REVIEW

by Prof. Dr. VALYA NIKOLOVA VASSILEVA
Institute of Plant Physiology and Genetics - Bulgarian Academy of Sciences

for the competition for the academic position of "Associate Professor"
in the professional field 4.3. Biological Sciences
scientific specialty "Biophysics"
for the needs of the laboratory "Transmembrane signaling"
at the Institute of Biophysics and Biomedical Engineering – BAS

1. General information about the competition and the submitted documents

By Order No. 632/01.08.2025 of the Director of the Institute of Biophysics and Biomedical Engineering (IBPhBME) – BAS, I have been appointed as a member of the Scientific Jury for the competition for the academic position Associate Professor in the scientific specialty Biophysics. The competition was announced in the State Gazette, issue 58/18.07.2025, for the needs of the laboratory "Transmembrane signaling" at IBPhBME. The only candidate who participates in the competition is Dr. **SONYA NIKOLOVA APOSTOLOVA**, who currently holds the position of Assistant Professor in the same laboratory. The submitted materials have been prepared in accordance with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria (ZRASRB), its Implementing Regulations, and the Regulations on the Conditions and Procedures for Obtaining Scientific Degrees and Holding Academic Positions at IBPhBME-BAS.

2. Career development of the candidate

Dr. Sonya Nikolova Apostolova obtained a Bachelor degree in Molecular Biology in 2011 and a Master degree in Virology in 2013 from Sofia University "St. Kliment Ohridski". During her studies, she worked as a biologist at the Institute of Experimental Morphology, Pathology and Anthropology with Museum - BAS, where she participated in research related to the immune response during viral infections. Since 2014, she has continued her professional development at IBPhBME-BAS, where she gained further experience with cell cultures, advanced microscopy techniques and the evaluation of *in vitro* antitumor effects of natural and synthetic compounds. In 2015, Dr. Apostolova was awarded a scholarship for PhD research at the Biomedical Research Institute of the University of Lleida (IRB Lleida), Spain, where she investigated the role of the RING domain of the *NSE1* gene in the stability of the Smc5/6 complex and the maintenance of genomic integrity in human cells. Her doctoral studies also included a research internship at the University of Barcelona in a group studying signaling and cell cycle control. In 2021, Dr. Apostolova successfully defended her PhD thesis with distinction (Cum Laude), and her results were published in renowned scientific journals such as Cell Reports and Cellular and Molecular Life Sciences. Upon her return to Bulgaria, she successively held the positions of biologist and, since October 1, 2022, Assistant Professor in the "Transmembrane signaling" laboratory at IBPhBME-BAS. Her research focuses on the analysis of the antitumor potential of natural and synthetic molecules, as well as on the modulation of signaling pathways in aging and neurodegenerative models.

Therefore, the career development of Dr. Apostolova is characterised by research in biophysics, cell biology and biomedicine, and shows steady growth in scientific independence and the complexity of the tasks she undertakes.

3. Compliance with the requirements for holding the academic position of "Associate Professor"

For participation in the competition, Dr. Apostolova presents 15 publications, of which 13 are in peer-reviewed international journals with a total impact factor (IF) of 40.068 and two with SJR. She is the first author in three of these publications. The papers were prepared in co-authorship with colleagues from the respective research teams and working groups within which the studies were conducted.

According to the submitted documentation, the H-index of Dr. Apostolova is 5, and according to the latest data in Scopus (as of 11 November 2025), it is 6.

The data from Web of Science/Scopus and the accompanying evidence confirm that the scientific record of Dr. Apostolova meets the minimum requirements set by ZRASRB, its implementing regulations, as well as the internal criteria of IBPhBME-BAS for the academic position of Associate Professor. The points for indicators A, B, G and D have been calculated in accordance with item 5 of the Rules for the Application of ZRASRB at IBPhBME-BAS, and fully comply with the requirements for this academic rank.

