

## REVIEW

By Prof. Dr Borislav Georgiev Vladimirov MD,  
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I have been appointed as an external member of the Scientific Jury by order № P-109-217/17.05.2021. of the Rector of MU-Varna "Prof. Dr Paraskev Stoyanov". By decision of the first meeting of the Scientific Jury, I was appointed to prepare a review of the dissertation entitled: "Serum expression of microribonucleic acids in patients with chronic inflammatory bowel disease" for obtaining scientific degree "Doctor of Science" for Higher Education in the field 7. Health and Sport, Professional Field 7.1. Medicine, Scientific specialty: "Gastroenterology" of Assoc. Prof. Dr. Antonia Yordanova Atanassova, MD, PhD, Clinic of Gastroenterology at the University Hospital "St. Marina" - Varna and Department of Anatomy and Cell Biology, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

The review was prepared in accordance with the requirements of the Bulgarian Law on the Career Development of the Academic Staff, as well as the local regulations of MU-Varna.

### ***Professional Development:***

Assoc. Prof. Dr Antonia Y. Atanassova, MD, PhD, graduated with honours in medicine at the Higher Medical Institute - Varna in 1986. Initially, she worked as a resident in the Department of Internal Medicine at the Primary Municipal Clinical Hospital- Shumen (01.12.1986 - 16.06.1987). Since 1987, she has worked as an assistant professor, senior assistant (since 1991) and chief assistant (since 1997) at the Clinic of Gastroenterology of the University Hospital "St. Marina" - Varna, Medical University Varna. In 1994, she acquired the specialisation "Internal Medicine", and in 1996 she acquired the specialisation "Gastroenterology". She has participated in a number of postgraduate courses in gastroenterology in Bulgaria, the Czech Republic, Denmark, Greece, Hungary, Austria, Serbia, Spain, Belgium and the United Kingdom. Antonia Atanassova speaks Russian, English and French. In 2014, she defended a dissertation entitled "Clinical

Evaluation of Patients with Ulcerative Colitis-Modern Approach". With this, Dr. Antonia Atanassova acquired a PhD in the scientific specialty "Gastroenterology", and since 2015 she has been an associate professor at the Department of Anatomy and Cell Biology, Faculty of Medicine at MU - Varna. The main focus of her scientific interests and scientific production is in the field of inflammatory bowel diseases. She has 67 original publications, incl. in journals with IF and 21 scientific papers. Her scientific works are original and valuable. She has been cited 48 times. She is the head of a project approved and financed by the Medical Science Fund at MU-Varna. She also participates in an international research project on celiac disease in the Danube countries. She is the supervisor of two PhD-students. Her teaching activity at MU Varna includes lectures and practical exercises for students and trainee doctors in Bulgarian and English; specialists and general practitioners.

I personally know Assoc. Prof. Dr Antonia Atanassova. She has in-depth and up-to-date theoretical knowledge; rich clinical and teaching experience and skills, and valuable scientific activity. She is constantly evolving and improving. She is polite, helpful, moral and dignified person, and a professional.

Assoc. Prof. Dr Antonia Atanassova is an established and highly respected specialist in gastroenterology and an expert in the field of inflammatory bowel diseases at the national and international level.

***Dissertation:***

The dissertation of Assoc. Prof. Dr Antonia Atanassova is dedicated to ***one of the most current problems*** in modern medicine, namely to assessing the changes and importance of some new non-invasive biomarkers, especially microribonucleic acids (miRNAs) in socially significant and complex inflammatory bowel diseases. The main role of miRNAs is to fine-tune gene expression by partially suppressing or breaking down target information RNAs. They are related to the molecular pathways involved in the progression of some diseases from the stages of cell damage / apoptosis and inflammation to fibrosis, dysplasia and invasive neoplasms. They regulate a number of metabolic processes and signals, as well as oxidative stress, inflammation, fibrogenesis, cell survival and proliferation pathways. Their in-depth study finds practical application in some areas and diseases, e.g., non-alcoholic steatosis, neoplastic diseases and

others. In contrast, in research into inflammatory bowel disease, there are a lot of unresolved issues. In this regard, this dissertation is relevant, modern, original, aimed at evaluating new biomarkers in a difficult, diverse and severe pathology, with great medical and social significance and severity.

