

## REVIEW

**by competition for the academic position of professor  
in the specialty of Clinical Hematology for the needs of the Second Department of  
Internal Medicine, Department of Hematology  
to the Faculty of Medicine of the Medical University  
Prof. Dr. Paraskev Stoyanov – Varna**

Regarding: competition for the academic position of professor in the scientific specialty Hematology and blood transfusion in the field of higher education 7. Health care and sports, professional direction 7.1. Medicine, for the needs of the Second Department of Internal Medicine, Department of Hematology at the Faculty of Medicine, MU - Varna, announced in SG no. 102/23.12.2022

Candidate (single): Associate Professor Ilina Dimitrova Micheva, Ph.D

Reviewer: Prof. Valeriia Ignatova Kaleva, Ph.D

Member of the Scientific Jury under order No. R-109-144/23.02.2023 of the Rector of the MU - Varna, designated as a reviewer

### **BIOGRAPHICAL DATA, PROFESSIONAL AND ACADEMIC DEVELOPMENT**

Assoc. Prof. Ilina Micheva is a graduate of the First Language High School with English language studies Hr. Kabakchiev, city of Varna. She completed his medical education with honors in 1993 at the Higher Medical University - Varna (series A 92000379). In 1998, she acquired a specialty in internal medicine (series AC #005436). Since 2000, she has been a full-time PhD student at the University of Patras, Greece, Department of Hematology, Department of Internal Medicine with a scholarship from the Hellenic Government Scholarship Foundation (IKY). In 2005, she defended a dissertation on the topic "The role of dendritic cells in the hematopoietic defects in patients with Myelodysplastic Syndrome". In the period 2000-2005, she worked in the Scientific Laboratory at the Department of Hematology of the Medical University of Patras and participated in a number of research projects in the field of hematology, immunology, cell and gene therapy.

Since 2006, she has been working in the Clinic of Clinical Hematology of UMBAL St. Marina, Varna. She acquired a specialty in clinical hematology in 2006 (series MUB-207 #1457). During the period 2014-2022, she was the head of the Department of Stem Cell Transplantation at the same clinic, and from 2019 she was also appointed as the head of the clinic. Since 2008, has been successively an assistant, chief assistant and associate professor at the Department of Internal Medicine, Department of Hematology at the Medical University - Varna, and since 2020 she has been the head of the Department of Hematology at the Second Department of Internal Medicine. In 2022, she defended his master's degree in health management (No. 049821).

Assoc. Prof. Micheva participated in a number of trainings on various topics in the field of clinical hematology and stem cell transplantation. There have been specializations in hematopoietic stem cell transplantation at SBALHZ - Sofia, Hannover Medical University, Germany and the University of Ljubljana, Slovenia. In 2016, she acquired a professional qualification in the highly specialized activity of Stem Cell Transplantation at the Medical University - Varna.

Assoc. Prof. Micheva's scientific interests and main contributions are mainly in the field of myelodysplastic syndrome (MDS), myeloproliferative neoplasia (MPN), lymphoproliferative diseases, acute leukemia, hematopoietic stem cell transplantation (HSCT), infectious complications in patients with oncohematological diseases and after HSCT.

Assoc. Prof. Micheva is the deputy chairman of the Management Board of the Bulgarian Medical Society of Hematology, chairman of the scientific group on myeloproliferative neoplasms and myelodysplastic syndromes and a member of the working group on hematopoietic stem cell transplantation at the same society. Since 2019, she has been a member of the Expert Council for Clinical Hematology at the Ministry of Health. Assoc. Prof. Micheva is the main coordinator for Bulgaria of the EUMDS register and an expert at the Program Committee of the European Commission. She is fluent in English, Greek and Russian, written and spoken.

## RESEARCH ACTIVITY

### • *Scientific indicators*

In the current competition, the candidate participated with a total of 97 scientific papers, of which 43 were full-text articles, 46 scientific announcements and reports with printed summaries at international and national scientific forums, 9 participations with reports at international and national scientific forums, a dissertation work for the acquisition of the National Academy of Sciences PhD and co-author of a clinical hematology manual. Of the attached lists of evidence, No. 24 and No. 25 are poster publications and cannot be accepted as actual full-text articles.

