Opinion

By Prof. Dr. Biliana Pancheva Nikolova

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By competition for the academic position "professor" in professional field 4.2. Chemical Sciences, scientific specialty 01.05.10 Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances, for the needs of the laboratory " Chemistry and Biophysics of Proteins and Enzymes", announced by IOCCP-BAS in State Gazette issue 40 of 16.05.2025.

With only one candidate who submitted documents for participation: Assoc. Prof. Dr. Vanya Nikolova Mantareva, laboratory "Chemistry and Biophysics of Proteins and Enzymes", IOHCF-BAS

By order of the director of the Institute of Organic Chemistry with a Center for Phytochemistry - BAS, I am appointed as a member of the scientific jury in the above-described competition.

At the first meeting of the scientific jury, we familiarized ourselves in detail with the materials provided by Assoc. Prof. Mantareva and established that they meet the requirements of the law on the development of the academic staff of the Republic of Bulgaria and the regulations of the IOHCF-BAS.

Assoc. Prof. Mantareva graduated from Higher Institute of Chemical Technology-Sofia (now University of Chemical Technology and Metallurgy) in 1990, acquired the scientific and educational degree "Doctor" in 1998, from March 2014 she holds the academic position "Associate Professor" at the IOCCP-BAS, and in 2021 she acquires the scientific degree "Doctor of Sciences".

The materials submitted for participation in the competition show the distribution of Assoc. Prof. Mantareva's scientific contributions by points according to the minimum national requirements of the law on the Development of the Academic Staff of the Republic of Bulgaria. The submitted documents show that the results achieved by Assoc. Prof. Mantareva cover, and in some indicators exceed, the requirements set out in the law.

The candidate participates in the competition after defending a dissertation for the award of the scientific degree "Doctor of Sciences" (2021), which has a contribution of 100 points (indicator B).

In group of indicators B (habilitation work), 5 scientific publications are presented (3 of them are published in journals with rank Q1, and the other two are in journals with rank Q2). In total, the publications carry 115 points, with a required 100.

In group of indicators D (scientific publications in journals that are referenced and indexed in world-renowned databases with scientific information), 19 scientific publications are presented, which carry 296 points, with a required 250, as well as one published book based on a defended

dissertation for the award of the scientific degree "Doctor". Of which 2 of them are published in journals with rank Q1, 5 in journals Q2, 3 in Q4 and 9 in publications with SJR without IF. Of the works presented in IF journals, 10 scientific articles have been published.

In the group of indicators D (citations in scientific publications, monographs, collective volumes and patents) with minimum national requirements of 200 points, which corresponds to 100 citations, a list of 249 citations (corresponding to 498 points) is presented, noted for the period from 2022 to July 2025, distributed among the articles.

In the group of indicators E, the candidate has presented a list of participation in scientific projects: Participation in a national scientific or educational project of the National Science Foundation 4 issues: 2014-2017 (Prof. L. Avramov, IE-BAS); 2019-2025 (Assoc. Prof. I. Angelov, IOCCP-BAS) 2019-2023 (Assoc. Prof. E. Borisova and Senior Asst. Prof. Ts. Genova, IE); 2018-2023 (Prof. Kr. Minkin, St. Ivan Rilski University Hospital, IOCCP - partner organization);

Participation in an international scientific or educational project 2: Russia (2020-2022); Poland (2024-2025);

Leadership of a national scientific or educational project: National Science Foundation (KP-06-N29/11, 2018-2022);

Leadership of the Bulgarian team in an international scientific or educational project - one: (Turkey, 2013-2016; China, 2024-2026);

Funds raised for projects led by the candidate (the total amount is filled in for each project) 120,000 BGN (KP-06-N29/11, 2018 - 2022) and 50,000 (KP-06-China/02, 2024-2026) = 170,000 BGN.

150 points are required for this indicator, and as can be seen from the attached reference, a total of 359 points have been collected.

The presented scientific contributions of Assoc. Prof. Vanya Mantareva are grouped as follows:

1. New phthalocyanine complexes as photosensitizers for PDT: synthesis and photo-properties.

New structures obtained on the basis of the phthalocyanine ring and biologically active fragments as substituents have been considered. The selected metal ions - palladium, nickel, gallium, zinc, aluminum and lutetium contribute to the transition of the molecule to a triplet excited state. The new structures have a different position of the substituents (methyl pyridoxy groups), in the four non-peripheral positions of the ring phthalocyanine molecule. This structure has the advantage of bathochromic shift in the absorption spectrum in the near IR region. Octa-substituted derivatives with peripheral substituent groups with a chemically unambiguous structure without positional isomers were obtained. A synthetic procedure was applied, in which the ligand was initially obtained, followed by formation of the complex. Higher yields and purity of the obtained complexes were established, compared to the procedure of direct synthesis from monomers.

Biologically active carbohydrate groups in a non-peripheral position linked by an ether bond to phthalocyanine derivatives, obtained as lutetium complexes, are considered as a second series of derivatives. The absorption and fluorescence properties of the synthesized complexes and conjugates were studied using UV-vis spectroscopy. The photophysical parameters of the

newly synthesized complexes show reliable properties for application in photodynamic therapy (publications B 1-6, G5, G7, G15).

