

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



**THE MICROSCOPIC FEATURES OF TUMORIGENESIS,  
A CONTINUUM FROM INFLAMMATORY LESIONS TO  
NEOPLASIA,  
WITH PROGNOSTIC AND THERAPEUTIC  
CORRELATIONS**

**ABSTRACT**

**Associated Professor Dr. Baderca Flavia**

**Timișoara  
2021**

## SCIENTIFIC ACHIEVEMENTS OF THE CAREER

### The research areas which include the scientific concerns of my career

The overall picture of doctor's roles in the society is saving life, but if you look closer, there are many other important aspects in treating humans, with significant impact on the individual and his family members' life quality.

The difficulty to find the right treatment for different disorders can't be disconsidered, but there is a bigger challenge in preventing their apparition by understanding the pathogenesis of many diseases. Since the very beginning of the humanity, the doctors observed that even if clinical aspects of the diseases looked initially similar, until the end the same condition at different patients could have completely opposed outcome.

Because cancer represents the main cause of death in almost three forth of the countries worldwide, for people under the age of 70s, being the most important enemy of increasing life expectancy, the oncologic diseases represent the main field of research for many scientific teams all around the globe. In order to find the best treatments with the most benefic impacts on patient life quality, the scientists try to understand the process by which the division of normal cells is perturbed and escape the control of tumor suppressive mechanisms, thus tumor development is an important field of research.

Moreover, the identification of the etiologic factors of different cancers is a *sine qua non* condition in order to prevent the tumorigenesis and to reduce the number of oncologic cases. Prostate cancer ranks first regarding incidence in many countries, being the second most diagnosed type of cancer worldwide, but little is known about its etiologic factors.

To identify some factors that may predict, at least in part, the behavior of a tumor and, if it is possible, to transform them in targets of individualized therapies is also as crucial as comprehending the mechanisms of tumorigenesis. Scientists try to identify new molecules with better results and delivered in some manner to reduce the side effects and to increase the treatment benefits. Thus, chemotherapeutic substances delivered in different type of nanoparticles occupies a main place in scientific projects.

In order to be approved and to have a best efficiency in the treatment of oncologic diseases, new drugs is better to be tested on *in vitro* models as cell culture or animal models, another important field of research worldwide.

There are some years since the importance of the epithelial-mesenchymal transition is recognized in the embryogenesis, and also in the response of the host tissue to injury. Moreover, in the last decades, it was emphasized the role of the epithelial-mesenchymal transition in both, chronic infection and carcinoma invasion. An important role in the transition from epithelial and endothelial cells to mesenchymal cells is attributed to the myofibroblasts, therefore their characterization by morphological, immunohistochemical and ultrastructural studies is crucial in the understanding of tumor genesis and cancer progression and represents the beginnings of my personal researches, starting with the graduating thesis "*The role of myofibroblasts in the evolution of chronic glomerulonephritis*" under the coordination of Prof. Dr. Raica Marius, with

highlights on morphological and immunohistochemical aspects of the myofibroblasts and their implication in the epithelial-mesenchymal transition.

My research continued in the same area of genitourinary disorders, switching from inflammatory conditions to the tumor lesions. Little were known about immunohistochemical profile of renal cancers and their prognostic factors. The human epidermal growth factor receptor (*Her2/neu*) oncoprotein expression was first studied in breast cancer and became later a target of biologic therapies. In the early 20<sup>th</sup>, the state-of-the-art oncologic treatment represented the use of Herceptin, that block the *Her2/neu* expression in breast cancer cells, with prognostics benefit. The important value of the studies focused on *Her2/neu* oncoprotein expression in urothelial cancers was recognized by approving, in 2005, the doctoral research project *Implicațiile prognostice și terapeutice ale identificării oncoproteinei Her2/neu în carcinoamele uroteliale*, [*The prognostic and therapeutical implication of Her2/neu oncoprotein expression in urothelial carcinomas*], a CNCSIS research Grant type TD, no. 20/2005, which I have coordinated as grant's director.