The presented scientific works, according to the requirements of the procedure, were published after the appointment of AD associate professor. A detailed summary of the available works is presented, as well as free links to most of them. In addition, a reference is presented for the scientific works for the appointment of AD associate professor, which is also available on the website of the MU - Varna.

The candidate provides a total of 10 publications, referenced and indexed in global databases (Scopus/WebOS) according to criterion B4 (required monographic work or at least 10 equivalent publications, indexed and referenced), thereby meeting the requirements under this criterion (156.02 items).

According to G7 criteria, it presents a total of 11 publications, published in scientific publications, referenced and indexed in world-renowned databases with scientific information. The publications provided have a point equivalent exceeding the requirements (219.05 points). A total of 12 publications and scientific works with a point equivalent exceeding the requirements (172.22 points) were presented according to G8 criteria. According to criteria group D, the candidate presents a total of 188 citations with a point equivalent of 2635 points. Additionally, Assoc. Prof. Micheva presents 17 full-text publications in scientific journals, which are beyond the minimum scientometric requirements for the position of AD professor.

Table 1. Compliance with the scientometric requirements of the MU - Varna for holding the academic position of professor according to the presented academic reference of the library at the MU - Varna.

Group of indicators	Required number of points	Number of points based on evidence presented by the applicant
A	50	50
B	100	156,20
G	200	391,27

D	100	2635
E	100	361,2

From the presented extended habilitation reference, the total number of scientific works is 171, of which 74 full-text publications and 97 scientific communications and reports with printed abstracts at international and national scientific forums, cited a total of 275 times with a total impact factor of 302,462 and h-index -7 (Google scholar):

- 13 publications in international journals with IF, indexed and referenced in the scientific databases Scopus and/or Web of Science
- 36 publications in non-IF journals, indexed and referenced in the scientific databases Scopus and/or Web of Science
- 25 publications in non-refereed journals with scientific review
- 61 scientific communications and reports at international forums with printed abstracts
- 36 scientific announcements and reports at national forums with printed abstracts.

• ***Thematic directions and contributions***

Assoc. Prof. Micheva's scientific career began in 1994 with participation in a scientific project of the Scientific Research Fund at the Ministry of Health on the topic of Clinical aspects of intercellular adhesions in pleural inflammation and tumor metastasis. After acquiring a specialty in internal medicine, in the period 2000-2005, scientific activity continued as a full-time doctoral student at the Department of Hematology, Department of Internal Medicine of the Medical University of Patras, Greece with a scholarship from the Hellenic Foundation for State Scholarships (IKY). During her doctoral studies, she mastered the principles of flow cytometry and fluorescence-activated cell sorting, as well as some specific research methods in the field of cell and molecular biology. During the mentioned period, she participated in the development of numerous research topics and projects in the field of hematology, immunology, dendritic cells, cell and gene therapy, culminating in publications in prestigious international journals. Developments on the mentioned projects have been awarded with three first prizes of the Hellenic National Congress of Hematology (2002, 2003 and 2005), as well as with the prestigious Akagatos Goutas Award of the Hellenic Society of Hematology. Since 2006, scientific interests have been focused on the biological and clinical aspects of myeloid and lymphoid neoplasias, and since 2015 on hematopoietic stem cell transplantation.

The main contributions of Assoc. prof. Micheva's scientific works after 2016 can be summarized in the following thematic areas: myelodysplastic syndromes, myeloproliferative neoplasias, lymphoproliferative neoplasias, acute myeloid leukemia, multiple myeloma, hematopoietic stem cell transplantation, infectious complications in patients with oncohematological diseases and after transplantation of hematopoietic stem cells.

**Myelodysplastic syndromes (10, 16, 17, 28, 37, 38, 39, 53, 77)**

For the first time in our country, an analysis of cases with chronic myelomonocytic leukemia is presented, assessing prognosis, survival and the risk of transformation into acute leukemia. The country's first large-scale study of 219 patients with MDS was conducted and overall survival was assessed according to socio-demographic characteristics, FAB and WHO2016 classifications and risk group determined by IPSS, IPSS-R and WPSS.

