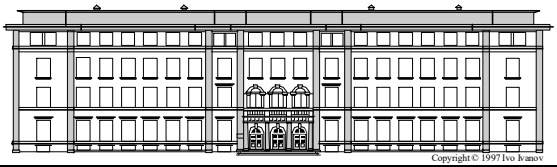

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R E V I E W

by **Irini Atanas Doytchinova - Tsekova,** DSc.,

Professor in the Faculty of Pharmacy at the Medical University of Sofia

RE: Competition for the academic position 'Professor' in the Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Area of higher education: 4. Natural sciences, Mathematics and Informatics, Professional direction: 4.3 Biological Sciences, Scientific Specialty: Application of the principles and methods of cybernetics in different scientific areas (*in silico* analysis of bioactive compounds)

In the competition for the academic position 'Professor', announced in the State Gazette, issue #18 from 28.02.2020, participated only one candidate – Assoc. Prof. **Ivanka Milosheva Tsakovska** from the Department of QSAR and Molecular Modelling in the Institute of Biophysics and Biomedical Engineering (IBPhBME) of the Bulgarian Academy of Sciences (BAS). The set of documents contains all applicable for the candidate documents according to the Rules for academic staff development in IBPhBME. Additionally, the documents were accessible on the Institute's website which was very convenient for my work on this Review.

Assoc. Prof. Tsakovska graduated from UCTM-Sofia in 1995. In 2003 she obtained a PhD degree from the Central Laboratory of Biomedical Engineering (CLBME), BAS. In the period 2002-2003 she was a fellow of the Alexander von Humboldt Foundation, and in 2005-2007 she held a postdoctoral/contract agent position at the Research Center of the European Commission in Ispra, Italy. In 2007 she returned to CLBME and a little later, in 2010, she was habilitated as a Research Associate II degree (Associate Professor) in the scientific specialty "Theoretical Chemistry".

Assoc. Prof. Tsakovska participated in the competition with 24 scientific papers, of which 17 publications in journals with IF, 3 publications in journals with SJR, 1 publication in conference proceedings without IF/SJR and 3 chapters in books. In group of indicators C (Habilitation thesis - scientific publications in journals that are referenced and indexed in Web of Science and Scopus) are included 9 publications in journals with Q1, which give 225 points at a required minimum of 100 points according to Annex 1 of the Rules for academic staff development in IBPhBME. The group of indicators D (item 7. Scientific publications and item 8. Chapters of books) includes 12 publications, of which 5 in Q1, 2 in Q2, 1 in Q4, 3 without IF, but with SJR, and 3 chapters of books that bring a total of 252 points at a required minimum of 220 points. In 8 publications, Assoc. Prof. Tsakovska is a leading author and/or author of correspondence. According to the additional requirements in the IBPhBME Rules, the candidates for the academic position 'Professor' should have at least 15 articles in journals with IF. This requirement has been met – Assoc. Prof. Tsakovska participates in the competition with 17 publications in journals with IF. Among them, 10 publications are in journals with IF > 3, incl. 2 reviews with own results published in the journal *Drug Resistance Updates* with IF (2019) = 11. The total IF of the publications in the competition is 65.65.

As of June 2020, Assoc. Prof. Tsakovska has reported 461 citations of her publications in Scopus without self-citations, which bring her 922 points at the required 120 points by group of indicators E (item 11). As of September 2020 (when this review was prepared) the citations reached 475. The candidate's H-index is 12.

The research activity of Assoc. Prof. Tsakovska is funded by 8 national and 3 European research grants. Assoc. Prof. Tsakovska is a Leading Investigator of 2 national and 1 European grant with a total sum of gained funds amounting to BGN 1,079,033.

Assoc. Prof. Tsakovska is a co-supervisor of the PhD students Marilyn Al Sharif and Antoniya Diukendjieva. Merilyn successfully defended her PhD thesis in 2016 and now is a Head Assistant in the Department of QSAR and molecular modeling of IBPhBME at BAS.

The total points in group of indicators F (from item 12 to item 20) is 431 at the required minimum of 150 points. Thus, **Assoc. Prof. Tsakovska participates in the competition with total points of 1880 at the required 640 points**, according to the Rules for academic staff development in IBPhBME, i.e. **3 times the requirements for holding the academic position 'Professor'**.

In habilitation report, Assoc. Prof. Tsakovska has divided her scientific contributions in two groups: contributions of the publications in the group of indicators C and contributions

of the publications in the group of indicators D. I fully accept such consideration. It shows that the candidate's work is focussed and systematic. In addition, such a separation facilitates the efforts of reviewers. Here, however, I will allow myself to consider the contributions of Assoc. Prof. Tsakovska from a methodological point of view, i.e. I divide the contributions according to the methods of drug design that have been used to achieve them. The methods in drug design are divided into two major groups: ligand-based design and structure-based design. In her research, Assoc. Prof. Tsakovska applies the whole spectrum of approaches and methods of molecular modeling and design of new molecules – from classical QSPR and 3D-QSAR techniques, through pharmacophore identification, virtual screening by pharmacophore search and molecular docking to molecular dynamic (MD) simulations.

