TO THE ATTENTION OF THE MEMBERS OF THE SCIENTIFIC JURY /SJ/, ACCORDING TO ORDER N 269/ 23.07.2025, ISSUED BY THE RECTOR OF THE BOURGAS STATE UNIVERSITY, "PROF. DR. ASSEN ZLATAROV", BOURGAS

REVIEW

BY Prof. Dr. Radka Mladenova Argirova, virologist, Clinical Laboratory, Tokuda University Hospital, Sofia

ON the scientific production of Miglena Antonova Koprinarova, senior assistant (2008-2021) in the section "Molecular Biology of the Cell Cycle", Institute of Molecular Biology "Academician Rumen Tsanev" – Bulgarian Academy of Sciences (BAS)

SUBJECT: acquiring of the academic position of "ASSOCIATE PROFESSOR" in the field of higher education 4. Natural Sciences, Mathematics and Informatics, professional field: 4.3. Biological Sciences, scientific specialty "Genetics" at Bourgas State University "Prof. Dr. Assen Zlatarov" according to a competition announced in the State Gazette, issue 42 of 23.05.2025.

Respected members of the scientific jury,

Miglena Koprinarova graduated with honors from the Faculty of Biology of Sofia University "St. Kl. Ohridski", speciality in Cell Biology and Developmental Biology, after which she worked at the Institute of Molecular Biology "Academician Rumen Tsanev", Bulgarian Academy of Sciences (BAS) in the group on molecular biology of the cell cycle. The leader of the group was the distinguished Bulgarian biochemist, corresponding member of the BAS Georgi Russev. Later, until 2021, she continuously worked in the same field, while simultaneously devoting herself to practical diagnostic activities related to molecular diagnostics. From 2017 to 2021, she was a co-founder, organizer and head of the Eurofins Scientific laboratory, Eurofins HOS Testing Bulgaria EOOD, dedicated to testing the quality of food and water. Here, her organizational talent was fully developed in relation to all the challenges and aspects that the creation and management of a laboratory in our country poses. Since 2022, she has been the organizer and manager for Bulgaria of RhineGene - Molecular diagnostics - specialized in products for In Vitro diagnostics and food safety. Additionally, from 2020 to 2024, she was also the creator and lecturer with an author's lecture

course on nutrigenomics and personalized nutrition at the University of Food Technologies, Plovdiv. From 2012 to 2022, she participated in 7 specialized courses in various areas of molecular biology in a number of European centers. She holds more than 20 training certificates in the areas of molecular diagnostics, healthcare, computer technologies, student education, etc. Miglena is fluent in English and Russian, also uses French.

Epigenetics is at the heart of Miglena Koprinarova's long-standing research activity, and it is inconceivable without knowledge of cell division and its regulation. The same is valid for the specific points (check points) that determine the transition from one phase of the cell cycle to another one and the possible transmission/slowing down/acceleration of cellular functions in the event of disturbances at the specific points.

Genetics studies DNA sequences, which transfer the fundamental code of life from generation to generation. Epigenetics is the study of how behavior and a range of environmental factors can alter the function and hence the impact of genes without changing the DNA itself. The key differences are: genetic information is stable and inherited, while epigenetic changes are reversible, influenced by external factors, can activate or silence genes, and therefore can impact our health and development. It is known that stably altered – partially or even missing – genetic structures are the basis of a number of hereditary diseases, the treatment approach for which requires gene modification/gene replacement therapy. At the same time, in other diseases – most often acquired and in particular a number of cancers – under the influence of known and unknown external factors, changes occur in the function of genes, without their changing.

The interplay between gene mutations and epigenetic changes is a key to the development of malignant neoplasms, where changes in the epigenome can lead to abnormal gene expression, tumorigenesis, and progression of tumor growth. And why not – regression in tumor growth? Today, this is among the main challenges, the goal of which is to slow down/stop the development of an already established tumor. In this sense, the scientific publications of Dr. Koprinarova submitted for the competition are actual and relevant.

Science metrics – The candidate presents a complete list of publications, specifically not mentioning those of them /3/ for which she was already evaluated in connection with the defense of her dissertation in 2008. Two scientific books are presented, published in 2024 and 2025 respectively, /one of them reviewed by 2 habilitated scholars/, 10 articles and 2 summaries in journals with an impact factor, 3 – in journals without impact factor, 2 articles in proceedings of scientific forums. It is noteworthy that 1 of the publications with IF is in a journal with

quartile Q1, 7 are published in journals with Q2 – of the ones listed so far, only in one publication is Miglena Koprinarova not the first author, the rest are in Q3 and Q4. In total, indicators from 5 to 10 make up 204 points – the requirement is 200 points. About citations - 75 citations /indicator 11/ - 150 points - minimum state requirements of 50 points and a requirement of the State University "Prof. Assen Zlatarov" - 100 points. The candidate's participation in research projects is as follows: leader of 4 projects funded by SMLD "Genika" and a participant in 2 projects funded by the National Science Foundation. Thus, in total, Miglena is presented in this competition with 604 points - minimum state requirements of 400 points and requirement of State University "Prof. Assen Zlatarov" - 550 points.

I completely agree with the candidate's reference, contributions, as well as the reflection and impact in the world specialized literature.

I will try to define the main topics, from the development of which the contributions to the scientific production of Miglena Koprinarova arise.