The research in genitourinary area continued, in 2006, with my dissertation for doctoral degree [*The morphological and immunohistochemical characteristics of malignant renal tumors and their implications in diagnosis, prognosis and treatment*] *Particularitățile morfologice și imunohistochimice ale tumorilor maligne renale. Implicații diagnostice, prognostice și terapeutice*, under the coordination of Prof. dr. Marius Raica and with the help of the colleagues from the Histology Department of Victor Babeș University of Medicine and Pharmacy Timișoara. In the following years, I characterized the immunohistochemical profile of renal and upper urinary tract cancers with emphasis on cytokeratins, epithelial membrane antigen expression.

Besides genitourinary areas, the other main subjects of my scientific career are represented by melanocytic lesions, inflammatory and lymphoproliferative disorders of the skin, lesions of squamous stratified epithelium, lesions of the oral cavity.

### **Experimental models and their use in therapeutical improvements**

Preclinical studies aiming to understand the etiology and mechanisms involved in the occurrence and progression of malignant diseases and to assess the effectiveness of new therapies imply most frequently *in vitro* and *in vivo* experimental models.

Cell culture is a very versatile tool for basic scientific investigation, the most important advantage of them being represented by reproducibility.

In the last decades, chorioallantoic membrane assay became a robust *in vivo* model utilized in many research fields with important implications in angiogenesis, tumorigenesis and drug screening.

Metal nanoparticles have entered the biomedical area due to their ability to act as both diagnostic and drug delivery agents, thus qualifying as theranostics. Betulin loaded silver nanoparticles effects on melanoma models consisted a part of my scientific career.

Numerous plants derived compounds were indicated to reduce chronic inflammation, their properties I have studied on *in vitro* and *in vivo* models.

All these represented useful tools in the tumorigenesis studies, concretized in important articles, published in ISI indexed peer-reviewed journals.

## **The Main Research Projects**

A better understanding of tumorigenesis cascade from inflammation to invasive malignant tumor could be obtained only on the basis of an exhaustive characterization of epidemiological, clinical and histopathological data of inflammation, benign, pre-malignant and malignant lesions, on cohort studies and, also, on *in vitro* and *in vivo* models.

All aforementioned issues represent significant points of my scientific career, concretized in many articles published in the field of otorhinolaryngology, dentistry, dermatology and pharmacology and participation in seven projects and three research centers.

## **Scientific Activity Results**

The scientific results were concretized in:

- two book chapters (one at international publisher, the other at national publisher);
- 41 articles published in ISI indexed peer-reviewed journals (22 articles as author [first, corresponding and main author] and 19 as coauthor);
- 12 articles published in CNCSIS B+ and B indexed peer-reviewed journals (4 articles as author [first, corresponding and main author] and 8 as coauthor.
- 27 articles published as abstracts in ISI indexed peer-reviewed journals, all representing posters at international congresses;
- one article published as abstract in CNCSIS B+ and B indexed peer-reviewed journals, representing poster at international congress;
- 16 articles published as abstracts in journals with ISSN or ISBN, representing posters at international congresses;
- 82 articles published as abstracts in journals with ISSN or ISBN, representing posters or oral presentations at national congresses with international participation;
- 24 articles published as abstracts in journals with ISSN or ISBN, representing posters or oral presentations at national congresses;

The value of the published articles was emphasized by 331 ISI peer-reviewed articles published in journals indexed on Web of Science ([https://apps-webofknowledge-com.am.e-information.ro/CitationReport.do?product=WOS&search\\_mode=CitationReport&SID=F3fea6UucGKEFPiqbcm&page=1&cr\\_pgid=1&viewType=summary&colName=WOS](https://apps-webofknowledge-com.am.e-information.ro/CitationReport.do?product=WOS&search_mode=CitationReport&SID=F3fea6UucGKEFPiqbcm&page=1&cr_pgid=1&viewType=summary&colName=WOS)) and by 546 articles published in journals indexed on Google Scholar. (<https://scholar.google.com/citations?user=GY8HiPoAAAAJ&hl=ro>)

I am member in two international and three national professional societies, I collaborate as pathologist expert in three research centers and I am reviewer for two ISI peer-reviewed journals.

