

## **RECENSION**

from

**Prof. Dr. Krasimira Ilieva Ikonomova, PhD,  
National Transport Hospital - Sofia  
Head of Clinical Laboratory and Immunology  
regarding**

**Selection competition for the academic position " ASSOCIATE PROFESSOR",  
Field of higher education 7. Health care and sports, professional direction 7.1. Medicine, by  
scientific specialty CLINICAL LABORATORY, announced for the needs of Faculty of  
Medicine, Department of Clinical Laboratory - MU - Varna, published in the State  
newspaper, no. 59 of 26. 07. 2022**

By order No. 381/26.09.2022 of the Rector of the MU - Varna, I have been designated as an official reviewer. For participation in the competition, documents were submitted by Dr. Irena Dimitrova Ivanova - head of the Clinical Laboratory of UMBAL "St. Ivan Rilski" EAD - Sofia. Criteria for awarding scientific degrees and titles and occupying academic positions in the MU - Varna, which are in accordance with the minimum national requirements, have been applied to evaluate the scientific-research, teaching-teaching and diagnostic-treatment activities of the National Center for Information and Documentation (NACID). The tender documentation is complete and contains the necessary data according to the existing requirements.

### **Professional Development**

Dr. Ivanova graduated in medicine in 2003 at the MU - Plovdiv. From 2003 to 2005, she was a resident in the Internal Department of Pazardzhik General Hospital AD. From 2005 to 2009, she was a specialist in the Clinical Laboratory of St. Ivan Rilski General Hospital, Sofia. From 2009 to 2010, she was a Clinical Laboratory specialist in the Clinical Laboratory of UMBAL "St. Ivan Rilski". From 2010 to the present, she is the head of the Clinical Laboratory of the "St. Ivan Rilski" UMBAL. In 2009, Dr. Ivanova obtained a specialty in Clinical Laboratory, and from 2014 to 2016 she was a part-time doctoral student at the Department of "Clinical Laboratory and Clinical Immunology", specialty "Clinical Laboratory", MU - Sofia, UMBAL "Alexandrovska". In 2016, she successfully defended PhD thesis in the specialty Clinical Laboratory. In 2018, she obtained the specialty "Public Health and Health Management". From 2016 to 2021, Dr. Ivanova is a part-time assistant, specialty Clinical laboratory, Bulgarian and the English language in the Department of Clinical Laboratory, MU - Sofia. From 2016 until now, he has been a part-time teacher in the specialty "Medical Chemistry" and "Clinical Practicum" in the Faculty of Science and Mathematics, Department of Chemistry, USU "Neofit Rilski", Blagoevgrad. From 2021 - 2022, she is a part-time teacher at the Faculty of Chemistry and Pharmacy, Department of Analytical Chemistry, specialty "Clinical Chemistry", SU "St. Kliment Ohridski", Sofia.

### **Research activity**

Dr. Ivanova's scientific activity includes over 28 scientific articles in medical journals at home and abroad. She has 29 participations in international and national medical congresses and

conferences. One monograph has been published. Dr. Ivanova's research studies include the following scientific directions

