

OPINION

by assoc. prof. Ekaterina Boyanova Softova-Zlatarova, MD, PhD

Scientific speciality "General and Clinical Pathology", MC "CityLab", JSC, Varna

Regarding: Competition for the academic position "ASSOCIATE PROFESSOR" in General and Clinical Pathology, in the field of higher education 7. "Health and Sports" professional direction 7.1. "Medicine", in the scientific specialty "General and Clinical Pathology", announced in "State Gazette" No. 28 / 28.03.2023 for the needs of the Department of "General and Clinical Pathology, Forensic Medicine and Deontology", MU-Varna and the Clinic "General and Clinical Pathology" at UMHAT "Sv. Marina" JSC, Varna.

By decision of a meeting of the FC of the Faculty of Medicine at MU-Varna according to protocol No. 02/04.05.2023 and by order No. P-109-266/25.05.2023 of the Rector of MU-Varna, I was elected as an external member of the scientific jury, and according to protocol No. 1/07.06.2023 of the meeting of the National Academy of Sciences, I am appointed to prepare an opinion on the procedure for occupying the academic position of "Associate Professor" in the specialty "General and Clinical Pathology" with an applicant according to the announced competition Kalin Petrov Kalchev, MD, PhD. assistant in the Department of "General and Clinical Pathology, Forensic Medicine and Deontology" at the Medical University of Varna. According to the regulation, the applicant has submitted a complete set of materials for the competition, on paper and on electronic media, including all the necessary documents specified in the Regulations for the conditions and procedures for acquiring scientific degrees and occupying academic positions at the Medical University – Varna.

Brief biography and career development of Kalin Petrov Kalchev, MD, PhD

Dr. Kalin Petrov Kalchev was born on 19.07.1974 in the town of Dobrich. After completing his secondary education, he entered MU-Varna as a student, where in 2001 he graduated as a medical doctor with the educational and qualification degree "Master" in "Medicine" /diploma series MU, №020638/2001/.

From December, 2001 till August, 2005 Dr. Kalchev works successively as a resident doctor in the Surgical dept. at the MHAT Tervel, a general practitioner in the village of Telerig, Dobrich distr. and resident doctor in the Department of Clinical Pathology at MHAT Dobrich.

Since August, 2005, with a short break, he is a resident in the Clinic for General and Clinical Pathology at the MHAT "Sv. Marina", Varna. Since July 2006 he was elected as an assistant professor at the Department of "General and Clinical Pathology, Forensic Medicine and Deontology" at the Medical University of Varna, where he's been working with a short break until now, as on 11.06.2021, when Dr. Kalchev was elected as chief assistant professor in the Department.

From February, 2008 till December 2012, he also held the position of donor-coordinator for the donation of bone and joint complexes at the "Osteocenter Bulgaria" tissue bank, Varna branch. From March, 2013 till July, 2016, with breaks, Dr. Kalchev worked additionally as a pathologist in England, Scotland, Wales and Sweden. From 15.08.2017 till 07.02.2018 he was

the head of the Department of Clinical Pathology at MHAT "Sv. Ivan Rilski", Razgrad, and from 12.02.2018, Dr. Kalchev works under a second contract as the head of the Department of General and Clinical Pathology, MHAT Dobrich.

Since 2010, Dr. Kalchev has a recognized specialty in "General and Clinical Pathology"/certificate with reg. No. 015143/20-01.20210, MUV series, No. 2939/.

Dr. Kalchev holds a number of certificates for individual trainings and courses held at home and abroad to increase his qualifications on various topics in the field of medicine: dermatopathology, thyroid diseases, placental pathology, tumors of the nervous and bone systems, melanocytic nevi and malignant melanomas, etc.; he participated in scientific-practical seminars related to: "IHC assessment of PD-L1 expression in non-small cell lung cancer;"/ held in Kassel, Germany;/ training on interpretation of HER2 and HER2 Dual ISH in stomach and breast cancer; educational courses in the field of lung and breast pathology (held in Ljubljana and Golnik, Slovenia); donor-coordinator training programs to the "Osteocenter"; training on "Working with video training systems"; qualification course "Pedagogical foundations of academic teaching" etc.

On 09/03/2020, Dr. Kalchev successfully defended his dissertation thesis on the topic "RIP3 Marker Expression for Necroptosis in Cases of Prostate Cancer" and acquired the ESD "Doctor" in the scientific specialty "General and Clinical Pathology", diploma No. 398 /29.12.2020.

