

**Review of the Official Reviewer on the Dissertation  
for the defense of the dissertation by Tokusheva Aliya Nurlanovna  
on the topic «Molecular and biological features of the course of aseptic inflammation associated with ecogenetic immunosuppression» submitted for the degree of Doctor of Philosophy (PhD) in the specialty 6D110100 – «Medicine»**

№	Criteria	Compliance with criteria (underline one of the response options)	Justification of the official reviewer's position (highlight comments in <i>italics</i> )
1.	The dissertation topic (as of the date of its approval) aligns with the directions of scientific development and/or state programs.	1.1 Compliance with priority areas of scientific development or state programs: <b>1) The dissertation was carried out within the framework of a project or targeted program funded by the state budget (indicate the name and number of the project or program);</b> 2) The dissertation was carried out within the framework of another state program (indicate the name of the program); 3) The dissertation corresponds to a priority area of scientific development approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan (indicate the direction).	The dissertation work was carried out within the framework of the scientific and technical project of the Ministry of Education and Science of the Republic of Kazakhstan “Molecular biological features of the course of aseptic inflammation associated with ecogenetic immunosuppression”, state registration No. 0115RK00600
2.	Significance for Science	The work <u>makes</u> /does not make a significant contribution to science, and its importance is well explained/not explained	The dissertation reflects the importance of the solving the problem of epigenetic regulation of the development of pathological conditions in the body is extremely relevant both for fundamental science and for practical application in the future. This study reveals the results of the study will significantly complement the understanding of pathogenetic mechanisms of inflammation by the data on the participation of gene expression in these mechanisms.

3.	Principle of Independence	Level of independence: 1) <b>high</b> ; 2) medium; 3) low; 4) no independence.	In the presented dissertation work, the doctoral student independently performed all stages of the study, performing experiments, statistical processing of data and interpretation of the results obtained during the study, preparing the publication and processing the obtained security documents. The author also participated in the design and conduct of transcriptomic and bioinformatics analyses.
4.	Principle of Internal Unity	4.1 Justification of the dissertation's relevance: 1) <b>justified</b> ; 2) partially justified; 3) not justified.	The significance of this exploratory study stems from its interdisciplinary approach. The originality of the proposed approach lies in a comprehensive study of immunophenotyping of T-regulatory cells, indicators of adaptive and innate immunity with next-generation sequencing. The planned results correspond to the world level of research and in the future can be used to create algorithms that predict the nature of the course of inflammatory diseases and new therapeutic agents, taking into account the environmentally unfavorable living conditions of the population. The results of the study will significantly supplement the understanding of the mechanisms of the pathogenesis of inflammatory processes with data on the participation of gene expression in them. In this regard, the dissertation research of A.N. Tokusheva is relevant.
		4.2 The content of the dissertation reflects the dissertation topic: 1) <b>reflects</b> ; 2) partially reflects; 3) does not reflect.	The content of the dissertation is fully consistent with the topic of the research. The work consists of an introduction, a literature review, a description of materials and research methods, a chapter of own research, conclusions, and practical recommendations.
		4.3. The aim and objectives correspond to the dissertation topic: 1) <b>correspond</b> ; 2) partially correspond; 3) do not correspond.	The purpose and objectives of the dissertation work were determined based on the analysis of the literature search and their own data on the problem under study. The purpose and objectives of the research are clearly formulated and solutions for each problem are consistently presented in certain sections of the dissertation.
		4.4 All sections and statements of the dissertation are logically interconnected: 1) <b>fully interconnected</b> ; 2) partially interconnected; 3) no interconnection.	Relevance, scientific novelty, practical significance, all sections of the dissertation work, as well as the main provisions submitted for defense, are united by the internal unity of the results obtained.



