REVIEW

On a competition for the academic degree "Professor"

In the field of higher education 4. Natural sciences, mathematics and informatics, professional field 4.1. Physical sciences, scientific specialty "Medical Physics", announced in SG no. 103 of 10 December 2021.

One candidate has submitted documents for participation in the competition - Dr. Genoveva Antonova Zlateva, Associate Professor in the Department of Physics, Biophysics and Radiology at the Medical Faculty of Sofia University "St. Kliment Ohridski ".

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

Associate Professor Dr. Genoveva Antonova Zlateva graduated the Faculty of Physics of Sofia University "St. Kliment Ohridski" as a Master of Physics, specialist in solid state physics in 1987. In 1992 she defended a doctoral thesis "Study of the phonon structure and the effects of cation substitution in some superconducting and non-conductive complex copper oxide systems" with supervisor Prof. Milko Nikolov Iliev, Doctor of Physics, in the Department of Physics of Condensed Matter at the Faculty of Physics, Sofia University. In 1999 she completed a postgraduate specialization in the healthcare system at the Department of Physics and Biophysics at the Medical University, Sofia, and was awarded with a position of a specialist in Biophysics.

During the period 1994 - 2007 Dr. Zlateva was a lecturer (assistant, senior assistant and chief assistant) at the Medical University, Sofia, at the Department of Physics and Biophysics, leading the following courses: Physics - for specialties "Medicine", "Dentistry", "Pharmacy" and "Sanitary Inspector", Medical Equipment in Nursing Practice - for the specialties "Nurse" and "Midwife" and Electrical Engineering - for the specialty "Sanitary Inspector". Since 2007 Dr. Zlateva has been a lecturer and researcher at the Department of Physics, Biophysics and Radiology at the Medical Faculty of Sofia University, leading the following courses: Physics - for the specialty "Medicine"; Biophysics - for the specialty "Medicine" (2007-2009); Medical Equipment in Nursing Practice - for the specialty "Nurse" and Biomechanics - for the specialty "Medical Rehabilitation and Occupational Therapy" (since 2019). For the period 2009 - 2012 Assoc. Prof. Dr. Zlateva has been Deputy Dean for Academic Affairs of the Medical Faculty of Sofia University, responsible for the organization of the entire educational process at the Medical Faculty. She was also the Chairman of commissions for

preparation of self-assessment reports on accreditation procedures at the Medical Faculty of Sofia University: Project for initiating the Professional Field "Health Care" with specialty "Nurse" - 2010; Project for initiating the Professional Field “Public Health” - 2011; Program accreditation of the specialty "Medicine" at the Medical Faculty of Sofia University - 2010. Since 2010 to 2019 Dr. Zlateva was the head of the Department of Physics, Biophysics and Radiology at the Medical Faculty of Sofia University and was also involved in the organization of teaching and research activities of the department. For the period 2019-2020, Assoc. Prof. Zlateva was the Director of the University Center for Quality Management and Organization of Activities. Since 2019 she is the Deputy Dean of the Medical Faculty of Sofia University and is responsible for the organization of the entire educational process at the Medical Faculty.

Assoc. Prof. Zlateva was a member and/or the chairman of Scientific Juries for obtaining the academic degree "Doctor of Science" (1), educational and scientific degree "Doctor" (4), in competitions for obtaining the academic degree "Associate Professor" (3) and for “Professor” (2). She is a reviewer for scientific journals such as: Chinese Journal of Cancer Research, International Journal of Automation, Journal of Experimental Clinical Medicine, for the Annual of Sofia University (for the Faculty of Physics), Bulgarian Journal of Physics. Dr. Zlateva is reviewing projects for the Bulgarian Science Fund of the Ministry of Education and Science as a member of Temporary Scientific Expert Commission. The expert activity of Dr. Zlateva includes chairmanship of an expert group for accreditation of doctoral programs at National Agency for Evaluation and Accreditation - for "Medical Physics" at Medical University, Varna (2016), at Shumen University "St. Konstantin Preslavski” (2018), and at Thracian University (2021); for "Biophysics" for Medical University, Sofia. She is also a member of the expert group for accreditation of doctoral programs at National Agency for Evaluation and Accreditation - on "Medical Biophysics" at Medical University, Pleven (2021). Dr. Zlateva was the co-supervisor of a successfully defended doctoral thesis.

Dr. Zlateva took part in implementation of 2 research projects at Bulgarian Science Fund, of 2 at the Medical Science Council at Medical University, Sofia and of 8 at the Scientific Research Fund at Sofia University. She was the principal investigator of 6 research projects at the Scientific Research Fund of Sofia University and of one project co-financed by the European Structural and Investment Funds - "Support for the development of doctoral students, postdoctoral students, graduate students and young scientists". Dr. Zlateva has also been the coordinator of an international bilateral project.

Assoc. Prof. Zlateva is a co-author of 99 scientific papers, which have been published in scientific journals and conference proceedings. 38 of the publications are in journals, referenced and

indexed in WoS and/or SCOPUS. Dr. Zlateva has presented her scientific results at 91 scientific forums. The H-factor of Assoc. Prof. Zlateva according to SCOPUS, after excluding the auto-citations of all authors is 7.