Dr. Kalchev has 28 published scientific works in home and international journals, 26 in co-authorship and 2 as an sole author, some of which are referenced in the world-acknowledged Web of Science and Scopus databases. According to the Google Scholar platform, the scientific works with the participation of Dr. Kalchev have been cited 85 times, and 10 of the articles with which the candidate participated in the competition for "associate professor" have a total impact factor of 36.528. Dr. Kalchev has participated in 14 national and international scientific events with 7 presentations and 8 posters, 7 in our country and 1 in Nis, Serbia. The applicant is fluent in English and Russian, as well as Swedish at B2 level. Has very good computer literacy. Dr. Kalchev is a member of the Bulgarian Medical Union, the Bulgarian Pathology Fellowship and the General Medical Council (Great Britain).

Dr. Kalchev has participated in 4 research projects under the "Science" fund at the University of Varna, relating to:

- "Expression of tetraspanin markers in benign prostate hyperplasia and in prostate cancer";
- "Analysis of immunohistochemical expression level of markers for necroptosis in breast cancer";
- "Predictive and prognostic role of immunohistochemical expression of apoptosis – inducing factor and RIPK3 marker for necroptosis in renal cell carcinoma";
- "Study on the expression levels of immunohistochemical markers for apoptosis and necroptosis in BCC and SCC"

Evaluation of scientometric indicators in relation to application in the competition for the academic position of "associate professor"

I. Scientific and research activity: The total publication activity of Dr. Kalin Kalchev obtains 28 scientific works, plus the 3 publications for granting the ESD "Doctor". In order to participate in the competition, he submitted:

- **Dissertation thesis** for the acquisition of ESD "doctor" on the topic "RIP3 Marker Expression for Necroptosis in Cases of Prostate Cancer", 2020.

- **Eleven (11) publications** in scientific journals, referenced and indexed in world-renowned databases with scientific information, equivalent to habilitation work, included in the academic reference in indicator Б4 /Б4.1-Б4.11/.

- **Fifteen (15) full-text publications** in scientific journals and collections other than those for the acquisition of the ESD "Doctor", included in indicators Г7 and Г8, of which 9 in international scientific journals, referenced and indexed in world-renowned databases with scientific information (WoS & Scopus), and 6 in non-referenced peer-reviewed journals. Of the mentioned 9, I do not accept publication Г7.7, as it is not full-text, but an abstract.

- **Two full-text publications** in scientific journals and collections beyond the minimum scientometric requirements for the granting the academic position "associate professor";

- **Three full-text publications** in scientific journals and collections in relation to the acquisition of ESD "Doctor", of which 1 in international scientific journal, referenced and indexed in world-renowned databases with scientific information (WoS & Scopus).

- **The dissertation thesis for ESD "doctor" on the topic "RIP3 Marker Expression for Necroptosis in Cases of Prostate Cancer"** has a positive assessment by the SJ, meaning that it meets criterion A of the minimum requirements for occupying the academic position of "associate professor" according to LDASRB.

The total number of points from the **11 publications** equivalent to a habilitation thesis presented is 113.68, with a required minimum of 100 points, i.e. **it meets criterium B of the minimum requirements for holding an AP "associate professor" according to the LDASRB.**

The total number of points from the indicators Г5 till Г9 of the presented 15 full-text publications in scientific collections and journals other than those for acquiring the ESD "doctor" is 209.5 (with a required minimum of 200 points), 121 pts from referenced, and 88 ,5 pts of publications in non-referenced journals and collections. **Criterion Г of the minimum scientometric requirements for holding the position of associate professor has been met.**

According to the reference submitted by the library of MU-Varna, **7 citations** of Dr. Kalchev's scientific works were found in international scientific journals, referenced and indexed in world-renown databases with scientific information /WoS & Scopus/. The indicated citations under indicators Д10-12 carry a total of 105 points, with a minimum requirement of 50 points, with meets criterion Д.

In two /2/ of the presented publications Dr. Kalchev is the **first author; second and third author is in 5** of the publications.

Research activity and contributions.

1. Alternative Molecular Mechanisms of Cell Death and Cell Survival scientific publications: № B4.2, № Г8.3
2. Prostate carcinoma: publications № Г7.1, Г8.1 и Г8.2
3. Rarely diagnosed diseases : publications B4.4; B4.6; B4.7; B4.8; B4.10 и B4.11/; Г7.2; Г7.4; Г7.6; Г7.8; Г8.4; Г8.5; Г8.6
4. Infectious diseases: publications B4.1 и B4.9; Г7.3; Г7.5; Г7.9
5. Experimental morphology: publications B4.3; B4.5/.