For the first time in our country, the role of the comorbid index and the degree of "vulnerability" for the outcome of MDS is examined. The Charlson comorbidity index, pre-HCT patient-specific comorbidity index (HCT-CI), MDS-specific comorbidity index (MDS-CI), adult

comorbidity evaluation 27 (Comorbidity Evaluation-27 (ACE-27)). Their use allows refinement of prognostic assessment and survival in patients with MDS.

The role of epigenetic mechanisms, the role of micro-RNAs and molecular genetic disorders in the pathogenesis of MDS is presented. Modern concepts of therapeutic influence through the search and development of new targeted therapies are presented.

### **Myelofibrosis (5, 8, 21, 25, 40, 41, 51, 68, 74, 83, 84)**

For the first time in Bulgaria, the role of regulators of iron metabolism (hepcidin and inflammatory cytokines (IL-6 and IL-8)) in the pathogenesis of the anemia in patients with myelofibrosis (MF) was studied. For the first time, a risk model in MF including hepcidin, IL-6 and IL-8 is developed and its relevance in the context of clinical and laboratory characteristics of patients is analyzed. The results are presented in 10 publications.

For the first time, a three-year multicenter experience with ruxolitinib in patients with primary myelofibrosis is presented.

### **Acute leukemia (6, 13, 18, 30, 33, 43, 47, 66, 73, 90)**

An original approach is published for the first time in the treatment of a patient with Ph + ALL with T315I mutation with inotuzumab plus ponatinib, followed by allogeneic HSCT and maintenance therapy with ponatinib.

A retrospective study was conducted on newly diagnosed adult patients with AML who underwent conventional cytogenetic analysis and 46% had an abnormal karyotype.

The first retrospective study for Bulgaria, aiming to evaluate the efficacy of azacitidine treatment in patients with MDS and AML is presented. Azacitidine therapy is an option in elderly patients with high-risk MDS and AML, with median overall survival of 12.6 and 5.4 months, respectively.

The possibilities of methods such as SNP-microarray, NGS, Sanger sequencing, multiplex ligation-dependent probe (MLPA) and PCR for genetic-molecular research in AML have been examined.

### **Multiple myeloma (3, 14, 15, 19, 27, 49, 50, 52, 60, 61, 62, 64, 65)**

A retrospective analysis of the cytogenetic profile of patients with newly diagnosed multiple myeloma (MM) was performed. All patients were evaluated by conventional cytogenetics and fluorescence in situ hybridization (FISH). The study confirms the informative value of these methods.

The pathogenetic mechanisms for the development of myeloma-induced bone disease (MBD) have been investigated. Multiple intra- and intercellular signaling pathways such as RANKL/RANK/OPG, Notch and Wnt/ $\beta$ -Catenin signaling have been examined, as well as a variety of chemokines, signaling and effector molecules such as DKK-1, sclerostin, periostin, activin A and transcription factors. Serum levels of periostin, sRANKL, osteopontin, sclerostin and DKK-1 in newly diagnosed MM patients were evaluated.

Results from the PORT study (NCT04412707) are presented, which aimed to compare the PK of melphalan after central and peripheral administration of melflufen and to assess the local tolerability of peripheral administration of melflufen. Systemic exposure to melphalan was found to be similar after melflufen PVC and CVC administration.

The role of 18F-FDG PET/CT in the diagnosis and staging of newly diagnosed MM patients was evaluated.

The experience with Bortezomib maintenance therapy in patients with MM after achieving complete response (CR) or very good partial response (VGPR) is presented.

### **Infectious complications in patients with oncohematological diseases and after hematopoietic stem cell transplantation (2, 4, 7, 22, 26, 46, 63, 71, 83)**

For the first time, the etiological spectrum and antibiotic resistance of the bacterial pathogens causing blood infections in patients with oncohematological diseases from the Hematology Clinic of UMBAL St. Marina, Varna for a six-year period (2015-2020) and 2828 blood cultures were examined. For the first time in our country, a study of slime production in *Staphylococcus* spp. isolates associated with bacteremia in patients after THSC is being conducted.

