

STATEMENT

**By Prof. Dr. Nina Gocheva - Cardiology Clinic in “National Cardiology hospital”
Multiprofile hospital for active treatment**

Member of the Scientific Jury of the call for the academic position “Associate Professor” in the higher education sphere 7. Health care and sport; professional field 7.1 “Medicine” and “Internal diseases” scientific specialty in the “Propedeutics of Internal Diseases” department, Medical University – Varna, appointed with order No R-109-242/26.07.2019 of Prof. Dr. Krasimir Ivanov.

In order to participate in the call for the position of “Associate Professor” in MU – Varna, “Propedeutics of Internal Diseases” department; documents have been submitted by one applicant – Dr. Yavor Kostadinov Kashlov, Ph.D., - and have been approved by the committee. Currently he is Chief Assistant in “Propedeutics of Internal Diseases” department. The committee which monitors admission in the call, has established that the documents have been submitted within the specified period and meet the requirements of the Law on the Development of the Academic Staff and the regulation for the academic position “Associate Professor” and the rules of MU – Varna.

Brief biographical background

Dr. Kashlov completed his Master’s degree in Medicine in 2009. He specialized Internal diseases /2011- 2016/ and was awarded the “Internal diseases” specialty in January, 2017. In 2011 he was also a doctoral student, with the right to defend his thesis in the “Propedeutics of Internal Diseases” department in MU – Varna. In 2013 he was a regular doctoral student in the “Propedeutics of Internal Diseases” department and was appointed Regular Assistant in the same department. In 2017 he was awarded the scientific degree “Doctor” in the “Internal diseases” scientific field after having defended successfully his thesis “Biological markers of necrosis and necroptosis in cardiovascular diseases.” Presently he teaches classes on Propedeutics of Internal diseases in German and English. He participates in scientific forums in the country and abroad, as well as in research projects.

Scientific research

1. Thesis on the topic “Biological markers for necrosis, necroptosis in cardiovascular diseases” for awarding the scientific degree “Doctor“in 2017.
2. Monograph “Cell death in myocardial infarction and heart failure”. Scientific data have been presented on the issue which includes the authors’ original research, too.
3. Publications and reports, published in abstracted and indexed magazines with Impact factor of 7. In two of them Dr. Kashlov is a first author, in 1 – second, in 4 – fourth author.
4. Publications and reports in abstracted magazines without impact factor - 5

5. Publications and reports, published in non-abstracted magazines – 20
6. Paragraphs, published in abstracted editions - 2
7. The Academic reference for citations by foreign and Bulgarian authors shows citations or reviews in scientific editions which have been abstracted and indexed in worldwide data bases – 18; citations in or reviews in non-abstracted magazines with scientific reviews – 8. Available material has been attached to prove citations by foreign authors in *Web of Science*; *Scopus*, *Google Scholar*.
8. Overall impact factor – 26,32

Profile of the scientific work

The main focus of Dr Kashlov's scientific interests is on current problems in the field of fundamental medicine and particularly, on the biomarkers, connected with the cardiovascular diseases. He has performed scientific work which is related to the diagnostics of the cardiovascular diseases value of miRNA, as well as research on the evaluation of the serum levels of RIPK3 and troponin as predictors of a worsening left ventricular function in patients with acute myocardial infarction with ST-elevation and normal levels of troponin I. Another analysis is focused on research data, which confirms the fact that patients with acute myocardial infarction with ST-elevation have higher levels of HMGB1, which leads to increased risk of death. According to the results, obtained by Dr. Kashlov, HMGB1 has the potential of being a biomarker for a more exact prognosis in this patient group. Another research in the same field of scientific work evaluates the possibility of measuring the NT- proBNP values and applying them as an assessment of the gravity of the ischemic heart disease.

In two extensive articles topics are discussed which are connected on one hand, with the role of autophagy in the development of acute myocardial infarction, and on the other hand – the role of the long non-coding RNA as potential markers for the diagnosis of acute myocardial infarction.

For the first time in Bulgaria the curtain is lifted on the problem of the connection between autophagy and cardiovascular diseases; with a description of the mechanism of this type of cell death. The possibility for therapeutical modulation of the autophagy processes is of exclusive interest for the clinical practice and the terms of treatment of acute myocardial infarction and heart failure, which follow accordingly.

In connection with these new trends in the diagnostics and treatment of acute myocardial infarction, the question about using the non-coding RNA is posed. It is a known fact that the non-coding RNA has a regulating role on the gene expression on an epigenetic control level. It turns out that some lnc RNA have impaired expression in the peripheral blood of patients with acute myocardial infarction. This fact is of special interest due to the possibility of establishing the prognosis.

To the group of analyses which are connected with the identification of different pathological mechanisms in the pathogenesis of cardiovascular diseases there is a publication which reviews the appearance of myocardial damage in patients with thalassemia major. Based on the known facts, it could be possible to improve the prognosis in this specific patient population. Another publication

on a possible participation in the patho-physiology and pathogenesis of cardiovascular diseases is based on a research of the potential role of ferroptosis in this area. Ferroptosis is a new, relatively unexplored form of cell death with a possible therapeutic and diagnostic potential in different forms of coronary disease of the heart and other areas of ischemia on the basis of atherosclerosis.

The significance of the metabolic syndrome is an important condition in the development of atherosclerosis. The article, connected with the analysis of the link of the serum levels of CK-18 with the histological changes in the liver, is extremely interesting. The questions, posed in it, could be of serious importance for the clinical practice. Particularly important is the fact of correlation presence between the histological changes as a result of a fructose-rich diet and the manifestations of the metabolic syndrome as a risk factor.

