

TO THE CHAIR OF THE SCIENTIFIC JURY
in accordance with Order No. R-1306/25.02.2026
of the Rector of the Medical University – Plovdiv

STATEMENT

by Prof. Tanya Ivanova Deneva, MD, PhD
Head of the Department of Clinical Laboratory
Faculty of Medicine, Medical University – Plovdiv

Regarding: Dissertation for awarding the scientific degree “Doctor of Sciences”

Field of Higher Education: 7. Healthcare and Sports
Professional Field: 7.1. Medicine
Doctoral Program: “Medical Biology”

Author: Prof. Maria Hristova Kazakova
Department of Medical Biology, Faculty of Medicine,
Medical University – Plovdiv

Title: “Molecular-biological and immunological studies on chitinase-like proteins
CHI3L1 and CHI3L2 in inflammation, tumorigenesis, and neurodegeneration”

Biographical Data and Academic Development

Prof. Maria Kazakova graduated in 2005 from Paisii Hilendarski University with a bachelor’s degree in molecular biology, and in 2006 obtained a Master’s degree in Cell Biology. From 2005 to 2007, she worked as a biologist at the Department of Developmental Biology at the same university. After successfully passing a competitive examination in 2007, she was appointed as an Assistant Professor at the Department of Medical Biology at the Medical University – Plovdiv. Alongside her teaching activities, she completed her PhD in Immunology, which she successfully defended in 2013. In the same year, she obtained a specialty in Medical Biology and was subsequently promoted to Chief Assistant Professor. In 2015, she also obtained a Master’s degree in management of applied research. Since 2016, she has been an Associate Professor, and since 2024 – Professor and Head of the Department of Medical Biology.

Relevance and Significance of the Dissertation

The relevance of the present dissertation is determined by the growing interest in the molecular and cellular mechanisms underlying chronic inflammation, autoimmune diseases, neurodegenerative processes, and malignant neoplasms—pathological conditions of substantial global medical and societal importance. Contemporary medicine faces an increasing need for a deeper understanding of the complex pathogenetic interactions between immune activation, tissue remodeling, mitochondrial dysfunction, and oxidative stress, which collectively determine disease progression, severity, and prognosis.

In this context, the chitinase-like proteins CHI3L1 (YKL-40) and CHI3L2 (YKL-39) emerge as key molecules at the interface between immune response, inflammation, and structural tissue alterations. While CHI3L1 has been relatively well investigated as a biomarker and mediator in various inflammatory, autoimmune, and neoplastic diseases, significant gaps remain regarding its regulatory mechanisms and its functional links to cellular metabolism and mitochondrial activity. Even more limited is the current knowledge of CHI3L2, whose expression patterns, biological role, and clinical relevance remain insufficiently elucidated, particularly in comparison with CHI3L1.

The scientific significance of the dissertation lies in its interdisciplinary approach, integrating molecular-biological, immunological, and clinical analyses to evaluate the role of CHI3L1 and CHI3L2 in autoimmune diseases, inflammation-associated neurodegenerative conditions, and tumorigenesis. The investigation of these proteins not only as serum or cerebrospinal fluid biomarkers, but also in relation to mitochondrial bioenergetics and oxidative stress, represents a modern and innovative research direction aligned with current trends in personalized medicine.

Particularly noteworthy is the analysis of CHI3L1 and CHI3L2 in diseases lacking sufficiently sensitive and specific biomarkers for early diagnosis, patient stratification, and therapeutic monitoring, such as rheumatoid arthritis, systemic sclerosis, osteoarthritis, ischemic stroke, central nervous system infections, and autism spectrum disorders. The parallel investigation of both chitinase-like proteins enables the delineation of both shared and distinct pathophysiological roles, which is essential for understanding the molecular heterogeneity of these conditions.

The practical significance of the study is reflected in the potential application of CHI3L1 and CHI3L2 as complementary or novel biomarkers in clinical practice—for assessing disease activity, prognosis, and therapeutic response. The accumulated data provide a foundation for the development of new diagnostic and prognostic panels, as well as for the identification of potential therapeutic targets aimed at modulating inflammation, tissue remodeling, and mitochondrial function.

In summary, the dissertation is both timely and highly significant from fundamental and applied perspectives, contributing to the expansion of knowledge regarding the role of chitinase-like proteins in key pathological processes and offering new perspectives for improving the diagnosis, monitoring, and treatment of socially significant diseases.

Characteristics and Evaluation of the Dissertation and Its Contributions

The dissertation is structured into the following main sections: introduction, literature review, aims and objectives, materials and methods, results, discussion, conclusions, and contributions. The bibliography includes 231 references, of which two are in Cyrillic, demonstrating a comprehensive and up-to-date knowledge of international scientific literature. The dissertation contains 41 figures and 31 tables, which effectively illustrate and support the presented results. Four appendices are included at the end, complementing the main text.

The literature review, spanning 34 pages, focuses on chitinases and chitinase-like proteins. It provides a detailed and systematic analysis of the role of CHI3L1 and CHI3L2 in diseases of diverse etiology, including rheumatoid arthritis, systemic sclerosis, and osteoarthritis. Additionally, summarized data are presented regarding their levels and clinical significance in ischemic stroke, autism spectrum disorders, and central nervous system infections. A separate section is devoted to their role in tumorigenesis, with emphasis on colorectal carcinoma and glioblastoma.

