

**”VICTOR BABEȘ” UNIVERSITY OF  
MEDICINE AND PHARMACY FROM TIMIȘOARA  
DOCTORAL SCHOOL  
MEDICINE DOMAIN**



**TRANSLATIONAL AND MULTIDISCIPLINARY  
APPROACH TO CHRONIC PULMONARY  
PATHOLOGY - FROM MECHANISMS TO CLINICAL  
IMPLICATIONS**

**ABSTRACT**

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The academic training in a **preclinical discipline, Physiopathology**, combined with the clinical professional specialization, initially in **Internal Medicine** and later in **Pneumology**, explains the beginning orientation of my scientific research activity, especially towards translational research with applicability in clinical medical practice of the results obtained under laboratory conditions.

Later, with the achievement of **clinical integration** and a more competitive transfer to the **discipline of Pneumology**, my scientific concerns were mainly focused in the direction of **multidisciplinary studies** (epidemiology, pathology, clinical medicine, functional explorations, radioimaging, pulmonary rehabilitation) regarding **patients with chronic pulmonary obstructive or interstitial pathology**.

The beginning of my scientific research activity was represented by the elaboration of the doctoral thesis entitled "**Experimental research on endothelial dysfunction in COPD**" completed and publicly supported on 16.02.2007. After the defense of the doctoral thesis, I capitalized on the results obtained by publishing a number of scientific works with great impact in the academic community: **1 monograph awarded by the Romanian Society of Physiological Sciences, 1 article published in the official journal of the Romanian Society of Pneumology, indexed by ISI, which received the award for best paper in the year of publication, 1 paper presented at the annual congress of the European Respiratory Society (ERS) under an ERS Gold Sponsorship.**

The experience gained during the doctoral studies in the management of scientific research in general and in organ-bath study on isolated vascular preparation regarding endothelial dysfunction was the rationament of my co-optation in the **Department of Research and Grant Management** within the university, as well as within the **Center of Studies in Preventive Medicine, UMF "Victor Babeș" Timișoara**, accredited by **CNCSIS** as a **type C research center**. From these positions, in between 2007-2013, I took part of the teams involved in implementation of **7 research projects financed on a competitive basis**.

The translational research results were presented through a series of full-length publications with international visibility, in the following research directions: (i) mechanisms incriminated (endothelial dysfunction, oxidative stress, mitochondrial dysfunction) in the etiopathogenesis of chronic diseases with a high impact on the population; **3 articles in ISI-listed journals, 1 chapter in a monograph edited by bilateral Romania-Hungary collaboration, 10 articles in BDI indexed journals;** (ii)

mechanisms incriminated in the restoration of nervous structures; **1 article in ISI indexed journal, 2 articles in BDI indexed journals**. Moreover, a series of studies were accepted to be presented at scientific events organized by prestigious international societies, 15 of them being published as abstracts in ISI journals with FI.

Given that since 2008 I have obtained clinical integration in the Department of Respiratory Medical Recovery within the structure of the "Dr. Victor Babeș" Timișoara, and since 2013 an **associate professor** title in the **discipline of Pneumology**, I have been co-opted into the multidisciplinary research team of the University Clinic of Pneumology. My expertise was initially mainly focused on the complex functional assessment (complex respiratory function tests, exercise testing, body composition analysis) of patients with obstructive pulmonary pathology included in pulmonary rehabilitation programs. Later, with my transfer to the Pneumology II clinical section, in 2015 and with my orientation of scientific concerns towards interstitial lung pathology, I was the promoter in the recognition obtained by the **Ministry of Health** for the Clinical Hospital for Infectious Diseases and Pneumophthisiology "Dr. Victor Babeș" from Timișoara as an **Expertise Center for Rare Pulmonary Diseases**.

In 2020, I was selected by file competition to participate in the implementation of **1 research project** in which our hospital gained coordinator role.

Notable research results from 2015-2020 determined the **Center for Research and Innovation in Personalized Medicine for Respiratory Diseases (CCIMPBR)/Center for Research and Innovation in Personalized Medicine of Respiratory Diseases (CRIPMRD)** within the discipline of Pneumology as an **Advanced Research Center** in 2020 by UMF "Victor Babeș" Timișoara through an internal competition. This status was reconfirmed next year (2021) also by competition. The statistics of research directions and studies of the University Clinic of Pneumology related to chronic lung pathology and to which I have contributed directly is listed as follows: **16 articles published in ISI listed journals, 1 chapter, 2 monographs with original data, as well as 14 articles published in BDI indexed journals**.