For the first time in Bulgaria, the clinical significance of the test for *Aspergillus* Galactomannan antigen (GM) in the diagnosis of invasive pulmonary aspergillosis (IPA) in patients with hematological malignancies, including patients undergoing HSCT, was assessed.

For the first time in our country, the species diversity of clinically significant *Staphylococcus* spp. isolates obtained from blood cultures of patients with a central venous catheter (CVC) after HSCT were tested for susceptibility to a range of antimicrobial agents. The spectrum of multidrug-resistant (MDR) bacteria, intestinal colonizers, was investigated.

The *in vitro* activity of ceftazidime-avibactam (CZA) against extended-spectrum beta-lactamase-producing (ESBL) and carbapenem-resistant (CR) Gram-negative bacteria recovered from blood and fecal samples of patients after THSC was analyzed.

The species diversity and profile of resistance to antimycotic drugs of *Candida* spp. isolates obtained from clinical materials of patients after HSCT were analyzed.

### **Hematopoietic stem cell transplantation (1, 45, 54, 57, 72, 75, 76)**

For the first time, the results of the application of autologous HSCT in patients with MM, treated in the transplant department at St. Marina, Varna for a period of 6 years. The efficacy and safety of ATHSC in patients with MM has been confirmed, demonstrating that achieving CR+VGPR before ATHSC is a factor in prolonged OS and PFS.

Outcome after haploidentical stem cell transplantation in a series of 11 patients was evaluated. An original study evaluated the outcome of patients with refractory non-Hodgkin's lymphomas (NHL) and Hodgkin's disease (HD) after salvage ATHSC. High-dose chemotherapy and ATHSC are still the modality of choice in patients with refractory lymphoma. Consolidation strategies after ASCT can significantly improve the outcome in bailout settings.

The results of the application of chemo-G-CSF protocols for the mobilization of peripheral stem cells in 40 patients with lymphomas who received ASCT in the transplant department of the clinic of hematology, UMBAL St. Marina, Varna. The results show that chemo-G-CSF protocols have comparable efficacy with acceptable toxicity and are superior to CY-G-CSF for stem cell mobilization in patients with lymphomas.

A complex case of successful desensitization in a patient with AML and donor-specific antibodies before haploidentical allogeneic hematopoietic stem cell transplantation is presented.

### **Lymphoproliferative neoplasms (9, 12, 23, 31, 32, 34, 35, 36, 55, 56, 58, 59, 81)**

The advantage of 18F-FDG PET/CT in the diagnosis and follow-up of a patient with generalized diffuse large B-cell lymphoma (DLBCL) with multiple extranodal lesions has been demonstrated.

A case is presented of a 63-year-old female patient with a severe form of myasthenia gravis (MG), possibly related to CLL relapse, treated with combined targeted and immunotherapy.

In the first multicenter study in the country, the "Bulgarian experience" in the treatment with Brentuximab Vedotin of patients with refractoriness or relapses after ASCT with Hodgkin's lymphoma was analyzed. The results obtained show an improvement in the therapeutic response, a prolongation of the time to progression and an increased overall survival with treatment with Brentuximab Vedotin.

The level of VEGF expression in 60 newly diagnosed patients with aggressive and indolent NHL was investigated, and significantly higher levels of VEGF were found in patients compared to healthy controls, in indolent vs. aggressive lymphomas and in high vs. normal LDH values.

For the first time in Bulgaria, the level of platelet-neutrophil complexes (PNC) was investigated in 88 patients with indolent and aggressive NHL and their relationship with clinical and laboratory indicators. Significantly higher levels of PNC were found in NHL patients compared to healthy controls, as well as in aggressive vs. indolent NHL.

A rare case of a young woman with Langerhans histiocytosis (LCH) with multisystem involvement including bone, orbit, lung, and central nervous system is reported.

For the first time in Bulgaria, the efficacy and safety of Truxima™ treatment in combination with chemotherapy was evaluated in 51 patients with NHL and CLL.

Two reviews present the therapeutic options following the inclusion of the monoclonal antibodies Polatuzumab vedotin and Obinutuzumab in the treatment of diffuse large B cell and follicular NHL.

