

REVIEW

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Regarding a competition for the academic position 'Professor' in the field of higher education 4. Natural Sciences, Mathematics and Informatics, Professional field 4.3. Biological sciences, specialty "Biochemistry", Faculty of Pharmacy, Department of Biochemistry, Molecular Medicine and Nutrigenomics, Medical University "Prof. Dr. Paraskev Stoyanov", Varna, Bulgaria, announced in the State Gazette, N: 7 of 23.01.2024.

The reviewing of the materials submitted for the competition is based on the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its implementation, as well as the Regulations on the Conditions and Procedure for Acquisition of Scientific Degrees and Occupation of Academic Positions at Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

The review is prepared on the basis of Order No. P-109-96/21.03.2024 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov", Varna and Protocol No. 1 of the scientific jury meeting on 03.04.2024.

1. General presentation of the competition materials

Only one candidate submitted documents for participation in the competition - Maria Atanasova Radanova, PhD - Associate Professor at Medical University Medical University "Prof. Dr. Paraskev Stoyanov", Varna. She is Associate Professor at the Faculty of Pharmacy, Department of Biochemistry, Molecular Medicine and Nutrigenomics.

The set of materials submitted by the candidate are in accordance with the recommended minimal scientific-metric requirements for academic positions in the Regulations of the Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

Assoc. Prof. Radanova participates in the competition with nine scientific publications in journals, refereed and indexed in world-known databases with scientific information (after acquiring the academic position "Associate Professor"), one monograph, two teaching manuals and one chapter of a textbook in co-authorship.

2. Career Development

Maria Radanova graduated in 1999 from the Faculty of Biology of Sofia University "St. Kliment Ohridski", Sofia, with a Master's degree in Molecular Biology with specialization in Clinical Chemistry. Immediately after graduation he started working as a biologist at the Bulgarian Academy of Sciences, Institute of Biology and Immunology of Reproduction "Acad. Kiril Bratanov", Sofia, then until 2006 he successively held the positions of biologist, assistant professor, senior assistant professor at the University of Rousse "Angel Kanchev", branch - Silistra.

Her academic career at the Medical University "Prof. Dr. Paraskev Stoyanov", Varna began in the Department of Biochemistry, Molecular Medicine and Nutrigenomics, where she has worked until now, passing through all levels of academic development – assistant professor, senior assistant professor, chief assistant professor, associate professor. Quite naturally, her candidacy for the highest academic position "professor" follows, which shows a purposeful and systematic work in one direction. It has already started in 2007 with her enrolment as an independent doctoral student in the same department. In 2012, she obtained a PhD degree after defending her thesis on the molecular effects of C1q inhibition in patients with lupus nephritis. Since 2015, after successfully passing the state exam, he is a certified specialist in biochemistry.

Assoc. Prof. Radanova is a researcher with serious training and clearly outlined professional interests. At the same time, she is engaged in active teaching and scientific supervision of PhD students.

3. General description and evaluation of the applicant's activities

- Teaching activities

Assoc. Prof. M. Radanova has 21 years of teaching experience from Rousse University "Angel Kanchev", affiliate - Silistra and Medical University "Prof. Dr.

Paraskev Stoyanov", Varna. The average teaching load for the last 4 years is 217 hours, of which 78 hours of lectures and 139 hours of practical exercises. Teaching work includes lectures and exercises in Bulgarian and English.

Under the supervision of Assoc. Prof. Radanova has defended three PhD students - Galya Mihaylova (2020) and with shared scientific supervision - Maria Kosturkova (2022) and Rostislav Manev (2022). All three dissertations are in the area of her research in the field of systemic lupus erythematosus and colorectal cancer.

- Scientific and applied activities

Assoc. Prof. Radanova is a researcher with a clear scientific profile. The main focus of her scientific work is the study of diagnostic, prognostic and predictive biomarkers in solid tumors. In this field, specific interests are focused on non-coding mRNAs and single nucleotide polymorphisms in their genes.

Another direction is related to the study of the molecular effects of inhibition of the C1q component of the complement system in autoimmune diseases.

In an interdisciplinary team, M. Radanova studies pathological dysregulation of metabolism in various diseases.

As a result of the long-standing work of the candidate, together with her collaborators from different specialties, significant contributions of a scientific-theoretical nature have been achieved. A database of circular RNAs with oncogenic function in colorectal cancer, mechanism of action, associations with clinicopathological features and potential as biomarkers has been established. Also of interest is the attempt to interpret the mechanisms by which transcribed ultraconserved regions regulate gene expression.

Of particular importance are contributions of applied nature, based on results published in reputable international scientific journals. Two novel circulating circRNAs have been identified that distinguish stage IV from stage III colorectal cancer patients, one of which has been evaluated for prognostic significance in metastatic carcinomas. The team demonstrated single nucleotide polymorphisms in miRNAs genes associated with prognosis of patients with metastatic colorectal cancer and risk of disease progression. Interestingly, these associations were independent of the levels of the respective miRNAs.

Original results demonstrate the predictive and prognostic role of RIPK3 in metastatic colon cancer and the association between expression levels in the primary tumor and disease aggressiveness. The report on the frequency of KRAS mutations in Bulgarian patients with advanced and metastatic colorectal cancer puts our country on the international scientific map with important epidemiological data.

Another solid tumor that is in the focus of M. Radanova is non-small cell lung cancer, where a high neutrophil/lymphocyte ratio and sarcopenia have been demonstrated to progress with platinum-based chemotherapy. These patients are at higher risk of disease progression after immunotherapy, an important observation for clinical practice.