### **Clinical - laboratory aspects in microelement analysis**

The laboratory aspects of the pre-analytical, analytical and post-analytical stages in the analysis of the trace elements copper and zinc are examined in detail in Dr. Ivanova's work. For the first time in the country, the biological variations of serum copper in healthy individuals were studied depending on the geographical location, smoking, alcohol use and physical activity. In the pre-analytical stage of trace element analysis, an important requirement is to protect the laboratory ware from contamination. In the works of Dr. Ivanova, a comparison was made between four types of test tubes widely used in practice for the analysis of copper and zinc. No clinically relevant differences in results were found for the respective micronutrients. All tested tubes are suitable for the assays, but it is necessary for each laboratory to validate the preferred vessels. This suggests that biological samples for clinical chemistry analysis can also be used for trace element analysis. There is no need to take material in a separate tube, which is beneficial both for the work in the laboratory and for the patient. During the study of copper in various biological matrices - serum, urine, liquor - the candidate paid special attention to standardizing the conditions in the pre-analytical stage. It is emphasized that 70-80% of errors in laboratory analyzes are precisely in the pre-analytical stage. Weaknesses in sample preparation for analysis and weaker automation of the pre-analytical stage are cited as the most common reasons. Regarding the analytical stage, Dr. Ivanova's research has validated methods for copper quantification - flame atomic absorption spectroscopy (AAS) and electrothermal AAS (ET - AAS). An immunoturbidimetric method for determining ceruloplasmin in serum was also verified. In the works of Dr. Ivanova, attention was paid to the proteins that help transport microelements - ceruloplasmin and albumin. Routinely in practice, ceruloplasmin is determined as a concentration (turbidimetric or nephelometric), but the need to determine the protein as an enzyme activity is increasingly emphasized. Ceruloplasmin exists in 2 forms: apoceruloplasmin - a protein not bound to copper and holoceruloplasmin - a protein bound to up to 6 atoms of copper. Copper ions are required for the activity of ceruloplasmin as a ferroxidase. In the works of Dr. Ivanova, it is proved that the enzymatic activity of ceruloplasmin gives more accurate information in determining the status of copper and the physiological fitness of the protein in performing its functions. In the development of the candidate, it is pointed out that microelement analysis is still limited to studying the deviations observed in rare diseases. The accumulation of more knowledge about the pathogenesis of these diseases will lead to the introduction of trace element analysis into routine practice. It is planned to introduce high-tech methods for analysis with the use of a smaller amount of biological material and shortened preliminary processing of the primary sample. Nanotechnology will be used as non-invasive approaches to obtain biological material.

### **Conditions associated with copper dyshomeostasis in the body**

In the works of Dr. Ivanova, it was pointed out that the classification of copper dyshomeostasis is still incomplete and there is no clear understanding of the distribution of copper ions at the cellular and systemic level. Modern terminology defines copper imbalance rather as toxic accumulation of non-ceruloplasmin-bound copper. Wilson's disease is a rare genetic disorder characterized by elevated levels of non-ceruloplasmin-bound copper and the

interest in the works of Dr. Ivanova is the study of vitamin D. Although our country has a prolonged solstice for more than 8 months of the year, the majority of the Bulgarian population is deficient in vitamin D. There is still no clarity about the influence of vitamin D deficiency on mother and fetus. The candidate studied healthy pregnant women and found that vitamin D levels in pregnant women were markedly higher than in non-pregnant women. It is likely that higher levels of vitamin D saturation in the maternal organism are a prerequisite for overcoming neonatal vitamin deficiency. When comparing healthy individuals and patients with autoimmune diseases, levels in the vitamin D-deficient zone were reported in both groups. The results indicate that the immunomodulatory effect of vitamin D may be a useful therapeutic tool in the treatment of various autoimmune conditions. In a number of studies by Dr. Ivanova, new and classic biomarkers of damage in patients with joint, kidney and liver diseases are compared. In patients with psoriatic arthritis, three new biomarkers - matrix metalloproteinase 3 (MMP3), vascular endothelial growth factor (VEGF) and cartilage oligomeric protein (COMP) were compared with the established inflammatory marker C-reactive protein. VEGF has shown the highest correlation with C-reactive protein, therefore it can be used as a potential biomarker in clinical practice. When comparing uromodulin with established laboratory parameters for the assessment of kidney damage, uromodulin is proposed as a potential marker for the diagnosis and early assessment of the progression of chronic kidney disease. As genetic markers of liver damage, the study of the PNPLA3 gene polymorphism, which is involved in the lipid metabolism of patients with obesity, hepatic steatosis and prediabetes, is proposed. Carriers of certain variants of the PNPLA3 gene are at higher risk of glucose disturbances, insulin resistance and metabolic syndrome.

The topic of the candidate's scientific works corresponds to the scientific specialty for which the competition has been announced. In the presented list for compliance with the minimum national requirements,

Dr. Ivanova has grouped her scientific works as follows:

**Indicators Group A**

Dissertation for obtaining the scientific degree "doctor" in the scientific specialty Clinical laboratory on the topic: Copper status - laboratory aspects and clinical application in some pathological conditions.