The dissertation presented to me for review complies with the requirements for **structure and volume**. It is written on 223 pages in plain language. It consists of the following main chapters: title (1 page), table of contents (2 pages), abbreviations used (3 pages), introduction (1 page), literature review (46 pages); aim, tasks and hypothesis (2 pages); methodology (5 pages); results (76 pages); discussion (36 pages); implications (2 pages), conclusion (3 pages) references to the contributions of the dissertation (1 page), publications in connection with the dissertation (1 page), reference (43 pages) and declaration of originality (1 page). It is illustrated with 59 tables and 55 figures.

**The literature review** contains the most important and up-to-date information related to the developed dissertation. It is comprehensive. The literature data is analysed in depth and summarised. The most important unresolved issues are also identified. Thus, the motives for the present dissertation are clearly outlined.

**The aim** logically derives from the analysis of the literature data. Both the aim and the 5 **tasks** set are formulated clearly and precisely and fully correspond to the topic of the dissertation. They focus on the most important characteristics of inflammatory bowel disease.

**The subjects and methods used** are clearly described and fully characterised, based on modern classifications, definitions and methods for examination and diagnosis, assessment of severity and location, follow-up and treatment. The subgrouping is real and correctly assessed. The subjects are sufficient in number for the applied statistical processing. A set of modern and reliable statistical methods is used. They are selected correctly in order to reliably prove or rule out the desired clinical dependencies.

**The results** fully correspond to the topic of the dissertation, the aim and the set tasks. They are presented clearly and accurately and are well illustrated. Original results with important theoretical and clinical significance have been obtained. The characterised population is Bulgarian. Thresholds of the selected panel of mRNAs in healthy individuals were developed. The spectrum of

changes in Crohn's disease and ulcerative colitis compared to the control group is shown. The similarities and differences between them have been established and characterised, as well as the correlation with disease activity, localisation, age and course of the disease, intestinal complications and extraintestinal manifestations, as well as with the type of treatment. The positive and negative predictive values of the individual mRNAs have been proven. Increased miR-28 expression predicts remission in Crohn's disease. A correlation has also been established to the main clinical and laboratory parameters assessing activity / remission, as well as to serum levels of iron, vitamin B12 and vitamin D. In addition, a correlation was found between the serum expression of some mRNAs and vitamin D levels.

In the "**Discussion**" section, the results are well interpreted, discussed and compared with those of other authors from the point of view of an expert in this field.

The **reference** is up-to-date and complete. About 20% of the cited authors are from the last 5 years. It contains a large number of literary sources - 574 titles, 8 of which in Bulgarian, and 566 foreign authors. The small number of Bulgarian authors is notable. It covers all aspects of the topic under discussion.

11 main **conclusions** were made, corresponding to the results obtained, as well as to the goals and tasks of the dissertation. A total of 11 **contributions** were proposed, namely 3 theoretical, 4 with practical application and 4 original ones.

Overall, I accept the conclusions and contributions made by the author, but they could be better formulated and presented. The conclusions are perceived as presenting results (e.g. using the word 'determined'). Regarding the contributions, the expression "for the first time in Bulgaria" can be replaced by "... in Bulgarian patients..."

The remarks made by me do not diminish the value and significance of the dissertation, which I highly appreciate.

**The abstract**, written on 80 pages, fully reflects what is stated in the dissertation.

The dissertation is mainly the work of the author. In connection with it, **10 publications** were made (8 in Bulgarian and 2 in English); one - published in a journal with IF, another one - in an indexed and referenced in Web of Science edition. In them, Assoc. Prof. Dr Antonia Atanassova is the first (3) or sole author (7).

***In conclusion***, based on the above, the dissertation of Assoc. Prof. Dr Antonia Atanassova, MD. is up-to-date, complete, with a clear goal and tasks, well-selected subjects and methods used, original results, conclusions and contributions of important theoretical and clinical significance. It meets the requirements of the Bulgarian Law on the Career Development of the Academic Staff, as well as the local regulations of MU-Varna for obtaining the scientific degree "Doctor of Science".

I recommend the members of the esteemed Scientific Jury to give a positive vote for the awarding of the educational and scientific degree "Doctor of Science" in the scientific specialty "Gastroenterology" to Assoc. Prof. Dr. Antonia Yordanova Atanassova, MD.

21.06.2021

/ Prof. Dr Borislav Georgiev Vladimirov MD /