

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



**GENERAL IN VITRO METHODS AND MODERN
TARGETED APPROACHES TO EVALUATE
POTENTIAL THERAPEUTIC COMPOUNDS**

ABSTRACT

Assoc. Prof. PhD. Mioc Alexandra Teodora

**Timișoara
2023**

The habilitation thesis entitled "General in vitro methods and modern targeted approaches to evaluate potential therapeutic compounds" outlines the personal academic, scientific and professional achievements accomplished in the postdoctoral period (2016-2023), as well as the main academic and research development directions.

The mitochondria, traditionally thought to be the principal energy generators or "powerhouses" of our cells, are involved in other numerous cellular processes such as the control of ion balance, cellular redox state, cell growth and communication, and consequently, they have a crucial impact on the mechanisms involved in both cell survival and cell death. Specifically, mitochondrial (dys)function has been shown to be ubiquitous in many frequently encountered pathologies in our society, such as cardiovascular diseases, cancer, type 2 diabetes and Alzheimer's disease. On this premise, compounds that can improve mitochondrial function in these pathological conditions gained substantially interest from researchers in this field.

Our scientific papers published so far, have made contributions regarding the involvement of mitochondria, but also the effect of natural compounds as well as novel semisynthetic and synthetic compounds with mitochondrial effects in ischemia/reperfusion injury and cancer and on platelet function and oxidative stress. Specifically, our scientific papers contributed to: i) evaluation of mitochondrial function/dysfunction and ROS production in various diseases, ii) the use of mitocans (compounds that target the mitochondria of cancer cells) as emerging anticancer agents, iii) the synthesis and assessment of mitochondrial targeted triterpenes in lung cancer, breast cancer and human melanoma cell lines and iv) improving the delivery systems of anticancer drugs and the chemical derivatization of pentacyclic triterpenes, compounds that influence mitochondrial function, to increase their anticancer activity.

The first chapter presents a synthesis of my scientific achievements. During my doctoral studies I evaluated the mitochondrial effect and potential use of novel benzopyran analogues, as cardioprotective agents against ischemia/reperfusion injury. The research was materialized through the publication of My PhD thesis entitled "*Characterization of novel benzopyran derivatives with cardioprotective properties*" under the supervision of Prof. Danina Muntean (Doctor in Medicine, 2017). Following the completion of my PhD studies, I won, by competition, one internal UMFVBT research grant, PII-C4-TC-2016 "The screening of functional bioenergetic reserve in peripheral blood in patients with malignant hemopathies". The skills required for the completion of the research grant were obtained by participating in a summer school in Copenhagen, Denmark, "*Mitochondrial Physiology - From Organelle to Organism*" where I gained valuable information regarding the methods used to evaluate the mitochondrial function of various types of cells. Also, during this time, I obtained through competition, a two-month internship "Interaction of zinc, ROS and superoxide dismutase in melanoma" provided by a Short-Term Scientific Mission (STSM) in Nijmegen, The Netherlands, where I gained knowledge and technical skills in the field cell culture, Western blot and fluorescence microscopy. During my PhD studies and also after its completion, I was co-opted as a member in 4 research

grants that were also researching mitochondria, cancer and therapeutically active natural compounds, especially pentacyclic triterpenes. Based on the various skills I acquired in cell culture techniques and molecular biology, I activated as an independent researcher in other research groups which were dedicated to investigating the derivatization, formulation, and impact of bioactive natural chemicals across different types of cancer, making major contributions regarding the *in vitro* biological evaluation of these compounds on cell viability and morphology, mitochondrial function (through high-respirometry studies) and a specific proteins (through immunoblotting-Western blot).

As a result of multiple research directions and the permanent accumulation of new information and working techniques skills in terms of cell culture and molecular biology, in addition to those for the assessment of mitochondria, the presentation of my scientific research and the sub-chapters were mostly organized chronologically in terms of evaluating mitochondrial function and the effect of various natural and new semisynthetic/synthetic compounds on mitochondrial function in cardiovascular diseases, platelet physiology and pathology, oxidative stress and finally, cancer.

