine", "Pharmacy", "Nurse", "Midwife", as well as selected lectures on physiology of trainee doctors. In the same specialties she also conducts seminar and practical classes.

According to the reference submitted by the Directorate of Educational Activities at MU-Varna, for the period 2018-2022 the total teaching load of Associate professor Velikova is 2477 hours,

of which 655 hours of lectures and 1822 hours of seminars and practicals in English with a norm of 126 hours, according to the decision of the AC of MU-Varna (Protocol № 30/11.04.2011).

The candidate is in the author's collective of 8 teaching textbooks, of which in 1 textbook is an independent author and co-author of 2 textbooks for medical or dental students in English language training. She is a member of the author collective of 5 other teaching textbooks in Bulgarian for medical, dental and pharmacy students. This earned her a total of 159.66 points in indicators E12-E20.

Associate professor Velikova has supervised the scientific work of two successfully defended PhD students at the Department of Physiology and Pathophysiology of MU-Varna, and is currently a supervisor of one PhD student at the same department with an upcoming defense, which brings her a total of 75 points in indicator E13. Associate professor Velikova has also supervised the scientific work of two foreign graduates from Casa college, Cyprus, who have successfully defended and obtained Master's degree in Public Health. She supervises the specializations of two graduate students in physiology.

4. Scientific production and scientific metrics

According to the Report prepared by the Library at MU-Varna, in the competition Margarita Velikova participates with a total of 54 full-text publications, beyond those for the academic position "Associate Professor" or for PhD, arranged according to a model proving the fulfillment of the minimum requirements for the academic position "Professor" and distributed as follows:

A1. PhD thesis for the degree "Doctor", carrying **50** points.

B4. Scientific publications in publications refereed and indexed in worldwide databases with scientific information (Web of Science and Scopus) equivalent to a habilitation thesis - **10** publications, carrying a total of **174** points with a mandatory minimum of **100** points. All submitted publications are indexed in Web of Science and Scopus, 7 of them (70%) are in journals with impact factor and the remaining 3 in journals with impact rank. The distribution of the submitted 10 publications by impact rank is as follows: Q1 - 1 (10%); Q2 - 4 (40%); Q3 - 3 (30%); Q4 - 2 (20%) publications. The publications cover the period 2012 - 2020 and 30% of them are from the last 5 years. All submitted publications are co-authored, and in 4 of them (40%) the candidate is the first author.

G7. Scientific publications in journals, refereed and indexed in worldwide databases with scientific information (Web of Science and Scopus) - **20** publications, carrying a total of **349** points with a mandatory minimum of **200** points. Of the submitted publications, 19 (95%) are indexed in Web of Science and Scopus, 1 publication is indexed only in Scopus. Of these, 12 (60%) are in journals with impact factor and the rest, in journals with impact rank. The distribution by impact rank is as follows: Q1 - 2 (10%); Q2 - 7 (35%); Q3 - 9 (45%); Q4 - 2 (10%) publications. The publications cover the period 2011 - 2023, of which 9 (45%) are from the last 5 years; 3 (15%) of

the submitted publications are in press. All submitted publications are co-authored, and in 5 of them (25%) the candidate is the first author.

D11. Citations in scientific publications, monographs and collective volumes and patents, referenced and indexed in world-renowned databases of scientific information (Web of Science and Scopus)

According to the Academic Transcript prepared by the Library at MU-Varna, the total number of citations in scientific publications, refereed and indexed in worldwide databases with scientific information (Web of Science and Scopus) is **116**, which brings **232** points and significantly exceeds the minimum requirements of 100 points for the academic position "Professor" in the professional field of the competition. Of all the citations, 33 (28%) are of publications submitted under indicators C4 and D7, concerning the minimum scientific metric requirements for the position of "Professor". Of these 33 citations, 19 (58%) are within the last 5 years.

Associate professor Velikova has active scientific profiles in Google Scholar, ORCID, Research Gate, SCOPUS.

5. Scientific and applied contributions

This section provides a brief analysis of the main scientific, applied and methodological contributions and a characterization of the main achievements of the candidate, as well as their relevance to science and practice and future development prospects.