For **Group A indicators**, Dr. Apostolova receives 50 points (minimum required - 50 points) for her successfully defended PhD thesis entitled "The RING domain of Nse1: roles in Smc5/6 complex stability and genome integrity in human cells". For **Group B indicators** (habilitation work - scientific publications indexed in Web of Science and Scopus), she earns 100 points (minimum required - 100 points) from five scientific publications: two in Q1, one in Q2 and two in Q3 journals. For **Group G indicators** (publications beyond the habilitation work), she presents 10 publications - six in Q1, three in Q2 and one in Q3 journals, which total 225 points (minimum required - 220 points). For **Group D indicators** (citations in WoS/Scopus), 44 citations have been recorded, which correspond to 88 points (minimum required - 60 points). The total of 463 points exceeds the required minimum of 430 points for holding the academic position of Associate Professor.

Currently, Dr. Apostolova is a co-author of 21 scientific publications in total, which, according to the submitted materials, have been cited 84 times, and according to Scopus (as of 11 November 2025) - 123 times. This reflects the recognition of her research within the scientific community. The publications and citations are primarily in specialised journals in the fields of cell biology, biochemistry, biophysics and biomedical technologies, which are fully consistent with the thematic scope of the announced competition.

4. Main areas of research and achievements

The scientific work of Dr. Sonya Apostolova focuses on the investigation of the mechanisms of cellular adaptation and stress responses through the use of in vitro (cellular and tissue) and in vivo models. She studies the effects of biologically active molecules and biomaterials on cellular

function by applying an integrated approach that combines cell biology, biochemistry and biophysics. The main research directions can be summarised as follows:

4.1. Study of antitumor activity and anti-metastatic potential of novel natural and synthetic molecules in human in vitro cell models

This research area focuses on the identification and characterisation of biologically active natural and synthetic compounds with potential for selective antitumor activity. The studies encompass analyses of cell proliferation, viability, morphology, cytoskeletal organization and programmed cell death in various tumor cell models, including breast cancer cell lines with different hormonal statuses and invasiveness, as well as myeloid tumors.

The main achievements are noteworthy in several aspects:

Natural biomolecules and their derivatives - the modification of marine hemocyanin (from *Rapana thomasiana*) with amino acid ionic liquids has been shown to alter the protein conformation and stability, accompanied by increased cytotoxicity toward breast cancer cells while normal fibroblast viability is maintained. This reveals a structure-function relationship important for the development of selective therapeutic molecules.

Triterpenoid derivatives – certain ester modifications of betulinic acid were found to enhance its cytotoxicity and specificity toward different cell types, which demonstrates potential for targeted therapy in tumors with varying receptor status.

Alkylphospholipids (erufosine) - erufosine was demonstrated to induce apoptosis in invasive myeloid tumor cells, accompanied by alterations in actin and microtubule organisation. This highlights the link between cytoskeletal reorganisation and cell death mechanisms.

Nanomicellar carriers - fluorescent micellar systems have been developed for controlled intracellular delivery and exhibit enhanced antiproliferative activity and selectivity toward tumor cells, with minimal effects on normal lines. This opens perspectives for theranostic applications (combined therapeutic and diagnostic use).

Plant extracts - the standardised extract from *Petasites hybridus* displays a selective pro-apoptotic effect in metastatic cells, associated with modulation of NF-κB signaling and oxidative status, which offers a promising approach for triple-negative breast cancer.

The presented results demonstrate a consistent scientific concept and the effective integration of biochemical, cell-biological and biophysical methods. The work by Dr. Apostolova contributes to the understanding of structure-function relationships between chemical modifications and cellular responses and lays the groundwork for the development of selective antitumor agents and combined therapeutic strategies.

4.2. Study of in vitro biocompatibility of different materials for applications in tissue engineering and regenerative medicine

The second research line in Dr. Apostolova's work focuses on the evaluation of biocompatibility, cellular adhesion and functional cellular responses upon interaction with natural, synthetic and hybrid materials that are potentially applicable in tissue engineering, regenerative medicine and implantology. The approach involves systematic assessment of cytotoxicity, genotoxicity, cell morphology and angiogenic potential.

Hydroxypropyl cellulose hydrogels with Ag nanoparticles - it has been established that at AgNP content ≤ 1.5 wt%, fibroblast (L929) viability remains high, whereas concentrations ≥ 2 wt% cause morphological alterations and increased cytotoxicity. The defined threshold concentration serves to optimise antibacterial 3D matrices for wound-healing therapies.

