



**ROMANIAN ACADEMY
INSTITUTE OF ONCOLOGY
“PROF. DR. ALEXANDRU TRESTIOREANU”
BUCHAREST**



HABILITATION THESIS

ABSTRACT

IONIZING RADIATION: FRIEND OR ENEMY? FROM FUNDAMENTAL RESEARCH TO TRANSLATIONAL MEDICINE

Habilitation domain: Biology

Dr. STANCIU ADINA-ELENA

Bucharest, 2021

The habilitation thesis entitled “Ionizing radiation: friend or enemy? From basic research to translational medicine” reflects the scientific, professional, and academic activity of the author, carried out after receiving the Ph.D. degree in chemistry in 2003, with an emphasis in the final chapter of career development prospects. The thesis comprises three sections: (I) Scientific, professional and academic achievements; (II) Plans for the evolution and development of the scientific, professional, and academic career and (III) References.

The first section is organized into two subsections (A) scientific achievements and (B) professional and academic achievements. Subsection (A) scientific achievements is divided into two chapters: 1. The action of ionizing radiation on biological systems - from basic research to clinical implications related to cancer treatment and 2. Biomarkers - a key element in precision medicine. The representative scientific results obtained following the two research directions are supported by the publications presented at each subchapter's beginning. The main results developed in the *Action of Ionizing radiation on biological systems - from basic research to clinical implications related to cancer treatment* can be summarized as follows: (i) rapid reaction kinetics studies combined with EPR technique have shown that gamma irradiation of molybdates ($\text{Mo}^{\text{VI}}\text{O}_4^{2-}$) and tungstates ($\text{W}^{\text{VI}}\text{O}_4^{2-}$) leads to paramagnetic species ($\text{Mo}\dot{\text{O}}_2^-$), ($\text{W}\dot{\text{O}}_2^-$) with Mo^{III} , W^{III} stable at 37°C, passing through unstable intermediate states and highly reactive ($\text{Mo}\dot{\text{O}}_4^{3-}$), ($\text{W}\dot{\text{O}}_4^{3-}$) with Mo^{V} , W^{V} , highlighted at 77 K; (ii) the concentration of free radicals induced by ionizing radiation in the analyzed systems was proportional to the absorbed dose - they can be used as biosimetric indicators; (iii) studies performed by EPR are the basis of the concept of radiation protection and chemical radiosensitivity, having multiple clinical applications in radiotherapy of malignant tumors. Chapter 2 *Biomarkers - a key element in precision medicine* is divided into two subchapters 2.1 *Tumor Markers* and 2.2 *Cardiac Markers*. Subchapter 2.1 presents the results of several clinical trials aiming to identify biomarkers of diagnosis, prediction, and prognosis in cancer: (i) the multi-biomarker panel (BTA, UBC, TPS) had a diagnostic accuracy of non-muscle-invasive bladder cancer superior to urinary cytology or panel consisting of variants of two biomarkers or independent biomarkers; (ii) hs-CRP, IL-4, and IL-10 biomarkers can be used in the early detection of tumor recurrence, especially in patients with papillary thyroid cancer associated with Hashimoto's thyroiditis, in whom Tg levels are unreliable due to cross-reaction with TgAb antibodies; (iii) the therapeutic efficacy of ^{131}I was illustrated by a reduction in the ratio of MMP-9 / TIMP-1; (iv) serum levels of MMP-2 and TIMP-2 were correlated with the degree of tumor differentiation in the head and neck squamous cell carcinomas; (v) the MMP-9 / TIMP-1 ratio was negatively correlated with the presence of lymph node metastases in head and neck squamous cell carcinomas; (vi) melatonin can be used as a predictive biomarker of proliferation and metastasis in oral squamous cell carcinoma.

The main results, obtained from clinical trials performed in groups of patients with heart failure and atrial fibrillation, presented in the subchapter *Cardiac Markers* can be summarized as follows: (i) multi-biomarker panel (NT-proBNP, IL-6, IL-8, MMP-2 / TIMP-2) may be useful in predicting patients' response to cardiac resynchronization therapy; (ii) NT-proBNP and CA 125 levels in venous blood and coronary sinus blood are dependent on

inflammation as a consequence of cytokine network activation (IL-6, IL-1 β , TNF- α) and provide an additional perspective on possible mechanisms by which these biomarkers lead to left ventricular remodeling; (iii) the development and progression of atrial fibrillation (from paroxysmal to persistent) has been associated with a gradual increase in serum NT-proBNP levels as a marker of hemodynamic stress; IL-6, as a pro-inflammatory and fibrosis marker and MMP-9 / TIMP-1, as an extracellular matrix remodeling marker; (iv) TGF- β 1, a marker of myocardial interstitial fibrosis, was negatively correlated with NT-proBNP and left atrium diameter, this interdependence allowing the progression of atrial remodeling in the development of atrial fibrillation.

The second part of the first section describes the main professional and academic achievements. Some of the data presented were obtained in collaboration with research groups in partnership projects. The number of national projects won through competition as a project director (2 projects) or partner manager (4 projects) attests the professional activity carried out after obtaining the Ph.D. degree. The results were published in ISI indexed scientific journals with impact factors (25 articles, of which 20 as the principal author). These include Cytokine, Clinical Biochemistry, Anticancer Agents in Medicinal Chemistry, Human Vaccines & Immunotherapeutics, Advances in Clinical Chemistry, Oncology Letters, and others. The author has published 6 books and 2 book chapters at international publishers (Pan Stanford Publishing, IntechOpen) and has a patent application filed for evaluation with the State Office for Inventions and Trademarks (OSIM). Dr. Stanciu AE received several awards, among which can be mentioned: the award for the best paper granted by the American Association for Clinical Chemistry Academy (2010 and 2011), the "Eugen Mody" award granted by the Romanian Association of Laboratory Medicine (2008), Diploma of the University Book Fair (2014 and 2019) granted by the University of Medicine and Pharmacy "Carol Davila" and Central University Library. The author is currently the coordinator of the Laboratory of Carcinogenesis and Molecular Biology within the Institute of Oncology "Prof. Dr. Alexandru Trestioreanu" Bucharest and a member of the Scientific Council of the Institute.

The second section of the thesis presents the scientific, professional, and academic development plans related to the current state of knowledge and the acquired professional experience. In the next period, the research activity will follow three development directions focused on: (i) internal dosimetry and radiobiology studies in the ¹³¹I therapy of differentiated thyroid cancer; (ii) the study of cardiotoxicity associated with cancer therapy; (iii) studies on management, assurance, and quality control in medical laboratories. The proposed objectives will not be achieved without the strengthen and development of scientific collaboration at the national and international level, without obtaining funding for research, and without recruiting young graduates who wish to carry on the personalized medicine dreams.

"Science is an ongoing process. It never ends.
There is no single ultimate truth to be achieved, after
which all the scientists can retire."

Carl Sagan