The presented by associate professor Velikova publications are thematically grouped in the following 5 main areas:

1. Studies in experimental neurophysiology related to the involvement of the brain endocannabinoid system (ECS) (cannabinoid CB1 receptors), brain renin-angiotensin system (RAS) (angiotensin II and angiotensin AT1 receptors) and brain vasoactive intestinal peptide (VIP) in the mechanisms of depression-like state, induced by bilateral olfactory bulbectomy (OBX) in rats (No. C4-1, C4-2, C4-6, C4-7, C4-8, C4-9, C4-10, G7-7, G7-8, G7-11, G7-12, G7-14, G7-16, G7-18, G7-19, 6, 8, 15, 18).

1.1. Study on the role of brain cannabinoid CB1 receptors in the mechanisms of anxiety, pain sensitivity, motor activity, learning and memory of depression-like state in bilateral olfactory bulbectomy (OBX) rats (No. C4-8, C4-9, C4-10, D7-7, D7-12, D7-14, D7-16, D7-18, 8, 15, 18).

In this field of research, the role of brain cannabinoid CB1 receptors in the mechanisms of anxiety, pain sensitivity, motor activity, learning and memory in rats with depressive-like state (OBX) was examined. A well-established experimental model of depression involving olfactory bulbectomy, resulting in behavioral, physiological, and neurochemical changes resembling clinical depression was used. Acute and subchronic stimulation of brain cannabinoid CB1 receptors by intracerebroventricular (i.c.v.) agonist administration was found to improve the anxiety-like state, by decreasing anxiety, normalizing impaired pain sensitivity, suppressing increased motor

activity, and improving learning and memory impairments, whereas their subchronic inhibition with a CB1 antagonist exacerbated the behavioral impairments associated with bulbectomy by increasing anxiety-like state, increasing motor activity and pain threshold, and worsening learning and memory performance. These original data establishing opposing effects of CB1-receptor ligands on learning and memory in OBX and sham animals reveal involvement of the endocannabinoid system in some behavioral disturbances characteristic of this model of depression.

Furthermore, the route of introduction of the CB1 antagonist, intragastric or i.c.v. exhibited opposite effects on learning and memory in the experimental model of depression that was used.

1.2. Study on the involvement of the hippocampal renin-angiotensin system angiotensin II (Ang II) and angiotensin AT1 receptors in motor activity, anxiety, learning and memory in depression-like state (OBX) (No. C4-6, C4-7, D7-11).

Using the same experimental model of depression, inhibition of hippocampal AT1 receptors with the specific AT1 antagonist losartan was found to suppress motor activity, favored bulbectomy-induced learning deficits, and significantly improved memory and reduced anxiety. These findings indicate that the level of AT1 receptor expression affects OBX-induced impairments in motor activity and anxiety-like state.

On the other hand, introduction into the same hippocampal field of angiotensin II agonist stimulated motor activity but did not affect the state of anxiety. The opposite and asymmetric effects of Ang II and losartan found in the left and right CA1 hippocampal fields indicate a marked lateralized effect of Ang II on motor activity of OBX rats and suggest the possible involvement of AT1 receptors in the mechanisms of olfactory bulbectomy syndrome in rats.

1.3. Study on the modulatory effect of neuropeptides, introduced into some brain structures, on motor activity, anxiety, learning and memory processes in depression-like state (No. C4-1, C4-2, C4-6, D7-17).

Using the same experimental model, has been investigated whether VIP receptors are relevant to cognitive abilities. For the first time, a lateralized modulatory effect of VIP was found after bilateral (left/right) introduction into the CA1 hippocampal field and its involvement in depressive-like state mechanisms such as anxiolytic-like effects and beneficial effects on learning and memory deficits.

2. Lateralization of behavioral responses of brain structures (hippocampus, amygdala) involved in the depression-like state upon introduction of neuropeptides (VIP, Ang II), their receptor antagonists and cannabinoid receptor ligands (No. B4-1, B4-6, D7-17, D7-19, 6, 16).

