To the chair person
of the Scientific Jury
appointed with order
no NR -109-242/26.07.2019
of the Rector of
Medical University
"Prof. Dr. P. Stoyanov"- Varna

REVIEW

By Prof. Dr. Zhaneta Georgieva Tyaneva, Ph.D., Member of the Scientific Jury, appointed with order No R-109-242/26.07.2019 of Prof. Dr. Krasimir Ivanov, Ph.D., Rector of Medical University "Prof. Dr. Paraskev Stoyanov", Varna, for holding the academic position "Associate Professor" in higher education 7. Health care and sport; professional field 7.1 Medicine, "Internal diseases" scientific specialty, promulgated in the State Gazette, issue 43/31.05.2019, for the needs of the Department of "Propedeutics of Internal Medicine" , Faculty of Medicine in MU - Varna and the Internal Diseases Clinic in "Sveta Marina" University Multiprofile Hospital for Active Treatment JSC – Varna.

An applicant has submitted documents for this call: Dr. Yavor Kostadinov Kashlov, Ph.D., Chief Assistant, " Department of Propedeutics of Internal Medicine", Faculty of Medicine in MU - Varna and the Internal Diseases Clinic in "Sveta Marina" University Multiprofile Hospital for Active Treatment JSC – Varna.
The submitted documents by the applicant are in conjunction with the requirements of the Rules of the academic position "Associate Professor" and the Rules of MU- Varna.

Biographical data

Dr. Yavor Kashlov completed his secondary education in 2003, in the town of Varna. In 2009 he successfully graduated Medicine in MU – Varna. For the period 2011 – 2017 he worked as resident medical officer in the Internal Diseases clinic at the Department of „Propedeutics of Internal Diseases" , "Sveta Marina" University Multiprofile Hospital for Active Treatment – Varna. He was awarded *Internal diseases* specialty in 2017.

Since April 2011 Dr. Kashlov has been a doctoral student with the right to defend his thesis in the " Department of Propedeutics of Internal Medicine" , MU – Varna. In 2011 he was appointed Adjunct Assistant in the "Propedeutics of Internal Diseases" and in 2013 he was appointed Regular Assistant at the department. In 2017 after a successful defense of his thesis he was awarded the scientific degree "Doctor" in the scientific field "Internal diseases".
The topic of his thesis is:"Biological markers of necrosis and necroptosis in cardiovascular diseases."Since 2017 he is Chief Assistant.
Dr. Kashlov specialized in Echocardiography in 2018, in Ausburg, Germany. He is a member of the Bulgarian Society of Cardiology, Bulgarian Heart and Vessel Association.

Professional experience
Dr. Kashlov has been working on the specialties Internal Diseases and Cardiology for over 8 years. He is definitely profound, conscientious and responsible towards the patients and the therapeutic and diagnostic process and highly professional. He has over 6 years of teaching experience.

2. Scientific research.

In view of covering the minimum state requirements in conjunction with the Law on the Development of the Academic Staff in the Republic of Bulgaria/ 2018 and the Rules of its application of Medical University – Varna/2018, Dr. Yavor Kashlov has submitted 32 scientific works in leading fields in the sphere of Internal Medicine, 29 full text publications in scientific editions with scientific review and 3 summaries in scientific editions, which have been abstracted and indexed in an international database with scientific information.
Dr. Kashlov is a first author in 10 (32%) publications and, respectively, a second author in 5 (15%). Citations and impact factor (IF): 18 citations in scientific editions, abstracted and indexed in renowned worldwide databases with scientific information; 8 citations in non-abstracted magazines with scientific review (the information is courtesy of the Library of MU – Varna).
Dr. Kashlov has an overall impact factor IF 26,32. The listed data is significantly higher than the minimum state requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Rules of its application of Medical University – Varna – regarding holding the academic position "Associate Professor".
I. Scientific contribution, connected with cell death, heart failure, and myocardial infarction

Monograph /habilitation thesis/ in Bulgarian with the title "Cell death in myocardial infarction and heart failure", 2019, ISBN 978-619-221-203-2., published by MU – Varna, with a total volume of 246 pages.
A total of 100 points.

