ROMANIAN ACADEMY
INSTITUTE OF CELLULAR BIOLOGY AND PATHOLOGY
"NICOLAE SIMIONESCU"

HABILITATION THESIS

ABSTRACT

TARGETED THERAPIES BASED ON NANOCARRIERS TO REDUCE VASCULAR INFLAMMATION

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Fundamental field: Biological and Biomedical Sciences
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ABSTRACT

The Habilitation Thesis "*Targeted therapies based on nanocarriers to reduce vascular inflammation*" summarizes the scientific results obtained in the field of nanomedicine by Dr. Manuela Călin in the period after receiving the Ph.D. degree in cell biology in 2005 and also presents the main professional achievements and the plans for evolution and development of professional, scientific and academic career.

The thesis is written in English and consists of three sections. The Section I "Scientific, Professional and Academic Achievements" describes the main scientific contributions and is organized in three chapters: Chapter 1. "Nanocarriers-based approaches to reduce vascular inflammation: State of the Art and personal contribution to the knowledge", Chapter 2. "Original contributions" and Chapter 3. "Professional and academic achievements".

The Section II „Plans For Evolution and Development of Professional Career" of the thesis presents the intentions for the future development of the academic, professional and scientific career and Section III „References" includes the list of references supporting the data presented in the habilitation thesis.

The representative scientific results are included in Chapter 2 "Original contributions" and describe three research directions, namely: 2.1. Development of suitable nanocarriers to perform specific and efficient delivery of pharmacological agents to dysfunctional endothelial cells; 2.2. Development of nanocarriers for delivery of pharmacological agents to monocytes/macrophages and 2.3. Development and testing of nanocarriers and nanoplatforms as vectors for gene delivery. The portfolio of published articles is mentioned at the beginning of each research direction. The main original results can be summarized as follows: (i) VCAM-1 is an appropriate target for specific delivery of drugs to activated endothelial cells employing nanoparticles; (ii) VCAM-1 directed target-sensitive liposomes carrying CCR2 antagonists bind to activated endothelium, diminish adhesion and transmigration of monocytes, reduce the atherosclerotic lesions in ApoE-deficient mice and prevent the generation of pulmonary metastases in a murine and a human xenograft model; (iii) Polyphenols-loaded lipid nanoemulsions directed toward VCAM-1 reduce monocyte infiltration by a mechanism involving the inhibition of NF-kB nuclear translocation and a reduced level of MCP-1 chemokine: (iv) Curcumin encapsulated in polymeric nanoparticles displays anti-inflammatory activity on TNF-α–activated endothelial cells by suppressing the phosphorylation of p38MAPK; (v) Cell-penetrating peptides-functionalized curcumin-loaded lipid nanoemulsions are efficiently internalized by the endothelial cells, producing anti-inflammatory effects; when administrated intravenously in mice exhibit increased accumulation in the liver and the lungs; (vi) P-Selectin targeted dexamethasone-loaded lipid nanoemulsions reduce selectively the endothelium activation and the consequent monocyte infiltration and diminish significantly the lungs' inflammation, in a mouse model of acute inflammation; (vii) P-selectin targeted PEGylated cationic liposomes bind specifically to activated endothelial cells and deliver with high-efficiency siRNA into the cells, that subsequently knockdown the mRNA expression of the target gene; (viii) Lipopolysaccharide-induced inflammation in monocytes/macrophages is blocked by the liposomal delivery of Gi-

protein inhibitor; (ix) fullerene (C60)-polyethyleneimine (PEI)/short hairpin (sh)RNA-Runx2 nano-polyplexes down-regulate Runx2 mRNA and protein expression leading to a significant reduction in the expression of osteogenic proteins in osteoblast-committed valvular interstitial cells; (x) validation of biomimetic nanocarriers and nanoplatforms able to act as safe and efficient gene transfection vehicles.

Some of the results were obtained in collaboration with research groups from Romania and abroad in the frame of research projects won in partnership. The results were published in ISI indexed scientific journals with impact factor (36 articles) such as Journal of Controlled Release, International Journal of Nanomedicine, Journal of Nanoparticle Research, Cell and Tissue Research, Pharmaceutics, European Journal of Pharmaceutics and Biopharmaceutics, Materials Science and Engineering: C, etc. I have also published 3 book chapters at prestigious publishing houses (Springer, Elsevier, John Wiley & Sons) and obtained a patent from the European Patent Office (EPO). Another 4 patent applications have been filed and are under evaluation, one at EPO and three at the State Office for Inventions and Trademarks (OSIM). The visibility of scientific research is proven by the number of citations (919/ WoS, 943/ Scopus, 1330/ Google Scholar) and the Hirsh index h = 18 (WoS); 19 (Scopus); 22 (Google Scholar).

A confirmation of the professional activity carried out after obtaining the Ph.D. degree is the number of national and international projects in which I was involved as project director (4 national grants), partner manager (2 European grants) or expert (7 national grants). I also received 7 awards, among which I mention Romanian Academy Award “Nicolae Simionescu” for the series of 10 papers published on the use of targeted nanotherapies for inflammation (2015), “Herbert-Berler” Prize of Excellence offered by Romanian Academy of Medical Sciences (2015), “Constantin Velican” Award of the Romanian Society for Cell Biology (2012) and Prize of Excellence offered by Romanian Medical Association (2010).

Currently, I coordinate the laboratory "Medical and Pharmaceutical Bionanotechnologies" within the Institute of Cellular Biology and Pathology "N. Simionescu” and I am a member of the Scientific Council of the institute.

The second section of the thesis is dedicated to the perspectives of scientific, professional, and academic development in relation to the current state of knowledge and professional experience acquired, being proposed a series of clear actions to achieve the objectives. The projects I envisage for the next period in terms of scientific activity aiming to develop innovative nanoparticles for the local delivery of therapeutic agents to improve existing therapies for the treatment of cardiovascular diseases are detailed. To achieve this scientific goal, we intend to strengthen existing collaborations and establish other collaborations with research groups in the country and abroad, obtain funding for research and recruit young graduates with the potential to evolve and build a career in scientific research. Therefore, I intend to continue and strengthen my mentoring activities as a Ph.D. advisor. I plan to guide Ph.D. students to continually improve their knowledge and encourage them to develop their ideas to become independent researchers who contribute to the advancement of science.