For the first time in Bulgaria the connection between the levels of HMGB1 and the liver damage, is researched and proven, based on an experimental model. The processes which lead to hepatocellular cell death, are traced; which in additional research could clarify part of the patho-physiological changes in patients with metabolic syndrome and their role in stimulating the development of atherosclerosis.

In Dr. Kashlov's monograph come together his in-depth knowledge on the processes of cell death, which are based on extensive personal experience as well as on medical literature on the matter. The main emphasis is on myocardial infarction and heart failure. The monograph consists of 190 pages and contains 16 figures and tables.

The second important field in Dr. Kashlov's scientific research is on the problems in cancer patients and chemotherapy. The quoted facts in it are connected with the presence of small RNA molecules (miRNA). Their concentration in the serum after the completion of chemotherapy can be used as a prediction of relapse.

Another research in the same sphere of scientific interest is the one which evaluates the serum levels of some VEGF isoforms as a prediction of the response to anti-angiogenic treatment. In this research group the presence of a potential link between the SUV values and the autophagy marker (Beclin – 1) is explored in the primary tumour.

The continuation of the posed questions is analysed in the next publication, in which the significance of Beclin – 1 is evaluated as a potential predictive marker of 5-FU based chemotherapy in patients with metastatic carcinoma of the colon.

The clinical importance of this research consists in the differentiation of these patients, too; who can turn out to be potentially resistant to the known chemotherapy methods so far. This, in turn, can help reduce the frequency of treatment failure cases of this type of carcinoma. In connection with the scientific research on the identification of prognostic markers in different kinds of carcinoma, for the first time in Bulgaria the potential role on the RIPK3 level expressions in primary tumours is reported in patients in metastatic colon cancer.

A synthesized review is presented on the autophagy processes in the area of cancer diseases. The results in many researches in this area are emphasized. One of the most important areas is connected with identifying the disorders in the autophagy processes, which in turn reflect sensibility to metabolic stress, genomic damage and accelerated tumorigenesis.

Important elements in this review are the facts which reflect the stress-induced autophagy in tumour cells and the emergence of treatment resistance; the emergence of new tumour growth and the accelerated degree of the disease development. Dr. Kashlov's and the other publication authors' on distress screening of cancer patients is specially noted with analysis of the proofs in its favour.

The problem discussed is important for our country, since we still do not have a developed concept by the health care authorities in this area. The personal participation of Dr. Kashlov in performing screening of cancer patients and in evaluating distress, as well as the factors which influence its manifestation level, is of extreme importance for the cancer clinical practice and not only for the medical practice but also for the patients who have been diagnosed with cancer. In a research with 225 cancer patients it is established that female patients and patients with a poor performance status experience higher distress levels.

The third important scientific area, in which Dr. Kashlov works, is on the interventional treatment procedures of aortic stenosis – catheter based implantation of the aortic valve. Two clinical cases have been published in patients who need interventional treatment. The results were obtained and analysed by the team who participated in the procedure and are of extreme interest. They enrich clinical experience in this area and show possible guidelines towards solving the problem.

Dr. Kashlov participates in a host of other scientific research topics, which proves a diverse clinical interest.

Scientific contributions

1. Dr. Kashlov's thesis was published in *Bioscience trends* – an impact factor medicine. The results have been quoted 4 times. Part of the data was presented at the International Cardiology Conference – Rome, 2018. The contributions from this research are based on testing the levels of the serum markers for necrosis and necroptosis in patients with cardiovascular diseases. This research was done for the first time in Bulgaria. It was proven for the first time that necroptosis as a cell death mechanism is at the root of the development of myocardial infarction with ST-elevation. Its importance was also proven regarding its manifestation after reperfusion treatment. The possible predictive value of RIPK3 is demonstrated in distinguishing patients with impaired systolic function in STEMI. The research also shows that patients, who died after myocardial infarction, had higher serum levels of the necrosis marker HMGB1.
2. The evidence material on the role of miRNA 208 as a biomarker in patients with cardiovascular diseases is a contribution to clinical practice.

3. Data on the serum levels of some VEGF isoforms and their application as a predictor in response to anti-angiogenic therapy.
4. Data on the role of HMGB1 in the pathogenesis of myocardial infarction and liver damage in patients with metabolic syndrome.
5. The application of values of NT-proBNP as a biomarker for assessing the gravity of ischemia.
6. The application of small molecules /microRNA/, according to their concentration, for early differentiation of patients with/ without relapse after successful chemotherapy.
7. The possibilities of SUV max for the prognosis of development of liver metastases.
8. The application of the screening method for distress in cancer patients.
9. The opportunities for therapeutic modulation of autophagy for the treatment of myocardial infarction and heart failure.
10. The application of a new biomarker for apoptosis in patients with metabolic syndrome.

Teaching activity

Dr. Yavor Kashlov started his teaching activity in 2013 with 220 hours workload pursuant to a decision of the Academic Council of MU- Varna. From 2015 to 2019, including the present, he has a total of 180 hours per academic year in the “Propedeutics of Internal diseases” department.

On the basis of the abovementioned facts for Dr. Kashlov’s scientific career and clinical development, including his teaching workload, it can be summed up that he has serious scientific achievements. Most of them are practically oriented. The submitted publications and the teaching activity is sufficient and fully meet the requirements of MU- Varna- for holding the academic position of “Associate Professor” in the “Propedeutics of Internal diseases” department.

Prof. Dr. Nina Gocheva, Ph.D. of Medical Science

16. 09.2019

Member of the Scientific Jury