Materials for endoprosthetics (Ti6Al4V, stainless steel, UHMWPE) - in vitro analyses show no decrease in cell viability or increase in micronuclei formation, which confirms the absence of cyto- and genotoxicity under the tested conditions and supports the biocompatibility of these materials for orthopedic applications.

Gelatin-based 3D matrices for vascular regeneration - cultivation of endothelial cells (HUVEC) on gelatin matrices with elastic properties comparable to vascular tissue results in enhanced adhesion and increased synthesis of fibronectin, VEGF and MMP-2, with the effect being amplified under a physiological electric field. Under the same conditions, tumor cells (MDA-MB-231) show reduced attachment and weakened angiogenic signaling, which demonstrates cell-type selectivity.

The obtained results have high applied relevance for the development of biomaterials that support vascular tissue regeneration and limit local tumor growth, offering potential for bioengineering innovations and clinical applications.

4.3. Models of diabetic neuropathy and neurodegenerative conditions

The third research direction in the work of Dr. Apostolova focuses on in vivo models of early and advanced diabetic neuropathy (streptozotocin-induced), as well as on models of age-related alterations in brain lipid metabolism. An integrated approach is applied, which combines behavioral tests, serum biochemical markers, and cellular and tissue analyses to elucidate the mechanisms of neuromodulation and cellular adaptation under chronic metabolic and neurodegenerative conditions. The main results include:

Riboflavin in diabetic neuropathy - two-week administration of riboflavin leads to a reduction in hyperalgesia and normalisation of neurometabolic parameters, which include the serum glutamate/glutamine ratio that is typically disrupted under diabetic conditions. The data support the role of riboflavin as a modulator of pathways related to neuronal excitability and pain sensitivity.

GLP-1 agonist and environmental factors - in early diabetic neuropathy, liraglutide, both alone and in conditions of environmental enrichment, affects antinociceptive behavior and serum levels of glutamine/glutamate and neopterin. The results indicate that pain perception and neurometabolic response are regulated simultaneously by pharmacological intervention and external factors, which supports the concept of combined therapeutic strategies.

Melatonin deficiency and aging – in a pinealectomy model in aged animals, increased levels of sphingolipid mediators, including sphingosine-1-phosphate, were detected in the hippocampus. This is interpreted as an age-specific adaptive or dysregulatory alteration in lipid metabolism under melatonin deficiency and reveals a possible link between melatonin status, sphingolipid signaling and susceptibility to neurodegenerative processes.

Thus, the studies demonstrate a targeted and well-substantiated experimental approach that integrates behavioral, biochemical and tissue-level analyses. The research highlights the

potential for multifactorial interventions aimed at cellular protection, adaptation and functional recovery in metabolic and neurodegenerative disorders.

4.4. Personal contributions of the candidate

The submitted materials demonstrate that Dr. Sonya Apostolova has a substantial and clearly defined personal contribution to the conducted research. She has participated in the planning, execution and analysis of experiments with cellular, tissue and in vivo models, as well as in the assessment of biocompatibility and cellular selectivity of novel materials. Her contribution includes the identification of structure-function relationships between chemical modifications and cellular responses, as well as the elucidation of neurometabolic mechanisms in diabetic neuropathy and aging. Information provided in the "Author contributions" sections of the published articles confirms her active involvement in the experimental work, methodology, data analysis, visualisation and manuscript editing. This is particularly evident in the publications where the candidate is the first author, demonstrating her independence and leading role in formulating the scientific conclusions.

Therefore, her personal contribution is convincingly demonstrated and fully corresponds to the criteria for holding the academic position of Associate Professor.

5. Relevance and significance of the research topic and prospects for development

The research topic is in full alignment with the strategic priorities of modern biomedicine and public health. Oncological diseases, regenerative medicine and diabetic neuropathy represent main challenges with a high social and economic impact. In this context, the development of selective antitumor compounds and targeted delivery systems, the evaluation of biocompatible materials for tissue engineering and the elucidation of neuromodulatory mechanisms in metabolic and age-related disorders possess direct scientific and applied value. Research on natural and synthetic bioactive molecules outlines promising directions for the creation of less invasive antitumor therapies with enhanced selectivity toward cancer cells. Work on hydrogels and implant materials reveals potential applications in tissue and vascular regeneration, which include the stimulation of angiogenesis. Studies that use models of diabetic neuropathy and melatonin deficiency contribute to a better understanding of neurometabolic mechanisms and highlight opportunities for combined therapeutic approaches.