Three of my published articles were prized at international and national congresses.

I participate in organizing committee of 10 national congresses with international participation as director (three), speaker (four), expert (six).

The list of articles can be consulted in the attached curriculum vitae.

## **ACADEMIC ACHIEVMENTS OF THE CAREER**

### **Academic course and most important academic responsibilities**

In October 2000, I have entered the Department of Histology from Victor Babes University of Medicine and Pharmacy Timisoara as assistant professor. Between February 2009 and April 2015, I have taught students as lecturer and since May 2015, as associate professor. During these years, I coordinated the lectures and laboratories of Histology for the Faculties of Medicine, Dental Medicine, General Medical Assistance, Radioimaging, Balneo-Physio-Kinesiotherapy, Nurse-Midwifery, Clinic Laboratory, at both, Romanian and English sections.

In order to improve my pedagogical methods, I have graduated, in 2014, the two modules of the course Pedagogy for Educators organized by the Department for Teachers Training.

In the desire to improve the quality of taught materials, I have yearly upgraded the information offered to the students, for both, electronic and printed version of lectures and lab materials, authoring and coauthoring nine printed supports for Histology, some of them could be considered as monographies.

Having in mind that a good teacher is who teach students how to learn, I have coordinated 35 graduating theses.

Because a good scientist has to be formed from the beginning of the faculty years, I have coordinated eight oral presentations at Student Congresses, two of them winning a prize for their hard and meticulous work and outstanding performances.

Since 2015, when I became associate professor, I worked together with 11 doctoral students under the concertation of PhD coordinator, in order to guide their wrestle in the science universe, in the field of oncogenesis.

Since 2006, as pathologist, I have coordinated the work of the residents of pathology, organizing lectures and slide presentations.

Since 2000, when I have entered to the Department of Histology, every year I participated as member in the board of examination for admission to faculty and for sustaining of bachelor degree.

## **PROFESIONAL ACHIEVMENTS OF THE CAREER**

Since 2006, when I became pathologist, I have participated at 34 post-graduate courses, 31 international scientific congresses, 10 national congresses with international participation and 20 national congresses. I have sustained 6 oral presentations at the national congresses with international participation, that represented proceedings published in books with ISBN or ISSN.

## **PLANS AND PERSPECTIVES FOR THE EVOLUTION AND DEVELOPMENT OF THE SCIENTIFIC, ACADEMIC and PROFESSIONAL CAREER**

### **Future directions in scientific career**

The next steps in my scientific career are going to be the continuation of the works that I have already started with my colleagues from different research teams, focused on tumorigenesis pathways in the fields of dermatology (melanocytic lesions [with extension also on primary extra-cutaneous melanomas], primary cutaneous T-cell and B-cell lymphoproliferative disorders and inflammatory and tumoral lesions nearby or developed from a squamous epithelium), otorhinolaryngology and dentistry.

While understanding the continuum of steps from inflammatory diseases to the malignant tumors, I will be looking forward to identify the turning points that can be diagnosed, treated or, better, prevented, in order to impair the transition of pre-malignant lesions to their invasive counterpart.

An important part of the activities involved in the care of oncologic patients is finding THE drug that can treat cancer, have the fewest, hardly any, if possible, side effects, and with best impact on the patient's quality of life. Even if the doctors deal with a condition that, nowadays, cannot be cured, to improve the therapies used against cancer means to gain time for patient and his family, time free of disease, to enjoy life, to create memories, to share moments and why not, to solve legacy issues. The new discoveries in the field, that confer to oncologist the possibility to design an individualized therapy centered on each patient, temporizing an undesirable event and offering to the researchers the time needed to find the long-awaited solution to cure cancer.

Together with the colleagues from Faculty of Pharmacy and from the Department of Biochemistry, we will be creating new bricks in this borderless building.

### **Future directions in the study of melanocytic lesions**

Together with the team of the Research Center for Pharmaco-Toxicological evaluation, we have already outlined a melanoma model on chorioallantoic assay and on Balb/c mice, and tested the properties of bare, PEGylated and betulin linked silver nanoparticles on four melanoma cell line, *in vitro* and *in vivo*, in order to find new therapies, area where our researches will be continued.

