



TITU MAIORESCU UNIVERSITY BUCHAREST
DOCTORAL SCHOOL MEDICINE FIELD



HABILITATION THESIS FOR DOCTORAL LEADERSHIP CERTIFICATION

Exploring the Relationship Between Mitochondrial Dysfunction Biomarkers and Early Detection of Pulmonary Cancer

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Bucharest 2026

ABSTRACT

The habilitation thesis entitled **“Exploring the Relationship between Biomarkers of Mitochondrial Dysfunction and the Early Detection of Lung Cancer”** brings together the main personal research, professional, and academic directions that I have pursued in my career following the completion of my doctoral studies. The present work is based on connecting the interdisciplinary studies I have carried out and addresses translational aspects derived from research conducted on experimental animals, current clinical practice, and the clinical studies in which I have collaborated. The results and future directions are focused on the early detection of bronchopulmonary cancer, the advanced study of mitochondrial dysfunctions, and their possible use for a better optimization of the results already obtained in the research and development of the bioinformatics platform for the early diagnosis of bronchopulmonary cancer, results patented at the international level. The topic addressed is of particular importance in the current context, in which prevention and early detection of bronchopulmonary cancer, an aggressive type of cancer, directly impact survival rate and response to targeted therapies.

The habilitation thesis is structured according to CNATDCU recommendations and comprises three main sections, in which the scientific, professional, and academic achievements from obtaining the title of Doctor of Medicine up to the present are presented, as well as the future directions of professional and academic development.

1. Scientific, academic, and professional activity

I graduated from the Faculty of Medicine of the “Grigore T. Popa” University of Medicine and Pharmacy in Iași. In October 2012, I enrolled in the doctoral university studies cycle (full-time contract, with scholarship). The thesis was carried out under the supervision of Prof. Dr. Magda Bădescu and was entitled **“Mitochondrial modulators in pain. Aspects and characteristics.”** Within the doctoral research, I evaluated the main mitochondrial modulators and their effect on visceral and neuropathic pain, pain associated with oncological conditions. During my doctoral studies, I won through competition a scholarship within the project **“Strategic partnership for increasing the quality of scientific research in medical**

universities by awarding doctoral and postdoctoral scholarships – DocMed.Net_2.0,” POSDRU/159/1.5/S/136893, co-financed by the European Social Fund through the Sectoral Operational Programme for Human Resources Development 2007–2013. This scholarship allowed me to improve a series of fundamental research techniques that I later applied also within the Center for the Study and Therapy of Pain, where I carried out the studies included in my doctoral thesis. Part of the experiments necessary for conducting my doctoral research were supported by the grant **“Experimental studies on the relationship between mitochondrial dysfunctions and pain,”** PN-II-ID-PCE-2011-3-0875, which was carried out during 2011–2016, having as Grant Director Assist. Prof. Dr. Cătălina Roxana Bohotin, where I collaborated as a scientific researcher in training.

At present, I am Associate Professor within the Department of Preclinical Disciplines of the Faculty of Medicine, Titu Maiorescu University of Bucharest, being course coordinator for the discipline of Pharmacology. Throughout my career, I have collaborated with several medical specialties, both in clinical and preclinical activity, collaborating both with researchers at national level and within international teams. The scientific activity carried out after defending my doctoral thesis materialized in the publication of 20 articles in ISI Web of Science indexed journals as first author or co-author, 21 articles in ISI-indexed journals as well as 15 articles in BDI-indexed journals, and an H-index of 11. During this activity, I collaborated within 14 research projects.

2. Research directions

2.1. Advanced methods of screening and early detection of bronchopulmonary cancer

Lung cancer is the second most frequently diagnosed cancer in both men and women, having a mortality higher than breast, colon, and prostate cancers combined. Early detection of bronchopulmonary neoplasms contributes greatly both to increased survival and to a better response to current therapies. The adaptive immune system represents a valuable source of information regarding present and past immune responses, being able to function as a biosensor. Considering the essential role of the immune system in numerous pathologies, correlated with machine learning techniques, it can be used to decipher how immunological

information is encoded in adaptive immune receptor repertoires, thus facilitating the prediction of immune responses and allowing the development of new diagnostic methods.

2.2. Exploration of identified and identifiable mitochondrial dysfunctions in patients with bronchopulmonary cancer with or without other associated neoplasms

Mitochondrial dysfunctions play an important role in cancer biology, being involved in the alteration of energy metabolism, regulation of apoptosis, and generation of oxidative stress. In bronchopulmonary cancer, these changes may contribute to tumor initiation and progression, as well as to the occurrence of treatment resistance. The analysis of mitochondrial dysfunctions in patients with bronchopulmonary cancer, in the presence or absence of other associated neoplasms, may provide relevant data regarding the molecular mechanisms involved in disease evolution. The relational exploration between these dysfunctions and bronchopulmonary neoplasm aims to identify potential mitochondrial-level changes through specific determinations, including alterations of oxidative metabolism, mitochondrial DNA, and the production of reactive oxygen species. Comparing the results from patients with isolated bronchopulmonary cancer with those presenting multiple neoplasms may contribute to the identification of modifications with high specificity in pulmonary neoplasms and open new opportunities for adjuvant pharmacological treatment.

2.3. The use of algorithms and artificial intelligence for the analysis, identification, and possible correlation of the early stages of bronchopulmonary neoplasm with certain mitochondrial dysfunctions, as well as the impact of possible pharmacological interventions on them

The use of artificial intelligence algorithms and advanced data analysis methods can significantly contribute to the identification of early biological changes associated with bronchopulmonary neoplasm. In this context, the application of predictive models and machine learning techniques, starting from the results already obtained, may allow the detailed analysis and correlation of the early stages of the disease with certain identifiable mitochondrial dysfunctions. Thus, it may facilitate the identification of molecular patterns relevant for the onset and progression of the tumoral process, as well as the correlation of

different pharmacological interventions with mitochondrial dysfunction and treatment responsiveness, allowing an individualized treatment.

3. Scientific, professional, and academic development plans

As a plan for scientific, professional, and academic development, I consider it is necessary to increase the visibility of the obtained results through the publication of specialty books, articles in prestigious journals, and through active involvement in the research activities of the faculty and the doctoral school. In addition to the aforementioned directions, I consider it a priority to attract funding for carrying out studies, as well as to involve future doctoral students in research activity, in the dissemination of results, and in the elaboration and submission of research projects. Regarding academic activity, my objective is to promote an individualized educational model, centered on the student's needs, but at the same time aligned with the current demands of medical knowledge, through the progressive integration of new directions and trends in international medicine. I also aim to strengthen interdisciplinary and international collaborations, in order to facilitate the exchange of experience, access to modern research infrastructures, and the development of projects with significant scientific and applicative impact. At the same time, I consider essential the development of an academic and research environment based on scientific rigor, mentorship, and the stimulation of critical thinking, which should support the professional training of students, residents, and young researchers.