Dr. Kashlov performs in-depth scientific analysis of the acquired knowledge on cardiovascular damage in cell death. He presents a large volume of evidence for the direct participation of known new types of cell death in the pathogenesis of myocardial infarction and heart failure. Dr. Kashlov reviews the types of cell death, their mechanisms and attitude to cardiac and other diseases. Dr. Kashlov has paid specific attention to new biomarkers in cell death.

II. Scientific contributions in the sphere of cardiovascular damage and assessment of the cardiac function

For the first time in clinical practice the role of necroptosis is admitted to be a new mechanism of cell death in patients with acute myocardial infarction with ST segment elevation after successful reperfusion; the role of necroptosis is supposed in the ischemic reperfusion injury when researching patients with STEMI. Data for the possible predictive value of the necroptosis marker – RIPK3 – is considered for bad ejection fraction when dehospitalising patients with myocardial infarction with ST segment elevation /4,5/.

Contribution and role of HMGB1 in the pathogenesis of myocardial infarction

For the first time in Bulgaria it has been reported that patients who were observed and who died after myocardial infarction, have higher serum levels of the necrosis marker – HMGB1. Defining the blood levels of RIPK3 and HMGB1 in patients with myocardial infarction with ST segment elevation before and after PCI, can play a significant part as biomarkers separately or in combination for adjusting the prognosis of these patients /4, 5, 30/.
Contribution in studying micro Ribonucleic acid 208a – biomarker of diagnosis in cardiovascular diseases./1/ The article considers miRNA as possible markers of injury in cardiovascular diseases. This is the first clinical article in our medical literature which treats the importance of miRNA in cardiovascular diseases.

Contributions regarding programmed necrosis and cardiovascular diseases

The article /25/ reviews a new type of cell death – programmed necrosis or necroptosis in cardiovascular diseases. This is the first clinical article in accessible literature which treats the significance of necroptosis in terms of ischemic reperfusion heart injury in patients with acute myocardial infarction with ST, who have been successfully treated with percutaneous coronary intervention.

In another research for the first time in Bulgaria NT-proBNP is reported to be used as a possible biomarker which evaluates the gravity of the ischemic heart disease /6/.
For the first time in Bulgarian medical literature the link between autophagy, myocardial infarction and heart failure is reported.
The mechanisms and the role of this type of cell death are listed. Therapeutic modulation of autophagy is of interest regarding the treatment of myocardial infarction and heart failure. /15/

Myocardial infarction and long non-coding RNA /16/
The article reports the potential role of four long non-coding RNA as biomarkers in the diagnosis of myocardial infarction. Non-coding RNA (LncRNA) have a regulating role on the genetic expression on epigenetic control, transcription and translation of RNA. In patients with acute myocardial infarction this can be used for diagnosis as well as improving the prognosis.

Contributions in other spheres of Internal Diseases
The article /17/ familiarizes the reader with mechanisms of heart injury in patients with Thalassemia Major. Therapeutic options of containing this injury are considered.
In the original study /23/ for the first time in Bulgaria a new biomarker is reported of apoptosis which participates in the pathogenesis of hepatitic impairment in metabolic syndrome. The elevated CK-18 serum levels correlate with the histological changes in the liver, caused by a fructose-rich diet. The research demonstrates the reliability of CK-18 as a biomarker of non-invasive evaluation of liver impairment in terms of metabolic syndrome.

Contributions on TAVI. Dr. Kashlov presents a case of transaortic catheter implantation of the aortic valve in a patient with a prosthetic mitral valve. He discusses another clinical case where he successfully used a new kind of technique of closure of paravulvar regurgitation after transcatheter aortic placement. Because of lack of official guidelines on how to solve the problem, this case presents a reliable and effective alternative for placing an additional valve. /19, 20, 21/

Contributions in Oncology. For the first time in Bulgaria the serum levels are tested of some isoforms of the VEGF family and their predictive value is researched for a response to the anti-angiogenesis therapy /2/. For the first time in accessible literature the presence of new small molecules (microRNA) is reported. Their concentration in the serum after the completion of adjuvant chemotherapy has the ability to recognize early patients with relapse (Nx nodal status).