The collaboration between pathology, molecular biology and dermatology teams resulted in miRNA characterization of cutaneous and extracutaneous melanomas, a research that is only at beginning and it will be continued on a bigger number of cases. Moreover, because of the association between ocular melanomas and dysplastic nevus syndrome, an interdisciplinary approach is necessary in order to diagnose earlier these rare tumors.

### **Inflammatory and lymphoproliferative disorders of the skin**

The small number of mycosis fungoides and parapsoriasis cases could be also an aspect of underdiagnosis of these conditions, their light signs being able to go unnoticed by the clinicians, therefore, the continuation of the research I have already done in the field, together with dermatology and molecular biology teams and the extension of the study to microRNA characterization of these diseases are part of my future plans in T-cell lymphoproliferative disorders field.

The paucity of primary skin B-cell lymphoma transforms the diagnosis of these lesions in a challenge, therefore, their exhaustive immunohistochemical characterization represents a real benefit for a correct diagnosis.

Thus, we consider important to fully describe from epidemiological etiologic, clinical, histopathological and immunohistochemical point of view all the B-cell lymphoma cases diagnosed in daily routine.

### **Lesions of squamous stratified epithelium**

Nasopharyngeal carcinoma is one of the few malignancies in childhood that emerge from the epithelium, and constitutes 1–5% of all pediatric cancers and 20–50% of all primary nasopharyngeal malignant tumors in children.

Therefore, in collaboration with my colleagues from Otorhinolaryngology Department, we will characterize these tumors from epidemiological, clinical and histopathologic points of view, with emphasis on the expression of immunohistochemical markers that can predict prognosis and can represents therapeutic targets, trying to assert the most probable **steps of carcinogenesis carousel regarding this type of tumor**.

Furthermore, based on the significant **male predominance** that we have already noticed in nasopharyngeal carcinomas and squamous papillomas ongoing study, in both benign and malignant tumors, we purpose to find if there is any immunohistochemical receptor expressions for sexual hormones in the benign and malignant lesions of nasopharynx and, also, if we can draw some evolutive factors that can predict the progression of the benign lesion to its malignant counterpart.

Moreover, on skin, we observed that **inflammatory disorders can progress to invasive tumor**, being known the apparition of squamous cell carcinoma at the site of hypertrophic lichen planus, pemphigus vegetans or chronic ulcer. All these conditions are systemic and can involve head and neck organs as oral cavity (how we already shown) and larynx. In a case of pemphigus vegetans affecting the larynx (data not published), we identified the acantholytic cells in a thick epithelium.

### **The interactions between infectious factors and tumor development**

Many types of cancer list viruses as main etiologic factor.

Hepatic cancers are the sixth most common type of cancer diagnosed worldwide and the third cause of deaths. Gastric cancer represents the fifth more important type of cancer by number of new cases and ranks four by mortality. These two types of cancers will represent new chapters in my future scientific career.

Kaposi's sarcoma is rare type of cancer worldwide. Its etiology is in all cases linked to Kaposi's sarcoma herpesvirus or human herpesvirus 8 (HHV8), but the only the HHV8 infection is not an enough condition to develop cancer.

In the light of the last months epidemiological context, we diagnosed a case of Kaposi's sarcoma in a patient with severe SARS-CoV-2 infection, where the lesions appeared on palms during the patient hospitalization in intensive care unit (data not published). The oncogenic potential of SARS-CoV-2, as singular infection or in association with other viruses, will be, also, a new chapter of my next researches.

### **Experimental models and their use in therapeutical improvements**

While it is well known that some microbes can act as etiologic factors for different malignancies, it is also recognized for more than 100 years already, that microorganisms and their products have the capacity to inhibit tumor growth without major side effects, being considered as potential therapeutic agents for cancer. The role of *Trichinella spiralis*

in the tumor environment it is not well documented, therefore the diagnosis of laryngeal trichinosis in a man with the parasitic infection 20 years before, with the presence of encysted *Trichinella spiralis* larva in the cytoplasm of striated muscle, some of them calcified, in the muscularis propria of larynx, lined by a thick squamous stratified epithelium with acanthosis (data not published), raise the question about the tumor suppressing role of the parasite.

