

OPINION

of **Prof. Dr. YOVCHO PETKOV YOVCHEV, MD, PhD** Faculty of Medicine, Trakia University, Stara Zagora, Director of UMBAL "Prof. Dr. Stoyan Kirkovich" member of the Scientific Jury for the competition for the academic position of "Professor" according to Order No. РД-134/12.04.2024 г of the Rector of the University "Prof. Dr. Asen Zlatarov" - Burgas.

**1. Regarding: Conducting a competition for filling the academic position**

"Professor" in the scientific specialty "Pathology and cytopathology", in the field of higher education 7. Health and sports, professional direction 7.1. "Medicine", announced in the Official Gazette, issue 13 of 13.02. 2024

Only Prof. Dr. Maya Vladova Gulubova, MD, PhD has submitted documents for participation in the competition.

The set of materials submitted by the candidate is in full compliance with the national regulatory requirements for holding academic positions and with the Regulations for the terms and conditions for acquiring scientific degrees and for holding academic positions at the University "Prof. Dr. Asen Zlatarov" - Burgas.

**I. Candidate's career profile**

Professor Dr. Maya Gulubova graduated from higher education in 1983 in the Medical Academy of Sofia, specialty "Medicine". She began to specialize in pathology in Stara Zagora in 1984. In the same year, she began her professional career as a teacher and researcher in the position of "assistant" in the Department of General and Clinical Pathology at VMI - Stara Zagora. In the period 1993-2002, she held the position of "principal assistant" at the Faculty of Medicine of Trakia University, after which she was elected to the position of associate professor, and in 2013 she held the position of professor. In 1989, she completed a specialization in liver pathology at the 1st Moscow Medical Institute "I In 1999, she obtained a doctorate in medicine on the topic of "Role of sinusoidal cells and the neoplastic process in the liver". experience covering the period 2004-2024, in the capacity of head of the department of general and clinical pathology, forensic medicine and deontology and dermatovenerology (2003-2023), deputy dean for scientific research at the Medical Faculty (2004-2007), dean of the Medical Faculty (2004-2019) at the University of Trakia, and current Head of the Clinic for General and Clinical Pathology at the UMBAL "Prof. Dr. Kirkovich" - Prof. Gulubova carries out program accreditation for a number of medical specialties such as " Medicine", accreditation of many doctoral programs (25 current, 16 in process, 6 new). She is actively involved in the development of research activities in the Medical Faculty by assisting in the equipment of laboratories in molecular biology, immunology, biochemistry, biophysics, physiology, molecular pathology, immunohistochemistry, confocal microscopy, as well as in the purchase of equipment for training and scientific activity at UMBAL "Prof. Dr. Stoyan Kirkovich" - JSC.

The scientific research activity of the candidate develops in several main morphological directions, which fully correspond to the field of higher education 7. Health care and sports", professional direction 7.1. "Medicine", scientific specialty "Pathology and cytopathology":

- Tumor microenvironment: colorectal, rectal, gastric, endometrial, lung and thyroid carcinoma, with an emphasis on cytokines and immune cells – myeloid and plasmacytoid dendritic cells, T-helpers, NK and NKT cells using precise and modern methods.
- Liver pathology including hepatocellular carcinoma, liver metastases, hepatic sinusoids, biliary tract pathology, peliosis, integrins, adhesion molecules, extracellular matrix.
- Experimental diabetes, focusing on insulin-producing cells in bile ducts, pancreatic duct and liver, and oxidative stress.
- Tertiary lymphoid structures induced by tumor, infectious agents and autoimmune processes
- Covid-19 or SARS-CoV-2 morphology of lung damage, cytokine storm, immune response
- Type II alveolocytes and tertiary lymphoid structures

Prof. Dr. Gulubova participated in her guidance and training of 22 doctoral students. He also participates in the training of specialists in the clinical specialty "General and Clinical Pathology". She won 4 research projects at the Ministry of Education and Culture for the Ministry of Education, corresponding to the scientific specialty "Pathology and cytopathology".

The original scientific results obtained have been published in referred international journals.

