

OVIDIUS UNIVERSITY OF CONSTANTA

HABILITATION THESIS

**GENETIC AND EPIGENETIC PROFILES IN COLORECTAL NEOPLASIA -
RESEARCH TRANSLATION INTO CLINICAL ACTIVITY**

ABSTRACT

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CONSTANȚA

2023

I am a senior medical genetics physician and senior scientific researcher (CS I) at the Research Team of Pathology Department, "Sfântul Apostol Andrei" Emergency County Clinical Hospital of Constanța and scientific researcher (CS II), coordinator of the Molecular Biology Platform, at the Research-Development Center for the Morphological and Genetic Study in Malignant Pathology (CEDMOG) of the "Ovidius" University of Constanța.

I obtained PhD degree in 2012 (Minister's order no 6351/07.09.2012) with the thesis entitled "Cytogenetic study of couples with reproductive disorders in order to establish the type and frequency of chromosomal abnormalities responsible for their production" at "Ovidius" University of Constanța.

The habilitation thesis "**Genetic and epigenetic profile in colorectal neoplasia – Research translation into clinical activity**" presents, in the synthetic manner, the main results of my postdoctoral research and professional activity, centered on colorectal neoplasia. In accordance with the recommendations of the specialized commission of the National Council for Attestation of University Titles, Diplomas and Certificates (CNATDCU), the thesis is structured in three main sections, preceded by the summary. The first section is organized into chapters that reflect my main research directions in the field of colorectal neoplasia.

Since obtaining the scientific title of doctor, I have been part of the team of more than 25 research projects, of which 7 as principal investigator. These projects allowed me to approach various research topics in the field of breast, ovarian, colorectal neoplasia, non-Hodgkin lymphomas, esophageal neoplasia, neuroendocrine tumors of the digestive tube. But out of all my research activity, I chose for the habilitation thesis to be centered on colorectal neoplasia, because in this field I have the most published works, in Web of Science, Clarivate Analytics, rated journals, with an important impact factor. The results of the scientific research activity were made concrete by the elaboration of over 140 scientific works, of which 88 (29 in extenso) were published in ISI Web of Science indexed journals, 39 in BDI indexed journals and 14 in other indexed databases.

The first research direction addressed is focused on the identification of the molecular profile of somatic mutations of the key oncogenes, KRAS, NRAS, BRAF, PIK3CA and AKT1, involved in colorectal carcinogenesis (CCR) and personalized therapy, through the Sanger sequencing technique. We chose to identify these mutations in the heterogeneous population of

Dobrogea and correlate them with clinical and pathological variables to determine diagnostically relevant changes. Our study showed that the occurrence of KRAS, BRAF, PIK3CA and AKT1 oncogene mutations are frequent events in CRC patients from Dobrogea, there is a significant association of KRAS and PIK3CA mutations. These findings have important implication for the personalized treatment of the Romanian CRC patients, thereby providing an opportunity to improve healthcare efficiency in these patients.

The next chapter is focused on the association of TCF7L2 (rs7903146, C/T), CASC21 (rs6983267, G/T) and GREM1 (rs1696981, C/T) polymorphisms with colorectal cancer, but also the risk of developing colorectal cancer in patients with type 2 diabetes mellitus. The rs7903146 TCF7L2 polymorphism has a low association with the development of colorectal cancer, and no association was identified between rs6983267, rs1696981 and colorectal cancer in our study. However, our study highlights the possibility of a high risk of developing colorectal cancer in patients with the TT genotype of rs7903146. On the other hand, TCF7L2 rs7903146, CASC8 rs6983267 and GREM1 rs1696968 are significantly correlated with the risk of developing CRC in patients with type 2 diabetes mellitus and could be considered as potential risk factors in these patients.

Another direction of research addressed is represented by the epigenetic profile of colorectal neoplasia, by identifying the expression of 14 microRNA species (miR-21, miR-141, miR-182, miR-183 and miR-370, miR-30c, miR- 144, miR-375, miR-214, miR-195 and miR-299, miR-92a, miR-143, miR-145), which function as potential liquid biopsy biomarkers, having the ability to discriminate colorectal neoplastic tissues. The results of the study demonstrated that miR-21, miR-183, miR-182, miR-14, miR-92a, miR-143 and miR-145 have increased sensitivity and specificity in discriminating between neoplastic and normal tissue, suggesting their importance as biomarkers, and their expression is deregulated in accordance with the evolution of the neoplasia.

Section II is dedicated to the presentation of career development plans, in scientific and academic terms. One of the most important projects in which I am involved as the coordinator of the Molecular Biology Platform, is represented by the Research and Development Center for the Morphological and Genetic Study in Malignant Pathology (CEDMOG), a project won through the POSCCE competition and completed with the construction of a center that has 11 research

laboratories. One of the research directions of this center is represented by the study of malignant pathology through molecular genetics and genomic techniques. I will be involved in attracting new research projects, improving national and international collaborations, attracting new members to the team I coordinate, especially doctoral and post-doctoral researchers. Future research directions are represented by the expansion of previous ones, emphasizing the clinical translation of research results. I therefore consider that the scientific supportive environment and access to research logistics offered by the CEDMOG center is of major importance for the mentorship of PhD students.

At the same time, one of my priorities is to establish and to take part in educational training programs for PhD students and postPhD researchers in the medical field. Therefore, I will be involved in educational programs Occupation and Education Program 2021-2027.

The third section includes the bibliographic titles associated with the scientific content contained in the first two sections.