Opinion

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on the materials submitted in a competition for the academic position of **Professor** at the Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences (IOCCP-BAS) in the higher education area 4. Natural science, mathematics and informatics, professional filed 4.2. Chemical science, scientific specialty "Bioorganic chemistry, chemistry of natural and physiologically active compounds" for the need of lab. "Chemistry and biophysics of proteins and enzymes"

1. General presentation of the procedure and the candidate

Assoc. Prof. DSc. Vanya Nikolova Mantareva from IOCCP-BAS, Lab. "Chemistry and biophysics of proteins and enzymes" is the only candidate in the competition for the academic position of Professor, announced in the State Gasette, issue 40 of 16.05.2025, and on the website of IOCCP-BAS.

The set of materials presented by Assoc. Prof. DSc Mantareva is in accordance with the Regulations on the terms and conditions for acquiring scientific degrees and for occupying academic positions at the IOCCP-BAS and meets the criteria of the Institute for occupying the academic position of "professor".

Assoc. Prof. DSc Vanya Mantareva participated in the competition with 27 scientific papers. Of these, 6 are equated to habilitation papers (indicator W), with 5 being in refereed and indexed scientific publications with a quartile: Q1 - 3 and Q2 - 2. The works under the group of indicators G are 21, of which 1 book based on a dissertation for the scientific degree of "Doctor of Science" and 19 publications in scientific journals, as follows: Q1 - 2, Q2 - 5, Q4 - 3 and with SJR without impact factor - 9 pcs. One publication each under indicators W and G are in journals with only impact factor. A list of all citations for the period 2022-2025 is presented, the number of which is 249. The citations for this period according to Web of Science and Scopus, as required, are 241. The candidate's H-index is 17 (Scopus). Lists of all articles are presented, for those under indicators W and G, and a list of participation in projects and scientific forums. The necessary evidentiary material is presented.

Vanya Mantareva graduated in 1990 as a chemical engineer at the Higher Institute of Chemical Technology-Sofia, now the University of Chemical Technology and Metallurgy. In 1995, she started working at the IOCCP-BAS as a chemist and over the years has successively held the academic positions of research fellow III degree, research fellow II degree, assistant professor, and since 2014 she has been an associate professor. In 1999, she acquired the title of "Doctor", and in 2021, the title of "Doctor of Sciences". She specialized in universities in Germany, the USA and Spain. She has made scientific visits, including project work, to universities in Israel, Turkey and India.

2. General characteristics of the candidate's activities. Evaluation of the works and their significance.

For participation in the competition, Assoc. Prof. DSc Vanya Mantareva has submitted 27 scientific works, including a book based on a dissertation for the Scientific degree "Doctor of

Sciences" (2025, first edition), not submitted in other competitions. Of the total of 26 publications, 23 are research papers and 3 are reviews, one of which is in memory of a scientist in the field of biophotonics. This publication is co-authored by 36 scientists, but there is no information of the personal contribution. The total scientific output of Assoc. Prof. DSc Mantareva is 90 papers (86 articles, 3 book chapters and 1 book on the dissertation for Doctor of Sciences) with a total number of citations over 950. The results of the research submitted in the competition have been presented at 14 international scientific forums.

Assoc. Prof. DSc Mantareva is the leader of 3 projects: with the National Science Fund (NSF) for fundamental research, with the NSF under a competition for bilateral cooperation with China, mobility (current) and under an agreement between BAS-Tübitak, Turkey. She is the coordinator on behalf of the IOCCP as a partner organization of 2 projects with the NSF and is a participant in another 4 projects with the NSF and an agreement between BAS-PAN (current). She is the supervisor of graduate students and one successfully defended full-time doctoral student (in 2019).

Assoc. Prof. DSc Mantareva's field of scientific research covers the development and study of photosensitizing compounds as potential agents for photodynamic therapy (PDT) - an unconventional method with applications in biomedicine and ecology. The topic is relevant given the need for alternative therapeutic approaches and agents against the backdrop of increasing drug resistance. The scientific interests of Assoc. Prof. DSc Mantareva are based on phthalocyanines, and the works submitted for participation in the current competition are presented in four areas: 1. New phthalocyanine complexes as photosensitizers for PDT: synthesis and photo-properties. 2. Natural photosensitizers for photodynamic method: cobalamin derivatives - properties and contributions and anthraquinones for PDT. 3. Conjugates of phthalocyanine complexes with proteins and enzymes: photo-properties and PDT effects. 4. Development of the photodynamic method with phthalocyanines for socially significant diseases. The achieved results and contributions are of a scientific and scientifically applied nature.