Future prospects include expansion of the research toward more complex disease models, application of multi-omics approaches and in-depth investigations of the molecular mechanisms that determine cellular responses in various biomedical contexts, as well as preparation for translational steps in collaboration with clinical units and industrial partners. In this regard, Dr. Apostolova's scientific work demonstrates strong research continuity and substantial potential for future practical applications in biomedicine.

6. Organisational and training activities

Dr. Apostolova is involved in the teaching process at the University of Chemical Technology and Metallurgy in Sofia, where she conducts practical classes in the disciplines "Immunology" and "Tissue Engineering" for Master degree students. Her role includes the preparation and delivery of laboratory exercises, the development of teaching materials, the assessment of student work

and the supervision of course projects related to cell line cultivation and evaluation of cellular parameters on biomaterials.

Her scientific and organisational activity is demonstrated by participation in 18 scientific forums, among which six international conferences, where she has presented her research results through seven oral and eleven poster presentations. Some of the presentations have received awards, which shows the high scientific quality of her research and her ability to communicate effectively in academic settings.

The candidate has participated in the implementation of eight national and five international research projects, and has served as principal investigator on one of them (under the National Programme "Young Scientists and Postdoctoral Researchers"). Some of these projects are ongoing. Within her project activities, she actively contributes to the planning, organisation and conduct of experimental work, the analysis of results, the preparation of reports and the coordination of team activities. Her involvement in many projects with partners from Bulgaria and other European countries demonstrates the high regard for her scientific competence and her ability to work effectively in multidisciplinary and international teams.

Dr. Apostolova also participates in science popularisation initiatives, such as the European Researchers' Night and educational demonstrations for pupils and students, which contributes to the promotion of public engagement with scientific research.

7. Critical remarks, recommendations and questions

I have no critical remarks regarding the candidate. It is recommended that in future studies, combined omics approaches (transcriptomics, proteomics, lipidomics) be more broadly applied. Such approaches would enable the correlation of functional changes with molecular profiles and assist in the identification of regulatory mechanisms involved in cellular adaptation to biologically active molecules. This type of comprehensive strategy would help clarify cause-effect relationships between the chemical structure of bioactive molecules, signaling pathways and the phenotypic cellular response.

In addition, the integration of mathematical and systems biology models for the analysis of signaling networks would allow a quantitative description of the dynamics of cellular processes and provide more accurate predictions of the effects of combined therapeutic strategies.

In this regard, I have two questions related to the practical aspects of the research approach:

1. Your studies combine in vitro and in vivo models. What are the main challenges in the comparison of results from these two systems and how do you approach their interpretation?
2. In some of your studies, you use biomaterials with potential applications in regenerative medicine. Do you see a possibility to combine these systems with biologically active molecules to achieve a synergistic effect?

8. Conclusion

Based on the submitted materials, the assessment of the scientific output, participation in research projects, teaching activities and scientific-organisational contributions, I consider that Dr. Sonya Nikolova Apostolova has established a consistent and sustainable research line in the fields of cell biology, biophysics and biomedical models, which fully corresponds to the profile

and requirements of the announced competition. Her research results have been published in reputable international journals, cited by the academic community and presented at national and international scientific forums. The candidate fully meets the regulatory requirements for holding the academic position of Associate Professor at IBPhBME-BAS and demonstrates strong potential for the further development of promising research activities within the laboratory "Transmembrane signaling".

In view of the above, I recommend that the members of the esteemed Scientific Jury propose to the Scientific Council of IBPhBME-BAS to elect Dr. Sonya Nikolova Apostolova to the academic position of Associate Professor in Professional Field 4.3. Biological Sciences, Scientific Specialty: Biophysics.

11 November 2025

Sofia

Prepared by:

Prof. Dr. Valya Vassileva