The reference for the contributions of Dr. Kalchev's scientific works testifies to a wide range of his scientific and diagnostic interests, while at the same time his ability to work in a team stands out. The various morphological and IHC methods of research used by the author show that Dr. Kalchev is a very well methodically prepared specialist who, in addition to his ability to interpret the results, shows a certain desire to build diagnostic algorithms in routine practice.

The main contributions in the scientific works of Dr. Kalchev refer to those related to the dissertation thesis, and contributions to the other publications submitted for the competition for "associate professor".

The contributions of the dissertation thesis:

Two original contributions stand out:

1. For the first time in our country, a scientific work with a systematic and in-depth study dedicated to necroptosis in prostate carcinoma in humans has been presented;
2. For the first time in our country, a semiquantitative assessment of the expression of the necroptosis marker RIP3 was made in order to clarify its prognostic and predictive role in prostate carcinoma;

Practical and applied contributions:

1. Evaluation of the the risk profile of patients with prostate carcinoma;
2. Analysis of the incidence and prevalence of prostate cancer morbidity and mortality in the world, in Europe and in Bulgaria;
3. Evaluation of the risk factors for low survival rate, including increased expression of RIPK3, Gleason score > 7 and perineural invasion, as well as for high survival, including low expression of RIPK3, Gleason score < 7, lack of PNI and metastases.

The main contributions in the scientific works of Dr. Kalchev submitted for participation in the competition are:

1. A correlation between higher RIPK3 expression and associated greater overall survival was found in patients with colorectal carcinoma, which can be used as an independent predictive marker for good response to treatment, and a lower risk of developing progression of the disease.

2. It's been shown that the expression of the necroptosis marker RIPK3, manifested by the H-score, cannot be used as an independent indicator of low survival, but only in some cases, as an addition to the classic T-stage and Gleason-score.

3. Tumor progression was monitored upon loss of the tumor suppressor gene Maspin through its epigenetic "silencing", and a correlation between the expression of the marker and indicators of age and inflammation at an early stage of tumor transformation was made; the possible role of basal cell hyperplasia in malignant transformation is considered.

4. An analysis of the role of the autophagic regulatory protein Beclin-1 was made as an antagonist of apoptosis, related to the survival of damaged cells in inflammation, degeneration and tumors; the importance of autophagy for the oncological practice is reported as a mechanism for cellular recovery: a contribution of a scientific and theoretical nature.

5. For the first time in our country, an analysis is made in the literature, dedicated to necroptosis as an alternative mechanism of cell death in various malignant diseases. From the data presented in the review, it is concluded that the induction of necroptosis can be an efficient therapeutic strategy in the treatment of malignant tumors, and can play an important role in the definition of targets and in the development of new drugs.

6. Substantial part of the applicant's publications, in the group of publications "equivalent to habilitation thesis", are devoted to rare diseases of various localizations, and in some cases a diagnostic algorithm's been developed and proposed. Particular attention has been paid to the cases of pediatric pathology, among which stand out: a. publication of a rare case of adrenal oncocytoma (only 5 such cases have been published in the scientific literature); a 9-year-old girl with virilization; b. a rare genetic syndrome with multiple internal and external malformations; a contribution to the article is the developed sample clinical-diagnostic algorithm for children with malformations; c. leiomyosarcoma of the bladder, with radical bladder and prostate ectomy and simultaneous bladder reconstruction (less than 200 cases have been described in the world-renown literature sources), etc.

7. For the first time in our country, a comparative analysis of rare oncological diseases is carried out based on data from the world-renown literature sources and those from the National Cancer Registry of Bulgaria; the analysis covers morbidity and mortality data disaggregated by age, incidence, tumor types and therapeutic behavior, with recommendations for therapeutic behavior in rare tumors.

8. For the first time in our country, a study is carried out covering autopsy cases of rtPCR-proven COVID-19, with analysis of morphological changes in the lungs, with assessment of the the dynamics of early and late changes in them, and indicating the probability of long-lasting and severe complications in patients with post-covid syndrome; the contribution in the publication is of a scientific and practical nature;

9. A scientific and practical contribution is the first published, histologically and microbiologically proven case of rhino-orbital cerebral mucormycosis in a patient after infection with COVID-19.

10. Contributions of an original nature are found in the studies dedicated to the problems related to CMV-infection, that arise from: the analysis of early postnatal diseases from CMV-infection in clinically symptomatic children up to 3 months of age in the city of Varna;

11. A comprehensive analysis of the problems related to vaccine prophylaxis was made; of a recommendatory nature is the guideline for mandatory screening of all suspected newborns.

