

To: Prof. Dr. Nikolay Lazarov
Chairman of the Scientific Jury in a competition for academic position "Professor" in the
scientific specialty "Pharmacology"
Institute of Neurobiology at the Bulgarian Academy of Sciences

REVIEW

Prof. Ivanka Ilieva Kostadinova, MD, PhD
Head of Department of Pharmacology and Clinical Pharmacology
Medical Faculty - Plovdiv University

By order № 274 dated 24.04.2019 from Prof. Dr. Reni Kalfin, director of INB-BAS, a composition of the Scientific Jury for a professor competition in the 7th area "Health and Sport", Professional Field 7.1 "Medicine" in the scientific specialty "Pharmacology" for the needs of the Department "Behavioral Neurobiology" at the Institute of Neurobiology, Bulgarian Academy of Sciences was appointed. The competition for academic position "Professor" was announced in State Gazette No. 10 from 01.02.2019 year.

In the announced competition participates Assoc. Prof. Ljubka Pavlova Tancheva, PhD from the Institute of Neurobiology, Bulgarian Academy of Sciences.

This review has been prepared in accordance to the Law of the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of the Academic Staff Development Law and the Regulations for the Conditions and the Procedure for Acquisition of Academic Degrees and Academic Position Occupation in the Bulgarian Academy of Sciences.

Assoc. Prof. Tancheva arranged the materials for the competition according to the requirements of the LDASRB and the INB Regulations. In the competition all documents are arranged in chronological order, which allows me accurately and objectively to make a general characteristic of the scientific, applied and pedagogical activity of the candidate. There are no data and documents regarding the procedure for acquiring the scientific diploma "Associate Professor" from 01.03.2011. However, this fact is noted in the CV of the candidate, in certificate №278/15.03.2019 of INB of Bulgarian Academy of Sciences and supplementary agreement to labor contract № 328/09.07.2018.

Brief biographical data of Assoc. Prof. Lyubka Tancheva

Assoc. Prof. Tancheva graduated as a Master of Pharmacy in 1975 at the Pharmaceutical Faculty of Medical University Sofia. For one year she worked as a master pharmacist in Pernik. From 1976 to 1987 she was an assistant in toxicology at the Department of Pharmacology and Toxicology of the Faculty of Medicine at the Medical University Sofia. Since 01.04.1987 she has been working at the Institute of Physiology (at present Neurobiology) at the Bulgarian Academy of Sciences consequently as a Research Associate II degree, Research Associate I degree and

Senior Scientist II degree. Since 01.03.2011 she has been an Associate Professor at the Institute of Neurobiology, BAS. Assoc. Prof. Tancheva's professional experience includes 44 years, of which 31 years, 11 months and 13 days at BAS - Institute of Physiology and Institute of Neurobiology. From January 13, 1983 Assoc. Prof. L. Tancheva has been a candidate of the pharmaceutical sciences with subject of dissertation "Influence of hydrocortisone and deoxycorticosterone on the activity of some drug metabolic enzyme systems". Assoc. Prof. Tancheva holds several post-graduate qualifications earned in 1988 (Vienna), in 1999 (Lithuania), in 2006 (Borovets). The main activities of the applicant are related to the management and implementation of tasks in research projects, training of PhD and MSc students. In 1988 Assoc. Prof. Tancheva specialized as a visiting scientist at the Institute of Pharmacology of the Slovak Academy of Sciences, Bratislava. In 1989 she held one-month specialization at Friedrich Schiller University, Jena, Germany and in 2009 specialized at Faraday Institute of Cambridge University. In 2015 and 2016 she was a guest professor at the Weizmann Institute of Science, Rehovot, Israel. The gained specializations abroad are proof for the international recognition and the professional qualities of Assoc. Prof. Tancheva in the scientific field in which she works. The candidate is a member of the Union of Scientists in Bulgaria, the Bulgarian Toxicological Society, the European Society of Toxicology, the International Toxicological Society, the Bulgarian Peptide Society, the Bulgarian Society of Toxicology, World Christian Doctors Network – Director for Bulgaria.