The identification of new therapies and, also, new prophylactic methods, using *in vitro* and *in vivo* models, will continue to be important parts of my scientific career.

### **Future directions in academic career**

The main goals of my academic activity are the formation of students and pathologists.

The students are the future doctors and keeping in mind that a good doctor must have an integrative mind with possibility to interconnect knowledges from many specializations, including histology and pathology, I will continue to focus on improving the lectures and lab presentations, making them more attractive to the students and correlating the histology and pathology curricula, with emphasis on the histology of organs whose impairment is the cause of high morbidity and mortality. Because the inner child will always enjoy to learn better while playing, during lectures and labs I will organize different games with histology subjects as jeopardy games, role play games, board games, cross words. In the same idea of helping them to learn, I will publish materials that can be consider learning supports for lectures and labs also, because it will include macroscopic and microscopic specimens' pictures presented as barcode, with the possibility to visualize them on electronic gadgets as high-resolution images.

The evolution of the technologies provides new possibilities for learning. It is a challenge to train new pathologist residents and medical students by providing online sources, access to online scanned slides, opportunity to attend "hands on" courses, summer schools, etc.

The training program will consist of acquisition of the theoretical knowledges of anatomy, physiology, pathology, etiology and symptomatology and treatment of diseases, because the diagnosis of a disease should always be the result of a teamwork, only correlating all this information.

A graded increase in the responsibilities of pathologist by creating for each patient an individualized therapy based on the features noticed at microscope, requires residents to be as well prepared as possible, therefore the experience gained by them will be recorded in the log book. Confirmation of the progression of the trainee to the competency level will be required.

Regarding academic study of Histology, I will optimize the curricula and the current textbook on which Histology is taught, edit new courses and practical workbook (laboratory) materials for students, implement the twelve tips for doing effective Team-Based Learning.

The topics for the graduation thesis proposed by our department are in the context with the international scientific concerns in order to maximize the value of scientific results.

Pathology field is vast and very often involves overspecialization. The fellow pathologist residents I work with are already used with all histopathological techniques



that usually are involved in a microscopic analysis: gross macroscopy, intraoperative diagnosis, morphological and histochemical stains, and immunohistochemical reactions, because I consider important to involve them in all the steps of laboratory workflow.

In the eager desire to offer them the possibility to learn, we will continue the online sessions of case presentation, and I will focus on organization of lectures of pathology that will cover the vast curricula of pathology exam. “Blitz” diagnosis on the slides with pathognomonic features of lesions will be a daily practice in our laboratory, in order to get them used to working under stress. A site of pathology, with the possibility to access clinical, radiological and histopathological aspects of interesting cases, will be set online.

Even if, in many cases, for histopathological diagnosis the state of art remains H&E staining, the urge to develop individualized therapies is the novelty in oncologic treatment in the last decades. Therefore, helping pathologist residents to become familiar with the newest histopathological techniques that imply hybridization in situ, molecular biology and genetic studies will be parts of my future directions in academic career.

Because a good scientist is sculpted from the early beginning, promoting of different active-participative strategies, by working with small groups of students and by their involvement in the writing process of scientific abstracts, presentations, papers and research projects will be another focus of my career.

### **Future directions in professional career**

My exciting future directions will include the development and introduction at Histology Department from “Victor Babeș” University of Medicine and Pharmacy and, also, at Service of Pathology from Timisoara’s Emergency City Hospital of highly sophisticated new technologies applied in histopathological diagnosis. New markers and prognostic factors will be assessed in order to improve the diagnosis and treatment options.

Under the coordination of “Victor Babeș” University of Medicine and Pharmacy Timișoara, we will organize of postgraduate CME events for the benefit of our local fellow pathologists: courses on specific research topics, curricular courses, summer schools, etc. as a continuation of previous congresses, conferences and courses.

In the same time, we would open new collaboration with professional and scientific research teams from our country and from abroad.