REVIEW

of the official reviewer of the thesis

Akimniyazova Aigul Nurlankyzy on the title "The interaction of miRNAs with mRNAs of candidate genes of gastrointestinal tract cancer" awarded for the degree of Doctor of Philosophy (Ph.D.) in the speciality "6D074000 - Nanomaterials and Nanotechnology"

№	Criteria	Compliance with criteria (one of the answer options should be marked)	Justification of the official reviewer's position
1.	The title of the thesis (as of the date of its approval) corresponds to the directions of scientific development and/or state programs	1.1 Relevance to priority areas of scientific development or government programs:	The thesis corresponds to the priority direction of science development: "Life and Health Science".
		1) The thesis was carried out within the frameworkof a project or target program financed from the state budget (specify the name and number of the project or program)	The thesis was conducted as part of the project "Development of test-systems for early diagnosis of cardiovascular, oncological and neurodegenerative diseases based on miRNA associations and their target genes" №AP05132460 MES RK.
2.	Importance for science	The work makes a significant contribution to science and its importance is well-disclosed	The work makes a significant contribution to science, its importance is well disclosed, because the work is devoted to the study of mechanisms of regulation of gene expression associated with the development of cancer diseases of the gastrointestinal tract, which occupy one of the leading places in mortality among the population of the world and including Kazakhstan. Recently, many studies have been devoted to the study of the role of miRNAs and their regulatory function in gene expression. It has been found that miRNAs are involved in the regulation of many processes. miRNAs can bind both to a single mRNA and to dozens and even hundreds of mRNAs. On the other hand, a single mRNA can bind to several miRNAs. Thus, the number of variants of miRNA binding to mRNAs is enormous. Due to the huge number of different variants of these bindings and combinations, computational technologies and methods of modern bioinformatics are required. Circulating miRNAs have many characteristics of a "valuable biomarker" for diagnosing, determining prognosis and selecting treatment methods for patients with various diseases, including gastrointestinal tract cancers. The integration of findings from the thesis is important for addressing a widespread global health challenge, focusing on early detection strategies of gastrointestinal tract cancer.
3.	Principle of self-reliance	Level of independence: 1) High;	All experiments were performed independently by the author. The author's publication history, encompassing two articles featured in international journals with impact factors within the Q1-Q2 quartiles, coupled with their individual scholarly contributions, serves to underscore her commitment to the

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			progression of knowledge within the domain of cancer research.
4.	Principle of internal unity	4.1 Justification of the relevance of the thesis: 1) Justified	The justification of the relevance of the thesis "The interaction of miRNAs with mRNAs of candidate genes of gastrointestinal tract cancer" lies in its potential to significantly contribute to the understanding of molecular mechanisms underlying gastrointestinal tract cancer. By investigating the intricate interplay between miRNAs and the mRNAs of identified candidate genes, the author of thesis aims to elucidate crucial regulatory networks involved in the development and progression of gastrointestinal cancers. This research may have an important role for advancing diagnostic approaches, prognostic assessments, and the identification of potential target genes, thereby addressing in current knowledge and offering avenues for improved strategies in the diagnosis of gastrointestinal tract cancer.
		4.2 The content of the thesis reflects the topic of the thesis: 1) Reflects;	In summary, the thesis contributes to the field of cancer research by providing valuable insights into the interactions of miRNA and mRNA genes in the development of esophageal, gastric, small intestinal and colorectal cancers.
		4.3. The aim and objectives are consistent with the thesis topic: 1) are consistent with;	The aim and objectives of the thesis, centered around exploring "The interaction of miRNAs with mRNAs of candidate genes of gastrointestinal tract cancer," clearly demonstrate a consistent alignment with the chosen thesis topic.
		4.4 All sections and statements of the thesis are logically interrelated: 1) fully interconnected;	The thesis exhibits a meticulous organizational framework, featuring cohesive sections that offer a thorough exploration of the research topic. The incorporation of supplementary materials contributes to heightened clarity and accessibility, rendering the thesis comprehensively presented and logically articulated. Upon thorough examination, no significant issues are discernible.
		4.5 New solutions (principles, methods) proposed by the author are argued and evaluated in comparison with known solutions: 1) There is a critical analysis;	The author substantiates and assesses the newly proposed solutions, encompassing principles and methods, within the context of "The interaction of miRNAs with mRNAs of candidate genes of gastrointestinal tract cancer" by conducting a thorough comparison with established solutions. This evaluation involves a meticulous examination of the strengths and weaknesses of both the novel and existing approaches, demonstrating a critical analysis that contributes to the scholarly discourse on the subject matter. Through this comparative analysis, the author establishes the merit and innovation of the introduced solutions in the context of miRNA-mRNA interactions in gastrointestinal tract cancer.
5.	Principle of scientific novelty	5.1 Are the scientific results and provisions new?	The author introduces novel findings and insights into the complex interactions between miRNAs and mRNAs specifically within the context of

