

REPORT

By Prof. Spiro Mihaylov Konstantinov, MD PhD DSc

Re. Competition for the academic position PROFESSOR at the IBBE-BAS with the only applicant associated professor Ivanka Milosheva Tsakovska; professional field 4.3 Biological sciences, scientific specialty: Application of the cybernetics principles and methods in different scientific fields (in silico study of bioactive compounds) for the needs of the Department “QSAR and molecular modelling”, IBPhBME-BAS, published in the State Gazette, No 18, p. 32, February 28, 2020

Order for the appointment of the scientific jury: 198/16.04.2020

Short biographic data

Ivanka Tsakovska finished high school in the National Gymnasium for natural and mathematic sciences ‘Academician L. Chakalov’ in 1990. In 1995 she graduated as MSc in chemical engineering at the University of Chemical Technology and Metallurgy in Sofia. Since 2004 she got the educational and scientific degree PhD in Pharmacology, and in 2008 she was took the position of associated professor in the Central Laboratory of Biomedical Engineering ‘Prof. Ivan Daskalov’ at the BAS. During her study as PhD student (2002-2003) she won a fellowship by the prestigious German Alexander von Humboldt Foundation (Stability Pact). In the period 2005-2007 she worked as a contract agent and post-doc at the Joint Research Center of the European Commission in Ispra, Italy. The applicant was a lecturer on QSAR and molecular modelling in the regular course of the Faculty of Chemistry and Pharmacy at the Sofia University ‘St Kliment Ohridski’. She knows English and Russian fluently and uses Italian at the basic level. Mrs. Tsakovska was granted with award ‘Evrika” in 2004 and with award for Best Junior research project ‘Jung Scientists’ in 200 of the National Science Fund. Mrs. Ivanka Tsakovsta is a member of the Union of the Scientists in Bulgaria and the Chemoinformatics and QSAR Society.

In the application for the competition for the academic position ‘PROFESSOR’ 24 publications were included and 17 of them are in journals with Impact Factor (total IF=65.65); 14 are in journals of category Q1; 3 publications are in journals with SJR; 1 publication is in a conference proceeding (without IF/SJR); and 3 are book chapters. Within the criterion B4 (equal to habilitation thesis) 9 publications with IF are included and some of them in journals with impressive IF of 11. According to criteria G7 and 8, 11

articles in referred and indexed journals are included as well as 3 book chapters. The total number of the publications of the applicant are 66. Recorded citations are 610 (461 in SCOPUS). According to SCOPUS the h-index is 12.

As indicated in the publication list the first two papers are review articles and the same is true for publications with the numbers 8, 9, 17, 20, 23 and 24.

The scientific interests of associated professor Ivanka Tsakovska are in the field of computer aided drug design. Publication No 3 is devoted to the possibilities for combined inhibition of Hsp90 and the xenobiotic pump MDR1. Valuable scientific experimental studies were done on malignant cells from solid tumors and derivative cell lines with induced multidrug resistance were included, too. Publication No 4 is devoted to the toxicological evaluation *in silico* of PPAR γ agonists with regard to the relation between mode of action and occurrence of side effects. The topic of publication No 6 is similar and includes molecular dynamic study of the interaction of PPAR γ with the antidiabetic drug Rosiglitazone (Avandia) as well. This antidiabetic drug is controversial because of its unacceptable ratio between benefits and risks due to data for elevated frequency of cardiovascular complications. Publication No 7 is devoted to the PPAR γ receptors as well, and drug candidates such as Farglitazar are included, too. In publication No 5 molecular dynamic simulations of ligand interactions with the estrogenic receptor alfa (ER α) are analyzed. Publication No 10 studies the applicability of the Inter Criterial analysis for evaluation of scoring functions in docking using the software platform MOE. Similar investigations are described in publication No 11, where the docking simulations are directed towards the serine proteases thrombin and trypsin, which are important pharmacological targets. Publication No 12 reflects a complex, excellently performed and well planned comparative study of natural compounds and BRAF inhibitors (Vemurafenib and Vismodegib), which reveals possibilities for anti-melanoma activity of *Sylibum marinum* components. In publication No 13 a complex study of compounds and their derivatives from *Sylibum marianum* (L.) Gaertn. is described. Here the aim of the study is to perform a comparative analysis to predict the gastrointestinal absorption application of *in vitro* Parallel Artificial Membrane Permeability Assay (PAMPA) and *in silico* (QSAR) models. Publication No18 describes a pure *in silico* study of sylibin derivatives. Publication No 14 is of methodological relevance and describes the above mentioned methods with applicability in *in silico* toxicological studies of the gastrointestinal absorption. In publication No 15 some interesting experimental studies of natural saponins from *Astragalus corniculatus* are described in the STZ-induced diabetes mellitus in rats with regard to the possibilities to interact with PPAR γ receptors. Publication No 16 reflects *in silico* studies of the drug metabolism of a broad spectrum of compounds by the use of ACD/Percepta software as well as the expert systems Meteor Nexus and Derek Nexus. Publication No 19 describes combined QSAR modelling of the antioxidant activity of series of polyphenolic compounds (curcuminoids, chalcones, etc.). A comparative study of 300 bioactive compounds is described in publication No 21 by the use of QSAR and available data from PAMPA experiments.