The group of contributions in the field of ligand-based design includes:

- Development of a 3D-QSAR CoMSIA model for prediction of transactivation ability of 83 PPARγ receptor agonists (publication 4).

- Development of a QSPR model for PAMPA permeability prediction of 269 natural compounds and its application for permeability prediction of 38 silibin derivatives (publications 13 and 21). The model is freely available in the database of the EU Reference Laboratory for Alternatives to Animal Tests.

- Development of a QSAR model for prediction of antioxidant activity of natural polyphenols, containing a quantum chemical descriptor (publication 19).

- Identification of a pharmacophore for binding of agonists to the α-estrogen receptor and its application for virtual screening (publication 5).

- Identification of a pharmacophore for binding of agonists to the PPARγ receptor (publication 7) and its application as part of a virtual screening protocol (publication 4).

- Identification of pharmacophores for binding of partial agonists to the PPARγ receptor (publication 15).

- Prediction of potential toxic effects and metabolic transformations by knowledge-based expert systems (Derek Nexus, Meteor Nexus, KNIME, ACD/Percepta) of natural modulators of non-alcoholic fatty liver disease (publication 16) and silibin derivatives (publication 18).

To the group of contributions in the field of structure-based drug design I consider:

- Definition of the mode of binding of 3 new HSP90 inhibitors to the P-gp transport protein by molecular docking (publication 3).

- Development, validation and comparative analysis of algorithms for molecular docking of PPARγ receptor agonists (publications 4, 6 and 10).

- Comparative intercriteria analysis of evaluation functions used in ligand docking (publications 10 and 11).

- Prediction of two new target proteins (BRAF kinase and SMO protein) of flavonolignans from *Silybum marianum* by molecular docking. Binding to these proteins was proved experimentally (Publication 12).

- Identification of a potential mechanism of action of saponin derivatives as partial agonists of the PPARγ receptor by pharmacophore-based docking (publication 15).

- Prediction the binding mode of the two stereoisomers of silibin to the α-estrogen receptor by molecular docking and explanation of the partial agonism of one of the stereoisomers observed experimentally (publication 18).

- Prediction of one additional element in the pharmacophore for binding to the α-estrogen receptor by MD simulations of ligand-protein complexes (publication 5).

- Prediction of the mode of binding and the intermolecular interactions of antagonists to PPARγ receptor by MD simulations of ligand-protein complexes (publication 6).

The review articles co-authored by Assoc. Prof. Tsakovska are also impressive. Two of the reviews examine the application of *in silico* methods for repurposing old drugs to fight multidrug resistant cancers (publication 1) and for improvement of conventional anti-cancer drugs as new tools against multidrug resistant tumors (publication 2). Remarkable is the analysis of the biochemical cascades at cellular, tissue and organ levels, which are triggered by the interaction of ligands with PPARγ receptors in hepatocytes and adipocytes (publication 8). The *in silico* approaches for modeling the toxicity of xenoestrogen compounds (publication 9), for modeling of PAMPA permeability (publication 14), skin permeability (publication 17), and antioxidant activity of phenolic compounds (publication 20) were also analyzed. The chapters in the books published by Springer, the Royal Society of Chemistry and Humana Press can be used as manuals on drug design (publications 22 - 24), illustrated with examples from the authors' own research.

Based on the quality and quantity of the above mentioned scientific achievements, I give a high positive assessment of the research activity of Assoc. Prof. Ivanka Tsakovska.

Although teaching is not necessary for the academic development of the scientists at BAS, I would like to emphasize on the teaching activity of Assoc. Prof. Tsakovska as a lecturer at Sofia University. This information was additionally provided to me by the applicant on my request. I believe that the good scientist should be able to present and communicate his research. Assoc. Prof. Tsakovska has been a lecturer in the course on QSAR and Molecular Modeling in the Faculty of Chemistry and Pharmacy since 2008 with a horarium of 30 hours lectures and 30 hours practicals. She has also co-supervised one graduate and two PhD students.

As a colleague working in the same scientific area, I know Assoc. Prof. Tsakovska personally and I have personal impressions of her work and her academic development. She is a worthy representative of the Department of QSAR and Molecular Modelling, successor of the Central Laboratory of Biomedical Engineering, led and developed by Prof. Ilza Pajeva, Corresponding Member of BAS. Prof. Pajeva's group has always been distinguished by good research practice and innovation, as evidenced by the many publications in prestigious scientific journals, the international collaborations, the guidance and participations in national and European projects, the successfully graduated PhD students.

Conclusion

The research activity of Assoc. Prof. Tsakovska not only meets, but qualitatively and quantitatively exceeds the criteria for acquiring the academic position 'Professor' in the field of biological sciences, considered by the Rules for academic staff development in IBPhBME.

I am voting positively for the selection of Assoc. Prof. Ivanka Milosheva Tsakovska at the academic position 'Professor' in the scientific specialty "Application of the principles and methods of cybernetics in different scientific areas (*in silico* analysis of bioactive compounds), in the Department of QSAR and molecular modeling at IBPhBME - BAS.

01.09.2020 Reviewer:

Sofia (Prof. Irini Doytchinova)