

STATEMENT

by Assoc. Prof. Dr. Eleonora Georgieva Dimitrova-Gospodinova, Head of the Department of Oncology, MU "Prof. Dr. Paraskev Stoyanov" - Varna

According to Order of the Rector of MU Varna № P-109-111 / 11.03.2022. I was elected as a member of the Scientific Jury, and on the basis of Protocol № 1 / 25.03.2022. I have been appointed to prepare a statement on the procedure for obtaining the educational and scientific degree "Doctor" in the scientific specialty "Oncology" with code 03.01.46., in the field of higher education "Health and Sports", professional field 7.1. Medicine

About a dissertation thesis entitled "Single nucleotide polymorphisms in the genes for non-coding RNAs as diagnostic and prognostic markers in patients with metastatic colorectal cancer"

Author: Dr. Rostislav Radoslavov Manev

Scientific Supervisors: Assoc. Prof. Dr. Nikolay Vladimirov Tsonev, Ph.D.

Assoc. Prof. Maria Atanasova Radanova, Ph.D.

1. Significance of the problem, formulation of the goal and tasks

Colorectal cancer is one of the socially significant diseases in modern medical science and is a challenge for the practicing oncologist. The improvement of diagnostic methods, surgical treatment, detection and application of various predictive biomarkers, personalized approach to drug treatment significantly improve the overall survival and quality of life of patients.

Single nucleotide polymorphisms are a common genetic variation related to various functional processes that determine individual susceptibility to certain cancers, including CRC, which is why they are used as a biomarker to predict the risk of its occurrence.

Microribonucleic acids are RNA molecules with an important role in a number of biological processes such as cell differentiation, proliferation, oncogenesis, apoptosis and others. They are important for regulating gene expression, including the expression of proto-oncogenes and tumor suppressor genes.

Single nucleotide polymorphisms in miRNA genes can modulate their expression and thus affect the risk of cancer, the effectiveness of treatment and the patient's prognosis. Such studies on the Bulgarian patient population have not been conducted so far.

All this has determined the formulation of the goal and the main tasks of scientific research, presented in the dissertation.

2. Structure of the dissertation

The presented dissertation contains 146 pages and is illustrated with 40 tables and 35 figures. The scientific work contains the following structure: "Introduction" - 2 pages, "Literary Review" - 58 pages, "Purpose and objectives of the study" - 2 pages, "Specific research methods" - 6 pages, "Results" - 46 pages, " Discussion "- 7 pages," Summary "- 1 page," Conclusions "- 1 page," Contributions to scientific work "- 1 page," Scientific publications and communications related to the dissertation "- 2 pages (9 scientific publications are presented, 7 of which have been published in international publications with an impact factor). The literature contains 257 titles, of which 3 in Cyrillic and 254 in Latin.

The structure of the dissertation is well balanced, the proportions between the separate sections are observed, it meets the requirements of the Law for development of the scientific staff of the Republic of Bulgaria.

3. Literature review

The doctoral student presents an in-depth literary analysis of a large amount of scientific information. It presents up-to-date data on the incidence, morbidity, survival of CRC, a current view of risk factors, the pathogenesis of the disease, known and used biomarkers, and the use of RNA as biomarkers. Because miRNAs have the ability to behave as tumor suppressors, as oncogenes, or both, the expression levels of certain miRNAs are related to the prognosis of patients with CRC in the metastatic stage, the levels of other mi RNAs are used for screening and initial evaluation. of patients. Modulation of Inc RNAs on the other hand can be considered as a therapeutic agent. General information about siRNA - biosynthesis, transcription and maturation, as well as their relationship with CRC is presented. The last part of the literature review is devoted to single nucleotide polymorphisms, as well as the possibility of SNP in miRNA genes to influence the risk of CRC, response to treatment and patient prognosis.

The results of global research conducted so far are also presented. It is obvious that such studies have not been conducted among the Bulgarian patient population.

4. Methodological level and design of scientific research

A retrospective study was presented with 101 patients meeting the formulated inclusion criteria and no exclusion criteria. Routine clinical trials and specific ones are described. The methods used for statistical processing of the obtained results are presented.

5. Correspondence between the goal, the results and the conclusions

There is a correspondence between the set goal, the formulated tasks and the reported results obtained, summarized in the discussion and the conclusions. The doctoral student presented the data from his own research with tables, figures and graphs. The main focus of the study was the search for single nucleotide polymorphisms in the genes of non-coding miRNAs as

diagnostic and prognostic biomarkers in the selected group of patients. A correlation was sought between the carrier of a certain genotype / allele of the studied five SNPs in the siRNA genes and their role in the assessment of the risk of developing CRC. Plasma levels of the mRNA in whose genes the polymorphisms studied were located were assessed in patients and in healthy controls.

6. Analysis of the conclusions and contributions

Ten conclusions are formulated, reflecting the obtained results. The conclusions are clear and concrete. I accept the contributions presented. For the first time in Bulgaria, data on the allelic frequency and genotypic distribution of polymorphisms in the genes for non-coding siRNAs among healthy individuals are reported. For the first time in Bulgaria, data have been obtained on the role of some polymorphisms as potential diagnostic biomarkers for CRC. The role of some single nucleotide polymorphisms as potential biomarkers of prognostic significance in patients with metastatic CRC has been reported for the first time. For the first time, a correlation was reported between the carrier of a particular genotype / allele of the SNPs studied and the overall survival in these patients.

The doctoral student presents 9 scientific publications related to the dissertation, of which he is a co-author.

The data summary is 84 pages and contains the main chapters of the dissertation.

7. Conclusion

The dissertation of Dr. Rostislav Radoslavov Manev is an in-depth and complex scientific development. The topic is interesting, dissertable, extensive. The applied methods are adequate for achieving the formulated goals and objectives, the results are convincing, the conclusions are clearly formulated, the contributions are significant with theoretical and potential practical value.

The dissertation on "Single nucleotide polymorphisms in the genes for non-coding RNAs as diagnostic and prognostic markers in patients with colorectal cancer in metastatic stage" covers the indicators for obtaining an educational and scientific degree "Doctor", meets the requirements of the Law for development of the scientific staff of the Republic of Bulgaria and the Regulations for its implementation.

Based on the above, I give a positive assessment of the dissertation of Dr. Rostislav Radoslavov Manev and propose to the members of the esteemed Scientific Jury to be awarded the educational and scientific degree "Doctor".

Assoc. Prof. Eleonora Georgieva Dimitrova - Gospodinova, Ph.D.