Main scientific contributions of the applicant include *in silico* modelling of the interactions between small biologically active molecules and proteins. The developed models have a potential for applications in the field of the rational drug design, which is a traditional focus of the scientific group, where Mrs. Tsakovska works. Moreover, the obtained results can serve to predict toxic effects of medicinal compounds and chemicals aiming the assessment of chemical risk (incl. supporting the risk evaluation within the European legislations, e.g. REACH). In the latter field the applicant plays a leading role and has significant contribution to introduce it as a new one for the research group.

I accept the main scientific contributions, which can be summarized as follows:

1. Molecular modelling of ligands and their interactions with P-gp by identifying the potential binding domain of a new class of HSP90 inhibitors to P-gp transporter. In that case the author uses an older nomenclature of transmembrane ABC-transporters without distinct indication on MDR1, MRP1 or other protein.
2. Molecular modelling of ER α ligands with broadened pharmacophore model of its agonists, based on complexes of strong agonists and validated with molecular dynamic simulations. The model includes an additional pharmacophore element, which remains to be within the free hydrophobic area inside the binding domain of ER α .
3. Modelling of ligands' interactions (full agonists, antagonists) with PPAR γ aiming to predict hepatotoxicity (liver steatosis). I do not accept the statement in the contribution 2.2.3 "Development of toxicological pathways initiated by ligand-dependent dysregulation of PPAR γ ...", because here no specific discovery of new signaling pathways is aimed rather than finding of interconnectivity and co-dependence of known pathways in terms of non-alcoholic liver disease initiated by PPAR γ agonists in hepatocytes and PPAR γ antagonists in adipocytes. I would suggest the contribution summarized as: *in silico* prediction of molecular initiating events such as interactions of PPAR γ full agonists (in hepatocytes) and antagonists (in adipocytes).

Noteworthy, I have specific remark about the use of 'cancer cells' and 'anticancer drugs'. Their translations in Bulgarian are not correct.

My terminological remarks do not reduce the value of the contributions of the associated professor Ivanka Tsakovska and do not change my highly positive evaluation of her published results, some of them being of fundamental importance, especially that related to the PPAR γ receptor system.

Numeric criteria: fulfilment of national and specific institutional requirements to get the academic position PROFESSOR by the applicant: associated professor Ivanka Milosheva Tsakovska:

Indicator (alphabetic)	Minimal national requirements	Requirements in BAS	Applicant's results
A	50	50	50
Б	-	-	0
B	100	100	225
Г	200	220	252
Д	100	120	922
E	150	150	431
Additional requirements in IBPhBME-BAS		15 publications with IF	17 publications with IF H_{index}(SCOPUS)=12

The SCOPUS database indicates 461 citations of the publications of the applicant and this fact confirms their importance.

Associated professor Tsakovska participated in 6 national research and educational projects and in 2 international ones. She leaded 2 national projects and was leader of the team in one international project. The financial contribution of these grants is impressive.

Mrs. Ivanka Tsakovska is co-supervisor of one successfully graduated PhD student.

CONCLUSION

Taken together all advantages above, I am stating that the presented by associated professor Ivanka Tsakovska materials in the competition for the academic position 'PROFESSOR' surpass the minimal national requirements, meet and also surpass the specific ones in IBPhBME-BAS, and regarding the requirements in the specific groups 'B, Д and E' exceed many times over the required minimum. With the broadly diverse profile of scientific research activities associated professor Tsakovska has demonstrated ability to work in team and to participate in nationally and internationally granted pharmacological and toxicological studies. The young applicant's publication activity impresses with its high quality. Therefore I recommend to all members of the Scientific Jury to award associated professor Ivanka Milosheva Tsakovska the academic position PROFESSOR. I am convinced to vote with "YES".

Sofia

Signature:

Date: August 23, 2020

/Prof. S. Konstantinov, MD, PhD, DSc/