

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



**CONTRIBUTIONS TO EXPLORING CELLULAR
DYNAMICS, SYSTEMIC INTERACTIONS, AND
THERAPEUTIC ADVANCEMENTS IN
PERIODONTITIS AND PERI-IMPLANT DISEASES
FROM THE PERSPECTIVE OF TIMISOARA
SCHOOL OF PERIODONTOLOGY**

ABSTRACT

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ABSTRACT

Since the defense of my doctoral thesis “Leziunile combinate endo-parodontale. Considerații clinice și terapeutice” (“Combined endodontic-periodontal lesions. Clinical and therapeutical considerations”, thesis director Academician Professor Dr.Andrei Iliescu) in 2011, my scientific interest was focused mainly on fundamental and clinical Periodontology. Additionally, part of the research was done also in basic research in Endo-Perio relationships.

The first part of the thesis contains a synthesis of my scientific achievements, after the completion of my doctoral thesis (chapters 1 and 2). The main results, all published in peer-reviewed and, most of them, in impact factor journals (as main author or co-author in national and international research teams) include:

1. The behavior of soft tissue cells involved in periodontal healing mechanisms. The published papers that cover this research topic are Cioban et al. Rom J Morphol Embryol. 2015; Rusu et al. BMC Oral Health. 2016; Roman et al. Microsc Microanal. 2016; Rusu et al. Quintessence Int. 2017; Rusu et al. Exp Ther Med. 2019; Roman et al. Sci Rep. 2019; Kardaras et al. Oral Health Prev Dent. 2023; Onet et al. Ro J Stomatol. 2023. One of the most important conclusions of this chapter is that *in vitro* assessment of different oral keratinocyte sub-populations after placing a 3D collagen matrix for augmentation of the keratinized gingiva, with a focus on progenitor cells, supports the claim that maturation of cytologic composition might take longer than expected, while clinical aspect and histological analysis at the same timepoint demonstrate a mature epithelial architecture. At the same time, the T-lymphocytes response induced by the matrix does not seem to hinder the healing process

2. Researches on periodontal-systemic interrelations. The published papers that cover this research topic are : Marian et al. Medicine in Evolution. 2017; Marian et al. Oral Health Prev Dent. 2019; Surlin et al. Exp Ther Med. 2020; Costea et al. J Clin Med. 2022; Butnaru et al. Romanian Journal of Medical and Dental Education, 2023. One of the valuable conclusions of this research topic suggests the role of vitamin D in the pathogenesis of periodontitis. Having the CC and CT genotype of the FokI polymorphism (rs2228570) and the AG genotype of the BsmI polymorphism (rs1544410) seems to predispose individuals; however, no associations between these two SNPs were identified in the Western-Romania population. At the same time, elevated levels of IL-1 α and IL-1 β , which have considerable implications in the pathogenic processes of both periodontal disease and chronic hepatitis C, could imply that the latter has a negative impact on the inflammatory status of periodontal patients, as assessed by interleukin detection.

3. Local and systemic antimicrobials as adjunctives to subgingival instrumentation during step 2 of periodontal therapy. The published papers that cover this research topic are: Rusu et al. Int J Dent Hyg. 2015; Radulescu et al. Medicine in Evolution. 2017; Boia et al. .Exp Ther Med. 2019; Soanca et al. Ro J Stomatol. 2022; Radulescu et al. Clin Oral Invest. 2022; Ilyes et al. Medicina. 2023; Lozon et al. Ro J Stomatol. 2023; Budală et al. J Clin Med. 2023; Soanca et al. J Clin Med. 2023. The main findings indicate that non-surgical periodontal therapy given in combination with a 7-day course of antibiotics proved more effective for improving clinical parameters when compared with a 3-day course of antibiotics. The detection of several pathogenic bacteria (*Aa* and *Td*) showed greater improvement with the 7-day antibiotic regimen,

as well as the systemic oxidative stress markers (decrease in d-ROMs). Bacterial resistance was found in fewer strains after treatment than prior to treatment. Also, various local antimicrobial medications adjunctive to subgingival instrumentation failed to show significant improvements over subgingival instrumentation alone.

4. The bacterial biofilm of endo-periodontal lesions. The published papers that cover this research topic are: Didilescu et al. Int Endod J. 2012; Rusu et al. Exp Ther Med. 2020. The results of these research indicate that the SEM investigation of radicular surfaces involved in endo-perio lesions (EPL) revealed less surfaces covered by biofilm than expected, while the positive association found between *P. micra-endo* and *P. micra-perio*, as well as significant association between *P. micra-endo* and symptomatic teeth, suggests the possibility of a role for these anaerobic Gram-positive cocci in endodontic–periodontal lesions.

