

REVIEW

In a competition for the academic position of “Associate Professor”

In the field of higher education 4. Natural sciences, Mathematics and Informatics, professional field 4.1. Physical Sciences and scientific speciality “Biophysics and medical physics”, announced in SN no. 99/20. 11. 2020

One candidate has submitted documents for participation in the competition - Dr. Desislava Anri Lazarova, Assistant Professor of Biophysics at the Department of Physics, Biophysics and Radiology at the Medical Faculty of Sofia University “St. Climent Ohridski”

Reviewer: Professor Dr. Antoaneta Vidolova Popova at the Institute of Biophysics and Biomedical Engineering, BAS.

Desislava Anri Lazarova was born on April 8, 1981 in the city of Sofia. In 1999 she completed her secondary education at 96 High school with intensive study of foreign languages “Lev Nikolayevich Tolstoy”, Sofia. In 2004 Desislava Lazarova completed her bachelor's degree at the Faculty of Biology of Sofia University “St. Climent Ohridski”, with obtained speciality “Molecular Biology”, and in 2006 defended with the highest mark her Master's degree in the speciality “Molecular Biology - Biophysics” at the Faculty of Biology of Sofia University “St. Cl. Ohridski”. In 2019 Desislava Lazarova defended her PhD thesis and received the educational and scientific degree “Doctor” in the professional field 4.1 Physical Sciences, scientific speciality “Biophysics” at the Faculty of Physics of Sofia University “St. Cl. Ohridski”. Supervisors of the PhD thesis "Contrast-enhanced magnetic resonance techniques for visualization of pathologies associated with disorders of cellular redox status" were Prof. Rumiana Balakalova-Jeleva and Assoc. Prof. Genoveva Zlateva. In the same year Dr. Lazarova acquired a speciality in the healthcare system - Biophysics, at the Medical Faculty of Sofia University “St. Cl. Ohridski”.

Since becoming an employee of the Medical Faculty of Sofia University in 2008 as an assistant in Biophysics in the Department of Physics, Biophysics and Radiology of the Medical Faculty of Sofia University “St. Cl. Ohridski” Dr. Desislava Lazarova was involved in the teaching and organizational activities of the department. From the very beginning Dr. Lazarova took part in the overall organization and conducting of practical classes in Biophysics and carried out organizational activities to ensure qualified educational process at the Medical Faculty of Sofia

University, participated in summarizing information on scientific assets of the academic staff of the Faculty, institutional accreditation of Sofia University and professional field of the Medical Faculty. Dr. Lazarova was also a long-term examiner in the university's candidate student campaigns for admission to the Faculty of Medicine. In the list of submitted documents for the present competition there is a reference from the Medical Faculty for the teaching hours of Dr. Lazarova for the period 2015-2020.

Since 2012 Dr. Lazarova is an administrative assistant at the Department of Physics, Biophysics and Radiology of the Medical Faculty of Sofia University, administrator of the system "Authors" for the Faculty, a member of the Faculty Committee on Quality, authorized person for the Medical Faculty at National Center for Information and Documentation (NACID), a representative of the Medical Faculty in the General Assembly of Sofia University and secretary of the Faculty Council of the Medical Faculty.

In the current competition for "Associate Professor" in the field of higher education 4. Natural Sciences, Mathematics and Informatics, professional field 4.1. Physical Sciences and scientific speciality "Biophysics and Medical Physics", the only one candidate Dr. Lazarova participates with a PhD thesis and abstract for obtaining the educational and scientific degree "Doctor". The total number of published articles by Dr. Lazarova is 31. For participation in the competition are included 20 articles published in peer reviewed and indexed journals in scientific databases and 5 articles in non-peer reviewed journals with scientific review. On the topic of the PhD thesis were published 4 articles in peer reviewed and indexed databases, and 2 in non-peer reviewed journals with scientific review. The total IF of the published articles is 41.68, and the personal IF is 6.86. The H-index of Dr. Lazarova by Scopus, after excluding the auto-citations of all co-authors, is 6.