## **II. General description of the submitted materials for the competition**

Prof. Dr. Gulubova has submitted 21 articles for participation in the competition (these are a small part of all her articles) in prestigious international and Bulgarian referred journals, of which 18 have an impact factor (IF= 22.385, and the total IF of all publications from 1984 until now is 106.006) and 2 with impact rank, quartiles: 2 with Q1, 4 with Q2, 13 with Q3, 1 with Q4. The extremely high H-index = 21 is an important indicator of the significance of her scientific output. A list of 32 citations in foreign specialized journals is attached. The total number of citations at the moment - 1621 reflected in the SCOPUS database - is impressive. Prof. Gulubova is the main organizer, executor and author of all the presented publications.

The candidate has participated in the implementation of 10 research projects corresponding to the scientific specialty "Pathology and cytopathology", 9 of which he is the leader of.

The significant contribution of Prof. Dr. Gulubova in the field of pathology gives her a well-deserved place in the prestigious ranking of Stanford University (USA, California), which, based on a complex analysis of her scientific output, determines Prof. Dr. Gulubova, together with another 48 Bulgarian scientists, as one of the best scientists in the world.

## **Evaluation of the candidate's scientific works**

Prof. Dr. Gulubova has attached a very well-prepared detailed report on the contributions from the scientific works, which accurately reflects her achievements in the individual scientific fields of important practical importance. The main scientific contributions of the candidate are related to:

#### **Studies of bile ducts:**

These include routine electron microscopy of endocrine cells and mast cells, light and electron microscopic immunohistochemistry in patients with extrahepatic cholestasis.

The deposition of type III and type IV collagen in sinusoids and portal spaces in livers of patients with extrahepatic cholestasis was studied by light microscopy and ultrastructural immunohistochemistry. For the first time in the Bulgarian literature, information is given about the expression of the adhesion molecule ICAM-1 in the liver sinusoids in cholestatic hepatitis, and for the first time in the world literature, the expression of ICAM-1 on the cell membrane of Ito cells is documented, which means that these cells are involved in the transport of inflammatory cells through the space of Disse to hepatocytes.

Liver sinusoids around metastatic and primary tumors were examined by light and electron microscopic immunohistochemistry and flow cytometry.

For the first time, electron microscopic differentiation was made between the granules of tryptase positive and chymase positive mast cells. Extracellular matrix proteins and their integrin receptors have been studied. In this regard, increased expression of tenascin and  $\alpha 9\beta 1$  integrin, which are markers of perisinusoidal fibrosis and sinusoidal transformation, was noted. Original data on adhesion molecules, their ligands and some cytokines in hepatic sinusoids are presented.

Immunohistochemical and flow cytometric studies of immune cells ( $CD83^+$  -  $S100^+$  dendritic cells) in the liver containing metastases from gastrointestinal carcinomas were performed. Flow cytometric typing of T lymphocytes ( $CD4^+$ ,  $CD8^+$ ,  $NKT CD3^+/CD56^+$ ) was performed in a homogenate isolated from a human liver resected due to metastases. Original data on the morphological features of human NK/pit cells in the liver of patients with primary malignant tumors of the gastrointestinal tract with and without metastases are presented.

The peptidergic innervation of the hepatic sinusoids was studied by immunohistochemical expression of SP, NPY, CGRP, SOM, SER in the liver of patients with primary malignant tumors of the gastrointestinal tract and liver cirrhosis.

#### **Immunohistochemical and genetic studies in colorectal carcinoma.**

Studies were conducted to establish the genetic polymorphisms of the genes encoding the protein expression of GST-p. Other studies have identified microsatellite instability in colorectal carcinoma. Endocrine cells and enzymes involved in antioxidant defense against free radicals GST-p, SOD1, SOD2, and the cytokine VEGF in tumor tissue in primary colorectal carcinoma were investigated. In survival analyses, carcinomats containing endocrine cells have been shown to have a worse prognosis. An original contribution was the expression of enzymes involved in the antioxidant protection of GST-p SOD1 and SOD2 in endocrine colorectal carcinoma cells.