#### **Others (11, 20, 24, 29, 44, 48, 86, 87, 91, 92, 93, 94)**

A retrospective analysis of all bone marrow samples was performed in the Laboratory of Medical Genetics of UMBAL St. Marina, Varna for a period of ten years. A total of 2653 outcomes from patients aged 0-93 years were evaluated. The most common indication is hematological diseases, occupying 90.9% of all examined samples.

The possibility that bispecific antibodies (BsAbs) induce reactivation of existing tumor-specific T lymphocytes was investigated. In an experimental model, a TCR-dependent blast-T cell interaction was studied after in vitro incubation with CD3xCD123 BsAb on bone marrow from AML patients.

The putative protective role of HLA-II alleles for the development of MPNs driven by JAK2V617F and CALRmut was investigated by NGS typing in 139 JAK2V617F positive, 46 CALR exon 9 positive MPN patients and 1083 healthy controls.

Over a period of 10 years, 1554 bone marrow karyotypes performed on both children and adults with hematological diseases were analyzed and three cases of unsuspected chromosomal disorder were identified.

Experience is shared with rare clinical cases of CLL, POEMS syndrome, Hodgkin's disease, gelatinous transformation with AML in a patient with post-thrombocytopenic MF, ALL, mantle cell lymphoma and MDS.

#### **• *Participation in projects***

Assoc. Prof. Micheva has participated in 17 research projects, of which eight are completed and nine are current. She is the supervisor of one of the graduate projects, which concluded with a successfully defended Ph.D. Three of the projects are international. Scientific research projects are in the areas of intercellular adhesions in pleural inflammation and tumor metastasis, pathogenesis of MDS, dendritic cells, invasive bacterial infections in patients after autologous and allogeneic bone marrow transplantation, creation of a database of blood donors in the Republic of Bulgaria for markers of transmissible infections, scientific approaches to complementary and alternative medicine, involvement of inflammatory cytokines and hepcidin in the pathogenesis of MF.

Assoc. Prof. Micheva's research interests extend to other areas of hematology, which is evident from the currently active projects: Role of plasma micro-RNAs as epigenetic markers in patients with MDS and MM; Serum Histones as Novel "Liquid Biopsies" in Human Malignancies; Molecular genetic analysis of newly diagnosed patients with acute myeloid leukemia; Novel molecular biomarkers to assess bone disease in multiple myeloma and One

Health-integrative research and scientometric approaches for better quality of life. Assoc. Prof. Micheva is a post-doctoral student at the TRANSTEM project, funded by the European Union, Horizon 2020.

Assoc. Prof. Micheva is the main coordinator for Bulgaria in a prospective, multicenter European registry for newly diagnosed patients with MDS. She is also a researcher in the unique for Bulgaria study of the safety and efficacy of immunoablative non-myeloablative autologous bone marrow transplantation in patients with multiple sclerosis.

### **GUILD AND EXPERT ACTIVITY**

Assoc. Prof. Iliana Micheva is deputy Chairman of the Board of Directors of Bulgarian hematology association. She is the Chair of the Scientific Group on Myeloproliferative Neoplasias and Myelodysplastic Syndromes and a member of the Working Group on Hematopoietic Stem Cell Transplantation of the same association.

She is the chairman of three working committees for the evaluation of health technologies at the NSCR and since 2019 she is a member of the Expert Council on Clinical Hematology at the Ministry of Health.

Assoc. Prof. Micheva is a reviewer in a number of journals such as British Journal of Hematology, Scripta Medica, Journal of IMAB, Folia medica, Asian Hematology Research Journal, Turkish Journal of Hematology. She is a reviewer for Scientific Research in the Projects Department of the Medical University of Plovdiv, a reviewer for the Scientific Research Fund of the Ministry of Health, a reviewer for D. Vankova's monograph: Integrative Medicine: History, conceptual development, informed choice and intelligent investment in the future. Varna, MU-Varna, 2021.

She is part of the editorial staff of Schwartz's Principles of Surgery, Ninth Edition and a member of the editorial board of the journal Hematology and Pro medica.

Assoc. Prof. Micheva is the main coordinator for Bulgaria of the EUMDS register and an expert at the Program Committee of the European Commission and at the AML Community of excellence.

