REPORT

on the materials presented for participation in the competition for the academic post of "Professor" in *Natural sciences, mathematics and informatics*, professional field 4.3. *Biological Sciences* (scientific speciality "*Application of the principles and methods of cybernetics in various fields of science (in silico study of bioactive compounds)*") announced for the needs of "*QSAR and Molecular Modelling*" Department at the Institute of Biophysics and Biomedical Engineering – Bulgarian Academy of Sciences

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The only candidate in the competition for "Professor" announced in the State Gazette, issue 18 (p. 32) of 28 Feb 2020 and on the website of IBPhBME–BAS (http://biomed.bas.bg/bg/procedures/concourse-professor-qsar/), is **Assoc. Prof. Dr. Ivanka Milosheva Tsakovska** from the same institute.

1. GENERAL PRESENTATION OF THE PROCEDURE AND THE APPLICANT

In the competition all documents and materials needed to fulfill the requirements for the academic post "Professor" are presented in accordance with the Regulations for the Development of the Academic Staff of IBPhBMI-BAS and the specific requirements of the Institute for the academic post "Professor".

Assoc. Prof. Dr. I. Tsakovska has presented 24 scientific papers published in the period 2011-2020, all on the topic of the competition, which are outside her PhD thesis and the "Associate Professor" competition and thus are accepted for review. Of them 17 are in journals with Impact Factor (IF), 3 are in journals with SJR, 3 are chapters in books of renowned scientific publishers (Springier, Royal Society of Chemistry and Humana), and one is a report in a conference proceedings. The articles are divided into categories as follows: 14 in journals with category Q1, 2 with Q2 and 1 with Q4 (the higher quartile is taken when? Web of Science and Scopus reported simultaneously). According to indicator B, 9 articles are indicated (all with Q1), and according to indicator D - 15 articles, of which 5 with Q1, 2 with Q2, 1 with Q4; the book chapters and the printed conference report are also referred to D section. The candidate's *Detailed reference for the implementation of the minimum national requirements* includes also information on: 461 citations of the candidate's works according to Scopus; leaderships of 3 research projects (2 national and one of a Bulgarian team in a FP7 project of the European Commission; currently Assoc. Prof. Tsakovska leads another national project) as well as participation in 8 other projects with international and national funding. Among the data on the project attracted funds led by the candidate, it is worth noting the impressive funding of approximately BGN 940,000 for the IBPhBME team in the FP7 project. As a supervisor Assoc. Prof. Tsakovska has a successfully defended PhD student, and another one with the right to defense after expiration of the PhD period. With these data on indicators C, D, E and E the candidate exceeds the required number of points set by IBPhBME-BAS and the threshold of minimum 15 publications in journals with IF, according to the specific requirements of the institute for the academic position "Professor".

The candidate's biographical record demonstrates a constantly ascending scientific development in the professional field of the competition, that is based on rich academic experience, both national and international. The scientific results and achievements presented by

Dr. Tsakovska in this competition have been obtained at IBPhBME-BAS; they are closely related to the scientific topics of the institute suggesting future benefits from her election as a "Professor" for the research staff of the institute, and in particular for her department "QSAR and molecular modelling".

2. GENERAL CHARACTERISTICS OF THE APPLICANT'S ACTIVITY

Contributions. I agree with the *Extended Habilitation Report* on the scientific contributions presented by Assoc. Prof. Dr. Tsakovska. All of them refer to *in silico* studies of biologically active molecules in accordance with the speciality of the competition and the subject of the section "QSAR and molecular modelling", for the needs of which the competition was announced. The candidate summarizes her contributions in two main groups (indicators B4 and G7 with G8, respectively), following the generally accepted requirements for the academic position "Professor". Below these contributions are summarized based on the publications:

1. Description of toxicological pathways, modeling of their molecular initiating events and evaluation of toxic effects of biologically active compounds.

This group of contributions of Dr. Tsakovska are closely related to her experience gained from her work in international research institutions and the international project COSMOS (http://www.cosmostox.eu/), implemented within the Bulgarian team led by her. The contributions are based on the results of 13 publications. The main subject of study is the nuclear peroxisome proliferator-activated receptor gamma (PPARγ) and its ligands to assess their potential toxic effects (publications 4, 6, 7, 8, 15, 16 from the presented list). The main research focus is on the full PPARγ agonists as potential molecular initiating agents in hepatocytes for development of non-alcoholic fatty liver disease. PPARγ partial agonists and antagonists have also been investigated to elucidate their pharmacophores, interactions with the receptor and potential effects. To this group of contributions I also relate the QSAR model for predicting membrane permeability based on the PAMPA (parallel artificial membrane permeability assay) methodology (publications 13 and 21), which is implemented in the platform for processing and analysis of free access data of the COSMOS project and included in the Database on Alternative Methods to Animal Experimentation of the European Union Reference Laboratory for Animal Testing Alternatives (https://ecvam-dbalm.jrc.ec.europa.eu/). To the same group I refer the studies on xenobiotic-induced dysregulation of the estrogen receptor ERα through a detailed analysis of the structure-activity relationships, pharmacophore modeling and virtual screening of compounds that could bind to this nuclear receptor (publications 5 and 9).

