ACADEMIA ROMÂNĂ
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Anexa nr.6

ABSTRACT OF HABILITATION THESIS

TITLE : **GENETIC AND EPIGENETIC MARKERS IN PRECISION MEDICINE**

Habilitation domain: *MEDICINE*

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Precision medicine is an innovative approach aimed to adapt the treatment to individual characteristics of patients or to a subgroup. Its goal is to maximize therapeutic efficacy and minimize treatment toxicity, thus contributing to more effective management of cancer, a complex and heterogeneous disease responsible for a significant proportion of morbidity and mortality worldwide. Precision medicine has shown the potential to improve treatment outcomes by personalizing therapy based on the distinct molecular features of tumors. Genetic and epigenetic testing are essential for the implementation of personalized medicine. Technological advancements, such as Next-Generation Sequencing (NGS), allow the identification of complex genetic and epigenetic patterns specific to tumor cells. This information is crucial for identifying new therapeutic targets and predictive biomarkers. For example, therapies based on epigenetic modulators could be viable for hematologic neoplasms and solid tumors.

This thesis presents a multi-faceted approach to identifying genetic and epigenetic biomarkers. The studies conducted have been carried out not only in oncogenesis but also in various pathologies.

Epigenetic and Genetic Markers in Oncogenesis

- **Epigenetic phenomena in virus-induced cancers:**

- HPV infection is correlated with the development of cervical neoplasia. Studies on the epigenetic changes induced by this virus have the potential to improve diagnosis and treatment.
- In laryngeal cancer, the increased expression of lncRNA H19 correlated with clinical stage and latent EBV markers suggests the significant role of epigenetics in the progression of this type of cancer.

- **Promoter methylation of tumor suppressor genes in thyroid cancer:** An example is the hypermethylation of the TET1 and TET2 genes, which significantly affects DNA methylation in thyroid cancer. Evaluating these processes could become an important diagnostic tool.
- **GNMT and pancreatic cancer:** Aberrant methylation of the GNMT gene is an indicator of tumor progression in pancreatic ductal adenocarcinoma (PDAC). The presented study shows that demethylation of this gene could constitute a potential therapeutic strategy.

- **Male infertility and epigenetics:** Epigenetic changes significantly influence male reproductive pathology. Identifying specific DNA methylation patterns in infertile patients highlights the importance of developing diagnostic tests and biomarkers for these conditions. Additionally, new directions indicate the need to explore the link between assisted reproduction and genetic imprinting disorders, such as Beckwith-Wiedemann syndrome and Angelman syndrome.
- **The importance of mutations in the diagnosis of myeloproliferative neoplasms (MPN):** Genomic studies highlight a predominance of mutations in genes encoding epigenetic factors in patients with MPN. These mutations, including in the EZH2 gene, are common and influence the evolution of tumor clones. Monitoring these changes is crucial for predicting disease transformation.
- **Epigenetics and rare diseases:** Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are associated with defects in imprinting mechanisms. Optimizing epigenetic diagnostic protocols for these conditions is an important step toward their effective management.
- **Epigenetic factors in COVID-19:** The presented study identified distinct lncRNA profiles in COVID-19, varying according to the severity of the disease. The increased

expression of GAS5 and ZFAS1 suggests a direct link to inflammation and infection severity, opening new perspectives for disease management and prognosis.

Future research directions:

1. **Artificial intelligence in oncology:** Integrating genomic and clinical data to develop diagnostic, prognostic, and therapeutic response prediction algorithms.
2. **Validation of epigenetic biomarkers:** Translating these into clinical practice requires extensive studies to demonstrate their utility.
3. **Virome-microbiome interaction and epigenetics:** Studying epigenetic profiles and integrating data into personalized medicine.

These directions emphasize the central role of epigenetics and genetics in understanding complex pathologies and developing innovative therapeutic strategies.