

**To the members of the scientific jury  
Defined by Order No. I-83/01.07.2020  
of the Director of Institute of Microbiology  
Bulgarian Academy of Sciences**

# **R E V I E W**

**OF**

**PROF. IVA STEFANOVA CHRISTOVA, MD, PhD, DSc  
NATIONAL CENTER OF INFECTIOUS AND PARASITIC DISEASES**

**Competition to hold the academic position ASSOCIATE PROFESSOR  
High education field 4. “Natural sciences, mathematics and informatics”  
Professional field 4.3. “Biological sciences”**

**And scientific specialty “Microbiology”**

**For the needs of Department of Infectious Microbiology  
Institute of Microbiology, Bulgarian Academy of Sciences**

**Announced in the State Gazette No. 47 of 22.05.2020**

With a single candidate

**ASISSTANT PROFESSOR MAYA MARGARITOVA ZAHARIEVA, DOCTOR OF  
PHARMACOLOGY**

## **CAREER DEVELOPMENT**

Assist. Prof. Maya Zaharieva is fluent in German, graduated from German college in Burgas and studied for 2 years German philology at Sofia University "St. Kliment Ohridski". She has graduated from the Medical University - Sofia with specialty “pharmacy”. In 2001,

she completed experimental part of her diploma thesis at German Center for Oncological Research in Heidelberg, Germany. Only four years later, at the same center, already as a DAAD scholarship holder, she completed the experimental part of her dissertation. From 2003 to 2006, she was a full-time doctoral student at the Department of Pharmacology at Medical University – Sofia. In 2007, she brilliantly defended her PhD thesis "Study on the pharmacodynamic effects of Erufosine in tumor-transformed and normal hematopoietic cells". Appropriate models of cell test systems have been used to establish the cytotoxic effect of Erufosine alkylphosphocholine on tumor-transformed hematopoietic cells, as well as the protective effect of Erufosine on normal hematopoietic cells; in vitro interactions of Erufosine with clinically administered cytostases have been tested, allowing its administration in synergistic combinations; mechanism of action of Erufosine was elucidated and for the first time the influence of Erufosine on the expression of the retinoblastoma protein Rb-regulator of the cell cycle was determined.

Several successful specializations in leading laboratories in Europe and ascending career development followed. Maya Zaharieva completed a one-week course in cell model systems at the University of Thor Vergata in Rome, Italy and two two-month specializations at the Institute of Agriculture and Fish Farming in Belgium, respectively in quantitative polymerase chain reaction with TaqMan probes and loop-mediated DNA amplification of pathogens in food matrices, the knowledge of which she successfully applies in her research. In 2008-2010 she led a research project under a program for young scientists of the Alexander von Humboldt Foundation, and in 2011-2012 she was a research associate in a project for a program for reintegration of the same foundation. She successively became an assistant professor of pharmacology at the Faculty of Medicine at Sofia University "St. Kliment Ohridski", assistant in microbiology at the Institute of Microbiology of Bulgarian Academy of Sciences and chief assistant at the same institute (from 2014 until now).

She is a member of prestigious scientific organizations - Union of Humboldtians in Bulgaria, Union of Scientists in Bulgaria, Union of Pharmacists in Bulgaria.

## **RESEARCH ACTIVITY**

In this competition, Assist. Prof. Zaharieva presents 85 scientific papers after obtaining a doctoral degree, distributed as follows:

- Publications in international scientific journals with SJR-IF: 21 issues, of which in 5 she is the first author, with a total IF 45,724;
- Chapters from books - 3 pieces, one of which is the first author;
- Publications in proceedings of international congresses - 3, 1 of which is the first author;
- Publications in magazines with SJR - 1 pc .;
- Scientific papers presented at foreign or national scientific forums with international participation - 57 pcs.

One can judge the significance of the results achieved by Maya Zaharieva not only by the high impact factor of her publications, but also by the numerous citations of her works in prestigious international publications. She participated in the competition with 235 citations and h-index 9.

Information on compliance with the criteria of Institute of Microbiology-BAS for holding the academic position of "Associate Professor" shows that for the required 20 pcs. publications with impact factor, monographs or published in full reports of international congresses, the candidate has 27 issues and is the first author of 7 of them with a requirement for at least 5, as well as 235 citations for the required 100 citations, the impact factor of her articles is 45,724 for the required 20, her h-index is 9 for the required 5, she has 14 participations in projects when the required are 3 pcs.

Summarized all these facts convincingly prove that Assistant Professor Maya Zaharieva has already established her reputation among Bulgarian and international scientific community as a scientist with high scientific achievements and opportunities, based on excellent theoretical and practical training.