Some of the multidisciplinary studies in which I was actively involved, especially those elaborated until 2013, also analyzed other aspects of pathology (**5 articles in ISI-listed journals, 3 ISI-indexed proceedings, 5 articles in BDI-indexed journals, 3 monographs with original data**). However, some other have etio-pathogenic links with chronic lung pathology and even clinical implications, in this case systemic

endothelial dysfunction (**2 articles in ISI indexed journals, 2 ISI indexed proceedings, 2 BDI indexed journal articles**).

Of the multidisciplinary studies presented at prestigious international events, **41 were published in abstracts in ISI journals with FI.**

Out of the total of 475 scientific papers that I developed throughout my university career, 328 (**99 articles, 229 abstracts**) were published after obtaining the title of doctor of medicine, and their statistics in terms of **international visibility** are as follows:

- **61 papers** out of a total of 63, indexed **Web of Science – Core Collection (ISI)**
  - **25 articles** in ISI rated journals (**cumulative FI 51,266**), of which 11 as main author (**cumulative FI 21,194**), all after 2007,
  - **4 proceedings papers**, all published after 2007,
  - **32 summaries** out of a total of 34, two being published before 2007;
- **46 Scopus indexed articles** out of a total of 50, four being published before 2007;
- **39 PubMed indexed articles** out of a total of 42, two of which were published before 2007.

Regarding **the impact of the published works**, the statistics of the main analyzed indicators are as follows:

- **324 citations** in the ISI system with a **Hirsch index (IH) of 11**;
- **369 citations** in the **Scopus** system with an **IH of 11**;
- **671 bibliographic references** in the **Google Academic system** with an **IH of 15**;
- **465 citations** in the **Research Gate system** with an **IH equal to 12**.

Regarding recognition status of **scientific results and research activity**, the main benchmarks are as following:

- **1 OSIM invention patent**;
- **director of the Center for Research and Innovation in Personalized Medicine for Respiratory Diseases**;
- **member from Romania in the Management Committee of Action COST CA 16125 "European network for translational research in children's and adult interstitial lung disease" acronym ENT-eR-child**;
- **diploma of Excellence for the activity in the field of scientific research**, International Salon of Inventions and Innovations "Traian Vuia" Timișoara, 2021;

- **5 awards** for papers presented at scientific events;
- **3 articles accepted for funding in the UEFISCDI research award competition;**
- **ERS Silver Sponsorship and ERS Gold Sponsorship;**
- **organization of scientific events; 9 of international level and 5 of national level;**
- **moderator in international (3) and national (50) scientific events;**
- **invited lecturer at international (2), national (67), regional (18) scientific events.**

**Research themes** I developed in relation to **chronic obstructive pulmonary pathology** and the **relevance of the studies** are carried out as the following:

- I. **Smoking is also a risk factor for the systemic manifestations of COPD – 4 studies**
  1. The study that documented that **passive exposure to cigarette smoke in guinea pigs induces a systemic endothelial dysfunction**. This allowed the validation of this animal model as a useful experimental tool for investigating the pathogenic mechanisms regarding the association of COPD with cardiovascular comorbidities of an atherosclerotic nature. Also how this combination could be influenced in a favorable way was demonstrated.
  2. The study that analyzed **the favorable vascular response of Juniperus Communis aerosols on isolated aortic rings from rats exposed to passive smoking**. This is the only study in the published scientific literature that analyzed the protective effect of this natural agent with antioxidant properties regarding cardiovascular damage initiated by smoking passive.
  3. The study that evaluated **the effect of smoking on the reactivity of internal mammary artery vascular rings taken from subjects undergoing aorto-coronary bypass interventions** is most likely the only study that documents, on an experimental model of a vascular sample isolated in an organ bath, the in vivo damage to the vascular endothelium induced by smoking.
  4. The study that assessed **the influence of cigarette smoking on endothelial function evaluated in vivo** revealed that the level of cumulative exposure to

cigarette smoke is reflected in the degree of structural and functional damage to the cardiovascular system.

