STATEMENT

From Prof. Dr. Vanya Alexandrova Gerova - Nankova, MD, PhD
Department of Gastroenterology, Clinic of Gastroenterology
UMHAT "Queen Joanna-ISUL", MU, Sofia

Subject: Dissertation for the award of scientific degree "Doctor of Science"
Field of higher education: 7. Healthcare and sports, Professional field: 7.1. Medicine, Scientific specialty: "Gastroenterology"
Author: Assoc. Prof. Dr. Antonia Yordanova Atanassova, MD, PhD
Topic: "Serum expression of microribonucleic acids in patients with chronic inflammatory bowel disease"

1. Protection procedure

By order № P-109-217/17.05.2021 of the Rector of MU "Prof. Dr. Paraskev Stoyanov" I was elected a member of the Scientific Jury, and under Minutes №1 of the first meeting of the Scientific Jury, I was appointed to present my an opinion on the procedure for defence of the dissertation for the award of educational and scientific degree "Doctor of Science" of Assoc. Prof. Dr. Antonia Yordanova Atanassova, Ph.D.

The set of materials provided to me on paper and electronic media is in accordance with the requirements of the Law for development of the academic staff in the Republic of Bulgaria, the Regulations for its application and the Regulations for development of the academic staff of MU-Varna.

2. Brief biographical data and professional development

Assoc. Prof. Dr. Antonia Atanassova graduated from the Higher Medical Institute - Varna in 1986 with excellent results. She started her career as an intern in the internal ward of Hospital - Shumen, and since 1987 she has been successively assistant, senior and chief assistant in the Department of Internal Medicine, educational and scientific sector of gastroenterology, MU – Varna. In 2014 she was awarded the educational and scientific degree "Doctor", after successfully defending her dissertation. Since December 2015, she is an "associate professor" in the specialty: "Gastroenterology" at the Clinic of Gastroenterology at the University Hospital "St. Marina" - Varna and the Department of Anatomy and Cell Biology at MU - Varna.

Assoc. Prof. Atanassova has acquired specialisations in "Internal Medicine" and "Gastroenterology". She also graduated from the Faculty of Public Professions at the Higher Medical Institute in Varna. She has certificates for professional qualification - III level in abdominal ultrasound and gastrointestinal endoscopy. Her impressive high qualification is also related to the 28 specializations, 23 of which are abroad. She speaks French, English and Russian.

3. Relevance of the topic

Significant progress has been made in recent years in understanding the multifactorial pathogenesis of chronic inflammatory bowel disease (IBD). Key pathophysiological factors include genetic components, environmental elements, intestinal microbiota, and immune responses. Information on the complex interaction between these factors is becoming increasingly available through the application of highly genomic approaches. miRNA-mediated gene regulation is involved in normal cellular processes such as cell cycle, differentiation, proliferation, apoptosis and immune function. The identification of different expression models of miRNAs in patients with IBD suggests that these molecules are involved in different pathophysiological mechanisms. Accumulating data suggest that some miRNAs may also serve as new biomarkers in diagnosis, prognosis, and response to therapy. This can help in early diagnosis and lead to the development of personalized therapies in patients with IBD. All this determines the relevance of the topic of the dissertation.

4. Knowledge on the subject

The literature review presented by Assoc. Prof. Dr. A. Atanassova is systematized in 16 subsections. The various aspects of IBD are described in detail and precisely - general characteristics, diagnostic methods, assessment of intestinal inflammation through the assessment systems for stratification of clinical, endoscopic and morphological activity. Serological and faecal biomarkers are considered as useful tools for diagnosis, monitoring of activity, severity and therapeutic response, as well as for predicting the course of IBD. Based on the literature data, the need for a wider use of genetic research at the molecular level to fill in the gaps in the pathogenesis, diagnosis, proactive monitoring and personalization of the approach in these patients is argued. The main characteristics of miRNAs, their biogenesis, their relationship to innate and acquired immunity, their role in maintaining the intestinal barrier, the families of TLRs and NOD-like receptors, apoptosis and autophagy are described in detail. Logically, special attention is paid to the expression of various miRNAs in IBD and the ability to distinguish Crohn's disease (CD) from ulcerative colitis (UC), to assess risk factors for aggressive disease, glucocorticoid resistance, and to predict the risk of colorectal cancer.

The review is written competently and clearly. The style of the exhibition is accurate and shows a good language and medical culture. The analysis at the end of the review reflects the unresolved issues on the problem and logically justifies the need and motivation for the development of the dissertation. Over 65% of the cited sources are from the last 10 years, and nearly 1/3 of them are from the last 5 years. This shows the excellent theoretical training and awareness of Assoc. Prof. Atanassova, as well as the impressive ability to analyse the well-known literature data on the problem.