5. The periodontium in patients with treated severe periodontitis during initial stages of orthodontic movements. The published papers that cover this research topic are: Zetu et al. Rev Med Chir Soc Med Nat Iasi. 2011; Calniceanu et al. Exp Ther Med. 2020. The main conclusion drawn was that there are no significant changes in the clinical parameters and microflora during the initial phase of orthodontic treatment in patients with periodontal support reduced by severe periodontitis once the primary disease is systematically treated and the residual inflammation controlled.

6. The middle- and long-term behavior of tooth- and implant-supported prosthetic restorations in patients treated for severe periodontitis. The published papers that cover this research topic are: Radulescu et al. Medicine in Evolution. 2018; Radulescu et al. Diagnostics. 2022; Rusu et al. Diagnostics. 2023. The findings revealed that, if a comprehensive and systematic periodontal treatment is performed prior to the prosthetic rehabilitation, and regular consequent supportive therapy is implemented, a successful medium-term retention of periodontally compromised teeth is possible for patients diagnosed with Stage IV periodontitis, through extended prosthetic restoration including these teeth, with predictable long-term results, regardless of the type of stabilizing prosthesis.

7. Experimental and clinical studies of peri-implant diseases: from histopathology to modern therapeutic solutions. The published papers that cover this research topic are: Boldeanu et al. Medicine in Evolution. 2018; Iorio Siciliano et al. Clin Oral Invest. 2020; Boldeanu et al. J Clin Med. 2022; Rusu et al. Medicine in Evolution. 2023; Boldeanu et al. J Clin Med. 2023. Among the conclusions, the most important appears to be that the adequacy of the experimental dog model based on ligature-induced peri-implantitis can be successfully challenged by the non-ligature models of spontaneously occurring peri-implant inflammation, while meeting the requirements for experimental designs with a very small numbers of animals. Of similar importance was the data-based confirmation of the reduced effectiveness of local antimicrobials on the reduction of peri-implant mucositis.

Since 2011, I have authored a *total of 42 papers*: 27 papers in peer-reviewed journals with impact factor (ISI) and 3 ISI Proceedings, 12 papers in peer-reviewed journals in international databases. 20 abstracts were published in ISI journals, 8 abstracts were published in ISBN or ISSN volumes, and 55 presentations were held in national and international scientific meetings. Up to July, 2023, the Citation report from Web of Science Core Collection refers to 27 published papers, with the following results: sum of the times cited: 79; sum of the times cited without self-citations: 74; citing articles: 78; citing articles without self-citations: 73; average citations per item: 2.72; h-index: 5.

I collaborated in interdisciplinary well-trained and well-functioning research teams, including prestigious national and international scientists and academics from the universities of Bern (Switzerland), Leipzig, Mainz and Aachen (Germany), Naples and Milan (Italy), Bucharest, Cluj-Napoca, Iasi, Craiova, Timisoara.

After having been involved in 5 national research grants funded through national competitions as researcher, collaborator, and scientific coordinator before the defence of my PhD thesis, from 2011 to 2017 I have participated in another 5 research grants funded through national and internal competitions: 1 grant as project director ("Characterization of the epithelial biological activity and of T-Lymphocytes response on a 3D bilaminar collagen matrix used for the augmentation of keratinized gingiva width during post-graft healing", internal grant of the Victor Babes University of Medicine and Pharmacy Timisoara (UMFVBT); 1 grant as scientific director („Microlaboratory for biopsy processing of non-demineralized tissues and complex bone-soft tissue-metal specimens in oral implantology" (internal grant of the UMFVBT within the program "Developing of capacities in applied and fundamental research"); 2 grants as team member: "Behaviour of the mesenchymal oral cells in relation with a new composite material in modern regenerative periodontal therapy" (funded in the 2013/2014 CNMP competition of partnerships, submitted by the Iuliu Hatieganu University of Cluj-Napoca); „Innovative and applicative fundaments of Optical Coherence Tomography in dental medicine. Alternative experimental validations" (internal grant of the UMFVBT within the program Partnerships in Innovative Fundamental Research); 1 grant as researcher: "Role of cognitive-behavioral psychotherapy during surgical periodontal therapy". The cumulated funding of these projects amounted to 7.467.894 RON and 40.000 EUR.