## **II. Systemic inflammation turning stone for cardiovascular comorbidities in COPD – 3 studies**

1. The study that confirmed **the association of cardiovascular comorbidities with the systemic inflammatory status expressed by persistently elevated C-reactive protein plasma levels in patients with stable COPD**. This study suggests that in current clinical practice, a limited set of usual parameters are most likely sufficient to be monitored such as white blood cell count, plasma fibrinogen, C-reactive protein. The use of other inflammatory biomarkers does not seem to yield additional information.
2. The study suggesting that **endothelial dysfunction is a possible link between cardiovascular comorbidities and the "inflammaging" phenomenon in COPD** indicates the use of specific biomarkers of endothelial dysfunction such as endothelin-1 (ET-1) for a more accurate assessment of COPD-associated cardiovascular risk in elderly patients without obvious signs of systemic inflammation.
3. The study that analyzed **the subclinical cardiovascular organ damage of at carotidian level in relation to other systemic effects in the context of persistent inflammatory phenotype in patients with stable COPD** provides arguments for the hypothesis that the systemic inflammatory status is responsible for both pulmonary and extrapulmonary effects of COPD.

## **III. Neuro-cognitive dysfunction in COPD – 4 studies**

1. The study that documented the **cognitive alteration in patients with COPD** is among the first studies in literature that reveals the fact that patients with COPD, especially those in severe stages of the disease or after exacerbations, the age-specific cognitive decline is statistically significantly accelerated, more likely through an inflammatory mediated mechanism.
2. The study that assessed **the impact on postural balance in patients with COPD** confirms the increased risk of falling in these patients induced by the presence of several potential risk factors: neuro-cognitive and/or muscular dysfunction, balance disorders, trophic-nutritional disorders, etc.

3. The study that analyzed **the relationship of postural balance disorders with systemic inflammation in COPD** suggests that simple tools to be implemented in clinical practice can bring valid information related to the risk of falling in these patients.
4. Practical implications of the study that assessed **the influence of body composition on postural balance disorders in COPD** derives from the association of obesity with sarcopenia present especially in the lower limbs. This significantly increases the risk of falling and also increases the fear of accidents in these patients.

#### **IV. Muscle dysfunction in COPD – 4 studies**

1. The study that evaluated **ventilatory muscle dysfunction in subjects with COPD** suggests that maximal inspiratory pressure is a useful functional parameter for evaluating skeletal muscle dysfunction for both respiratory and peripheral muscles, in patients included in pulmonary rehabilitation programs.
2. The study that analyzed **the level of physical activity in patients with COPD** offers data on the sedentary lifestyle in our country, not only regarding COPD patients, but also the healthy population. This is largely explainable due to cultural differences and improper habits.
3. The study that evaluated **the usefulness of pedometry for assessing the level of daily physical activity of patients with COPD**. Results showed that using pedometry as an alarm threshold for a possible complication or exacerbation when observing decrease of more than 10% in the level of daily physical activity.
4. The study that evaluated **the usefulness of radioimaging techniques for the evaluation of skeletal muscles in patients with COPD** suggests that chest CT can provide important information for the combined evaluation of peripheral and respiratory muscle dysfunction.

#### **V. Personalized management in obstructive pulmonary disease – 4 studies**

1. This study represents a consensus material regarding **the early diagnosis and individualized treatment of patients with COPD according to the realities in Romania**, which allowed the development of a phenotype-specific monitoring



and treatment algorithm adapted to the specific needs and possibilities of our country.

2. The study based on **the development in our clinic of a mobile training application on the inhalation technique for patients with obstructive lung pathology** demonstrated that it is a particularly valuable tool in clinical practice for the patients with chronic obstructive disease in order to learn the correct use of control medication and implicitly obtaining a better control of it.
3. The study that analyzed **the impact of medical education programs on the management of patients with COPD** documented their real benefit, even if they are not provided within a complex pulmonary rehabilitation program.
4. The analysis of **the usefulness of oscillometry in the management of patients with obstructive pulmonary pathology** allowed drawing of future directions for in-depth research of pulmonary mechanics with the help of this promising functional evaluation tool, applicable also within our research team.