For the participation in the present competition is included a list of the participation of Dr. Lazarova in 23 national and international scientific forums. Dr. Lazarova was a member of the project teams of 16 research and training projects. Ten of the projects were one-year long and were funded by the Research Fund at Sofia University "St. Cl. Ohridski", and two of the projects were running three years and were funded by the National Research Fund. For one of the projects (BG051PO001-3.3.06-0040 under the Operational Program "Human Resources Development" with Principal Organization - Sofia University "St. Climent Ohridski", Faculty of Medicine 2013-2015) Dr. Lazarova was the coordinator. Under project BG051PO001-3.3.04 / 42 under the Operational Program "Human Resources Development", co-financed by the European Social Fund of the European Union with the Principle Organization Institute of Biophysics – Bulgarian Academy of

Sciences - 2009-2011 Dr. Lazarova was a member of the target group. Under project BG051PO001-3.3.05-0001 “Science and Business” under the Operational Program “Human Resources Development” Dr. Lazarova was a beneficiary of a scholarship and was an academic mentor to two students (BG05M20P001-2.002-0001 of MES “Student Internships - Phase 1” Funded by Operational Program “Science and Education for Smart Growth“, 2017).

Dr. Pazarova submitted a completed reference for the implementation of the minimum national requirements under Art. 2b of The Law on the Development of the Academic Staff of the Republic of Bulgaria (ZRASRB) for scientific field 4. Natural Sciences, Mathematics and Informatics, professional field 4.1. Physical Sciences, scientific speciality “Biophysics and Medical Physics” for the academic position “Associate Professor”. By the groups of indicators A and B, Dr. Lazarova covers the required 50 and 100 points, respectively, according to the minimum national requirements. By the groups of indicators C and D Dr. Lazarova exceeds the minimum national requirements as follows: by indicator C collects 261 points at a required value of 200 and by indicator D - presents 214 points at a required value of 50. According to indicator E, which is not required by the minimum national requirements for the academic position “Associate Professor”, Dr. Lazarova presents 130 points.

The scientific achievements of Dr. Lazarova are presented in two main sections. **The first section** summarizes the scientific achievements of the publications related to the PhD thesis “Contrast-enhanced magnetic resonance techniques for visualization of pathologies associated with disorders of cellular redox status”, that are definitively practically orientated in the field of medicine. Evidence is presented for the development of new methodological approaches for the application of EPR for the identification of isolated cultured cell lines of the same origin but with different proliferative activity, as well as for early diagnosis of renal damage in vivo. The contributions included in this section have been reviewed for the defense of PhD thesis of Dr. Lazarova.

The second section of the scientific contributions summarizes the significance of the achievements in the published articles, included in the present competition. The achievements are grouped into 7 subsections. The first 5 summarize the contributions in the field of medicine, and the last two - research related to abiotic stress-induced alterations in the photosynthetic activity of higher plants. The achievements, related to medical topic are practically orientated, while the last two subsections represent interest for the basic science.

1. Modulation of redox status and increasing the sensitivity of tumor cells to conventional chemotherapeutics.

Conventional and new generation antitumor drugs in combination with docosahexaenoic acid (DHA) have been applied to sensitize leukemic lymphocytes. It has been shown that the cytotoxicity of the studied drug combinations was accompanied by strong induction of apoptosis and ROS production. A synergistic ROS-dependent cytotoxicity between docosahexaenoic acid and a new generation of antitumor drugs has been reported for the first time [8]. When various antitumor drugs were used in combination with vitamin C and provitamin K3, it was possible to modulate redox homeostasis, which would make possible to reduce the therapeutic doses of chemotherapy and its negative side effects [6]. When treating tumor cells with a combination of a conventional chemotherapeutic and combination of provitamin K3/ascorbate, the antitumor effect of provitamin K3/ascorbate has been shown to be due to a specific interaction with tumor cell mitochondria. The results of this investigation would be useful for the development of new protocols for cancer therapy [2]. The cytostatic and cytotoxic effect of a large number (over 20) of antitumor drugs in terms of their effect on the redox status of isolated cancer cell lines has been evaluated [14]. It has also been found that the anticancer effect of a combined chemotherapy with SN38 and electroporation was associated with changes in redox regulation that led to higher levels of apoptosis and ferroptosis [3]. The application of low or moderate concentrations of the flavonoid quercetin hydrate demonstrated a good anti-proliferative activity [4].

