

## STATEMENT

by Prof. Maria Stoyanova Panchovska-Mocheva, MD, PhD,  
Department of Propaedeutics of Internal Diseases  
Medical University, Faculty of Medicine - Plovdiv,  
on dissertation for awarding the educational and scientific degree of  
Doctor of Sciences  
Professional field 7.1. Medicine,  
Specialty: 03.01.18. Rheumatology  
Author: Rositsa Valerieva Karalilova, MD, PhD  
Department: Propaedeutics of Internal Diseases

**Subject: Imaging and serum biomarkers for pulmonary and joint involvement in patients with systemic sclerosis**

### **1. General description of the procedure and the doctoral candidate.**

The statement was prepared as per order No. P 1843 / 22/10/2020 of the Rector of Medical University - Plovdiv, Prof. Mariana Murdzheva, MD, PhD, MHM.

The set of materials, presented to me on paper and electronically, complies with Art. 123 (1) of the Procedure for Awarding the Scientific Degree of Doctor of Sciences at Medical University – Plovdiv, the Regulations of MU - Plovdiv as of 06/11/2014, and includes the required documents.

Rositsa Valerieva Karalilova, MD, PhD, was born on October 10, 1979. She acquired her Master's degree in Medicine at MU – Plovdiv in 2005 and in 2013 she obtained specialization in Rheumatology. She has been Assistant at the Department of Propaedeutics of Internal Diseases since 2013. As a free PhD student, she worked out a dissertation on the subject: “Diagnostic capabilities of new ultrasonographic techniques for the assessment of skin, articular, periarticular and pulmonary involvement in systemic sclerosis”. Following the successful defence of the thesis

in 2018, she was awarded the scientific degree of PhD. At present, she is Assistant at the Department of Propaedeutics of Internal Diseases, Supervisor of academic activities and Chief Administrative Assistant. Since 2005, immediately after acquiring her Master's degree, Rositsa Valerieva Karalilova, MD, PhD, has been working at the Rheumatology Clinic at University Hospital Kaspela. She is a member of the Bulgarian Medical Association, the Bulgarian Scientific Society of Rheumatology, the Bulgarian Rheumatology Society, the Bulgarian Medical Society of Osteoporosis and Osteoarthritis, the Bulgarian Association of Musculoskeletal Ultrasound. Since 2017, Karalilova, MD, PhD, has been a certified European professor of Musculoskeletal Ultrasound at the European League Against Rheumatism (EULAR). From 2016 to date, she has taught several courses in joint ultrasound under the auspices of the EULAR as a lecturer and trainer. The scientific interests of Karalilova, MD, PhD are in the field of systemic sclerosis and other autoimmune inflammatory and systemic connective tissue diseases, as well as musculoskeletal ultrasound.

## **2. Relevance of the subject.**

The dissertation examines important aspects of progressive systemic sclerosis (SSc): identification of the disease biomarkers enabling the differentiation of disease subtypes, the predictors of disease progression, the involvement of internal organs and, as a logical consequence – the selection of an appropriate treatment approach.

Systemic sclerosis poses a considerable number of challenges to specialists in Rheumatology. Over the last years, researchers' efforts have been focused on studying new disease biomarkers. The presented thesis is the first study in Bulgaria, which investigates the relationship between serum biomarkers and specific organ involvement, pulmonary and joint involvement in systemic sclerosis by using validated imaging methods.

The study was carried out with the financial support of MU - Plovdiv under project DP 06/2018, as well as the Bulgarian Association of Musculoskeletal Ultrasound.

### **3. Knowledge of the problem.**

The dissertation consists of 200 pages, 34 tables, 34 figures and 15 appendices.

The literature review is presented on 68 pages. It shows data from 917 literature sources, of which 7 are in Cyrillic and 910 in Latin. It offers an in-depth analysis of scientific data on the significance and informativity of imaging and serum biomarkers for pulmonary and joint involvement in progressive systemic sclerosis, namely, YKL-40, IL-6, CXCL-4, ICAM-1, TNF- $\alpha$ , IL-12p40, IL-17A, TGF- $\beta$ 1 in blood serum; the levels of gene expression in inflammatory-response-associated genes, as well as the expression levels of specific miRNAs. In the thesis, a consideration is given to the points of dispute in the studied field. The thesis examines the informative value of specific instrumental approaches enabling the assessment of skin, joint and tendons and pulmonary fibrosis by ultrasound elastography, lung radiography, and the role of capillaroscopy and transthoracic echocardiography.

The analysed information demonstrates detailed knowledge of the subject and is comprehensive. There is a critical approach to the data as a prerequisite for a proper analysis of the results obtained by the author.