**Research themes** developed regarding **interstitial lung pathology** and the **relevance of the studies** carried out are the following:

**I. Particular clinical profiles with prognostic implications in idiopathic interstitial pneumopathies – 2 studies**

1. The study that analyzed the natural disease evolution of patients included in the database of our center of expertise for rare lung diseases sorted as having unclassifiable idiopathic interstitial pneumopathies. This study appreciates the prognostic implications of different clinical profiles of patients with interstitial lung disease in our country.
2. The analysis **of pulmonary fibrosis associated with mutations of the telomerase complex** presents the potential clinical implications of the identification of telomere shortening: (i) marker for an increased predisposition to the development of the disease; (ii) prognostic significance, short telomeres being associated with low survival and rare systemic complications post-lung transplantation reflecting the syndromic aspect of this molecular defect.

## II. Multidimensional assessment of interstitial pathology – 4 studies

1. The study recommending **somnographic screening in patients with pulmonary fibrosis** documents the presence of mild cognitive deficit only in forms of idiopathic pulmonary fibrosis that associate various types of sleep disorders.
2. The case study reveals the possibility that **diffuse interstitial pneumopathies can be the initial or dominant manifestation of an underlying autoimmune disease**. Implicitly it confirms the need for screening of collagenases in any form of diffuse interstitial lung damage and, moreover, the presence of a rheumatologist at both initial and subsequent multidisciplinary discussions at the diagnosis of a new case of PID.
3. Starting from a clinical case from my own experience and based on the analysis of few existing data in the specialized literature, I suggested that the **association of idiopathic pulmonary fibrosis with ANCA-positive vasculitis could represent a distinct phenotype with therapeutic and prognostic implications**. Nevertheless, immunological screening for detection of ANCA antibodies in idiopathic pulmonary fibrosis should be considered in both diagnostic and monitoring phases of these patients.
4. The study on the **utility of bronchiolo-alveolar lavage in the diagnostic approach of diffuse interstitial pneumopathies based on an atypical case** presented and expert recommendations suggests that in patients with lung histiocytosis with Langerhans cells bronchiolo-alveolar lavage (BAL) may still have diagnostic value. Especially in patients in whom histopathological examination is also needed, and surgical lung biopsy is contraindicated. Moreover, the molecular genetic examination could, in this type of patients, bring additional diagnostic arguments by highlighting the BRAF-V600E type mutation in the LBA fluid or differentiating phenotypes. This can occur by highlighting other mutations in the MAPK/ERK intracellular signaling pathways through techniques of peripheral blood next-generation sequencing.

**Regarding my academic course, the main milestones and achievements are the following:**

- Firstly, my university career took shape within the **discipline of Physiopathology**, UMF "Victor Babeș" Timișoara, where in between 1994-2013 I went through all academic levels by competition, up to associate professor;
- Since I was the promoter of the accreditation within the Master's Department of the university of one of the first master's study programs "**Prevention and recovery in cardiopulmonary diseases**" (starting from the academic year 2009/2010), and based on the experience I've gained through participation in various training programs in quality assurance in university education according to the Bologna Process, I was appointed **department director in between 2012-2020**;
- In 2013, I became **assistant professor in the Pneumology discipline** through competition, following I've been appointed **head of discipline in 2019** and elected **director of Department XIII – Infectious Diseases** from the structure of which my current discipline descends in 2020;
- I am an expert evaluator of **ARACIS Commission 12 Medical Sciences** since 2020, in which capacity I participated in **8 external evaluations** of some undergraduate programs;
- I contributed to the editing of **6 books** themed from the analytical program of the Pneumology discipline (**2 co-authored books**, respectively author of **8 chapters in 4 other books**), and also **9 books** themed from the analytical program of the Physiopathology discipline (**1 single-authored book, 7 co-authored books, 1 chapter author**);
- I coordinated **3 graduation theses** of students from the Medical University College, **5 undergraduate theses** of Faculty of Medicine students, **18 dissertation theses** of students from the master's study programs in the field of Medicine;
- I **co-supervised the research activity** of students, which resulted in **4 awards for papers presented at scientific events** dedicated to young researchers;
- I was a **referent member in 9 commissions** to analyze and support **doctoral theses**;
- I participated in **18 competition commissions** for vacant teaching positions.