This is one of the few articles in accessible literature which treats the same problem for the patients in the IInd and IIIrd stage, too and which demonstrates the superiority of these molecules over the standard marker, used up to now – CEA. For the first time in Bulgaria the serum levels are tested of some isoforms of the VEGF family and their predictive value is researched for a response to the anti-angiogenesis therapy /8/.
For the first time in accessible literature the potential link between the SUV max values and the autophagy marker – Beclin-1 in the primary tumour is reported. The prognostic value of SUV max in the liver metastases is shown /9/.
In this review the authors consider some main pathways and regulators, connected with cell death and surviving, which provide metabolic resistance in tumours. This leads to resistance to chemotherapy and failure in treating cancer /10/. For the first time in Bulgaria the process autophagy is reviewed in Oncology.
Although autophagy participates in tumour suppression, it also provides tolerance for cellular stress and helps tumour cells survive in adverse conditions. Stress-induced autophagy in tumour cells can read to treatment resistance and tumour latency, with a possible repeated tumour growth and progression /11/.

Contributions regarding distress screening in cancer patients
The interest towards distress screening in cancer patients grows considerably. The screening process of a certain disease or health problem depends on some basic factors: the health problem itself (in this case cancer), the type of screening test and the national health care system. /12/
In a research with 225 cancer patients /14/ it is established that the female patients and those with a poor performance status experience higher distress levels. Diagnosing cancer leads to the same distress levels in patients with metastatic and non-metastatic disease.

Neurotoxicity of anticancer drugs – The neurotoxic effects of chemotherapy appear relatively often and are the cause of modification of the medicine dosage. The risk of developing neurotoxicity is increased with upping the applied dosage and there is no standard behaviour to limit it.

Radiation treatment and cell death. Importance of types of cell death radiation treatment of cancer. Current forms of cell death are considered, which are induced by radiation treatment. The revealing of the exact mechanisms of cell death, which was induced by ionizing radiation, provides opportunities for the development of new target therapies. Their combination with radiation contributes to the individualization and approval of the complex treatment of cancer. /22/

Expression of the liver HMGB1 levels in fructose induced fatty liver

For the first time in Bulgaria we prove the connection between the HMGB1 levels and the liver damage in rats with fructose induced fatty liver. The research of the processes which lead to hepatocellular cell death is important for clinical practice for the evaluation of the gravity of liver damage, as well as the application of effective interventions towards preventing it. /23/

Analysis of the connection between distress levels and the list of problems

Distress screening in cancer patients is recommended by many organisations, including The National Comprehensive Cancer Network (NCCN).

The research measures distress levels before the beginning of treatment of patients in the Medical Oncology Clinic in "Sveta Marina" University Multiprofile hospital for active treatment – Varna and the connection with some parameters of the problem list, pointed out by the patients.

The necessity of introducing a concept on combating and treating psychosocial distress on a national level is emphasized in view of improving the prognosis of cancer patients in Bulgaria./24/ For the first time in Bulgaria there is a report on the potential role of the levels of expression of RIPK3 in primary tumours in patients with metastatic cancer of the colon as a potential and promising prognostic marker. /25/

Cardio-toxicity. The article reports a current problem, connected with the introduction of effective, but toxic medication for the heart tissue and informs us about new biomarkers (presented for the first time in Bulgarian medical literature) for diagnosis and new therapeutic strategies. /26/

4. Teaching activity

Dr. Yavor Kashlov has been Internal Diseases Assistant since 2013. His teaching workload is between 170 to 180 hours per year (the information is courtesy of the Administration office of MU – Varna for the last 5 years). He has been Chief Assistant since 2017.

Dr. Kashlov's teaching workload meets the requirements of teaching workload to hold the academic position "Associate Professor".

In conclusion:

According to the minimum requirement of MU Varna and the National Centre for Information and Documentation for holding the academic position "Associate Professor" Dr. Yavor Kostadinov Kashlov meets more than the minimum requirements and can be defined as a researcher who is capable of independent scientific work in the Internal Diseases sphere; an erudite doctor of high professionalism.

Dr. Yavor Kashlov is an approved specialist in the Internal Diseases sphere. As a teacher he is respected and loved by his students. The submitted scientific work, citation references and IF meet the approved scientometric criteria, outlined in the Law on the Development of the Academic Staff in the Republic of Bulgaria and in the Rules of development of the academic staff in MU – Varna – for the academic position "Associate Professor".
I propose with confidence to the Science Jury to consider Dr. Yavor Kostadinov Kashlov awarding him with the academic position "Associate professor" in the medical professional field in speciality " Internal Medicine"

10.09.2019

(**Prof. Dr. Zhaneta Georgieva Tyaneva, Ph.D.,**)