Academic work

Assoc. Prof. Tancheva has taught practical lab classes and lectures on "Pharmaceutical Toxicology" for students in Pharmacy from 11.06.1976 to 01.04.1987. As an assistant professor in the Department of Pharmacology and Toxicology at the Faculty of Medicine, Sofia Medical University, she holds lectures for postgraduate qualification of Master Pharmacies for "Side and Toxic Effects of Drugs". The candidate has not provided data on the workload hours as an assistant at the Faculty of Medicine at the Medical University, Sofia. Assoc. Prof. Tancheva has 10 years, 10 months and 20 days of work experience in the specialty as an assistant in the Department of Pharmacology and Toxicology at the Faculty of Medicine of the Medical University Sofia. Assoc. Prof. Lyubka Tancheva, has been supervisor to several PhD candidates - Eleonora N. Encheva (2009) acquired PhD in 2015, Stella T. Dragomanova (2014), Simona A. Miteva (2014), Svetlana M. Stoeva (2013), Julia I. Karaivanova (2019). Assoc. Prof. Tancheva is a guest professor at the Faculty of Mathematics and Physics, Southwest University "Neofit Rilski" in Blagoevgrad with additional labor contract № 589 from 15.03.2019. From 2018 to 2019 she held lecture courses on Drug Toxicology at the Faculty of Mathematics and Physics of the South-West University "Neofit Rilski" in Blagoevgrad.

During the post habilitation period, Assoc. Prof. Tancheva has been a supervisor to post graduate and master students from several prestigious universities: Sofia University - Biological Faculty, two students from the Pharmaceutical Faculty of Medical University Sofia one of which was an assistant at the Department of Pharmacology and Toxicology of the Faculty of Medicine at Sofia Medical University from 2015 to 2019, and three students from Sofia University from a Mentor Program in 2016. The participation of Assoc. Prof. Tancheva as a co-author of the textbooks in Pharmacology and Toxicology confirms her professionalism and pedagogical skills. Fluency in English and Russian languages helps her in raising her qualifications as a lecturer and scientist

and in updating her teaching materials. According to this index, Assoc. Prof. Tancheva covers the requirements for “Professor” of INB at the Bulgarian Academy of Sciences.

General description of the materials presented

In a common list of scientific papers, Assoc. Prof. Tancheva has stated:

1. Publications for Acquisition of the PhD title “Doctor” in 1982 - 2 publications in *Acta Physiol. Pharmacol. Bulg.*, 4, 36-42, 1978 and *Arch. Toxicol. Suppl.* 1.4, 68, 328-330

2. Publications for the Academic Position "Associate Professor", acquired in 2007:

a/ 5 publications in books and monographs (in one publication the candidate is the first author)

b/ Publications and abstracts in periodic journals – 44 (23 publications and 21 abstracts). In 12 of the publications Assoc. Prof. Tancheva is the first author. The applicant has not indicated the journals with their impact factor.

3. Publications in the competition for academic position "Professor" for scientific specialty "Pharmacology"

Publications in the competition for the academic position "Professor" in the specialty "Pharmacology" - 23 publications. Of these, 17 are in Impact Factor journals. Total Impact Factor - 21,095. Six publications are in SJR, total of 1.415. In Scopus there are 23 publications with the participation of Assoc. Prof. Tancheva, of which in 1 publication the candidate is the leading author. Assoc. Prof. Tancheva has a total of 45 participations in scientific forums in Bulgaria and abroad, of which 16 are abroad. Participations with posters in scientific forums in Bulgaria and abroad are 81. In 6 of them Assoc. Prof. Tancheva is the leading author. Assoc. Prof. Tancheva presents a list of publications and reports in unreferenced journals and collective chapters from a collective monograph in a total number of 13. This list also includes two publications No 6 and No 19, which are presented in a list of publications referred in world-wide databases (Scopus). The publications Tancheva L., Encheva E., Novoselski M., Petkov V., Klisurov R. “Sex-dependent effect of a new peptidomimetic on cognitive function of isolated rats maternal deprivation, *Scripta Scientifica Medica*, 44 (1), Supplement 1, 19-21, 2012 and Dragomanova S., Tancheva L., Georgieva M. Biological activity of myrtenal and some myrtenal-containing medicinal plant essential oils, *Scripta Scientifica Pharmaceutica*, 5 (2), 22-33, 2018 are excluded from a list of publications in scientific journals referred in a world-renowned databases, presented by Assoc. Prof. Tancheva. The total number of publications after earning the Academic Position "Associate Professor", from 2008 to 2019 is 23 articles in scientific journals, referenced in a world-renowned databases, and 13 publications in scientific publications not listed in a world-wide databases, a total of 36 publications, of which 17 in journals with IF and 6 in magazines with SJR. The number of citations after earning the title