In all the research activity, I have gained substantial knowledge and experience in the study of mitochondria as both an effector and therapeutic target in cancer and other pathological conditions. Additionally, I have developed skills in the formulation of chemical compounds and the evaluation of their biological activity, particularly in relation to their anticancer properties. Furthermore, I have acquired practical proficiencies in assessing mitochondrial respiratory function and reactive oxygen species (ROS) production, in cellular viability and cytotoxicity assays and in techniques such as Western blot analysis and fluorescence microscopy. This entire work resulted in the publication of 43 ISI articles (total IF > 150, 6 Q1 and 20 Q2 articles; 20 – as main author, IF > 100, 3 Q1 and 10 Q2 articles), 1 book chapter, 35 conference papers and the participation in 6 research grants (1 as project coordinator) and 1 doctoral scholarship. The Hirsch index values are: WOS – 11 (with 383 citations from which 331 are without self-citation), Google Scholar – 13, Scopus – 12.

The second chapter is dedicated to my academic development and achievements. My academic journey started in 2014 when I became Assistant lecturer at Department of Anatomy, Physiology, Pathophysiology, Faculty of Pharmacy, followed by my promotion to Lecturer, in 2021, and to Associate Professor in 2022. In parallel, from February 2020 up until June 2023 I was a clinical pharmacy resident at Spitalul Clinic Județean de Urgență „Pius Brînzeu”, Timișoara Romania. During these years, I followed the increase of teaching quality, by participating in the preparation of the documents that were necessary to order and purchase new equipment that was used by/for the students at our department. From the beginning of my teaching activity, I was also involved in the development of the curricula, I delivered and constantly improved courses and practical works material, presentations, and reports. Specifically, I collaborated on the writing of four books, contributed to the modernization of Anatomy, Physiology and Physiopathology courses and practical works/interactive seminars (PowerPoint presentations,

presentation of clinical cases, analysis bulletins, interactive exercises), writing evaluation grids for the course material and that of practical works in Romanian and French. I held a post-graduate course and was involved in the coordination of the students' research activity, which resulted in the writing of 38 diploma theses, while also guiding students that participated in scientific communication sessions and coordinating student volunteers within the program "Volunteering in academic development activity" (VADA), "Victor Babeş" University of Medicine and Pharmacy in Timisoara.

The third chapter presents my professional activity and is divided in two sub-chapters that displays the professional path and certificates and also the recognition of the professional activity. Immediately after graduating from "Victor Babeş" University of Medicine and Pharmacy, Faculty of Pharmacy, in October 2013, I followed the doctoral school studies at the University of Medicine and Pharmacy "Victor Babeş" Timișoara, under the coordination of Prof. Dr. Danina Muntean. In July 2016 I publicly presented my Ph.D. thesis entitled: *Characterization of novel benzopyran derivatives with cardioprotective properties* and in 2017, I received the Doctor's Diploma in the Field of Medicine, Excellent qualification. During my PhD studies, I won a doctoral scholarship through a competition within a POSDRU project and as a result I participated in a 4-month research internship at the University of Szeged, Hungary, Department of Pharmacology and Pharmacotherapy (period 01.06.2015 - 30.09.2015). From September 2015-June 2016, I participated in a postgraduate psycho-pedagogical training program designed for teachers, successfully completing the requirements to receive both Level I and Level II certificates. After the completion of my doctoral thesis, I won an internal UMFVBT grant, namely the PII-C4-TC-2016. The necessary skills for the research grant were acquired by attending a summer school in Copenhagen, Denmark. The summer course, titled "Mitochondrial Physiology - From Organelle to Organism". Also, in 2016 I obtained through a competition an internship in Nijmegen, The Netherlands.

The fourth chapter is the final part of this thesis and presents the future perspectives regarding the academic, scientific and professional achievements. The academic skills will be constantly improved by adopting the latest and the finest teaching methods while ensuring a continuous update of the students' materials. Also, another aim is to attract students who possess an interest in research, encouraging their active participation and subsequent publication of their findings at student scientific gatherings. In order to increase my personal visibility and recognition, as well as the reputation of the discipline, the faculty, and the university where I am affiliated, I propose a fruitful development of my academic career complementary to that of a researcher. I will maintain and also expand existing collaborations, establishing both local and international collaborations with academics from other universities or research institutes, a crucial step for diversifying and improving the scientific performance while also enhancing financial support prospects. The existing research directions will be further pursued, expanded upon, and utilized, while the newly identified directions will be connected to the ongoing ones. In the future, the focus of my research efforts will also be on the acquisition of

new information, methodologies, and the development of additional capabilities in order to increase research initiatives and grants obtained. By participating in various workshops, scientific meetings and mobilities programs, I wish to accumulate new skill sets and expand my knowledge in the field of my research and beyond that, to related topics of research. This process will increase my ability to coordinate and to teach new methods used in modern research and hence, will increase my students and co-opted graduates research activity outcomes.