

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



**MONOAMINE OXIDASE-RELATED OXIDATIVE  
STRESS IN CARDIO-METABOLIC PATHOLOGIES:  
A TRANSLATIONAL APPROACH**

**ABSTRACT**

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The Habilitation thesis entitled "*Monoamine Oxidase-Related Oxidative Stress in Cardio-Metabolic Pathologies: A Translational Approach*" summarizes the scientific, academic and professional activities conducted after the defence of the PhD thesis, "*The Role of Monoamine Oxidases in the Pathogenesis of Experimental Endothelial Dysfunction*" under the supervision of Prof. Danina M. Muntean, Chair of Pathophysiology, Faculty of Medicine from "Victor Babeș" University of Medicine and Pharmacy of Timișoara, Romania in co-tutorship with Prof. Ralf Brandes, Director of Institute of Cardiovascular Physiology, Goethe University, Frankfurt, Germany, in 2013.

Currently, I am Associate Professor of Pathophysiology at the Department of Functional Sciences - Chair of Pathophysiology, Faculty of Medicine from "Victor Babeș" University of Medicine and Pharmacy of Timișoara, and Consultant in Diabetes, Nutrition and Metabolic Disorders at the Centre for Diabetes from Timișoara County Hospital. I am also a member of the Centre for Translational Research and Systems Medicine, approved by the University Senate in 2014 and ranked as Advanced Research Centre of the university in 2020; since 2020 to date I serve as its treasurer.

The present thesis complies with the recommendations of the Romanian Ministry of Education and Research, the requirements of the National Council for Attestation of University Degrees, Diplomas and Certificates and has been written according to the Guideline of Preparation and Writing of the Habilitation Thesis within "Victor Babeș" University of Medicine and Pharmacy from Timișoara.

The thesis is organized in 3 parts:

The **first part, *Scientific Achievements***, includes information about the most significant research findings and the participation in research projects/grants won through national and international competitions. My research interests span the fields of metabolic and cardiovascular diseases and were focused over the past decade on two intertwined topics, which are also two main research directions of the centre: i) *endothelial dysfunction: novel pathomechanisms and innovative, drug-repurposing therapeutic approaches* and ii) *assessment, prevention and management of the oxidative stress in pathology*, with particular emphasis on ***the contribution of monoamine oxidase (MAO)-related oxidative stress***. The results of the translational research carried out in both experimental models and human samples were published

in over 30 papers mostly in international journals, among which the most prestigious are: Hypertension, Arteriosclerosis, Thrombosis and Vascular Biology, International Journal of Molecular Sciences (Q1), Molecular and Cellular Biochemistry, Canadian Journal of Physiology and Pharmacology and Life (Q2).

During my 10 months doctoral mobility abroad in the Institute of Cardiovascular Physiology, Goethe University, Frankfurt, Germany I gathered the expertise to study the experimental endothelial dysfunction and oxidative stress and I firstly demonstrated that MAO, a mitochondrial enzyme with 2 isoforms, MAO-A and MAO-B, is a mediator of endothelial dysfunction in mouse aorta (1). When back, I implemented these techniques in our research centre, which are all currently in use by the members and collaborators of the centre. Also, I have standardized 2 experimental models of diabetes and diet-induced obesity (and prediabetes) that were used for a couple of research projects in our centre. The major scientific contributions in the past decade belong to the evolving field of MAO-related oxidative stress in the pathophysiology of cardiometabolic disease. The original findings can be summarized as follows (chronological order): **1)** first demonstration that MAOs are sources of cardiovascular oxidative stress in experimental type 1 and 2 diabetes (2, 3) , **2)** the expression of the MAO-B isoform and oxidative stress are increased in atrial appendages and mammary arteries harvested from diabetic and non-diabetic obese patients with coronary artery disease undergoing elective cardiac surgery (4), **3)** MAO inhibition improved endothelium-dependent relaxation and reduced reactive oxygen species level in human brachial artery collaterals isolated from patients with end-stage renal disease subjected to hemodialysis, suggesting that MAO inhibitors might be useful in the management of the vascular access in these patients (5), **4)** MAOs are expressed in human visceral adipose tissue (6) and mesenteric artery branches contain and the MAO-A isoform is upregulated in obese (but not in the non-obese) patients with chronic inflammation (7), **5)** chronic (6 mo) administration of an obesogenic hypercaloric, cafeteria-type diet in rat elicited an increase in aortic (8) and ventricular (9) expression of both MAO isoforms and contributed to cardiovascular oxidative stress. The effect was mitigated by acute *ex vivo* incubation of the ventricular samples with either a MAO-A inhibitor (clorgyline) or a MAO-B inhibitor (selegiline) (9). Also, Metformin, the classic biguanide used in the treatment of type 2 diabetes, reduced vascular and ventricular gene and protein expression of MAO isoforms after acute incubation of the samples with the lowest clinically relevant concentration in obese and

