

**"VICTOR BABEȘ" UNIVERSITY OF
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**PRECLINICAL METHODS FOR TOXICOLOGICAL
SCREENING APPLIED IN THE ASSESSMENT OF
THERAPEUTICAL POTENTIAL COMPOUNDS**

ABSTRACT

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The present thesis entitled " *Preclinical methods for toxicological screening applied in the assessment of therapeutical potential compounds*" represents a synthesis of my scientific research activity that I conducted during the last 10 years since I finished my PhD thesis, and also a presentation of my academic career.

Cancer is recognized worldwide as a major public health problem, since affects not only the health of the patient, but also its psychological and social status, and has a financial negative impact on the public health system. Moreover, in recent years it became the main cause of mortality in most of the countries (75% of the countries). Even though the number of treatment options for cancer is increased recently, the adverse effects of these treatments are significant and severe, and, also it was observed that some cancer cells develop resistance to these treatments, so their therapeutical effect decreases and become ineffective. On this basis, considerable efforts are conducted to discover new targeted anticancer therapies with low/no adverse effects, and natural compounds gained a lot of interest in this field of research.

My pivotal research directions were established since my late years of faculty when I started to elaborate my bachelor thesis (coordinator Prof. Cristina Dehelean) and consisted of cancer, mainly skin cancer, and particularly melanoma and the analysis of natural compounds with therapeutical potential in terms of elucidating the antitumoral mechanism of action. My PhD studies represented a follow-up of these research ideas which were concretized with the PhD thesis entitled " *Mechanistic insight into antitumor effects of betulinic acid* " under the supervision of Prof. Danina Muntean (Doctor in Medicine, 2013). During my PhD I improved my knowledge and my technical skills in the field of cell culture, molecular biology, mitochondrial respiratory studies and animal models of skin cancer with the help of my colleagues from the Department of Toxicology, Pathophysiology and the team of Prof. Bernhard Bruene (Goethe University, Frankfurt am Main, Germany), forming the background for the following years.

The years after my PhD thesis were decisive regarding my research activity since I managed to win by competition one intern grant (UMFVBT grant - PII-C2-TC-2014-16498-10 entitled: „*Pharmaco-toxicological evaluation of betulinic acid formulated as nanoemulsion effects on tumor progression and metastasis in a human melanoma mouse model*”) and 3 national projects (2 Young Teams – Tinere echipe and 1 – postdoctoral

grant): PN-II-RU-TE-2014-4-2842 (2015-2017) entitled: *“In vitro and in vivo evaluation of pharmacokinetic and pharmacodynamic profile of triterpenic compounds nanoformulations with antitumoral effect (NANOBET)”*, PN-III-P1-1.1-PD-2016-1982 (2018-2020), entitled: *“New insights into the antimelanoma mechanism of action of betulinic acid (MELBA)”* and PN-III-P1-1.1-TE-2019-2134 (2020-2022), entitled: *“Delivery to the dermocosmetic market of a modern topical formulation with betulinic acid encapsulated in proniosomes (BAPRONIO)”*.

The collaborations established during these projects added new research directions that I followed, directions that are tangential to my initial pivotal work, and I contributed with my expertise in cell culture techniques and molecular biology that I gathered during my years of research.

Taking into account the above-mentioned information, I decided to organize my habilitation thesis in 2 main chapters: chapter 1 that describes the main scientific achievements and chapter 2 that focuses on the academic and professional activity.

Due to the multiple and somehow different directions of research that I followed during these years, the presentation of my scientific research was organized in 2 main directions, as follows: *in vitro* methods applied for the toxicological screening of compounds with therapeutical potential and *in vivo* models, directions that are summarized in chapter 1 of the present thesis. The *in vitro* methods presented are assays used for the verification of cellular viability (MTT and Alamar blue), cytotoxicity tests (cellular morphology monitorization, nuclei staining using DAPI and Hoechst 33342, Annexin V/PI, etc), immunofluorescence and other complementary techniques (LC/MS, etc). As *in vivo* models I described the models of melanoma and skin cancer obtained during my studies, and also some animal models of hepatic cancer.

In summary, the scientific results obtained after finishing my PhD consisted of:

- ❖ 86 ISI indexed full-text articles – 22 as main author
- ❖ 6 BDI indexed full-text articles
- ❖ 5 book-chapters published in international publishing houses (2 as main author)
- ❖ 24 ISI indexed abstracts

- ❖ **Research grants:** member in 14 international and national research scientific projects (project manager in 4)
- ❖ **H-index:** 21 (Web of Science), 26 (Google Scholar)

Chapter 2 of the thesis refers to the academic activity that comprises the presentation of the lectures and practical works that I taught, the bachelor and dissertation theses that I coordinated, participation as member in committees for students evaluation, for admission to the faculty, for bachelor thesis assertion, coordinator for student programs (VADA program) and organizing member committee for different student manifestations (summer schools, workshops), and also as member in committees for professional promotion. I had also some administrative responsibilities as member in several committees (Faculty of Pharmacy board, Department II board of the Faculty of Pharmacy, Scientific Committee within the Scientific Vice-chancellorship, UMFVBT Ethics Committee, DEACE) and as president (Bioethics Committee and the Scientific Research Committee of the Faculty of Pharmacy).

My academic journey started in 2013 when I became Assistant Professor at the Department of Toxicology, Faculty of Pharmacy, followed by my promotion to Lecturer (2014) and Associate Professor (2016). During these years, I attended multiple training courses to improve both my academic and scientific skills, that are detailed in the second chapter of the thesis.

The final part of the thesis presents the future academic and scientific perspectives that can be synthesized to an improvement of my academic skills by adopting the newest and the best teaching methods and by updating continuously the courses for students, and as regards the scientific part I intend to continue my previous work and to add new research directions using state-of-the art methods, to gain new projects and to establish research collaboration with researchers from the same field or connected fields.