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		1) partially new;	gastrointestinal tract cancer. This is substantiated by a comprehensive review of current research, highlighting the uniqueness of the methodology, results, and interpretations presented in the thesis. Additionally, the acknowledgment or absence of similar concepts in prior literature further reinforces the originality of the scientific contributions made by the author in advancing the understanding of miRNA-mRNA interactions in gastrointestinal tract cancer. Throughout the investigation, the author uncovered that a majority of candidate genes are subjected to targeting by one or more miRNA molecules, with their binding sites distributed independently on the mRNA. In contrast, certain candidate genes exhibit a configuration where miRNA binding sites overlap in nucleotide sequences, forming clusters that accommodate two or more miRNAs. These clusters of miRNA binding sites are distinguished by their closely packed arrangement, leading to competition among miRNA molecules due to the overlapping placement of their binding sites on nucleotides. Also, author uncovered that the quantitative aspects of the interaction between miRNAs and the mRNA of candidate target genes suggest a potentially significant reliance of these genes' expression on the concentrations of miRNA molecules and mRNA and suppose that these findings form the foundation for identifying specific associations between miRNA and mRNA for the diagnostic potential in gastrointestinal tract cancer.
		5.2 Are the conclusions of the thesis new? 1) completely new;	The novelty of the conclusions in the thesis is evident through the identification of unique insights and implications stemming from the research. The author's thorough analysis of the data reveals distinctive interpretations and connections, offering a fresh perspective on the intricate relationship between miRNAs and mRNAs in the context of gastrointestinal tract cancer.
		5.3 Technical, technological, economic or managerial solutions are new and justified: 1) partially new;	Technological solutions to the defined goals and objectives are completely new and justified. The bioinformatics technologies used made it possible to obtain many original results with novelty. The use of these technologies is justified, since they are more effective in solving the problems of the thesis.
6.	The validity of the main findings	All main conclusions are based on scientifically sound evidence or are sufficiently well-substantiated.	All conclusions are based on scientifically sound evidence and reasonably well founded. This was achieved by the application of bioinformatics technologies and adequate approaches to studying the set goals and objectives.
7.	The main provisions for the defense	7.1 Is the statement proven? 1) proven;	The provisions for the defense have been proven. The majority of the findings in the study are displayed through tables, providing an analysis of the associations of miRNAs and candidate genes of gastrointestinal tract cancer. This constitutes the primary outcome of the research, and it is comprehensively

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			achieved for all specified tasks. 1. Create a database for miRNA nanomolecules and genes involved in the development of gastrointestinal tract cancer. The findings are provided in Table C1, which represents the compilation of candidate genes of gastrointestinal tract cancer, accessible in Supplementary Materials C. 2. To study the characteristics of the interaction of miRNA nanomolecules with mRNA genes involved in the development of esophageal cancer. In thesis, most of the results are presented as tables and descriptions of the associations of miRNAs and candidate genes. Also the results of the research are presented in the following paper: Akimniyazova, A. N., M. Régnier, Sh. A. Atambayeva, R. E. Niyazova, and A. T. Ivashchenko. 2018. "Characteristics of MiRNA Interaction With MRNA of Candidate Genes of Small Intestinal Cancer". *International Journal of Biology and Chemistry* 11 (2):11-20. https://doi.org/10.26577/ijbch-2018-2-340. 3. To study the characteristics of the interaction of miRNA nanomolecules with mRNA genes involved in the development of gastric cancer. The results of the research are presented in the following paper: Akimniyazova, A., Pyrkova, A., Uversky, V., and Ivashchenko, A. (2021). Predicting Associations of miRNAs and Candidate Gastric Cancer Genes for Nanomedicine. *Nanomaterials (Basel, Switzerland),* 11(3), 691. https://doi.org/10.3390/nano11030691. 4. To study the characteristics of the interaction of miRNA nanomolecules with mRNA genes involved in the development of small intestinal cancer. In the work, most of the results are presented in tables and a description of associations of miRNAs and genes. 5. To study the characteristics of the interaction of miRNA nanomolecules with mRNA genes involved in the development of colorectal cancer. The results of the research are presented in the following paper: Akimniyazova, A.N., Pyrkova, A.Y., Aisina, D.E., Ivashchenko, A.T. miRNA Binding Site Clusters in mRNAs of Colorectal Cancer Candidate Genes. *Nanotechnologies in Russia*, 15, 807–818 (2020). https://doi.org/10.1134/S1995078020060038. 6. To establish the associations of miRNA nanomolecules and mRNA genes involved in the development of gastrointestinal tract cancer. The author represents most of the results are presented as tables and