### **Main scientific directions**

The main direction in the research activity of Assistant Professor Maya Zaharieva is research in the field of experimental chemotherapy of malignant diseases and concomitant

bacterial infections. In her studies, she focuses on the selective antineoplastic and antibacterial activity of synthetic compounds from the group of alkylphosphocholines and a series of plant extracts and biologically active substances isolated from various plants with potential application in human medicine.

The most important scientific contributions are in the field of studying the mechanism of action of compounds with combined antineoplastic and antimicrobial activity. Research on the pharmacodynamics and antibacterial activity of the alkylphosphocholine erufosine is central.

Maya Zaharieva conducts targeted oncopharmacological research on the antineoplastic activity and the possibilities for combined application of triterpene saponins from the plant *Gypsophila trichotoma* in order to synergize and potentiate the effect of classical cytostatics at lower doses.

Her scientific contributions in the field of antimicrobial activity include pilot studies on the antibacterial activity of plant extracts, biologically active substances derived from them, new strains of microalgae, synthetic compounds and human neutral peptides (defensins).

**The main scientific contributions can be systematized as follows:**

***Antineoplastic activity and mechanism of action of alkylphosphocholine erufosine in leukemic, lymphoma and tumor cell lines***

For the first time, she proved the antineoplastic activity of alkylphosphocholine erufosine in cell lines of chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, squamous cell carcinoma of the oral cavity and breast cancer. For the first time, she elucidated the modulating effect of erufosine on the activation and expression of PI3K / mTor / PKB-Akt signaling proteins, the phosphorylation of the retinoblastoma protein Rb, and the regulation of the cell cycle at the R restriction point, where cell division is controlled. She establishes the key role of retinoblastoma protein in the antineoplastic effect of erufosine in SKW-3 cells (T-cell leukemia). She demonstrates the antineoplastic activity and potential of erufosine to induce apoptosis in multiple myeloma cell lines. A significant contribution is the evidence that erufosine is an inhibitor of protein kinase B, which plays a key role in the regulation of cell growth and proliferation and is often overexpressed or constitutively activated in malignantly transformed cells. The publication with the participation of Maya

Zaharieva in Cancer letters is among the 25 most read articles of the journal for period January-March 2012, which is a huge success and is indisputable proof of the importance of her scientific results.

***Cytotoxicity and mechanism of action of GOTCAB saponins in combination with etoposide***

The contribution of Assist. Prof. Zaharieva is in demonstration of the antineoplastic activity of extracts from the roots of the plant species *Gypsophila trichotoma* L. and the potential of saponins isolated from the extracts to potentiate in non-toxic concentrations the antineoplastic effect of the clinically applied cytostatic etoposide. The conclusion is that triterpene saponins are suitable compounds for inclusion in synergistic combinations with the clinically administered cytostatic etoposide.

***Cytotoxic effect of the biotechnological product justicecidin B in lymphoma cell lines***

For the first time, she established antineoplastic potential of biotechnologically derived plant product justicecidin B in human lymphoma cell lines. Cytotoxicity studies with justicecidin B have shown that it inhibits cell proliferation by 50% in vitro while they are not toxic to mice.

***Cytotoxic activity of lignans from the plant *Linum tauricum* W. in human malignant cell lines***

For the first time, she evaluates the cytotoxic potential of lignan from the plant *Linum tauricum*, which induces apoptosis in two of the three leukaemic cell lines tested.

***Cytotoxic activity of lanthanum complexes with biscoumarin in leukemic cell lines***

For the first time, she established the cytotoxic potential of lanthanum (III) complexes with bis-coumarins in cell lines of chronic myeloid leukemia that express the Bcr-Abl oncoprotein and in SKW-3 T-cell leukemia cells. She found that these compounds showed antineoplastic activity in micromolar concentrations and induced apoptosis in the BV-173 cell line, which has a wide response in the scientific literature and a huge number of citations (97).

***Antimicrobial activity of combinations between alkylphosphocholines erufosine or miltefosine and micelle drug delivery systems with curcumin***

She demonstrates for the first time the antibacterial activity of the alkylphosphocholine erufosine against pathogenic strains of *Staphylococcus aureus* with or

without resistance to metacillin. She found that the antibacterial effect of erufosine was more pronounced against methicillin-resistant staphylococci than against methicillin-sensitive ones.

#### ***Antimicrobial activity of African plant species***

She established for the first time antibacterial activity of extracts extracted from the African plants *Geigeria alata* and *Solanum schimperianum* Hochst. A new compound, N-feruloyl lysine, was isolated for the first time from the plant *S. schimperianum* H., which is promising for future studies on its antibacterial activity.