2. Nitroxide-enhanced EPR for visualization and evaluation of cellular redox potential.

A new methodology has been proposed for recording superoxide overproduction in living cells and the differentiation of cancer and non-cancer cells based on intracellular redox status through the application of nitroxide-enhanced EPR [5, 12].

3. Optical image

By applying in vivo chitosan-modified quantum dot-labeled polymersomes to colorectal cancer models, it has been shown that this type of polymersomes could be used for the diagnosis and treatment of cancer [9, 10]. Combined treatment with polymersomes and electroporation accelerated the process of penetration into tumor cells [13].

4. Contrasting multimodal samples

The application of cell-penetrating contrast multimodal probes made possible to simultaneously monitor the oxidative and reducing capacity of cells and the balance between oxidizing and reducing substances both *in vitro* and *in vivo*, by simultaneously applying three different imaging techniques - EPR, magnetic resonance imaging, tomographic images (MRI) and fluorescent imaging [1].

5. Algorithm for image processing for extraction of contrast-enhanced signals from magnetic resonance tomography (MRT).

An algorithm for extracting contrast-enhanced signals from magnetic resonance imaging (MRI) using an ImageJ script has been proposed. By applying this approach to data processing, an objective assessment of the differences between kinetic curves by statistical methods was achieved. It was possible to analyze the degree of functional impairment based on changes in redox status of the studied tissue and contrast dynamics [7].

6. Abiotic stress in plants and reactive oxygen species .

This section systematizes the contributions to the study of the photosynthetic activity of isolated thylakoid membranes and PS1 particles under conditions of abiotic stress (high light intensity, high temperature, UV-B treatment) and the role of various scavengers of active oxygen species for protection of photosynthetic apparatus.

Photoinhibitory treatment of PS1 particles leads to different degrees of photobleaching of photosynthetic pigments. The presence of histidine significantly reduced the degree of photobleaching of xanthophyll lutein and long wavelength chlorophyll species in PS1 antenna [19].

The changes in the activity of oxygen-evolving system and photochemical activity of PS2 under illumination with high light intensity at normal (22 °C) and at low (4 °C) temperature were investigated. The sensitivity of the oxygen-evolving system of thylakoid membranes was more pronounced when treated with high light intensity at normal temperature. ROS quenchers (histidine and DMSO) retarded the inactivation of oxygen evolving process. Histidine realized a more effective photoprotection at room temperature, while DMSO was more effective at 4 °C [18].

The sensitivity of the two photosystems (PS1 and PS2) after decrease of the fluidity of the lipid phase with integration of stigmasterol and cholesterol was studied. The reduction of fluidity of the lipid phase changed the stoichiometry of the two populations of PS2 and affected the thermotropic characteristics of the pigment-protein complexes [20].

The changes in the structural organization and functional activity of the photosynthetic apparatus as a result of treatment of thylakoid membranes with UV-B irradiation at low (4 °C) and normal (22 °C) temperature were studied and the protective role of different scavengers of reactive oxygen species - histidine, DMSO and nPG was evaluated. The most effective at room temperature was nPG, and at low temperature - DMSO [11].