Studies on the hippocampal hemispheric asymmetry in motor activity induced by the introduction of Ang II and losartan (an AT1 receptor antagonist) into the CA1 field of OBX rats showed that Ang II introduced only into the left but not into the right CA1 field stimulated the increased motor activity due to OBX, whereas inhibition of AT1 receptors only in the left CA1 field

suppressed it. These original data also revealed a hemispheric asymmetry in learning and memory processes in the OBX model induced by the topical introduction of the neuropeptides VIP and Ang II into the hippocampus and amygdala: a right-dominant hemispheric asymmetry when VIP was introduced into the CA1 field of the hippocampus and a left-dominant hemispheric asymmetry when Ang II and losartan were effective.

3. Modulation of hippocampal RAS and brain ECS activity and their effects on behavioral responses in rats (No. C4-3, C4-4, C4-5, C4-10, D7-1, D7-10, D7-15, D7-19, 10, 12).

The research in this field shows that inhibition of hippocampal AT1 receptors with losartan, bilaterally or unilaterally in the left CA1 field, exerts antinociceptive and anxiolytic effects and suppresses exploratory activity. Lateralized effects of Ang IV on learning and memory processes after microinjection into the hippocampal CA1 field have been demonstrated.

The modulatory influence of ligands (agonist and antagonist) of brain cannabinoid receptors during subchronic and/or acute (i.c.v.) stimulation or inhibition of CB1 receptors in the hippocampal CA1 field on state anxiety, motor activity and nociception has been demonstrated.

4. Research on the effects of hormones of the hypothalamic-pituitary-thyroid (HPT) hormonal axis on hemostasis and fibrinolysis in rats (No. D7-2, D7-3, D7-4, D7-5, D7-6).

On experimental animals, have been shown that thyroid hormones modulate the activity of coagulation factors V, XI, XII, and XIII, the protein C anticoagulation pathway, and the fibrinolytic activity by lowering the major parameters of fibrinolysis, α 1-antitrypsin, α 2-macroglobulin, vitronectin and plasmin- α 2-antiplasmin complex, as well as parameters characterizing the functional status of the fibrinolytic system such as fibrin degradation products and D-dimer.

5. Assessment of the mental health of medical students (questionnaire surveys) and the reactivity of human organism to stress (№ D7-13, D7-20, 3)

Research in this area is on the assessment of academic stress among international medical students and stressors such as "Demands related to academic duties", "Postponement," "Exam worries", "Difficulties remembering the study material", as well as socio-demographic factors related to lifestyle and academic environment that affect the mental health of international medical students and influence the risk of developing depression.

Based on the analysis of the submitted materials, I can assess that to a very large extent, sufficient for the level of this competition, the contributions of the candidate in the relevant publications, formulated contributions and the obtained results are her personal merit.

I accept all contributions as ranked by significance and scientific criteria. The candidate's contributions in the above scientific areas show high professional competence and interdisciplinary knowledge in the field of medical-biological sciences.

6. Critical comments and recommendations

I have no significant critical comments on the materials submitted for the competition.

CONCLUSION

The documents and materials submitted by Associate Professor Margarita Stefanova Velikova meet all the requirements of the Academic Staff Development Act in the Republic of Bulgaria, the Regulations for its Implementation, and the Regulations for the Development of the Academic Staff at MU - Varna.

The candidate has submitted a sufficient number of scientific works published beyond those for the PhD degree and for the academic position "Associate Professor". The submitted materials contain original scientific and applied contributions, a representative part of which has been published in journals of International academic publishers. The excellent results in teaching and scientific research achieved by Margarita Velikova fully comply with the minimum national and additional requirements of the Academic Staff Development Act in the Republic of Bulgaria, the Regulations for its implementation and the Regulations for Academic Staff Development at Medical University – Varna.

After critical analysis of the materials and scientific works presented in the competition and assessment of her scientific production, I can confidently give a positive assessment and recommend to the esteemed Scientific Jury to award to Associate Professor Margarita Stefanova Velikova the academic position "Professor" in the field of higher education **4. Natural Sciences, Mathematics and Informatics**, professional field **4.3. "Physiology"**, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

April, 27th, 2023

Varna

REVIEWER 
/prof. Bistra Kaltcheva, PhD/