#### ***Antimicrobial activity of new strains of microalgae***

For the first time, antibacterial potential of newly isolated strains of microalgae was characterized. Antibacterial activity of biomass and extracts of the species *Poterioochromonas malhamensis* against *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Staphylococcus aureus* and *Streptococcus pyogenes* has been established.

#### ***Antimicrobial activity of alpha-defensin 2 in pharmacopoeial buffers with different pH***

She established that a buffer of pH 9.0 was most suitable for stabilizing the peptide and for exhibiting its inhibitory activity against *Escherichia coli*.

#### ***Toxicity study of ethyl acetate extract of the plant *Geum urbanum* L. on intestinal epithelium and Peyer's patches***

For the first time, acute toxicity of ethyl acetate extract of the plant *Geum urbanum* L. on intestinal epithelium and Peyer's patches in mice was evaluated.

#### ***Study of cytotoxic effect of GOTCAB saponins***

For the first time, in vitro cytotoxicity of 11 GOTCAB saponins isolated from the roots of the plant *Gypsophila trichotoma* L. on the standardized cell line of normal murine fibroblasts CCL-1 was evaluated.

#### ***Study of cytotoxic effect of eye prostheses with antimicrobial action***

Lack of cytotoxic effect of Al<sub>2</sub>O<sub>3</sub> silver-coated eye prostheses with antibacterial and antifungal action was established.

#### ***In vitro toxicological evaluation of platinum (II) complexes with acetate ligands***

Toxicological potential of platinum (II) bis- (aceto) diamine-bis-1-aceto diplatin (II) dihydrate complex in *in vitro* models of nephrotoxicity, bone marrow toxicity and neurotoxicity was studied for the first time.

*Modeling of the processes of inhibition of proliferation of human malignant cell lines with mathematical software MAPLE*

For the first time in Bulgaria, software has been created that overcomes the shortcomings of the linearization of nonlinear kinetic models. The results obtained from this program are compared with those obtained from the software programs CompuSyn and GraphPad Prism using the same experimental data. The program encoded in MAPLE® showed a higher correlation coefficient (R) and IC50 values had better biological significance for all samples of experimental data. For the first time in Bulgaria, modeling of metabolic activity in bacteria was performed with mathematical software MAPLE.

### **Participation in research projects**

Assistant Professor Maya Zaharieva participated in the competition for associate professor with an impressive list of participations and leadership of research projects, a total of 14 research projects. Most of them are with Medical University of Sofia or are funded by the Research Fund of the Ministry of Education and Science. One of the projects on which Assistant Professor Maya Zaharieva is the leader, is funded by Alexander von Humboldt Foundation. A total of three research projects are leaded by Assistant Professor Zaharieva. The presented data show the active participation of the candidate, as well as the fact that she is a sought-after and preferred partner for joint research.

### **TEACHING ACTIVITY**

Assistant Professor Maya Zaharieva is actively involved in supervising of graduates, participation in writing textbooks and teaching activities. She is a research supervisor of three diploma theses at the Faculty of Pharmacy of MU-Sofia, two of which are of foreign students. She took part in writing of two chapters in the Guide to Pharmacotherapy. She did exercises during the period 2011-2012 at Medical Faculty of Sofia University "Kliment Ohridski" in the specialties "Medicine" (270 teaching hours), "Nurse" and "Medical Rehabilitation and Occupational Therapy" (45 teaching hours).

## CONCLUSION

Assistant Professor Maya Zaharieva, Ph.D. is a famous and respected scientist with innovative ideas, excellently prepared and highly valued by her colleagues at home and abroad, who has proven his professionalism over the years.

The results of research activities of Assistant Professor Maya Zaharieva present her as a graduate scientist and a respected expert in the field of experimental chemotherapy of malignant diseases with plant extracts and active substances isolated from plants of potential importance in human medicine.

Summarizing the scientific contributions of her research achievements, highly appreciated by the scientific community, an indicator of which is the huge number of their citations, I can confidently say that they fully meet the quantitative and qualitative criteria of ZRASRB, the Rules for its application and the Rules of the Institute of Microbiology, BAS for holding the academic position of "Associate Professor".

Based on all this, I recommend to the respected members of the scientific jury to support the candidacy and to propose to the Scientific Council of the Institute of Microbiology at BAS, Assistant Professor Maya Margaritova Zaharieva, Ph.D. to be elected to the academic position "ASSOCIATE PROFESSOR" in the scientific specialty "MICROBIOLOGY" for the needs of the Department of Infectious Microbiology, Laboratory of Cytotoxicity and Signal Transduction, Institute of Microbiology at the Bulgarian Academy of Sciences.

25.08.2020

Signature:

/ Prof. Iva Christova, MD, PhD, DSc./