“PhD” is 60 from Scopus. I accept the table presented by Assoc. Prof. Tancheva for the quoted and calculated points in the set of Index E.

Since 2008, Assoc. Prof. Tancheva has participated in 18 national projects and two international projects. She was also a leader of two international projects. The participation of Assoc. Prof. Tancheva in national and international projects and the management of such projects show her skills to work in a team, to lead and organize scientific research. This is proof of her professional and personal qualities.

Assoc. Prof. Tancheva has submitted a patent application No. 112806/25.09.2018 entitled "Adamantane derivative with antiviral and antiparkinsonian activity".

Assoc. Prof. Tancheva has indicated in the report on the contributions of her scientific works five directions:

- Directed synthesis and drug design for the selection of biologically active substances in vitro and in vivo;
- Neurobiological and psychopharmacological studies of newly synthesized analogues on experimental models of diseases with social impact;
- Experimental models for protection and therapy of neurodegenerative disorders with newly synthesized substances;
- Multitarget strategies in the treatment of neurodegenerative diseases with substances of natural origin;
- New mechanisms of neurodegenerative processes and social isolation.

In **Direction 1** (Articles 2,3, 5,6,7,8,10,12,13,14,25) the effects on training and memory of newly synthesized L-valine peptidomimetics (P-6 and M-6), canavanin and neurotensin analogues and new derivatives of galanthamine and amantadine are studied. An improvement in the memory functions of rodents from two newly synthesized isomeric L-valine peptidomimetics (P-6 and M-6) has been reported. These effects are related to the levels of neurotransmitters serotonin and acetylcholine. Original data on analgesic action and on learning and memory from cannavanin and neurotensin analogues have been identified. It was established for the first time that neurotensin analogues more easily cross the blood brain barrier than neurotensin. These data can be used in further studies in humans. The improved pharmacokinetics of the studied neurotensin analogues gives them an advantage over the referent neurotensin in terms of both therapeutic doses and adverse drug reactions. Genuine data are available for binding to three types of neurotensin receptors in rats and humans. For the first time effects on the cognition of new derivatives of galanthamine and amantadine as well as their toxicity in rodent experiments were studied. Galanthamine derivatives showed improvement in rat memory and significant

inhibition of brain anticholinesterase activity in contrast to amantadine derivatives having moderate antioxidant activity.

Direction 2 (Articles 6, 7, 14, 21). Experimental models of diseases with significant social impact such as aggressive behavior, social isolation, maternal deprivation, and autism were used to study the therapeutic effects of new valine and neurotensin derivatives. It has been demonstrated on a model of aggression by social isolation that newly synthesized L-valine peptidomimetics M-6 and P-6 modulate the altered memory functions in aggressive rodents, as their effect being dependent on gender and social isolation. Both peptidomimetics have opposite effects on serotonin levels. M-6 increases them while P-6 lowers them. The results obtained support the complex mechanism of action of M-6 and P-6, which includes not only the influence on neurotransmitters. Together with scientists from Israel, a new neurotensin analogue NT4 has been studied on a genetic model of autism. Scientific contribution is the established difference in the effects of NT4 on the social behavior of two mice species.