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			descriptions of the associations of miRNAs and candidate genes. The provisions set forth previously unknown information about the interaction of miRNA with mRNA of candidate genes of gastrointestinal tract cancer. They are original and expand the understanding of the relationship of the associations of miRNA and mRNA of candidate genes as novel molecular markers of gastrointestinal tract cancers.
		7.2 Is the position trivial? 2) no	The provisions for the defense are not trivial. There are no elements of triviality in this thesis work. All discovered patterns and features of the researched processes were considered not oversimplified, but from the perspective of modern knowledge in the field of computational nanomedicine.
		7.3 Is it novel? 1) yes	The provisions are novel because they are based on original results obtained for the first time.
		7.4 Level for application: 3) average;	The scientific results obtained by the applicant Akimniyazova A. were carried out using modern bioinformatic approaches. A database of nucleotide sequences of human miRNAs was created, which will facilitate the search and analysis of sites to identify and predict associations for rapid diagnosis of gastrointestinal cancer. Based on the findings, specific miRNA associations involved in the pathogenesis of esophageal, gastric, small intestine and colorectal cancers are proposed. The results of comparative in silico analysis of miRNA binding sites in the mRNAs of orthologous genes (presented in Chapter 3.2.2), set the stage for the selection of an experimental animal model in order to confirm the regulation of the investigated target genes by miRNAs in experiment. Besides, the results obtained in the course of the thesis are implemented in the educational process during the reading of the elective course "Omics technologies in medicine and pharmacy" in the groups of Master's degree of the 1st year of the educational program 7M101 "Health care".
		7.5 Is it proven in the article? 1) yes;	The proof of all provisions is confirmed by the publication of research results in 13 printed works, of which 2 articles in international journals cited in the databases Web of Knowledge and Scopus, 5 articles included in the list of the Committee for Control in the Sphere of Education and Science and 6 abstracts reported at international conferences.

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8.	Principle ofreliability Validity of sources and information provided	8.1 Choice of methodology - justified ormethodology is described in sufficient detail 1) yes;	Chapter 2 of the thesis describes in detail the methodology for conducting the experiment, and also outlines the rationale for its choice. In particular, in order to substantiate the choise of the MirTarget program, author provides a comparison of the known programs for searching for miRNA binding sites with mRNA. To compare and demonstrate the effectiveness of MirTarget program over other programs, author represents the results from such programs as DIANA-MicroT-CDS (http://www.microrna.gr/microT-CDS), TargetScan (https://www.targetscan.org/vert_80/) and RNA22 (https://cm.jefferson.edu/rna22/) programs. Author showed that the following examples of search for binding sites by the MirTarget program and other programs show the great advantage of the MirTarget program.
		8.2 The results of the thesis are obtained using modern methods of scientific research and techniques of data processing and interpretation with the use of computer technologies: 1) yes;	Yes, the results of the thesis were obtained using modern methods of scientific research and techniques of data processing and interpretation with the use of computer technologies. The miRNA binding sites in mRNAs of the target genes were predicted with the MirTarget program. The MirTarSeq program (The copyright certificate "MirTarSeq" No. 15600 dated March 2, 2021) was used to search for oligopeptides encoded by the nucleotide sequences of miRNA binding in CDS of mRNA genes.
		8.3 Theoretical conclusions, models, identified interrelationships, and regularities are proved and confirmed by experimental research (for areas of training in pedagogical sciences, the results are proved on the basis of pedagogical experiment): 1) yes;	Yes, theoretical conclusions, models, identified relationships and regularities are proved and confirmed by the experimental study using computer simulation.
		8.4 Important claims are supported by references to relevant and credible scientific literature	Important claims are supported by references to relevant and reliable scientific literature.
		8.5 Literature sources used sufficient for literature review	The 296 literature sources used comprehensively cover the current study and are sufficient for a literature review.
9	Principle of practical value	9.1 The thesis is of theoretical significance: 1) yes;	The given scientific work brings a good contribution to the study of molecular and genetic mechanisms of gastrointestinal tract cancer development. The results of studying the effect of miRNAs on candidate genes of esophageal, gastric, small intestinal and colorectal cancer can directly initiate other theoretical and fundamental researches.
		9.2 The thesis is of practical significance and	The results of this study of miRNA interactions have practical significance and

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		there is a high probability that the results obtained will be applied in practice: 1) yes;	potential for practical applications.
		9.3 Are the proposals for practice new? 1) partially new;	The proposals outlined in the thesis are new for practice, as previous studies have examined a small fraction of target genes and miRNAs, which do not reflect the full picture of multigenic diseases such as cancer. This work is based on an integrated approach to the study of molecular genetic mechanisms of diseases.
10.	Quality of writing and design	Quality of academic writing: 1) High;	Thesis written at professional level, meets the requirements of the Rules of awarding scientific degrees of the Committee for Control in the sphere of education and science of the Ministry of Education and Science of the Republic of Kazakhstan. The thesis represents is a logically completed scientific work, possessing internal unity. Clearly formulated goal and objectives of the study found a consistent theoretical and methodological solution in each section of the thesis, formed in the form of the main provisions put forward for defense.

By considering the thesis of Akimniyazova A.N. on the topic «The interaction of miRNAs with mRNAs of candidate genes of gastrointestinal tract cancer» meets the requirements for a PhD thesis in the specialty 6D074000 - Nanomaterials and nanotechnologies, and the candidate deserves a PhD degree.

Official reviewer:
PhD, Head of Laboratory of Molecular Biology,
Institute of Plant Biology and Biotechnology
MSHE RK

(signature)

Gritsenko D.A.

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