12. A contribution of a scientific and theoretical nature is made in the extensive analysis concerning problems related to vaccine prophylaxis.

13. An original contribution is made in the study monitoring cases of patients with lymphomas infected with CMV-infection; a very high rate of infection was found in these patients /90%/, with about 10% reactivation of a latent infection.

14. A certain scientific and practical contribution is made by the publication in which CMV-infection is considered most common cause of congenital infections worldwide, and emphasizes the pathological changes developing in unscreened children.

15. In two experimental studies the role of toxicity of alcoholic and aqueous extracts of sumac are presented, which show that both infusion of alcoholic extract and subchronic administration of aqueous sumac extract doesn't show toxicity in the concentrations applied, which gives reason to use them to study treatment effects in vivo.

16. A comparative analysis of the rates of incidence and morbidity of prostate cancer is made on a global, European and national scale, using data from Globocan and the National Statistical Institute of Bulgaria. The role of PSA screening for early diagnosis and prevention of carcinoma has been marked; morbidity and mortality rates are monitored in age, race, geographic origin differences, etc.

17. The role of the necroptosis marker RIPK3 in prostate carcinoma was monitored and its association with some morphological parameters and patient survival is analyzed. A prediction is presented regarding the increase of the morbidity rate in the developed countries and increase of the mortality rate in developing countries.

II. Teaching activity:

Dr. Kalchev is a chief assistant professor in the Department of "General and Clinical Pathology, Forensic Medicine and Deontology" at MU-Varna. According to the teaching report presented, his total teaching experience as of 31.03.2023. is 15 years, 9 months and 20 days. Dr. Kalchev actively participates in the training of Bulgarian and English-speaking students in: Faculty of Medicine, discipline "General Pathology", English and Bulgarian language lectures and seminars; discipline "Clinical Pathology" English and Bulgarian language; Faculty of Dental Medicine - discipline "Pathoanatomy" - English and Bulgarian language; Faculty of Pharmacy - "Pathoanatomy" discipline for Bulgarian students; lectures and seminars; Medical College, Varna, specialty "Medical Laboratory Assistant", discipline "General Pathology" - for Bulgarian students; participation in specialists training and in thematic courses. His academic employment is:

- in the academic year 2017/2018 the total workload is 222 hours; - in the academic year 2018/2019 - 274 hours; in the academic year 2019/2020, the total workload is 278 hours; in the academic year 2020/2021 - the total workload is 232 hours and in the academic year 2021/2022 the total workload is 320 hours. **Dr. Kalchev's teaching workload exceeds the required 220 hours for the positions he held.**

III. Therapeutic and diagnostic activity.

Dr. Kalchev's professional experience is 20 years, 2 months and 18 days. As a resident-assistant-professor, and later as a resident-chief-assistant-professor in the "General and Clinical Pathology" clinic at the UMHAT "Sv. Marina", Varna, Dr. Kalchev takes an active part in the overall diagnostic process, including post-mortal examinations, and diagnosis of histological and cytological biopsies. Dr. Kalchev has a special merit doing highly specialized tests of malignant tumors of the breast, stomach, non-small cell lung carcinoma, head and neck, etc.

Dr. Kalchev is elected member of some of the committees at the UMHAT "Sv. Marina", Varna, namely: the Oncology General Committee and Children's Oncology Committee; Breast Cancer Subcommittee at the Oncology General Committee, and in the multidisciplinary team for complex medical care of child patients with sexual differentiation disorders.

Dr. Kalchev's professional interests are mainly related to oncological diseases and the opportunities for application of the molecular pathology to help in oncological diagnostics. I know Dr. Kalchev since the beginning of his professional career and my impressions of him are excellent. He is a responsible young colleague, able of teamwork, with an interest in scientific activities and a continuous striving to improvement.

Conclusion:

Dr. Kalchev is a proficient and methodically trained pathologist, with extensive clinical and pedagogical experience. The scientometric indicators presented by the applicant, as well as the teaching workload report, meet the criteria that lay down in the LDASRB and the Regulations for the conditions and procedures for acquiring scientific degrees and holding academic positions at the Medical University-Varna, as a requirement for holding the academic position "associate professor". Considering these facts, and in accordance with my own personal impressions, I believe that Dr. Kalchev has all the necessary qualities to hold the position of associate professor. This gives me the ground to give my positive vote and to recommend to the esteemed Scientific Jury to award Kalin Petrov Kalchev, MD, PhD, the academic position of "Associate Professor".

14.08.2023

Varna

assoc. prof. Ekaterina Softova Zlatarova, MD, PhD