For participation in the current competition for the academic degree "Professor" Assoc. Prof. Zlateva presents 19 publications in referenced and indexed in world-famous databases (Web of Science and SCOPUS). The total IF of the presented papers is 24.15, and the personal IF is 10.85. According to the classification of scientific journals by quartiles, the published articles are as follows: Q1 - 4, Q2 - 4, Q3 - 4, Q4 - 6. The publications presented in non-refereed journals with scientific review are 30, of them 22 are in Bulgarian. Dr. Zlateva presents as well 54 participations in scientific forums, 25 of them in Bulgarian. Dr. Zlateva took part in implementation of 21 scientific and educational projects. The up-to-date of the scientific topics Assoc. Prof. Zlateva is dealing with is demonstrated by the noticed citations of her publications. A list of the noticed citations of her publications (285) in SCOPUS/WoS is applied. The significant scientific contribution of Dr. Zlateva to the published articles is demonstrated as well by the fact that in 7 of the articles she is the first author, in 9 she is the second and in 8 - last author. It is worth noting that one of the publications (number 4 of the list of scientific publications after acquiring the academic position "Associate Professor") is in a journal with impact factor 6.785, Analytical Chemistry.

A fulfilled table for implementation of the minimum national requirements under Art. 2b set in The Low for the Development of Academic Staff in the Republic Bulgaria for scientific field 4. Natural sciences, mathematics and informatics, professional field 4.1. Physical sciences, scientific specialty "Medical Physics" is also applied. By criterion Group A and B are presented the required 50 and 100 points, respectively. For the other groups are presented more than the required points - for G - 212 (required 200), for D - 370 (required 100) and for E - 396 (required 150 points).

An academic report is attached which summarizes the main scientific achievements of Dr. Zlateva, which are systematized in 5 sections.

I. Application of redox modulators as cytotoxic agents in tumor cells alone or in combination with conventional chemotherapeutics with the aim to increase the sensitivity towards them as well as to reduce their side effects.

Part of the research of Assoc. Prof. Zlateva is focused on searching of appropriate approaches for selective treatment of cancer cells and reducing their viability, without affecting healthy cells.

Many natural products such as ascorbic acid, polyphenols, melatonin, docosahexaenoic acid and others exhibit antitumor activity and, unlike conventional anticancer drugs, alter intracellular redox homeostasis and induce apoptosis in tumor cells without causing unwanted side effects in normal cells. The effect of alpha-tocopheryl succinate (the main component of vitamin E) on the redox status of leukemic and normal lymphocytes, as well as their sensitization to four conventional and eleven new generation anticancer drugs was studied. The molecular mechanisms of action of this natural product, in combination with anticancer drugs, for the regulation of vital metabolic processes in leukemic lymphocytes, but not affecting the processes in normal lymphocytes, are discussed. It has been suggested that alpha-tocopheryl succinate may be used as an adjunct to tumor therapy, especially in **acute lymphoblastic leukemia**, to reduce the therapeutic doses of drugs used to date and to minimize their side effects on healthy cells.

The possibility of targeting the **glioblastoma tumor** of the redox-active menadione/ascorbate combination was investigated and shown to induce highly selective cytotoxicity in isolated glioblastoma cells, but normal microglial cells remain unaffected. This effect is accompanied by concentration-dependent overproduction of mitochondrial superoxide only in **glioblastoma cells**. This effect was compared with the effects of the chemotherapeutic standard for the treatment of cancer, temozolomide, which is cytotoxic to both glioblastoma and normal cells. The menadion/ascorbate combination is thought to selectively alter tumor cell dysfunctional mitochondria.

II. Optical imaging

The method of Optical Imaging, based on the fluorescence of quantum dots encapsulated in polymer vesicles, to which antibodies, peptides, DNA are selectively attached, is the subject of intensive research. This method demonstrates a number of advantages over conventionally used fluorophores due to the ability to develop multimodal quantum dots with additional functionalities used in the diagnosis and treatment of cancer.

- **Optical Imaging in investigation of the theranostic potential of polymersomes.**

The use of chemically modified chitosan-based polymersomes are suitable drug carriers and selective targeting of tumors. The results of in vivo experiments with the application of quantum dot-labeled polymersomes (QD^{750} polymersomes) on colorectal cancer models are presented. The data suggest that these long-circulating polymersomes are promising carriers of drugs, small nanoparticles, and contrast agents to solid tumors. This makes them suitable for use in the diagnosis and treatment of cancer.

The effectiveness of in vivo and in vitro monitoring of chitosan-based polymersomes marked with quantum dots (QD) or conventional organic dyes (fluorescein isothiocyanate - FITC) was compared. The data obtained suggest that FITC-dextran is not suitable for the monitoring of polymersomes due to the rapid release of organic dye, while QD-labeled vesicles are suitable fluorescent markers for quantitative monitoring of the pharmacodynamics of polymersomes in vivo and in vitro. The application of electroporation accelerates the release of the organic dye FITC-dextran but does not cause the release of QD from the polymersomes.