1.Special targeted search and successful determination of increased sensitivity of cancer cells to antitumor agents through epigenetic regulation of cell cycle checkpoints / publications 9,10,11,14,19,20/. This formulation covers the proven sensitazion (albeit via different mechanisms) of the HDAC inhibitor butyrate to the action of cisplatin in the HeLa cells, UV-irradiation and radiotherapy. In summary, these experiments not only prove, but also stimulate the possible inclusion of sensitizing agents in combination antitumor therapies. For the purposes of the current competition, 30 of the total number of citations of these publications are presented.

2.The role of histone H4 acetylation in cell cycle progression and arrest at different phases of the cell cycle has been investigated. It has been convincingly demonstrated that histone H4 acetylation is part of an epigenetic code that determines the functional activity of specific regions in chromatin. This observation is of particular interest because it suggests that acetylation occurs in parallel with the control of complex signal transduction pathways. This in turn shows how important the level of acetylation is for the correct course of the cell cycle /publications 1,7,21,22/. For the purposes of the competition, 20 of the total number of citations of these publications are presented.

3. Among Miglena's contributions, the monograph dedicated to the role of butyrate in maintaining homeostasis in the body through endogenous stimulation of butyrogenic bacteria in the colon stands out. This is a completely new concept, directly linking the HDAC inhibitor butyrate to modulation of gene expression

with protective and even therapeutic function in a number of diseases. For me, the facts and conclusions in this monograph are innovative, very well theoretically and practically substantiated, and with clear possibilities for practical application - I mean the promotion of sourdough bread. In my opinion, this is one of the most important contributions of the candidate and it defines her as a scientist firmly in real life and aware of a number of health problems /publication 2/. I am convinced that citations of this interesting monograph are forthcoming.

4. The candidate also presents numerous experimental results on epigenetic changes related to DNA methylation and the progression of various diseases and stress conditions – type 2 diabetes and HPV-induced cervical dysplasia. It is very likely that such studies will show prognostic significance in the near future for chronic conditions and diseases, especially if it is known which genes are active in these conditions. In fact, the methylation test for CIN2/3 is already applied for triage purposes and is considered to have early prognostic significance for the course of the infection, more precisely for already existing malignant transformation /publications 8,13,15,18/. For the purposes of the competition, 15 of the total number of citations of these publications are presented.

5. Very interesting are the studies on the molecular pathogenesis of spontaneous abortions of unknown etiology. The proven increased expression of major angiogenic factors and the chemokine SDF-1/CXCR4 is an expression of increased angiogenesis without fetal aneuploidy. This conclusion requires an active search for drugs with antiangiogenic activity.

6. A promising contribution is the demonstration by several methods of a cytotoxic effect on cancer cell lines compared to non-cancerous ones, i.e. the antitumor properties of aloe-emodin. This is an important contribution today, when natural therapeutic agents are increasingly sought after.

Without belittling the unmentioned contributions, I see an image emerging before me of a geneticist with broad and diverse interests in the field of epigenetics. Being a student and long-time collaborator of one of the greatest Bulgarian biochemists – Academician Georgi Rusev, Miglena Koprinarova has developed an unusual and uncommon triad – experimentator, analyst, and organizer - with a clearly outlined sequence in the goals of her research, specific conclusions of a fundamental scientific nature, leading to the next experiments. In Miglena's intense scientific life and activity, each publication gives rise to a new perspective, her works seem complete , but the new challenge is lurking behind each of them predetermining a new challenge as if it were endless... And another thing – she always has a thought for possible practical application and practical

benefit. A particularly valuable example in this regard is her peer-reviewed monograph /publication 2/ - a combination of fundamental contribution with practical application.

The position of associate professor requires teaching experience and training. In this regard, Miglena Koprinarova presents herself with a full cycle of author's lectures on NUTRIGENOMICS AND PERSONALIZED NUTRITION - a new discipline, created and introduced for the first time at this university by her and taught for 4 academic years, with an annual teaching load of 50 hours. The discipline is included in the curriculum for masters in the specialty: FOOD, NUTRITION AND DIETETICS at the UNIVERSITY OF FOOD TECHNOLOGIES - PLOVDIV. The well-prepared annotation of the discipline and the distribution of the teaching material are impressive. Her report on academic workload was accepted at a meeting of the Faculty Council. Her students have shared their excellent impressions of her lectures.

Miglena Koprinarova is a sought-after colleague, collaborator in national and international projects, lecturer, reviewer of scientific articles, author of wonderful popular science articles on genetics and epigenetics. Her deep and solid knowledge is well-respected by the international scientific community – according to Google Scholar, her publications have been cited 320 times, and according to Web of Science - 180 times. Her cumulative IF is 41.98.

In conclusion, the comprehensive assessment of the scientific and teaching activities of Miglena Antonova Koprinarova presents the candidate as a highly erudited scientific researcher in the field of fundamental molecular genetics and epigenetics, a lecturer with an author's lecture course with 4 years of experience, meeting and exceeding the requirements for holding the academic position of "associate professor" according to the specialized law and the Internal Rules of the Bourgas State University "Prof. Dr. Asen Zlatarov". Based on the materials presented, I will confidently vote "FOR" the acquiring by Miglena Koprinarova the academic position of "ASSOCIATE PROFESSOR" and also call on the other members of the scientific jury to join my vote and assessment.

Sofia,

Sept.11th, 2025

Reviewer:

(Prof. DrSc. R.Argirova)