prediabetic rats and had no effect in control animals (8, 9), **6**) both MAO-A and B isoforms are upregulated in mammary arteries harvested from overweight, cardiac patients with heart failure with mildly reduced ejection fraction (HFmrEF) subjected to bypass grafting, after acute stimulation with angiotensin II (to mimic the activation of the renin-angiotensin-ALDO system) and high glucose (to mimic dysregulated diabetes); *ex vivo* incubation of the samples with either Metformin (the classic antidiabetic drug) or Empagliflozin (the novel antidiabetics, the SGLT2 inhibitors) alleviated endothelial dysfunction and mitigated oxidative stress (10), **7**) both MAOs are expressed in right atrial appendages isolated from overweight, cardiac patients with HFmrEF undergoing elective cardiac surgery and Incubation with either dapagliflozin or empagliflozin mitigated oxidative stress and downregulated MAO expression in a dose dependent manner, suggesting a novel off-target class effect of these drugs (11, 12). Last but not least, we have demonstrated in obese patients that a low serum level of vitamin D was associated with increased inflammatory markers and reactive oxygen species generation in two types of samples harvested during elective abdominal surgery, visceral adipose tissue and mesenteric artery branches and (ii) *ex vivo* incubation with the active vitamin D alleviated oxidative stress in both adipose tissue & vascular preparations and also improved the vascular function (13). Also, in diabetic rats we observed that incubation of the aorta with vitamin D was able to reduce MAO expression and to improve vascular relaxation (14).

In the past decade, after the award of the PhD degree in Medicine, I have published 39 articles in extenso. Of these, 31 are published in ISI journals (17 as principal author, 14 as co-author), and 10 are in international databases (6 principal author, 4 co-author).

In the Web of Science database, the indices of scientific activity (<https://www.webofscience.com>, data valid on 23 January 2024), are as follows: total number of citations - 675, total number of citations without self-citations - 534, Hirsch index - 13. For the Google Scholar Citations platform the total number of citations is 911 and the Hirsch index is 15 (<https://scholar.google.com>, data valid on 23.01.2024). The scientific activity indices in the Scopus database (<http://www.scopus.com>, data valid on 23.01.2023) are as follows: total number of citations - 724 and Hirsch index equal to 14. **Cumulative principal author impact factor – 53,263.**

I was the recipient of several **international awards**, the most representative being: *Distinguished Service Award In Cardiovascular Science, Medicine and Surgery*

offered by International Academy of Cardiovascular Sciences at the 9<sup>th</sup> European Section Meeting of the International Academy of Cardiovascular Sciences, Timișoara, 2023; *Early Career Investigator Competition Award* at The 5<sup>th</sup> European Section Meeting of the International Academy of Cardiovascular Sciences, Slovakia, 2018; *First Prize for Poster Presentation* at The 2<sup>nd</sup> European Section Meeting of the International Academy of Cardiovascular Science, Serbia, 2015; *Pavel Braveny Poster Competition Award* at the International Symposium "Advances in Cardiovascular Research", Bratislava/Smolenice, Slovakia, 2015, as well as of **national prizes** awarded during the annual meetings of the Romanian Society of Diabetes (2023, 2022, 2017, 2016), Romanian Society of Cardiology (2022) and Romanian Society of Pathophysiology (2017).

In 2014 I received the **Eminent Researcher Award** of the year granted by Association "University Horizons" and the **Diploma of Merit for outstanding merits in scientific research activity** offered by the City Hall of Timișoara (Mayor Nicolae Robu). In 2018 I was the winner of the **Prize for Scientific Activity** awarded by "Victor Babeș" University of Medicine and Pharmacy of Timișoara in recognition for the capability to carry out original, international visible research.