Since 2011, I have authored and co-authored three textbooks and contributed to one international textbook: "Leziunea endo-parodontala: notiuni de clinica, terapie si teme particulare de cercetare" (The Endodontic-Periodontal Lesion: Clinical Description, its Therapy and Particular Related Research Topics), Ed.Curtea Veche, Bucuresti, 2014; "Furcatiile radiculare: notiuni de clinica, imagistica si teme particulare de cercetare" (The Furcation Lesion: Clinical & Imagistic Description, and Particular Related Research Topics), Ed.Victor Babes, Timisoara, 2014; "Managementul Spațiului În Dentiția Temporală si Mixtă" (Space management in temporary and mixed dentition), second edition, revised and completed, MIRTON, Timișoara, 2017; "Periodontology – New Insights". Edited by Gokul Sridharan. IntechOpen, 2022. Advances in Locally Delivered Antimicrobials for Periodontitis Treatment. Open Access Peer Reviewed Chapter.

One of the innovative results of my post-doctoral scientific activity is the patenting of a "Device for splinting of mobile teeth affected by periodontal disease" (National Patent 126086 B1, RO-BOPI 11/2013 of 29.11.2013). Three scientific awards granted by the National Research Authority UEFISCDI (2012, 2019, 2020) were over the last decade a form of recognition for my scientific activity.

Up to present, I have participated in over 70 international scientific meetings in Romania and abroad (Spain, Germany, Greece, Turkey, the Netherlands, Croatia, Sweden, Serbia, Ireland, Bosnia-Herzegovina, Cyprus, Lithuania, Hungary, Austria, Belgium, Portugal, Switzerland, Italy, Finland, Israel, UK, Malta, France) with 31 personal research papers. So far, I have delivered 23 lectures in postgraduate and CME courses on topics of Periodontology and Implantology.

Chapter 3 of the habilitation thesis describes my academic percourse. In 2004, as an associate assistant professor, I joined the recently created Department of Periodontology of the Faculty of Dental Medicine of the Victor Babes University of

Timisoara. In 2007 I became assistant professor and in 2018 reader in the same Department. My main academic assignments include currently: courses and periodontal clinical training in Periodontology for the 6th grade students of the Faculty of Dental Medicine; courses, clinical courses and clinical supervision in the postgraduate program of Periodontology; CME courses of Periodontology for postgraduates organized by the Victor Babes University in cooperation with scientific societies; coordination and supervision of graduation dissertations. Since 2011 I have contributed to two textbooks of Periodontology for undergraduates, I have participated in all admission and graduation exams organized by our University, in several exams for promotion to academic positions in Timisoara, and in commissions for PhD defence in Iasi and Cluj-Napoca. Our University honoured me with appointments to several administrative and managerial positions, like membership in the Commission for Evaluation and Assurance of Educational Quality, the Executive Board of the Student Entrepreneurial Society and as executive director of the Anton Sculean Centre for Periodontal and Peri-implant Diseases Research CCBPPAS.

Chapter 4 of the thesis follows the achievements of my professional activity. Between 2007-2010, following the introduction of new dental specialties, I attended the postgraduate program in Oral Surgery of the Victor Babes University of Timisoara. In 2012, I received the recognition as specialist of Periodontology, and in 2017 as *Medicus Primarius* of Periodontology. In 2008, after having attended a one-year curriculum, according to the current regulations, I was granted the competence in Dental Implantology. I have attended numerous postgraduate courses and workshops in Periodontology, Implantology, Dental Microscopy and Endodontology, in Romania and in Germany, Switzerland, USA, Ireland, Denmark, the Netherlands, Lithuania, Sweden, Spain. The professional recognition led since 2011 to several professional engagements: repeated memberships between 2014 and present in commissions for the examination for the title of specialist in Periodontology at the Victor Babes University of Medicine Timișoara, and in commissions for the examination for the Title of *Medicus Primarius* of Periodontology at the Victor Babes University of Timișoara in 2020 and 2022.

Although focused on Periodontology, my early interest on Endodontology and dental microsurgical techniques required a systematic structuring of the knowledge and experience achieved over years. Therefore, a Master Program in Endodontology (Management of Pulpal Diseases) was completed in 2006-2007 at the Carol Davila University of Medicine and Pharmacy Bucharest (program director – Academician Professor Dr. Andrei Iliescu).