The results and contributions of the publications, equivalent to a habilitation thesis (**indicator W**) in all areas include:

- New phthalocyanine complexes, coordinated with Pd, Zn and Ga, respectively, and with methylpyridyloxy substituents in four non-peripheral positions, were synthesized and characterized. Their photophysical and photochemical properties and effects under conditions of PDT therapy, such as safety, efficiency and selectivity on normal and tumor cell lines, were studied. The photostability was determined under non-specific conditions such as the spectrum of the light source and radiation doses.
- Cobalamins (vitamin B_{12}) were studied for the first time as potential photosensitizers for PDT. Hydroxycobalamin has been shown to be photosafe over a wide concentration range on mouse embryonic cell lines. When tested as an additive to non-peripherally methylpyridyloxy substituted Zn(II)-phthalocyanine, a positive effect was found, expressed in a reduction in the dark toxicity of the phthalocyanine complex and increased selectivity through accumulation in tumor cells.
- Physical conjugates of phthalocyanine complexes with physiologically functional biomolecules were synthesized and characterized - tetramethylpyridyloxy substituted Ga(III)-phthalocyanine with collagen hydrolysate and octamethylpyridyloxy substituted Zn(II)- and Ga(III)-phthalocyanines with α-chemotrypsin. Stability was proven under physiological conditions and concentrations suitable for biomedical applications. A decrease in cytotoxicity and reduced phototoxicity were found when using conjugated forms in *in vitro* conditions in normal and tumor

cell lines. Photoirritation factor (PIF), phototherapeutic index (PIF) and selectivity index (SI) values were calculated, indicating their safety and potential as PDT agents.

- Antimicrobial PD effect of peripherally substituted methylpyridyloxy Pd(II)-phthalocyanines was established against antibiotic-resistant and sensitive strains of Gram(-) *Aeromonas hydrophila*, with complete photodynamic inactivation of both strains at concentrations >5 μM. Non-specificity in their accumulation in bacterial cells and biofilms was established by fluorescence detection, which is important for the broad-spectrum efficacy of PDT. A similar study was conducted on Gram(-) bacteria *Flavobacterium hydatis*, a cause of losses in fish farms, with two methylpyridyloxy Pd(II)-phthalocyanines. It was shown that non-peripherally substituted complexes show a lower effective concentration for complete inactivation of the bacteria.
- The photooxidative potential of Zn(II)-phthalocyanines and their mestranol tetra-azidoethoxy substituted derivatives on cholesterol was evaluated with a view to their effect in photodynamic therapy, with a lower potential being established for the substituted complexes.

The results and contributions in the publications included in **indicator G** and the book based on the dissertation work are in the outlined scientific directions. Phthalocyanine complexes with different coordinating metal ions and substituents were obtained and characterized, synthetic approaches were developed. The potential of the complexes as antimicrobial, antiviral and antitumor agents *in vitro* was evaluated and approaches for photodiagnosis and assessment of the effectiveness of phthalocyanine complexes in PDT of tumors *in vivo* were developed. The perspective for the development of a "green PDT method" based on photosensitizers of plant origin such as anthraquinones, as an environmentally friendly and sustainable alternative to synthetic compounds, was outlined.

The perspective for future research is outlined, aimed at expanding the current ones by use of "green solvents" for the synthesis, use of natural substances through structural modifications as photosensitizers, as well as obtaining new phthalocyanine complexes for the PDT method for inhibiting tumor-associated matrix metalloproteases.

3. Personal contribution

The conducted scientific research is in a multidisciplinary field, which requires the participation of scientists from different fields. The presented habilitation report partially outlines the personal contribution to such research. The leading and personal contribution of Assoc. Prof. DSc Vanya Mantareva is undoubted, supported also by the fact that she is a corresponding author of 10 publications, in 9 of which she is the first author. She is the head of national and bilateral projects, and is the head of 1 defended doctoral student. I would like to note that currently under her leadership an assistant is working and training with the prospect of being enrolled as a doctoral student in independent preparation.

4. Critical remarks

The submitted materials are well arranged and I have no remarks. I have some remarks on the habilitation report - it is partly written too generally and there are errors related to references to the relevant publications, which makes it difficult to track and analyze them; publications 3, 10 and 11G are not reflected in the report.

CONCLUSION

The research and research metric indicators of Assoc. Prof. DSc Vanya Mantareva, reflected in the materials submitted for the competition, meet the requirements for holding the academic

position of "professor", according to the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation, the Regulations of the Bulgarian Academy of Sciences and the Regulations of the IOCCP-BAS.

After reviewing the materials and scientific papers presented in the competition, analyzing their significance and the contributions contained in them, I give my **positive assessment** and recommend to the Scientific Jury to prepare a report-proposal to the Scientific Council of the IOCCP-BAS for the **election of Assoc. Prof. DSc Vanya Nikolova Mantareva** to the academic position of **"professor"** in professional field 4.2. Chemical Sciences, scientific specialty "Bioorganic chemistry, chemistry of natural and physiologically active compounds".

Sofia, 22 September 2025

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/Prof. Dr. Milena Popova/