Direction 3 (Articles: 11, 14, 15, 18, 21). Experimental approaches for protection and treatment of neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease with newly synthesized substances. The importance of these studies is determined by the prevalence, the poor quality of life and the social significance of the above mentioned diseases. Parkinson's disease (PD) is the second most common neurodegenerative disease in the world. Parkinson's disease affects 1-2 per 1,000 of population. PD spread increases with age and it affects 1% of the population over 60 years of age.

As the disease progresses, the life quality of patients significantly worsens, patients' social contacts are disrupted. Non-motor symptoms of PD have become increasingly important for the treatment of the disease. Motor and non-motor features are already included among the supporting criteria. Cognitive deficits are one of the non-motor symptoms of PD, which may range from mild abnormalities in the ability of memorizing and training to severe impairment of intellectual functions and dementia. The study of two newly synthesized neurotensin analogues revealed the presence of prognostic effects on the memory of an experimental model of Parkinson's disease in rats. The neuroprotective and neuromodulatory effect of the analogues is more pronounced than that of neurotensin, which may be related to improved pharmacokinetic parameters of the analogues. Both analogs increase the dopamine content in the brain of rats with an experimental model of Parkinson's disease. This effect is more pronounced in NT. On a toxin-induced experimental model of Parkinson's disease in rats, a neuroprotective effect of an original newly synthesized molecule (Amantir) has been identified with improved neurobiological and biochemical effects. The neuroprotective effect of the new molecule is similar to the neuroprotective effect of amantadine in efficacy, but the therapeutic doses of Amantir are about 2.5 times lower than the reference, and the toxic doses are lower than those of amantadine. According to the researchers of importance to the neuroprotective effect of the new molecule is its antioxidant properties. The results of the Amantir study were submitted as a joint patent application from INB of the Bulgarian Academy of Sciences and the Southwest University in Blagoevgrad.

Direction 4 (Articles: 1, 4, 16, 17, 19, 20, 22, 23). Searching for and researching the pharmacological effects of compounds from plant origin and combinations of plant sources has a preference for the synthesis of new drug molecules (according to the WHO,

about 80% of the world's population uses prophylactic and therapeutic medicinal products of plant origin). These products have an easy and convenient route of administration that provides better patient involvement in the prophylaxis and treatment of various diseases. Due to the prolongation of life, the number of people with Alzheimer's disease, vascular dementia, social phobias and anxiety increases. The treatment of these socially significant diseases with traditional medicinal products is prolonged with many registered ADRs. About 44 million people are affected by Alzheimer's disease or dementia associated with the disease. Alzheimer's disease is the sixth leading cause of death in the United States. One out of 3 elderly people die with Alzheimer's disease or other dementia. Social anxiety disorder in the United States occurs in 7% of people. It is a risky factor for the subsequent depressive illness. These facts determine the demand for medicinal products that slow down the development of the disease and can be used prophylactically to preserve training and memory. Prevention and treatment of dementia and anxiety disorders will slow down the course of illness, improve quality of life, and reduce the mortality from these socially significant illnesses. In this scientific field, the studies are divided into: Natural compounds and Alzheimer's disease and Natural compounds and Parkinson's disease. Dementia and Alzheimer's disease have been investigated with myrtenal, ellagic acid and lipoic acid. The data from these experiments are the basis for a further study of the pharmacokinetic and pharmacodynamic characteristics of these compounds on experimental animals and humans with Alzheimer's disease. Under experimental conditions, it has been found that myrtenal slows the progression of Alzheimer's disease by exerting protective effects on the memory functions of experimental animals with an Alzheimer type dementia model. A complex mechanism of action of myrtenal has been established. In the experiments, it has been found that polyphenol ellagic acid improves memory of animals with a dementia pattern. The protective effect of ellagic acid on cognitive functions is enhanced under conditions of scopolamine induced oxidative stress. Ellagic acid increases the level of dopamine in the brain of animals with an experimental model of Alzheimer's disease. Original data on antioxidant mechanisms of neuroprotective action of lipoic acid in rats with experimental dementia induced by scopolamine were obtained. Lipoic acid has been found to significantly improve cognitive function and reduce oxidative lesions by restoring glutathione levels and activation of catalase and superoxide dismutase in three brain structures related to memory. Interesting data have been obtained for the effect of myrtenal, ellagic and lipoic acid on an experimental Parkinson's disease model. The levels of dopamine, acetylcholine, noradrenaline, adrenaline and serotonin have been investigated with myrtenal, ellagic and lipoic acid application.