**Regarding my academic course, the main milestones and achievements are the following:**

- In 2002 I promoted the **internal medicine specialist exam**;
- In 2007 I promoted the exam for the **certificate in Special Functional Explorations**;
- In 2010, I obtained the **certificate in Health Services Management** by exam;
- In 2012, I became a **medical specialist** by exam, and in 2016, I became a **primary doctor Pneumologist**;
- In 2020, I obtained the **certificate in General Echocardiography** through exam.
- My **expertise in cardio-pulmonary exercise testing** was acquired through theoretical courses and practical internships abroad;
- Since 2008 I've achieved **clinical integration in the Respiratory Medical Recovery Department**, and since 2015 I have transferred to the **Pneumology II** clinical section, both within the structure of the Clinical Hospital for Infectious Diseases and Pneumophthisiology "Dr. Victor Babeş" Timișoara. In 2018 I became the **head doctor of the department**;
- **Coordination of the Laboratory of Functional Explorations** within the Clinical Hospital of Infectious Diseases and Pneumophthisiology "Dr. Victor Babeş" Timișoara during 2011-2019;
- Eligible person to apply as a **trainer in the European Spirometry Driving License Program**;
- **Residency coordinator in Pneumology** specialty in Timișoara University Center since 2018.
- **Member of the Pneumology Advisory Committee of the Ministry of Health** in the period 2015-2016, respectively the period 2020-2022;
- **Coordinator of the Diffuse Interstitial Pneumopathies and Sarcoidosis Working Group** within the Romanian Pulmonology Society for the 2021-2025 mandate;
- **9 Diplomas of excellence** from the Romanian Society of Pneumology;
- **2 awards** for reports of clinical cases that were presented at the **annual conferences of Pneumology resident doctors** and that were carried out under my coordination;

- **11 chapters as an author in 4 treatises** (two awarded by the Romanian Academy, one being edited under my editorship) **2 national clinical guidelines and 1 monograph**;
- participation as a member or president in **12 specialist physician commissions, 4 senior consultant physician commissions, and 12 Pneumology discipline position commissions.**

As benchmarks of **my personal development plan** resulting from the SWOT analysis of the route of my scientific, academic and professional achievements, I would mention the following:

**I. Specific objectives of educational activity:**

1. Coordination within a collective representation of diffuse interstitial pneumopathy and sarcoidosis working group of the SRP, re-editing the national PID diagnosis and treatment guide with inclusion of all the relevant information that has appeared in the field since the previous edition and optimization of the editorial format;
2. Coordinating in partnership with other people with national expertise in pulmonary function testing: editing a practical manual of complex respiratory functional exploration that includes all current recommendations of the consensus guidelines of the main professional societies in the field of pulmonary pathology;
3. Publication in collaboration with the staff of functional exploration laboratory from our center of an editorial material based on answers to a series of questions frequently encountered in current practice;
4. A distinct objective will be obtaining accreditation of the Functional Exploration Laboratory within the Timișoara University Pulmonology Clinic as an European Spirometry Driving License training and certification center.

**II. Specific objectives of the research activity:**

1. Publication of articles in ISI rated journals with preferably in those with red or yellow zone of their scientific subfield;
2. Participating as partner in a Clinical Research Collaboration (CRC) research program in the field of respiratory tract pathology, interstitial lung disease or vascular disease;

3. Acquire acceptance for our center of expertise within the European Reference Network on rare respiratory diseases ERN-LUNG: European Reference Network on rare respiratory diseases;
4. Promotion of translational research directions through interdisciplinary collaboration in order of generating innovative research-development ideas with increased potential for financing, publication and innovation.

### **III. Research projects:**

1. Encounter the diversity of fibrosing interstitial pneumopathies by capitalizing on the database of patients from the Expertise Center for Rare Pulmonary Diseases Timișoara;
2. The identification of most appropriate tools for evolution-monitoring of progressive pulmonary fibrosis and their implementation in clinical practice;
3. Remote monitoring of patients with fibrosing interstitial pathology;
4. Telemedicine as a tool for obtaining disease control in adolescents with bronchial asthma;
5. The importance of prevention and treatment of respiratory diseases in children through balneary, alimentary, emotional and physical factors.

In **conclusion**, this habilitation thesis, which presents my scientific, academic and professional achievements and route, brings potential arguments in favor of certification as a supervisor for doctoral thesis.