7. Mechanisms of resistance to extreme drought of the resurrection plant *Haberlea rhodopensis*.

The effects of high temperature and extreme drought of the resurrection plant *Haberlea rhodopensis* on the activity of the photosynthetic apparatus, the ability to restore membrane integrity, the activity of oxygen release and energy distribution between the main pigment-protein complexes were studied. Temperature has been shown to play a significant role during desiccation.

Photosynthetic activity was more sensitive during desiccation at high (38 °C) than at normal (23 °C) temperature. The energy transfer to PS1 was increased at high temperature as a result of some destacking of the thylakoid membranes. Plants from different habitats in Bulgaria have been used in investigation [15, 16, 26, 29].

The research of Dr. Lazarova is extremely important for establishing of new possibilities for application of innovative approaches in the treatment of various types of cancer. Her research activity is related to monitoring the effects of various antitumor drugs, both conventional and new generation. Special attention is paid to elucidating the effects of various combinations of antitumor drugs with docosahexaenoic acid, provitamin K3/ascorbate, vitamin C/provitamin K3 and others in order to monitor ROS-dependent cytotoxicity, reducing the dose of chemotherapeutic drugs, development of new protocols for treatment of cancer, which is extremely important from a medical point of view for the treatment of various types of cancer. Some of the obtained results represent new scientific data.

The significant scientific contribution of Dr. Lazarova in the published papers is illustrated by the fact that she is the first author in 5 publications on the topic of this competition (3 in peer reviewed and indexed journals and in 2 publications in non-peer reviewed journals with scientific review). In 8 of the publications Dr. Lazarova is the second author (6 in peer reviewed journals and 2 in non-peer reviewed journals with scientific review in the current competition for “Associate Professor”) and in one she is the last author. Five of the published articles on the topic of this competition are in Bulgarian language - 2 in peer-reviewed and 3 in non-peer-reviewed journals. In 2020 3 papers were published, and one manuscript was accepted for publication in 2021 in a journal with high impact factor - *Analytical Chemistry*, IF 6.785.

The distribution of published articles in peer reviewed journals with high IF is as follows: 1 in *Analytical Chemistry*, IF 6.785; 2 in *Oxidative Medicine and Cellular Longevity*, IF 5.076. 10 papers have been published in journals with IF from 1 to 2: in *Anticancer Research* - 6, and one in each of the following journals - *Revisita de Chimie*, *Biologia Plantarum*, *Photosynthetica*, *General Physiology and Biophysics*.

The state of art of the scientific problems that Dr. Lazarova is dealing with is also demonstrated through the citations of her publications. A reference of the observed 144 citations in Scopus and Web of Science is presented. It is noteworthy that two of the articles published in 2019 have already been cited. The article under number 10 in the list of publications is cited 13 times, under number 23 - 34 times, and under number 24 - 62 times.

Along with research Dr. Lazarova is also involved in the teaching activities of the Medical Faculty of Sofia University, as evidenced by the attached reference list from the Medical Faculty for the period 2015-2020.

Conclusion:

After acquaintance with the documents and references submitted by Dr. Lazarova for participation in the current competition for the academic position of “Associate Professor”, it became clear to me that Dr. Desislava Lazarova is a qualified researcher and lecturer in the field of Biophysics, which is managing in an excellent way with the scientific, teaching and organizational activities. The scientific achievements of Dr. Lazarova significantly exceed the minimum national requirements set out in the Law on the Development of Academic Staff in the Republic of Bulgaria

(ZRASRB) for the position of “Associate Professor” in Biophysics at the Faculty of Medicine of Sofia University “St. Cl. Ohriski”.

Taken into account of all mentioned above, I would like to recommend to the members of the Scientific Jury to award the academic position “Associate Professor” in Biophysics for the needs of the Medical Faculty of Sofia University “St. Cl. Ohriski”, Sofia, to the assistant Dr. Desislava Anri Lazarova.

15. 02. 2021

Sofia

Prof. Dr. Antoaneta Popova