**Indicators Group B**

Monograph presented in connection with a habilitation procedure: Copper metabolism - physiological mechanisms and clinical applications.

**Indicators group G**

Publications and reports in scientific publications, referenced and indexed in world-famous databases with scientific information (Scopus and Web of science) - 12 items.

Publications and reports in non-refereed peer-reviewed journals or in edited collective volumes - 10 items.

**Indicators group D**

Citations or reviews in scientific publications, referenced and indexed in world-famous databases with scientific information (Scopus and Web of science) – 4 citations

The compliance of Dr. Ivanova's scientific output with the quantitative and qualitative criteria for awarding scientific degrees and titles and holding academic positions at the MU - Varna and their comparison with the minimum requirements of the National Center for Information and Documentation (NACID) is presented in table 1.

<b>Group of indicators</b>	<b>Content</b>	<b>Associate professor Number of points</b>	<b>Candidate's points</b>
<b>A</b>	Indicator 1	50	<b>50</b>
<b>B</b>	Indicators 3 and 4	100	<b>100</b>
<b>Г</b>	Sum of indicators from 5 to 9	200	<b>225,55</b>
<b>Д</b>	Sum of indicators from 10 to 12	60	<b>60</b>
			<b>Total: 435,55 p.</b>

**Tabl. 1**

It is clear from the attached table that the scientific production of the candidate meets all qualitative and quantitative criteria. The analysis of the works shows sufficient volume and quality of scientific production. 28 scientific papers were submitted for review in the competition. In 48% of these scientific publications, Dr. Ivanova is independent or first author, in 20% she is second author. The candidate's presented list of 29 printed abstracts (14 in Bulgaria and 15 abroad) of scientific reports from participation in congresses confirm her scientific research activity. Eleven of Dr. Ivanova's scientific works have been cited 42 times in Bulgarian and foreign scientific sources. Dr. Ivanova is a member of the Bulgarian Clinical Laboratory Society. She is a member of the European Society of Clinical Chemistry and Laboratory Medicine and the Russian Federation of Laboratory Medicine. Dr. Ivanova is a member of the editorial board of the journal "Pathology and Laboratory Medicine".

### **Teaching and learning activity**

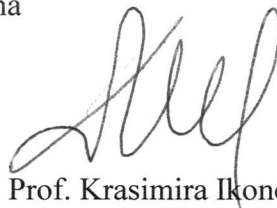
Dr. Ivanova's academic and teaching activities are related to the educational process at the University of Sofia - Sofia, "Neofit Rilski" High School - Blagoevgrad and "St. Kliment Ohridski" University - Sofia. She has developed curricula and programs, a lecture course and exercises. The study and workload includes: MU - Sofia, Clinical Laboratory, III course, English language, Medicine - 258 study hours, Clinical laboratory, III course, Bulgarian language, Medicine - 606 study hours, Clinical laboratory, V course, Bulgarian language, Medicine - 90 study hours. "Neofit Rilski" UZU - Blagoevgrad, Medicinal Chemistry, 4th year, Bachelor - 465 hours, Clinical practicum - 135 hours. SU ..St. Kliment Ohridski" Pharmacy in English, 60 study hours.

### **Conclusion**

Based on an analysis and assessment of the attached documentation, I consider that Dr. Ivanova fully meets the requirements of the law on the development of the academic staff in the

Republic of Bulgaria and the qualitative and quantitative criteria for the development of the academic staff specified in the regulations of the MU - Varna with the criteria of NACID, for acquiring the academic position of "associate professor". The complex evaluation of the candidate's qualities gives me reason to recommend to the members of the respected scientific jury to choose Dr. Irena Dimitrova Ivanova, PhD for ASSOCIATE PROFESSOR in clinical laboratory at MU "Parashkev Stoyanov" - Varna

02.11. 2022



Prof. Krasimira Ikonomova, PhD