She is the chairman of the Blood and Blood Products Committee at the UMBAL St. Marina, Varna.

Participated as the chairman and member of a scientific jury for the appointment of the academic positions of professor, associate professor, chief assistant and acquisition of the scientific degree doctor at the University of Varna, University of Pleven, University of Plovdiv and Academy of Medical Sciences Sofia.

The importance of Assoc. Prof. Micheva's research activity is also evidenced by the Akagatos Gutas awards of the Hellenic Society of Hematology for 2005 and the three first prizes of the Hellenic Society of Hematology for the best presentation for 2002, 2003 and 2005.

Assoc. Prof. Micheva was awarded the title of Doctor of the Year in the field of Innovations for 2018 and 2019 by the Bulgarian medical society, Varna.

### **EDUCATIONAL AND TEACHING ACTIVITY**

Assoc. Prof. Iliana Micheva has over 15 years of teaching experience, of which 7 years as a qualified teacher. Since 2020, he is the head of the Clinical Hematology Department at the Second Department of Internal Medicine. As part of her teaching experience, she combined lecturing and practical exercises with English-speaking (AEO) and Bulgarian-speaking (BEO) medical students (academic reference provided). Independently develops a lecture course for AEO and BEO medical students and conducts semester and state exams. According to the presented reference, her educational workload significantly exceeds the norm for the relevant position, which shows commitment to the educational process and a desire to bring the training in the discipline to a relevant and high clinical level.



Assoc. Prof. Micheva is the supervisor of two interns who have successfully acquired the Clinical Hematology specialty and three active interns (reference provided).

Assoc. Prof. Micheva is the scientific supervisor of three successfully defended doctoral students - Dr. Stella Dimitrova (specialty Clinical Hematology), Dr. Merlin Efraim (specialty Clinical Hematology) and Dr. Denis Niazi (specialty Microbiology and Virology).

She is also the supervisor of seven current PhD students. Five of the doctoral theses are in direction 7.1 Medicine, scientific specialty Hematology and blood transfusion and two - in direction 4.3 Biological Sciences at the Department of Medical Genetics.

### **PERSONAL IMPRESSIONS OF THE CANDIDATE**

Assoc. Prof. Micheva is an excellent specialist, erudite teacher and thorough researcher with extensive clinical and pedagogical experience. As her university professor and longtime colleague, I have witnessed her upward professional and scientific growth in both clinical hematology and stem cell transplantation. She continues to impress me with her enviable work ability and leadership skills to achieve a highly professional and equal combination of the highly specialized and multifaceted clinical, educational and scientific activities in the entrusted clinic.

### **CRITICAL NOTES AND RECOMMENDATIONS**

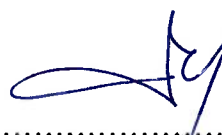
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### **IN CONCLUSION,**

The candidacy of Associate Professor Iilina Micheva fully meets the state and institutional requirements for holding the academic position of Professor. Her scientometric indicators in some of the criteria exceed the mandatory requirements many times over. The scientific activity and achievements are wide-ranging and have been realized both in independent studies and in studies with compact author groups, incl. within large-scale projects. Assoc. Prof. Micheva's participation in multidisciplinary teams, both at the level of scientific and at the level of expert activity, makes her a recognizable and reference specialist in the specialty of Clinical Hematology. Apart from the purely scientometric data and the required documentary attributes, Assoc. Prof. Micheva also implements a corresponding professional and career development, fully corresponding to what is expected for holding the title of Professor. In his work with students, specialists and doctoral students, the candidate has continuous commitment and control to the teaching activities in the Department of Hematology, which is an inalienable part of the content of AD Professor.

In the context of everything stated in this review, I recommend the Scientific Jury to award Assoc. Prof. Iilina Dimitrova Micheva, PhD, the academic title of Professor in the scientific specialty of Clinical Hematology for the needs of the Second Department of Internal Medicine at the University of Medicine - Varna and Clinic of Clinical hematology at UMBAL "Sveta Marina" - Varna.

25 April 2023



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Prof. Valeriya Kaleva, Ph.D