#### **Immunohistochemical studies in gastric carcinoma.**

They allow the distribution of immature (CD1a<sup>+</sup> and S100<sup>+</sup>) and mature (CD 83<sup>+</sup>) dendritic cells to be determined. Increased HER2/new expression in tumor cells was observed, which correlated with shorter patient survival. VEGF expression in tumor cells correlates with the presence of distant metastases.

### **Immunohistochemical studies in thyroid carcinoma**

The involvement of the Th2 cytokine TGF- $\beta$ 1 and molecules from the TGF- $\beta$ 1 signaling pathway Smad4, Smad7, TGF- $\beta$  RII as well as dendritic cells in the tumor tissue of primary thyroid carcinomas was studied.

### **In the last 3 years**

Prof. Gulubova studies the tertiary lymphoid structures that are inducible by tumor, infectious agents and autoimmune processes. There is an accepted review on this topic from the American Journal of Clinical and Experimental Immunology IF=0.800. She studies immune cells, namely T helpers, cytotoxic T lymphocytes, macrophages and dendritic cells, in colon carcinoma and rectal carcinoma before and after radiotherapy. With Assoc. Merhar, they study type II pneumocytes in Covid-19 and in tumors and pneumoconioses. Together with Prof. Tolekova, they study the biliary-hepatic pathology in experimental metabolic syndrome. They have interesting findings, namely the appearance of  $\beta$ -cells in the extrahepatic bile ducts in hepatocytes and in the sinusoidal endothelium. Some of these data were published in the Journal of Metabolic diseases IF=3.471. At the same time, she continues to study 500 colorectal carcinomas for immune cells in the tumor microenvironment. These patients have been followed up for several years, for chemotherapy and radiation therapy and recently for mutations, investigated at Stoyan Kirkovich UMBAL, Stara Zagora. Several significant publications have been published in journals with an impact factor.

**The teaching activity of Prof. Dr. Gulubova includes conducting a significant number of hours of exercises and lectures for the period 1984-2024. in the following disciplines:**

- "General and clinical pathology", for students majoring in "Medicine" from the 3rd and 4th year.
- For the "Medicine" specialty, he gives lectures in English on general and clinical pathology
- "Somatopathology and oncopathology" of second-year students, majoring in "Social activities" - full-time and extramural studies.
- "Clinical Pathology" of first-year students, specialty "Nurse" and specialty "Midwife"

Prof. Gulubova has a total teaching experience of 39 years, and her total annual workload varies from 360 to 480 hours.

The complex analysis of the teaching and research activity shows that the candidate has fulfilled the required criteria for occupying the academic position of "professor", laid down in the Regulations for the terms and conditions for acquiring scientific degrees and for occupying academic positions at the University "Prof. Dr. Asen Zlatarov" - Burgas, which are included in a group of indicators A, B, D, D and E. It is important to note that the points of the indicators for groups D and E significantly exceed the minimum required points.

### III. Critical notes and recommendations

I have no comments on the presented scientific works and materials.

### IV. Conclusion

The career development of Prof. Dr. Maya Gulubova, her scientometric indicators, the contributions of her scientific research activity fully correspond to the requirements specified in the Regulations for the terms and conditions for acquiring scientific degrees and for holding academic positions at the University "Prof. Dr. Asen Zlatarov" - Burgas regarding the occupation of the academic position of "Professor".

The accumulated rich professional experience defines the candidate not only as a successful researcher, but also as a leader of research teams, doctoral students and specialists.

For these reasons, I confidently give my positive assessment to Prof. Dr. Maya Vladova Gulubova and recommend to the members of the esteemed Scientific Jury to support her selection for the academic position of "Professor" in the scientific specialty "Pathology and Cytopathology", in the field of higher education area of higher education 7. Health care and sports", professional direction 7.1. "Medicine" to the Department of "Anatomy, Histology and Embryology, Pathology, Forensic Medicine and Deontology", MF, University "Prof. Dr. Asen Zlatarov".

19.06.2024

(Prof. ~~Dr.~~ Yovcho Petkov/ Yovchev, MD, PhD)