A similar finding with direct clinical implications is based on a study of PIK3CA mutations in Bulgarian patients with metastatic breast cancer in whom the presence of the mutation did not affect response to endocrine therapy as first-line treatment.

No less significant are the observations regarding the molecular effects of inhibition of the C1q component of the complement system in autoimmune diseases. Functional deficiency of C1q was discovered for the first time, indicating the critical role of functional sites located in the region of collagen stems of the protein in maintaining tolerance to its own structures. The functional consequences of autoantibody binding to globular domains of C1q, which could account for the insufficient clearance of immune complexes and CRP-associated apoptotic cells in lupus nephritis, have also been established.

Pilot studies have shown that the minor G-allele, GG genotype of rs172378 and AA genotype of rs292001 are associated with the risk of rheumatoid arthritis and have focused the interest of the Bulgarian rheumatology community on the role of the complement system in the pathogenesis of rheumatoid arthritis.

As a result of the interdisciplinary studies in which Assoc. Prof. Radanova participated, the first meta-analysis evaluating the relationship between variants in dynein-related genes and male infertility was conducted, which distinguished pathogenic variants in dynein-related genes from harmless variants. The study has strong potential for practical application in conditions of impaired sperm motility and infertility.

In addition to molecular biological and immunological analyses, the author has detailed knowledge of many biochemical techniques as a specialist in medical biochemistry. This knowledge naturally led her to the study of pathological dysregulation of metabolism. In her publications, a cytoprotective effect on hepatocytes of S-adenosylmethionine has been established by increasing the expression of the enzyme heme oxygenase-1 under conditions of fructose-induced disorder. We demonstrate that serum cytokeratin-18 levels are consistent with histological and biochemical changes in liver injury and can be used as a biomarker for noninvasive assessment of its progression in metabolic syndrome.

From the methodological point of view, the protocol for detection of anti-C3 autoantibodies in plasma by ELISA is an original achievement of the team led by M. Radanova team.

The candidate's scientific results would have been largely impossible without the financial support received from project activities.

A significant part of the published data has been sponsored by projects - e.g. those on autoantibodies against complement in lupus nephritis have been supported by INSERM in a competitive session "International Research Projects" - 2022. The autoimmune response against plasma proteins was supported by the Bulgaria/France bilateral cooperation programmes, the Research Fund, the Ministry of Education and Science.

Advanced studies on non-coding RNAs in colorectal cancer are the subject of a project funded by the "Scientific Research Fund", Ministry of Education and Science, and the study of single nucleotide polymorphisms in non-coding RNAs in the same pathology and awarded by the "Science" Fund at the Medical University "Prof. Dr. Paraskev Stoyanov", Varna. The identification of biomarkers in systemic lupus erythematosus was also carried out under an intra-university project.

The total amount of funds attracted by projects in Bulgaria is 176 927 BGN and 60 000 Euro from international contracts, which is a guarantee of the possibility to fully implement all published high-tech methods and analyses.

In conclusion, the research activity of Assoc. Prof. M. Radanova is clearly defined, interdisciplinary and fruitful. In the course of these studies, the candidate has

proven that she can work in a team, supervise collaborators and successfully implement project contracts.

The journals in which the research papers have been published for the period 2017 - 2023 have an overall Impact Factor of 44.892 and an overall SJR Rank of 10.732.

For the same period Assoc. Prof. Radanova has presented the results of her research to the scientific community in the country at 3 forums and 11 abroad.

The most significant recognition of the quality and significance of each candidate's work is citations. Assoc. Prof. Radanova participated in the competition with 119 citations, which earned her 238 points. I believe that her citations will increase significantly in view of the interesting data published in recent years.

4.Evaluation of the personal contribution and personal qualities of the candidate

I do not personally know Assoc. Prof. Maria Radanova, but the analysis of the documents submitted for the competition shows that she is an excellently trained specialist with methodological competences in various biomedical fields - biochemistry, immunology and molecular biology. She combines fundamental knowledge with methodological skills and precision, which is extremely important when interpreting scientific results.

The fact that she has experience in scientific supervision of PhD students, teaching work and in project funding outline a profile of a reliable academic teacher and researcher.

Analyzing the presented scientific production and comparing it with the scientific criteria set out in the Regulations of the Medical University "Prof. Dr Paraskev Stoyanov", Medical University of Varna, the following data emerge:

Indicators	Minimal requirements	Assoc. Prof. Radanova
A -1	50	50
B - 3 or 4	100	102
Г - 5 to 10	200	210
Д - 11	100	238
E – from 12 till end	150	316,98
Total	600	916,98

CONCLUSION

The documents and materials presented by Assoc. Prof. Maria Atanasova Radanova, PhD meet all the requirements of the Academic Staff Development Act in the Republic of Bulgaria (ASDA), the Regulations for the Implementation of the ASDA and the Regulations of Medical University "Prof. Dr. Paraskev Stoyanov", Varna. Her research activity exceeds the minimal national requirements for the academic position of Professor.

The candidate has submitted a sufficient number of research papers with original scientific and applied contributions that have received international recognition, a representative part of which have been published in international journals or have been cited in such journals.

After reading the submitted materials and scientific works, analysis of their significance and scientific and applied contributions contained in them, I give my positive assessment and recommend the Scientific Jury to award Assoc. Prof. Maria Atanasova Radanova, PhD the academic position "Professor" in the field of higher education 4. Natural Sciences, Mathematics and Informatics, Professional field 4.3. Biochemistry", Faculty of Pharmacy, Department of Biochemistry, Molecular Medicine and Nutrigenomics of the Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

Заличено на основание чл. 5,
§1, б. „Б“ от Регламент (ЕС)
2016/679

May 9th, 2024

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