OPINION

on the materials submitted for the competition for the academic position of "Associate Professor," announced in the State Gazette, issue 104/10.12.2024, for the needs of the "Molecular Biology of the Cell Cycle" department at the Institute of Molecular Biology "Acad. R. Tsanev."

The sole applicant for the competition is Dr. Emil Damyanov Parvanov.

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1. I. Brief Biographical Information about the Candidate

Dr. Emil Parvanov earned his Master's degree in Molecular Biology from the Faculty of Biology at Sofia University "St. Kliment Ohridski." He obtained his PhD in 2006 from the University of Bern, Switzerland, specializing in yeast genetics. His scientific career includes postdoctoral and research positions at prestigious international institutions, including The Jackson Laboratory (USA), Masaryk University (Czech Republic), the Institute of Molecular Genetics at the Czech Academy of Sciences, as well as Medical University, Varna. Since 2024, he has held the position of Assistant Professor at the Institute of Molecular Biology "Acad. Roumen Tsanev" – BAS.

His research activities span several thematic areas:

1. Mapping recombination events along mouse chromosomes.
2. Identifying trans-acting factors that determine the location and activity of individual recombination hotspots during meiosis.
3. Determining the mechanism of action of Prdm9.
4. Analysis of trends in digital healthcare, patient safety, and personalized medicine.

2. II. Publication Activity and Compliance with the Requirements of the Academic Development Act

The candidate is applying with 15 scientific publications, with a total impact factor exceeding 122. These publications appear in reputable international journals, most of which (11) are ranked in the first quartile (Q1) according to WoS/Scopus. Dr. Parvanov is a co-author of 32 publications indexed in Scopus/Web of Science, cited over 1050 times.

He has supervised a successfully defended PhD student, participated in national and international projects, and led two research projects. His cumulative score across evaluation indicators amounts to 2782.4 points, far surpassing (especially in indicator "D" - citations) the requirements of the national academic regulations and those of IMB-BAS.

3. III. Scientific Contributions

Dr. Parvanov's scientific work has received high recognition from the international research community, evidenced by over 1000 citations in prestigious databases. These results highlight the depth and impact of his research.

His work focuses primarily on meiotic recombination, with significant contributions to understanding its fundamental mechanisms:

III.1. Mapping Recombination Events in Mouse Chromosomes (B4.1)

Dr. Parvanov conducted studies to map recombination events along mouse chromosomes using genetic crosses between two mouse strains (C57BL/6J and CAST/EiJ) and genotyping the offspring from backcrosses to C57BL/6J. A key achievement is the detailed identification of the location and frequency of recombination events on mouse chromosome 1, representing the first of its kind for a mammalian chromosome.

His analysis revealed that while global levels of meiotic recombination are evolutionarily conserved, local variations along the chromosome exist. Most recombination events (90%) occur at a small number (10%) of highly active hotspots. He also showed that recombination frequency in females is 1.2 times higher than in males, likely due to differing chromosomal compaction during male versus female meiosis. Furthermore, crossover interference varies between sexes, with females exhibiting shorter distances, allowing more simultaneous crossovers. In contrast, gene conversions do not follow interference patterns. Crossover lengths range from 200 to 1200 base pairs, and gene conversion events from 10 to 280 base pairs, highlighting the dynamic regulation of recombination at multiple levels.

III.2. Identification of Trans-acting Factors Determining Recombination Hotspot Activity

By comparing recombination maps in mice with a fixed heterozygous region on chromosome 1 (B6 × CAST) and variable genomic backgrounds, Dr. Parvanov identified hotspots influenced by CAST alleles in distant genome regions—some enhanced, some suppressed, and others unaffected. Analysis of recombination activity in sperm revealed dependency on a single Mendelian factor, Rcr1 (Recombination Regulator 1), mapped to a 5.30-Mb region on chromosome 17. Rcr1 acts early in the process, during DNA break initiation by SPO11 (B4.2).

Subsequent studies (B4.3) involving phenotyping and genotyping males with recombination events on chromosome 17 helped narrow down the region. The gene identified as responsible is *Prdm9*, encoding a histone methyltransferase essential for fertility in both sexes. Sequencing *Prdm9* alleles from various mouse lines revealed a conserved KRAB domain, a catalytic PR-SET domain, and a variable C-terminal region with zinc fingers responsible for DNA binding. The diversity in the zinc fingers explains the differing recombination hotspot positions across mouse strains. The discovery of *Prdm9* as a master regulator resolves the "hotspot paradox" by providing a stable set of recombination sites. Notably, the study describing these results, with Dr. Parvanov as lead author, was published in *Science*.

III.3. Mechanism of Action of Prdm9 and Epigenetic Marking of Recombination Hotspots (B4.4)

Dr. Parvanov continued by elucidating *Prdm9*'s mechanism of action. In vivo experiments showed that *Prdm9* trimethylates lysines 4 and 36 of histone H3 during meiosis I. These two histone modifications co-occur almost exclusively at recombination hotspots and not elsewhere in the genome. They determine both the hotspot location and D-loop length during DNA repair.

In vitro enzymatic activity assays with purified *Prdm9* confirmed these findings: *Prdm9* methylates lysine 36 at a slower rate than lysine 4. Additional studies revealed interactions between *Prdm9* and a set of proteins that help tether hotspot-containing DNA to the chromosome axis, facilitating recombination. Yeast two-hybrid screens and co-immunoprecipitation from mouse spermatocytes showed that *Prdm9* interacts via its KRAB domain with other histone modifiers (CXXC1, EWSR1, EHMT2, CDYL), meiotic cohesins (REC8), and synaptonemal complex proteins (SYCP3, SYCP1). A mechanistic model was proposed, detailing *Prdm9*'s

DNA binding, enzymatic activity, and interactions, establishing it as a central regulator of meiotic recombination in mammals.

III.4. Applied and Interdisciplinary Research

Dr. Parvanov also engages in digital health, patient safety, and personalized medicine research. He co-authored articles examining the effects of various plant compounds on liver diseases such as jaundice and alcohol-induced damage, and reviewed molecular mechanisms underlying hepatocellular carcinoma. These papers present key plant species, their active compounds, and trends in treatment development (publications G7.1–G7.4).

He has also conducted bibliometric studies related to the COVID-19 pandemic, including research on the use of rapid antigen tests (G7.7) and various types of protective masks (G7.9), as well as the role of social media in spreading medical misinformation (G7.5).

Other studies include a bibliometric analysis of digital technologies in cardiology (G7.6), patent analysis of non-invasive blood pressure sensors for hypertension monitoring (G7.8), and an overview of digital glucose sensors based on existing patents (G7.10). These studies compare the characteristics, advantages, and limitations of different technologies and patents.

4. IV. Conclusion

Dr. Parvanov meets and greatly exceeds all criteria for the academic position of Associate Professor. His scientific output and research contributions are impressive in volume and even more so in scientific significance. His research establishes a strong presence in contemporary molecular biology. I firmly recommend the esteemed academic panel vote in favor of awarding the academic position of Associate Professor to Dr. Emil Damyanov Parvanov.