		<p>4.5 The new solutions (principles, methods) proposed by the author are substantiated and evaluated in comparison with known solutions:</p> <ol style="list-style-type: none"> <li>1) <b>critical analysis is present;</b></li> <li>2) partial analysis;</li> <li>3) the analysis consists of quotes from other authors rather than the author's own opinions;</li> <li>4) no analysis.</li> </ol>	The dissertation contains a detailed analysis of modern literature data on the topic under study.
5.	Principle of Scientific Novelty	<p>5.1 Are the scientific results and statements new?</p> <ol style="list-style-type: none"> <li>1) <b>completely new;</b></li> <li>2) partially new (25-75% are new);</li> <li>3) not new (less than 25% are new).</li> </ol>	The main scientific results and provisions of the dissertation do not raise doubts about their novelty, which is confirmed by the presence of publications in international peer-reviewed journals.
		<p>5.2 Are the conclusions of the dissertation new?</p> <p>Выводы диссертации являются новыми?</p> <ol style="list-style-type: none"> <li>1) <b>completely new;</b></li> <li>2) partially new (25-75% are new);</li> <li>3) not new (less than 25% are new).</li> </ol>	The conclusions formulated in these dissertations, according to the research conducted, are completely new and justified.
		<p>5.3 Are the technical, technological, economic, or managerial solutions new and substantiated?</p> <ol style="list-style-type: none"> <li>1) <b>completely new;</b></li> <li>2) partially new (25-75% are new);</li> <li>3) not new (less than 25% are new).</li> </ol>	A patent of the Republic of Kazakhstan for a utility model was obtained for a new method developed by the author for predicting the chronicity of the inflammatory process under conditions of intoxication with vanadium and chromium salts.
6.	Justification of the main conclusions	All main <b>conclusions are</b> /are not based on scientifically sound evidence or are sufficiently well substantiated (for qualitative research and fields of study in arts and humanities).	All conclusions, scientific provisions, and practical recommendations of the dissertation follow from the results of the research and are reasoned, justified and reliable.

7.	Main statements submitted for defense	<p>It is necessary to answer the following questions for each statement separately:</p> <p>7.1 Has the statement been proven?  1) <b>proven</b>;  2) rather proven;  3) rather not proven;  4) not proven;  5) it is impossible to verify the proof of the statement in its current form.</p> <p>7.2 Is it trivial?  1) yes;  2) <b>no</b>;  3) it is impossible to verify the triviality of the statement in its current form.</p> <p>7.3 Is it new?  1) <b>yes</b>;  2) no;  3) it is impossible to verify the novelty of the statement in its current form.</p> <p>7.4 Level of applicability:  1) narrow;  2) <b>medium</b>;  3) wide;  4) it is impossible to verify the level of applicability of the statement in its current form.</p> <p>7.5 Has it been proven in the article?  1) <b>yes</b>;  2) no;  3) it is impossible to verify the proof of the statement in the article in its current form.</p>	<p>The provisions submitted for defense are proven by research materials, are new, the level of application is average and the provisions are proven in 13 scientific publications, of which: 1 article in a journal indexed in the Scopus database, 4 articles in periodicals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Education and Science of the Republic of Kazakhstan, 4 theses in collections of foreign international conferences indexed in the databases Scopus and PubMed, 4 articles in international journals, 1 utility model patent.</p>
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8.	Principle of Reliability. Reliability of sources and provided information.	8.1 Is the choice of methodology justified or sufficiently detailed? 1) <b>yes</b> ; 2) no.	The choice of research methodology is justified and described in detail in the corresponding section of the dissertation work. The methods used in the dissertation work are modern and generally accepted.
		8.2 The results of the dissertation work were obtained using modern methods of scientific research and techniques for data processing and interpretation with the use of computer technologies: 1) <b>yes</b> ; 2) no.	The data obtained during the experiments were statistically processed using the program STATISTIKA 6,0, SPSS version 15. Quantitative indicators were presented as M (SD, where M is the mean value and SD is the standard deviation). To check the coincidence of the distribution of studied quantitative indicators with the normal distribution in the groups, the Kolmogorov-Smirnov test was used. If the law of distribution of the studied numerical indicators differed from the normal one, then the statistical significance of differences was tested using the Mann-Whitney U-test (in the case of paired independent samples) and the Kruskal-Wallis test (in the case of multiple independent samples). Differences were considered significant at $p < 0,05$ . To determine the existence of functional relationships between parameters, the R Spearman correlation coefficient was calculated, which was considered significant at $p < 0,05$ . Genomic data analysis was performed with R, packages DESeq2 and Reactome.
		8.3 Theoretical conclusions, models, identified relationships, and patterns are proven and confirmed by experimental research (for fields of study in pedagogical sciences, results are proven based on a pedagogical experiment): 1) <b>yes</b> ; 2) no.	The conclusions and main provisions of the dissertation work were obtained on the basis of experiments conducted in comparison groups, are interconnected and reflect the purpose and objectives of the study.
		8.4 Important statements are: <b>confirmed</b> / partially confirmed / not confirmed by references to relevant and reliable scientific literature.	Each scientific claim is supported by reference to current and reliable scientific literature.