5. Research methodology

The chosen research methodology allows accurate and clear formulation of the goal. The set 5 tasks follow logically the goal and allow good implementation of the planned study. The research hypothesis is very well formulated - Serum expression of certain miRNAs is related to the distinction between the two inflammatory bowel diseases - CD and UC and can

serve as a non-invasive biomarker for assessing disease activity, monitoring inflammation and the effectiveness of the chosen therapeutic approach.

6. Characteristics and evaluation of the dissertation

The dissertation is structured according to the procedural requirements. It is written on 223 standard pages. The connection between the different parts of the dissertation is logical and meaningful. The literary reference is extensive and modern. It includes 574 literary sources, of which 8 in Cyrillic and 566 in English.

The clinical study included 70 patients with IBD divided into 2 groups of 35 patients, respectively 35 CD (20 in the active stage and 15 in remission) and 35 UC (20 in the active stage and 15 in remission) who visited the Clinic of Gastroenterology from 04.2019 to 10.2019. 30 healthy volunteers participated as a control group. The study was approved by the Research Ethics Commission at MU-Varna and all participants signed an informed consent.

The methods are appropriately selected, described clearly and in detail. Serum expression of miRNAs was examined in all participants. Standard clinical and laboratory tests were performed, serum levels of vitamin B12 and vitamin D, faecal calprotectin and faecal microbiological tests, ileocoloscopy with biopsies for histological examination, abdominal ultrasound and / or CT / MR enterography were also performed. The statistical methods used for data analysis are appropriate and fully consistent with the objectives.

The results are presented in great detail in 6 subsections of 76 pages. They are presented in chronological order, following the set tasks. The evidence is well illustrated with 55 figures and 59 tables.

The 35-page "Discussion" section discusses the data obtained on miRNAs expression models for the assigned tasks. The discussion is detailed, competent and reasoned, based on the results compared with the literature data. The citations are correctly marked. The dissertation concludes with a conclusion, which clearly shows what has been achieved in the study, outlining the unclear problems and future guidelines for research on the problem.

Conclusions. Based on the obtained results, 11 conclusions are formulated, which follow the logically set goal and tasks of the research.

7. Contributions and significance of the development for science and practice

I fully accept the proposed 11 contributions of the dissertation, which are grouped in three areas: 3 with a theoretical nature, 4 with a practical-applied nature and 4 with an original character.

8. Evaluation of dissertation publications

In connection with the acquisition of the Scientific Degree "Doctor of Science", Assoc. Prof. Atanassova has published 10 articles, of which 2 in English and 8 in Bulgarian. One of these articles was published in a publication referenced and indexed on the Web of Science. An article was published in an international journal with IF (JCC): 4.3241. Assoc. Prof. Atanassova is the first author of all articles. The attached list fully meets the requirements for obtaining the scientific degree "Doctor of Science".

9. Personal participation of the dissertation

The presented dissertation is an original product. The research, the obtained results and the formulated contributions are a personal merit of Assoc. Prof. Atanassova. The present work does not repeat her dissertation for obtaining a scientific and educational degree "Doctor".

10. Abstract

The abstract consists of 80 pages and is prepared according to the procedural requirements. In abbreviated form, it competently and correctly reflects the main positions and scientific contributions in the dissertation.

In conclusion, Assoc. Prof. Dr. Antonia Atanassova, Ph.D. is a respected and established gastroenterologist and lecturer, with high professional qualification and clinical experience, dedicated to her professional life in the study of IBD. She is one of the national experts on these diseases.

The dissertation presented for an opinion on the topic: "Serum expression of microribonucleic acids in patients with chronic inflammatory bowel disease" is a current, significant and excellently completed scientific work, with a clearly set and achieved goal, with well-formulated and completed tasks. The conclusions made are accurate and correspond to the set goal. The contributions are theoretical, practical and original. Such a study is being conducted for the first time in Bulgaria.

The dissertation shows the in-depth theoretical and practical knowledge of Assoc. Prof. Atanassova in the scientific specialty "Gastroenterology" and demonstrates her qualities and professional skills for conducting a large and complex study.

I believe that the dissertation of Assoc. Prof. Dr. Antonia Atanassova fully meets the requirements of the Law on the Development of the Academic Staff of the Republic of Bulgaria and the criteria of MU "Prof. Dr. Paraskev Stoyanov "- Varna. All this gives me reason to give my positive assessment and to recommend to the members of the esteemed Scientific Jury to vote positively for the award of the educational and scientific degree "Doctor of Science" to Assoc. Prof. Dr. Antonia Atanassova, Ph.D. in the scientific specialty "Gastroenterology".

15. 06. 2021
Sofia

Prof. Dr. Vanya Gerova-Nankova, MD, PhD