The **second part, Academic and Professional Achievements** includes information about professional recognition, teaching activity, coordination of licence/dissertation theses, affiliations to professional organizations, and other academic activities. With respect to the teaching activity, I have delivered lectures and laboratories of Pathophysiology for students enrolled in the following study programs of the Faculty of Medicine within the university: Medicine (Romanian section), Medicine (English section), Nursing, and Nursing for Nutrition and Dietetics. Also, I have participated as lecturer in several postgraduate courses and coordinated 2 courses in the past 2 years. During my academic activity I have coordinate 29 dissertation thesis at Faculty of Medicine, some of the coordinated students have participated in scientific meeting and obtained 4 international awards.

Throughout my career I was: i) *director of 3 research grants*, ii) *member in other 7 (3 international and 4 national) scientific projects* won through competition, and iii) *recipient of 3 research fellowships*. I was also representative for Romania in the Management Committees of 2 European COST (Cooperation in Science and Technology) actions. Recently, I served as co-leader for an Erasmus+ project

*Strengthening capacities and digital competences in biomedical education through internationalization at home – BIOSINT.*

Since 2020 I have been an Editorial Board Member of *Molecular and Cellular Biochemistry, Oxidative Medicine and Cellular Longevity* and *Timișoara Medical Journal* and I have served as ad-hoc reviewer for several international journals.

Since 2020 I am member of the following university academic structures: the Council of the Faculty of Medicine (where I have been re-elected for the mandate 2024-2029), the Commission for Ethics of Scientific Research and the Commission for Evaluation and Assurance of Educational Quality of the Faculty of Medicine.

I am member of the following international and national societies: International Academy of Cardiovascular Sciences – European Section, Romanian Society of Pathophysiology, Romanian Society of Physiology, Romanian Society of Diabetes, Nutrition and Metabolic Disorders and Romanian Society of Cardiology. In my social life, I am member in *Eparchial Council of the Romanian Orthodox Archdiocese of Timișoara*.

The **third part**, includes ***Perspectives for Academic Development and Future Research Directions***. In terms of strategies for my further professional development I will be focused on the following key aspects: translational research activity and interdisciplinary collaboration, implementing new research methods, publishing in high-impact journals, research team development, research funding, dissemination and continuous learning. I am focus on bridging the gap between scientific discoveries and clinical applications and to ensure that my research has direct relevance with benefits for the patients; this will be possible with collaboration closely with clinical departments and healthcare professionals.

Regarding my future plans for the **scientific research**, *firstly*, I will continue to encourage undergraduate students to start doing research as soon as possible. This might help to improve the number of students who will become enrolled and will complete PhD programmes in basic and translational research and help our research team become more competitive, enabling us to join international research networks and giving us the foundation to seek for EU financing and thus, secure funding for research. I am committed to further submit applications within the national calls and also, to participate in consortia that will apply for project under the umbrella of cross-border, interregional or European calls. *Second*, in order to further raise our university's profile internationally, I will continue and deepen our partnerships and

support the formation of multidisciplinary research teams (with surgeons, cardiologists, cardiovascular surgeons, diabetologists, nephrologists, haematologists, geneticists, public health specialists etc.), which will increase the capability of producing original research and publish the findings in higher impact factor journals. *Thirdly*, I am driven to keep our translational research centre further implementing cutting-edge research techniques, especially in the area of molecular biology, so that we can advance our existing research directions, mainly the MAO-related oxidative stress by dissecting its signal transduction pathways and also, explore novel research directions.

**At the academic and professional level**, I plan to: update the Pathophysiology courses and the ppt presentations the both in Romanian and English for the students in the 3<sup>rd</sup> year at the Faculty of Medicine, in the field of Pathophysiology as well as to publish two manuals (lectures and practicals) for the students in the 1<sup>st</sup> year at the Nursing for Nutrition and Dietetics program; support the introduction of a novel optional course, Clinical Pathophysiology, for medical students in the IV<sup>th</sup> or V<sup>th</sup> year of study, in collaboration with the colleagues from clinical departments in order to recall the fundamental concepts of Pathophysiology and integrate them in the clinical setting, as prerequisite for the preparation of the residency exam; continue to propose postgraduate courses focused on the understanding the pathomechanisms of various diseases and therapeutic strategies in terms of the mechanisms of action of therapeutic agents, respectively, as a way of both keeping us updated and maintaining the visibility of the chair of Pathophysiology; use of combined teaching methods: interactive teaching, case studies, diagrams/algorithms, group/team work, training students in interpretation of lab tests, encouraging students to use the medical language.

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