I define the contributions in this group as those that **most clearly outline the personal academic profile of Dr. Tsakovska**. Together with a number of her other activities in recent years as a lecturer, expert and reviewer, they give me reason to identify Assoc. Prof. Tsakovska as **a leading specialist in the field of computational toxicology** not only institutionally and nationally but also internationally. The contributions rely on publications that report original research results (publications 4, 5, 6, 7, 8, 13, 15, 16, 21), as well as review articles and chapters in books (publications 9, 14, 17, 24). Most of them have been published in journals and books specialized on toxicology, such as *Toxicology, Computational Toxicology, Food and Chemical Toxicology, Toxicology and Applied Pharmacology, Big Data in Predictive Toxicology*. The results and knowledge gained in this field serve as a basis for research in another group of contributions (publication 10) through the developed database with structural and biological data

on PPARγ agonists, which, according to our information, is currently the largest publicly available curated? database of ligands of this receptor (http://biomed.bas.bg/qsarmm/).

2. In silico modeling of small molecules, incl. drugs, drug-like compounds and natural substances, with respect to: prediction of ADME/Tox properties; derivation of "structure-activity" relationships; analysis of ligand-receptor interactions; finding new potential target proteins.

The subject of research in this group of publications are different classes of biologically active molecules and their target proteins studied by applying various in *silico* ligand-based and structure-based methods of drug design. **It is worth noting that in the original research on this topic, the model results find their experimental confirmation**.

Some of the results are a continuation of research started in the dissertation of the candidate related to the transport protein of multiple drug resistance, P-glycoprotein (P-gp), but at a new level due to the presence of new experimental data on the structure and function of P-gp (publications 1, 2 and 3). In the article with the original study on the problem (publication 3) a structure of human P-gp is used, which ranks it as the first such study after the deposit of the structure in the Protein Data Bank. The expertise gained over the years determines the invitation to Assoc. Prof. Tsakovska to participate as a co-author in two review articles on this topic, published in the prestigious journal *Drug Resistance Update*.

Another part of this group of contributions is based on the results of modeling and studying interactions and biological effects of natural compounds: in *silico* prediction of ADME/Tox properties of flavonolignans from silymarin (publication 18), modeling and experimental study of membrane permeability of major components of silymarin (publication 13) and prediction of their novel biological targets (publication 12); review of QSAR models and 3D QSAR modeling of natural, semisynthetic and synthetic polyphenols to evaluate their antioxidant effect (publications 19 and 20).

3. Using mathematical methods to evaluate the results of applying structure-based methods of drug design.

In this group of contributions, Assoc. Prof. Tsakovska has presented two publications (10 and 11) related to the most recent developments in her department on application of a new method for data analysis and decision making in structure-based virtual screening of biologically active molecules, based on index matrices and intuitionistic fuzzy sets. With her expertise in modeling of PPARγ ligands and using also other groups of compounds, she shows with the new method of mathematical analysis that, depending on the subject of study, docking scores can have different levels of consonance?.

The candidate's contributions can be classified mainly as scientific achievements in the field of computational toxicology and computer-assisted drug design. A number of *in silico* models have been developed, modes of interactions with target biomacromolecules have been elucidated, and mechanisms of action of various biologically active molecules have been identified and elucidated. The presented scientific contributions give room for potential practical applications of the obtained results. Her results constitute a solid base with potential for use in further research, for which Dr. Tsakovska has a clear vision.

Scientific metrics. The majority of the papers are published in renowned scientific journals, referenced and indexed in the world-renowned databases for scientific information Web of Science and Scopus. In fact, **83% of the research papers have been published in journals with IF or SJR**, among them: *Drug Resistance Update* (IF=11.00 for 2019), A*ntioxidants* (IF=5.014 for 2019), *International Journal of Molecular Sciences* (IF = 4.556) for 2019), *Phytomedicine*

(IF= 4,268 for 2019), *Toxicology* (IF=3,265 for 2017) and others. **The high impact factor of the publications of Dr. Tsakovska is impressive, especially in recent years**. Of the scientific papers, 82% fall into the Q1 category, which is an indicator of the high quality of the presented scientific results. This is confirmed by the data on her citations that, according to the reference are 461 (dated 17.06.2020), of which about 1/4 are of the publications included in the competition list. The report in Web of Science shows an even higher total number of citations (over 500, without auto-citations), and according to the personal data of the candidate the overall number exceeds 600 (with h index = 12). These results illustrate **the candidate's intention to maintain a consistently high level of quality of her publications.** They also testify to **the recognition of her results by the international scientific community**.

3. CONCLUSION

The documents and materials presented by Assoc. Prof. Dr. Ivanka Tsakovska meet the requirements of the Act for the Development of the Academic Staff in the Republic of Bulgaria (ADASRB), the Regulations for the Implementation of ADASRB, the Regulations for the Implementation of ADASRB of BAS and the specific Regulations of IBPhBME-BAS.

The candidate has submitted a sufficient number of scientific papers published after the defense of her PhD thesis and the competition? for the academic post "Associate Professor". According to the main indicators she collects points significantly above the required thresholds. In this way, the research results achieved by Dr. Tsakovska fully comply with the specific requirements of IBPhBME - BAS Regulations for the implementation of ADASRB.

Assoc. Prof. Dr. Tsakovska has achieved a number of original scientific results published in renowned scientific journals with high impact factors, which have received recognition from the academic community in Bulgaria and abroad. In many of the publications she has a leading position and outlined personal contribution to the presented results, which defines her as a scientist with an outlined academic profile.

The above gives me a reason **to assess positively** the candidature of Dr. Tsakovska and to recommend to the Scientific Jury to prepare a report-proposal to the Scientific Board of IBPhBME-BAS **for the election of Assoc. Prof. Dr. Ivanka Milosheva Tsakovska as a Professor** in the professional field. 4.3. *Biological sciences* (scientific specialty "*Application of the principles and methods of cybernetics in various fields of science (in silico study of bioactive compounds)*").

1st September 2020 ....

Prof. Ilza Pajeva