		8.5 The literature sources used are: <b>sufficient</b> / not sufficient for the literature review.	The dissertation work carried out a comprehensive analysis of modern data from domestic and foreign scientific literature. The list of sources used includes 319 items.
9	Principle of Practical Value	9.1 The dissertation has theoretical significance: 1) <b>yes</b> ; 2) <b>no</b> .	The theoretical significance of the scientific work is beyond doubt and its results can be used, including lectures and classroom training.
		9.2 The dissertation has practical significance and there is a high likelihood of applying the results in practice: 1) <b>yes</b> ; 2) <b>no</b> .	<ol style="list-style-type: none"> <li>1. Data obtained in the course of experimental studies can be useful in conducting applied research devoted to the study of medical problems within the framework of the corresponding priority area.</li> <li>2. Data on the immunotoxic effects of vanadium and chromium, as some of the common anthropogenic pollutants, can be useful in assessing risk factors for the disease, taking into account the region of residence of the patient and preventing its chronicity, including an assessment of the immune status in the diagnosis.</li> <li>3. The findings of this study may also be useful for government and commercial structures interested in the development and promotion of new domestically produced medicinal brands.</li> <li>4. The dissertation materials can be used in the educational process at medical and biological faculties, as well as in postgraduate education courses for immunologists, therapists and general practitioners.</li> <li>5. Based on the results of the research, two utility model certificates were obtained. A monograph was published based on the dissertation materials, which is included in the list of recommended literature for 2nd and 3rd year students of general medicine in preparation for practical training.</li> </ol>
		9.3 The proposals for practice are: 1) <b>completely new</b> ; 2) partially new (25-75% are new); 3) not new (less than 25% are new).	The proposals for practice are completely new.



10.	Quality of Writing and Formatting	<p>The quality of academic writing:</p> <p>1) <b>high;</b>  2) medium;  3) below medium;  4) low.</p>	<p>The dissertation consists of an introduction, four chapters, such as a literature review, a description of materials and methods, the results of one's own research, a discussion, a conclusion including conclusions, and a list of references.</p> <p>Based on the results of the review of Aliya Tokusheva's dissertation work on the topic "Molecular and biological features of the course of aseptic inflammation associated with ecologenic immunosuppression" it can be noted that the work is a completed scientific and qualifying work. It presents a solution to a current scientific problem that is important for experimental pathophysiology. Work by Tokusheva A.N. fully complies with the requirements for obtaining a PhD degree in the specialty 6D110100 - "Medicine", its author deserves to be awarded the required degree due to proven relevance, scientific novelty, practical significance, completeness of presentation and validity of the conclusions of his research.</p>
11.	Comments on the Dissertation	There are no fundamental comments on the work.	
12.	The scientific level of the doctoral student's articles on the research topic (in case of dissertation defense in the form of a series of articles, the official reviewers comment on the scientific level of each article on the research topic)		
13.	<p>Official reviewer's decision:</p> <p><b>1. Award the degree of Doctor of Philosophy (PhD) or Doctor of Profile (in case of defense in a dissertation council at a higher education institution with special status), or petition the Committee to award the doctoral student the degree of Doctor of Philosophy (PhD) or Doctor of Profile (in case of defense in a dissertation council at a higher education institution without special status);</b></p>	<p>I recommend awarding the degree of Doctor of Philosophy (PhD) to Aliya N. Tokusheva, who presented a dissertation on the topic: "Molecular and biological features of the course of aseptic inflammation associated with ecologenic immunosuppression," submitted for the academic degree of Doctor of PhD in specialty 6D110100 – "Medicine"</p>	

<p>2. Send the dissertation for revision if it does not comply with paragraph 4 and/or 6 of the Rules and/or partially complies with the principles (except for the principle of academic integrity) listed in paragraph 5 of the Rules, and/or there are comments that require correction. In case of defending a dissertation in the form of a series of articles, the dissertation is not sent for revision;</p> <p>3. Deny the awarding of the degree of Doctor of Philosophy (PhD) or Doctor of Profile in case of violation of the principle of academic integrity or non-compliance with the principles of scientific novelty, internal unity, and reliability.</p>	
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**Official Reviewer:**  
**PhD, associate professor,**  
**Department of Biomedical Sciences**  
**at the Nazarbayev University School of Medicine**

**Jeannette Kunz**

«НАЗАРБАЕВ УНИВЕРСИТЕТИ» ДЕРБЕС БІЛІМ БЕРУ ҰЙЫМЫ THE AUTONOMOUS ORGANIZATION OF EDUCATION «NAZARBAYEV UNIVERSITY» Медицина мектебі / School of Medicine	
Шығыс/Outgoing №	_____
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