Chapters 5 and 6 of the thesis contain plans and perspectives for the future evolution and development of my scientific, academic and professional career. The latter is introduced by a subsection on the role and place of periodontal research in a global vision and a list of interest topics in contemporary periodontal research. Below a brief selection of the future directions of research: in-depth exploration of the current research directions (as documented with the published papers); Introduction of new research directions: the microbiological diagnosis of periodontitis based on Next Gen Sequencing (NGS) techniques (in collaboration with the Department of Biochemistry of the Victor Babes University of Medicine and Pharmacy Timisoara); the evaluation of new techniques and protocols (the Guided Biofilm Therapy) and substances designed for the causative (anti-inflammatory & antibacterial) therapy of periodontitis and peri-implantitis (in collaboration with the University of Leipzig, the Iuliu Hatieganu University of Medicine of Cluj-Napoca, the Gr.T.Popa University of Iasi, the Federico II University of Naples, the RMW University of Aachen); the evaluation of the safety

profile of various antimicrobial medications used in Step 2 of periodontal therapy (in collaboration with the Department of Toxicology of the Faculty of Pharmacy Victor Babes University of Medicine and Pharmacy Timisoara); the regenerative treatment of suprabony defects using hyaluronic acid and enamel matrix proteins (in collaboration with the Federico II University of Naples, Italy); the pathogeny of the peri-implant disease and the recent advances in the research of factors, materials, substances and techniques involved in peri-implant healing and regeneration (in collaboration with the Federico II University of Naples, Italy, the University of Bern); the particular research of periodontal-systemic associations: associations of periodontitis with diabetes, C hepatitis, atherosclerotic cardiovascular disease, adverse pregnancy outcomes/obstetric complications, periodontitis - chronic obstructive pulmonary disease, chronic kidney disease, rheumatic arthritis, cognitive impairment, metabolic syndrome and cancer (in collaboration with the University of Craiova); 3D assessment of the tissues involved in root coverage using modern scanning techniques (in collaboration with the University of Milan).

A selection of both undergraduate and post-graduate proposal for future directions of my academic career includes: contributing to the improvement of the existing knowledge database of the Department of Periodontology, as a common editable collection to be used by the undergraduate students of all academic programs of the Faculty, e.g. Dental Medicine, Dental Technique, Dental Assistance; aligning the chapters on periodontal therapy in the course support with the recent S3-level Clinical Practice Guides for Treatment of Periodontitis stages I-III and IV (2020, 2022) and the CPG for Peri-implant Diseases (2023); editing a support for the practical exercises for dental laboratory students; renewal and completions to the demonstrative and research equipment of the Department; providing the clinical spaces of the Department with modern recording and broadcasting equipment, to be used for clinical demonstrations and live surgeries; providing the teaching staff, the students and residents with subscriptions to electronic databases of scientific papers and clinical demonstrative movies of Periodontology, based on the self-financing provided by the Research Centre of the Department; enlarging the existing academic and scientific relations with foreign prestigious Universities and to develop relations with new ones; contributing to the creation of an open, multidisciplinary and integrated clinical classes system, involving all dental clinical disciplines hosted by the main building of the Faculty of Dental Medicine of Timisoara; contributing to the re-thinking of the global residency program of Periodontology, which should increase its content of "pure" specialty to reflect the 2019 Quality Standards For Graduate Programs In Periodontology, Periodontics And Implant Dentistry of the EFP; contributing to the specific improvement of the knowledge thesaurus of the Department of Periodontology using the modern e-learning facilities of the Victor Babes University (Moodle platform), as a common editable knowledge database to be also used by the postgraduate program of Periodontology; contributing to the creation of an "inter-residential clinical research unit", with state-of-the-art equipment of clinical research (a number of modern ergonomically fully equipped dental units, dental operating microscopes, microsurgical & endodontic kits, latest imaging, networking and documentation technology etc.) to be used in common by the residents of the 5 new specialties; finding further funding support for the academic development by using the self-financing resources provided through the CCBPPAS Research Centre.

One of periodontology's greatest strengths is that it is not a static field; rather, it continues to evolve and readjust its focus on the basis of contemporary research spanning a vast array of scientific endeavors. These developments are expected to

help reshape periodontal therapy over the next 10 years and are oriented towards an evidence-based personalized periodontal medicine, as required by the emerging standards of care of the European Union, to which the Romanian dental medical education is aligned.