Direction 5 (Articles: 6.7, 9, 11, 15, 16, 17, 18, 19, 21, 23)

For the first time it was investigated the dynamics of the brain plasticity to recover spontaneously over time, with early and later changes in the memory functions of animals treated with scopolamine. New relationships between the studied changes in oxidative status, anticholinesterase activity, and neurotransmitter levels in brain structures associated with memory as well as memory impairment, spatial orientation and motor coordination of animals in neurodegenerative processes have been identified.

The publication of experimental results in impact-factor journals is a criterion for the value of the research. The significance of developments in these areas is related to the social significance of Parkinson's disease and Alzheimer's disease, autism, anxiety.

Summarized Table of Indexes for Academic Position "Professor" of Assoc. Prof. Lyubka Tancheva

Index	Content	Index “Professor” INB-BAS	Assoc. Prof. Lyubka Tancheva
A	Index 1	50	50
B	Index 3 and 4	100	100- from monograph
C	Index 4,5,6,7,8,9,without those for Associate Professor and scientific title “Doctor”	220	337,28
D	Index 10, 11 and 12	120	540
E	Index	150	460
Total Points		640	1487,28

Index A: Doctorate work for the candidate of science Sofia 1982 "Influence of hydrocortisone and deoxycorticosterone on the activity of some drugs metabolizing enzyme systems" Scientific coordinator Prof. Tsanko Stoychev, PhD

Index B: Published monograph, not presented as habilitation work: Assoc. Prof. L. Tancheva, "Drug metabolism and oxidative stress in influenza virus infection. Experimental Approaches to Antioxidant Protection", 2019, 111 pages. The monograph corresponds to the requirements of the Regulations to the Law on Development of the Academic Staff in the Republic of Bulgaria.

Index C: Correction of the points given by Assoc. Prof. Tancheva was made. Two of the publications have been moved from a list of scientific journals referenced in world-renowned databases to a list of scientific publications not referenced in a world-famous database.
Index D: There is no change in the points submitted by Assoc. Prof. Tancheva on the table when submitting the documents.

Index E: Assoc. Prof. Tancheva has participated in 18 national projects since 2008. /270p./ Assoc. Prof. Tancheva is a participant in two international projects (40 points) and head of two international projects (80 points) for the same period of time. Supervisor of Doctoral Students / 30 points /. Scholar principal of one PhD student, who acquired the Doctor of Physical Education title- 40 points. Total points based on Index E = 460.

Recommendation: In order to make the documents easier to check when applying for a competition for academic positions, candidates should be registered with NACID. This will facilitate the verification and writing of an opinion or review for the participants in the competition in acquiring the academic title "Professor" at INB-BAS.

After carefully reviewing the research and teaching activities of Assoc. Prof. Lyubka Tancheva, I can summarize that the accumulated scores of Assoc. Prof. Tancheva for some of the indicators exceed those indicated in the requirements for choosing "Professor" in INB at the Bulgarian Academy of Sciences. As a result of complex scientific research, national and international projects, cooperation with scientists from universities from Bulgaria and abroad, Assoc. Prof. Tancheva has achieved original results with a contributive character in science and in applied science. Assoc. Prof. Lyubka Tancheva is an established professional, researcher, lecturer and scientific supervisor. She is a scientist with authority and international recognition.

Based on the reasons provided, I will vote positively to award the academic position "Professor" to Assoc. Prof. Lyubka Pavlova Tancheva, PhD. I would like to recommend to the honorable members of the scientific jury to appreciate the merit of the overall activities of Assoc. Prof. Tancheva in the competition for awarding the academic position "Professor" in the scientific specialty "Pharmacology" at the Department "Behavioral Neurobiology", Institute of Neurobiology at the Bulgarian Academy of Sciences.

06.06.2019
Plovdiv