The aim of the dissertation is to investigate the complex expression and biological role of the chitinase-like proteins CHI3L1 and CHI3L2 in inflammation, tumorigenesis, and neurodegeneration. Two main objectives are defined, one of which includes three sub-objectives logically aligned with the overall research concept.

The Materials and Methods section, developed over 24 pages, encompasses a broad spectrum of molecular-biological, immunological, and cell-biological techniques. The applied methodologies range from innovative experimental approaches to established routine methods, ensuring reliability, reproducibility, and interdisciplinary validity of the results.

The Results section is the most extensive (72 pages), with data logically organized into subchapters according to the studied disease entities. The use of 41 figures and 31 tables enhances clarity and facilitates interpretation.

As a result of the conducted investigations, **seven main conclusions were formulated:**

1. Gene and protein expression of CHI3L1 and CHI3L2 is significantly elevated in patients with rheumatoid arthritis prior to therapy and decreases substantially depending on treatment, reflecting reduction of inflammatory activity.
2. Elevated plasma levels of CHI3L1 in systemic sclerosis, together with their association with clinical scores and pro-inflammatory cytokines, illustrate chronic autoimmune inflammation and support its role as a patient stratification marker.
3. CHI3L1 expression in central nervous system infections may aid in early differentiation between viral and bacterial etiology.
4. CHI3L1 and CHI3L2 exhibit distinct expression patterns associated with tumor aggressiveness in colorectal carcinoma and glioblastoma.
5. Tissue expression of CHI3L1 in colorectal carcinoma, combined with tumor budding, represents a reliable indicator of metastatic potential.
6. CHI3L1 may serve as a marker of mitochondrial dysfunction correlating with clinical scales in autism spectrum disorders.
7. Novel aspects of the relationship between CHI3L1, CHI3L2, and mitochondrial function/dysfunction are presented, expanding possibilities for assessing inflammation, disease progression, and therapeutic response.

Contributions

1. Novel original data are presented on gene and protein expression of CHI3L1 and CHI3L2 in diseases associated with inflammation, tissue remodelling, and neurodegeneration.
2. Early identification of mitochondrial dysfunction is demonstrated as a basis for improved antioxidant strategies and optimized therapy monitoring in autism spectrum disorders and rheumatoid arthritis.
3. CHI3L1 is shown to promote tumor cell proliferation, invasion, and metastatic potential through modulation of inflammation and the tumor microenvironment, supporting its prognostic and potential therapeutic relevance.

Publication Activity and Scientific Contributions

The results of the conducted comprehensive study have been published in 17 scientific articles, with Prof. Maria Kazakova serving as first author in six of them. The research findings have been presented at 30 scientific forums, including 15 international congresses, demonstrating high scientific visibility and international recognition of the results obtained.

The implementation of the dissertation research was supported by funding from several intra-university projects, two national projects, and one European project, further emphasizing the scientific and practical significance of the study.

Compliance with Mandatory Quantitative Criteria and Scientific indicators

Prof. Maria Kazakova has submitted a self-assessment demonstrating compliance with and fulfilment of the mandatory quantitative criteria and scientific indicators in accordance with the Academic Staff Development Act in the Republic of Bulgaria and the Regulations for the Development of Academic Staff at the Medical University – Plovdiv, for the awarding of the scientific degree “Doctor of Sciences”.

Group of Indicators	Content	Doctor of Sciences (Required)	Candidate: Maria Kazakova
A	Indicator 1	50	50
B	Indicator 2	100	100
C	Sum of Indicators 5–9	100	133
D	Sum of Indicators 10–12 (MU–Plovdiv Supplement)	100 (+100)	166 × 15 pts = 2490
Total	—	450	2,773

Based on the candidate’s documented academic activity, the requirements set forth in the Academic Staff Development Act of the Republic of Bulgaria and its implementing regulations at the Medical University – Plovdiv for the awarding of the scientific degree “Doctor of Sciences” are fully met and substantially exceeded.

CONCLUSION

The dissertation entitled “Molecular-biological and immunological studies on chitinase-like proteins CHI3L1 and CHI3L2 in inflammation, tumorigenesis, and neurodegeneration” represents a comprehensive, large-scale, and interdisciplinary scientific investigation, distinguished by its high scientific value, originality, and significance from both fundamental and applied perspectives. The work demonstrates profound theoretical knowledge, excellent command of contemporary molecular-biological, immunological, and cell-biological methodologies, as well as a strong capacity for critical analysis and interpretation of complex experimental data. The formulated conclusions and contributions are logically substantiated and convincingly supported by the obtained results.

In view of the above, I confidently express my positive evaluation of the dissertation and recommend that the esteemed members of the extended Department Council vote in favour of proceeding with the official defence of the dissertation entitled “Molecular-biological and immunological studies on chitinase-like proteins CHI3L1 and CHI3L2 in inflammation, tumorigenesis, and neurodegeneration”, authored by Prof. Maria Kazakova, for the awarding of the scientific degree “Doctor of Sciences” in the field of Medicine, doctoral program “Medical Biology”.

Prof. Tanya Deneva, MD, PhD



Заличено на основание
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