III. Methods and techniques for visualization of pathologies associated with disorders of cellular redox status.

Cellular redox status determines the regulation of cellular signaling in the body and maintains cellular homeostasis within normal limits. Disturbance of redox balance in cells is closely related to the pathogenesis of many diseases, which makes the creation and implementation of new methodological approaches for the registration of cellular and tissue redox status in clinical practice especially relevant.

- **Contrasting multimodal samples**

A two-component sensor system is described - a sensor for total antioxidant capacity (TRC) and a sensor for the level of oxidative stress (OxiStress) based on quantum dots that can penetrate cells and mitochondria. With these sensors, the total antioxidant capacity and the level of oxidative stress can be monitored using EPR, MRI and fluorescent optical imaging. It has been shown that with the help of proposed sensors, based on contrast multimodal samples able to penetrate cells, the oxidative and reducing capacity of cells and the balance between oxidants and reductors can be registered both in vivo and in vitro.

- **Contrast-enhanced magnetic resonance techniques**

The possibilities for precise visualization of the redox status of cells, tissues and organs with the help of nitroxide radicals and the application of magnetic resonance techniques (electronic paramagnetic resonance and nuclear magnetic resonance) have been studied. The penetrating mitochondria mito-TEMPO was used to record renal dysfunction in mice as a result of redox imbalance and oxidative stress in renal tissues by recording magnetic resonance imaging. The mito-TEMPO probe is suitable for recording hypercholesterolemia-induced renal dysfunction and for evaluating the effect of antilipidemic drugs by magnetic resonance imaging.

• Algorithm for processing image processing to extract contrast-enhanced signals from magnetic resonance imaging (MRT).

An algorithm for extraction of contrast-enhanced signals from magnetic resonance tomographic images using the ImageJ script is described. Tomographic images are transformed into digital data for describing the kinetic curves of contrast-enhanced MRT signal for objective assessment of differences between the kinetic curves and analysis of the extent of functional disorders based on alterations in redox status of the respective tissue.

IV. Investigation of surface and interface polariton modes of optical phonons (SPP and IPP) in low-dimensional structures.

• In nanofilms and nano-inclusions of Mg_2Si and $FeSi_2$ in silicon matrix.

Raman spectra of samples representing Si matrix with ion-implanted nanolayers and nano-inclusions from the semiconductor silicides β-$FeSi_2$ and Mg_2Si were studied. Various features in the spectra as a result of generating surface and interface polariton modes of optical phonons (SPP and IPP) have been interpreted. The obtained results are closely correlated with the technological conditions for obtaining the low-dimensional structures and with the electron-microscopic interpretation of the structure of the studied samples. The energies of the inter-band transitions in the studied energy range were determined from studies of resonant Raman scattering.

• In InN / AlN nanofilms

Raman and infrared spectra of InN nanofilms on an AlN buffer layer deposited on a sapphire substrate (Al_2O_3) were studied. Peculiarities in the spectra related to the occurrence of surface and interface polariton modes of optical phonons (SPP and IPP), whose frequencies are theoretically derived from calculated dispersion ratios of SPP and IPP, were interpreted.

V. Issues of students training in medical specialties

This section summarizes and analyzes the results of various methods and approaches in the training of students in physics of medical specialties at the Medical Universities. Methodical solutions are offered to increase the motivation of students and their success. In this section are summarized the achievements described in 25 publications on the topic.

The research interests of Assoc. Prof. Zlateva are focused on extremely up-to-date and important scientific field of establishment and application of innovative approaches in diagnostic and treatment of various cancers. Her research is related to monitoring the effects

of different anticancer drugs, both conventional and new generation. Special attention is paid to the monitoring of ROS-dependent cytotoxicity, the target effect on reducing the viability of cancer cells without affecting healthy cells, the application of optical imaging for the diagnosis and treatment of cancer, which is extremely important from a medical point of view for detection and treatment of various oncological diseases. Some of the results are new to science.

CONCLUTION

All documents and references submitted by Associate Professor Dr. Genoveva Zlateva for participation in the current competition for the academic position "**Professor**" clearly indicate that Dr. Zlateva is a researcher and lecturer in the field of "Medical Physics" that is managing excellent with her scientific, teaching and organizational activities and that significantly exceeds the minimum national requirements set out in the Law for the Development of Academic Staff in the Republic Bulgaria (ZRASRB) for obtaining the academic position "**Professor**" in the field of higher education 4. Natural sciences, mathematics and informatics, professional field 4.1. Physical sciences, scientific specialty "Medical Physics".

Based on all listed above I strongly recommend to the members of the Scientific Jury to award the academic position "Professor" in "Medical Physics" for the needs of the Medical Faculty of Sofia University "St. Kl. Ohriski" to Associate Professor Dr. Genoveva Antonova Zlateva.

23.03.2022

Sofia /Prof. A. Popova/