### **4. Methods of the study.**

The aim of the study is clearly defined: "To reveal some of the cellular and molecular mechanisms for pulmonary and joint involvement in SSc and to develop a panel of biomarkers with possible organ association".

Five tasks were set on the path to that aim and immunological and instrumental evaluation approaches were included.

Modern statistical methods for analysis of the obtained results were applied that allow for achieving the set aim.

The study included 95 individuals – 90 women and 5 men, mean age of  $52.76 \pm 14.12$  years. The patients were assigned to several subgroups depending on the specific types of progressive scleroderma, including the overlap syndrome and very early systemic sclerosis. The group of healthy controls included individuals of similar age. The patients were examined at the

Rheumatology Clinic at University Hospital Kaspela and in outpatient settings, including the healthy volunteers (mostly healthcare workers).

The selection of study participants was carried out in accordance with clear and precise criteria, which is a prerequisite for credible results. The samples are sufficient for the data statistical analysis.

## **5. Characteristics and assessment of the dissertation.**

The results of author's study are presented in several sections:

- 1) Clinical characteristics of the patients;
- 2) Comparative assessment of the patients' and controls' serum cytokine concentrations, determination of the genetic expression levels of inflammatory-response-associated genes, determination of the expression levels of miRNAs;
- 3) Significant correlations between the studied values - serum cytokines and ultrasonographic examinations with scores related to skin thickness, pulmonary fibrosis and pulmonary arterial hypertension (PAH).

The studied parameters IL-6, YKL-40, ICAM-1, CXCL4 and IL-12p40 were found to be significantly correlated with the degree of skin thickness, PAH, pulmonary fibrosis, the GUESS, SEC and US10SSc scores.

The "Discussion" section presents an analysis of the author's results against the data from the world scientific literature. Discussion issues were discussed critically and in depth.

The 10 conclusions are derived logically and reflect in an objective manner the data from the conducted study. There are 9 contributions divided into 3 groups. Five of them are original for Bulgaria and the world literature - this is the first Bulgarian study of certain anti-inflammatory cytokine serum levels (8 serum biomarkers) in SSc patients, the role of specific biomarkers for specific organ involvement and their correlation with the imaging biomarkers for pulmonary and joint involvement. This is the first Bulgarian study of the gene expression levels of inflammatory-response-associated genes and the expression levels of specific miRNAs.

## **6. Evaluation of the publications and personal contribution of Rositsa Karalilova, MD, PhD.**

A list of 15 publications, related to the subject of the dissertation, is presented. The candidate is the first author of 6 of the publications and co-author of 5 of the papers which confirms her undeniable contribution to scientific research.

The candidate's IF includes a total IF of 19.017 for the articles, a total IF of 63.539 for participations in congresses, and a total IF of 38.67 for citations of the dissertation-related publications.

According to the scientometric criteria for achieving the scientific degree of Doctor of Sciences, the results of Rositsa Karalilova, MD, PhD fully meet and exceed the required.

## **7. The author's abstract.**

The author's abstract is structured in compliance with the requirements and reflects the main results of the dissertation.

## **Conclusion.**

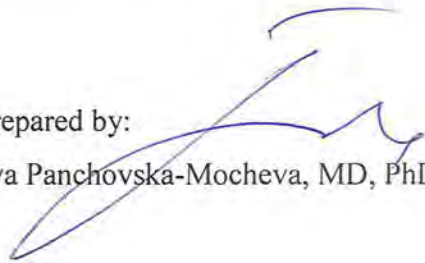
The submitted dissertation of Rositsa Valerieva Karalilova, MD, PhD, with scientific consultants: Prof. Marco Matucci Cerinic, MD, PhD and Prof. Anastas Zgurov Batalov, MD, PhD, contains scientific and applied results which comply with the Academic Staff Development Act (ASDA) in the Republic of Bulgaria, the Regulations for the implementation of the ASDA and the corresponding Regulations of Medical University - Plovdiv. The dissertation demonstrates that Rositsa Karalilova, MD, PhD, has an in-depth knowledge and professional skills in the scientific field of Rheumatology. Rositsa Karalilova, MD, PhD shows capabilities and competencies to independently conduct scientific research.

In view of the above, I hereby confidently give my **positive assessment** of the presented scientific work with the obtained results and contributions, and recommend to the members of the honorable scientific jury to vote positively for awarding the scientific degree of Doctor of Sciences to Rositsa Valerieva Karalilova, MD, PhD, in the field of higher education 7. Healthcare and Sports, professional field 7.1. Medicine, specialty 03.01.18 Rheumatology.

December 12, 2020

The statement was prepared by:

Prof. Maria Stoyanova Panchovska-Mocheva, MD, PhD

A handwritten signature in blue ink, consisting of several fluid, overlapping strokes that form a stylized representation of the name Maria Stoyanova Panchovska-Mocheva.