2. Natural photosensitizers for photodynamic method: (1) cobalamin derivatives - properties and contributions; (2) anthraquinones for PDT

2.1. Cobalamins: photo-physicochemical and biological properties.

The role of cobalamin (vitamin B12) in tumor therapy is well studied and it finds clinical application. Its effect is due to increased accumulation in tumor tissues with the help of a receptor molecule - CD320. The study of cobalamin for photosafety showed a wide concentration range of non-toxicity in the treatment of embryonic cells - BALB 3T3. In vitro experiments on human breast cancer cell lines (MCF-7 and MDA-MB-231) both alone and in combination with phthalocyanine complexes under conditions of photodynamic therapy have demonstrated a dependence on the structure of the complexes. It has been established that cobalamin is a weak photosensitizer when irradiated with a spectrum with a maximum of 660 nm. The contribution of cobalamin is in reducing the dark toxicity of the main photosensitizer and increasing the selectivity index and phototherapeutic efficiency (publications B3, D12).

2.2. Anthraquinones of plant origin: available results and prospects for the development of new photosensitizers.

Compounds with anthraquinone structure are being developed, based on a literature review. Anthraquinones of higher plant origin are assumed to be a good basis for the development of new photosensitizer structures (publication D4).

3. Conjugates of phthalocyanine complexes with proteins and enzymes: photo- properties and PDT effects.

Conjugates of phthalocyanine complexes with collagen hydrolysate and α-chemotrypsin were investigated as potential photosensitizers for photodynamic therapy. The results obtained show properties for the conjugates, such as stability in neutral medium, a suitable transport system for phthalocyanines and fluorescence in the far red region with an intensity suitable for diagnostics. Compared to pure phthalocyanines, the conjugates were evaluated with lower cytotoxicity and better selectivity, with the conjugate with chemotrypsin being particularly promising due to lower toxicity to normal cells at relatively high selectivity and phototherapeutic index. Conjugation of phthalocyanines with biomolecules increases their biocompatibility, transport and reduces unwanted toxicity. Particularly promising is the conjugate with chymotrypsin, which demonstrates the lowest toxicity to normal cells under conditions of high phototherapeutic effect (publications 2B, 4B, 14D).

4. Development of the photodynamic method with phthalocyanines for socially significant diseases (1-2B, 4-5B, 7B, 2D, 4D, 6-9D)

4.1. Antimicrobial photodynamic therapy

Photodynamic therapy with Pd(II) and Zn(II) phthalocyanine complexes against pathogenic bacteria, including multidrug-resistant strains Aeromonas hydrophila and Flavobacterium hydatis, as clinical isolates, was studied. Pd(II) complexes showed complete inactivation of bacteria at concentrations above 5 μM, the effect being due to their nonspecific accumulation in pathogenic cells, such as suspension and biofilms. It has been found that non-peripherally

substituted Pd(II) phthalocyanines are more effective than peripherally substituted analogues, achieving complete inactivation at lower concentrations.

4.2. Photodynamic inactivation of viruses

Photodynamic therapy can also be considered as a reliable method for inactivating enveloped viruses. It effectively blocks the infection of host cells at all stages of the virus-cell interaction. PDT is established as a promising approach for controlling and reducing viral activity in experimental conditions.

4.3. Photodynamic therapy in tumors

Photodynamic therapy is an effective method for treating tumors by preventing the development of resistance. The third generation of photosensitizers is distinguished by improved selectivity and controlled toxicity, with non-peripherally substituted complexes showing higher activity on tumor cells. The candidate's personal contribution includes the synthesis of new photosensitizers and the development of protocols for their application.

A plan for future research is presented, which includes the development of sustainable "green" methods for the synthesis of phthalocyanines using low-toxic solvents, ionic liquids and deep-eutectic mixtures, with the aim of their introduction into laboratory practice. In tumor therapy, matrix metalloproteases (MMPs) are being investigated as a natural target and the effect of photosensitizers and PDT on them is planned to be studied using an "organ-on-a-chip" model. In addition, projects are being developed with natural photosensitizers, including anthraquinones, for structural modifications and study of their applicability in various photodynamic applications.

The attached documents show that the candidate has experience in teaching a doctoral student who has defended a dissertation on this scientific topic. I believe that there is a good prospect for training young associates and developing a subsequent dissertation work.

I have no critical remarks or questions for the candidate.

In conclusion, I believe that the scientometric indicators presented above, the scientific contributions made, as well as the overall work of Assoc. Prof. Vanya Mantareva fully meet, and in some indicators exceed, the requirements for acquiring the academic position of "Professor" set out in the regulations to the law on the Development of the Academic Staff of the Republic of Bulgaria.

My personal impressions of the candidate's work, as well as the duly submitted documents for the competition, give me reason to confidently recommend to the scientific jury to prepare a proposal to the Scientific Council of the IOCCP-BAS for the election of Vanya Nikolova Mantareva for the academic position of "Professor" in scientific field 4.2. Chemical Sciences, scientific specialty 01.05.10. Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances.

15.09.2025

Prof. Biliana Nikolova