

ABSTRACT OF THE HABILITATION THESIS

CANDIDATE: *ALEXANDRU ȘCHIOPU*

THESIS TITLE: *Development of immunomodulatory therapies in cardiovascular disease*

I graduated from the Faculty of Medicine of the University of Medicine, Pharmacy, Sciences and Technology (UMFST) "G. E. Palade" Târgu-Mureș, General Medicine profile, in 2001. After graduating, I worked full-time as a PhD student at the Department of Clinical Sciences Malmö of Lund University, Sweden. I completed my doctorate in 2006 with the thesis "Development of a Passive Immunization Strategy against Atherosclerosis". I then continued my research activity with a short period in the Cardiovascular Research Laboratory of the Cedars Sinai Research Center in Los Angeles, USA, followed by full-time post-doctoral studies for 2 years in the Transplantation Research Immunology Group, University of Oxford, UK (2007-2009). In 2009 I returned to Sweden, where I continued my scientific career in parallel with my clinical and teaching career. On the scientific side, I established my own line of research, focused on the development of immunomodulatory treatments against inflammation in heart diseases. In 2014 I became an Associate Professor, and in 2022 I was appointed as Senior Lecturer at Lund University, awarded in competition. In 2022 I founded my own research group, the Cardiac Inflammation Research Group within the Department of Translational Medicine of Lund University. So far, I have supervised to completion one PhD student as main coordinator, two PhD students as co-supervisor, and I have supervised two researchers at the post-doctoral level. I currently manage 4 active PhD students at Lund University as the main coordinator, and I supervise two researchers at the post-doctoral level. Clinically, in 2015 I completed the specialty of Internal Medicine, and in 2018 the specialty of Cardiology. Starting 2020, I work as a primary physician at the Internal Medicine Clinic of Skane University Hospital in Lund. In parallel, I developed my teaching career, including courses, seminars and clinical teaching in cardiovascular diseases (atherosclerosis, coronary disease, heart failure, EKG) and Internal medicine for students of the Faculty of Medicine of Lund University and UMFST Tg-Mureș. Starting 2014, I teach the course "Applied biomedical research" within the program "Scientific Master of Medico-Pharmaceutical Research" within UMFST Tg-Mureș. I currently hold a teaching management position at Lund University, as coordinator of the clinical education of the 6th semester students placed at Skane University Hospital Lund.

Until now, I have published 42 original peer-reviewed articles (7 as first author and 11 as last author) and 6 reviews (4 as first author and 1 as last author) in international ISI-rated journals (H-index 21). The best rated journals where I have published articles as first or last author are European Heart Journal, Circulation, JACC (Journal of the American College of Cardiology), Circulation Research, ATVB (Atherosclerosis, Thrombosis and Vascular Biology), Atherosclerosis, Journal of Internal Medicine, and Journal of the American Heart Association. As a co-author I have published articles in Nature Medicine and Science Translational Medicine. As a PhD student, I demonstrated that therapy with antibodies directed against

certain peptides from the ApoB-100 protein, which is part of LDL particles, inhibits the progression of atherosclerosis and leads to the regression of already developed plaques in hyperlipidemic mice prone to atherosclerosis. During my post-doctoral studies at Oxford University, I worked with a murine model of transplant arteriosclerosis. We demonstrated that the hyperlipidemic environment significantly accelerates the progression of transplant atherosclerosis, due to the accumulation of inflammatory monocytes and foam cells in the sub-endothelial space. In another project, conducted in collaboration with researchers from the same group, we showed that therapy with regulatory T cells (Treg) developed in-vitro inhibits transplant atherosclerosis in allogeneically transplanted murine or human aortic fragments. After returning to Lund University in 2009 I focused on the study of acute cardiac inflammation. We studied in particular the role of the heterodimeric protein S100A8/A9 (calprotectin), produced in large quantities by neutrophil leukocytes, in myocardial infarction. In two studies published in the *European Heart Journal* (2019) and *Circulation Research* (2020), we showed for the first time that inhibiting the function of this protein with a pharmacological blocker (ABR-238901) prevents cardiac inflammation, reduces myocardial injury and improves long-term cardiac function. At the same time, we demonstrated that the optimal therapeutic period for this treatment is the first 3 days after the myocardial infarction, when cardiac inflammation is at its maximum. Later, together with collaborators from Lund University and the Institute of Cellular Biology and Pathology (ICBP) N. Simionescu from Bucharest, we demonstrated that ABR-238901 reduces the presence of inflammatory proteins in the myocardium, prevents conversion to pro-inflammatory N1 neutrophils, and reduces the severity of abdominal septicemia through a systemic anti-inflammatory effect. Part of these studies were carried out at UMFST Târgu-Mureş, where I established and led a research team funded by UEFISCDI through a PED project (2017-2018) of 150 000 EUR, followed by a PCCF project of 2 000 000 EUR (INNATE-MI, 2018-2022) obtained in collaboration with Prof. Maya Simionescu (ICBP Bucharest) and Prof. Dan Vinereanu (University of Bucharest). In parallel with the experimental studies, we also conducted clinical studies in cohorts of participants recruited from the general population and in patients with myocardial infarction from the Elderly Project cohort recruited at Malmö University Hospital (550 patients). We demonstrated that increased levels of S100A8/A9 in the blood are associated with an increased risk of developing cardiovascular events in both cohorts. Increased plasma levels of the soluble variant of RAGE, one of the receptors for S100A8/A9, are also associated with an increased risk of complications in patients with myocardial infarction. Through these studies we demonstrated the importance of S100A8/A9 as a biomarker and therapeutic target in myocardial infarction. The importance of our results was highlighted by other researchers in two review articles published in the *European Heart Journal* (2020) and *Nature Reviews in Immunology* (2021). In 2020, we sent to the European Patent Office (EPO) a patent application to protect the intellectual property related to the therapeutic blockade of S100A8/A9 in myocardial infarction, but also in myocarditis and septic cardiomyopathy.

In the next period, my scientific activity will focus on elucidating the protective mechanisms induced by S100A8/A9 blockade in myocardial infarction, and on continuing to

develop this therapy for clinical implementation. In murine models, we will study the effects of S100A8/A9 blockade on the systemic and myocardial immune response, myelopoiesis, myocardial metabolic and mitochondrial activity, the susceptibility of the myocardium to develop arrhythmogenic complications, and the development of atherosclerotic plaques. In parallel, in collaboration with researchers from Finland and Spain, we will test the therapy in a porcine model of myocardial infarction, which is much closer to the clinical scenario than murine models. In preliminary studies, we observed that the treatment reduces myocardial inflammation and improves cardiac function in experimental models of myocarditis and septic cardiomyopathy. We will continue these studies, trying to adapt the therapy to these pathologies with a very important inflammatory component, against which there are currently no adequate therapies. In clinical studies, I will continue the exploration of new pathogenetic mechanisms and prognostic biomarkers in the cohort of patients with myocardial infarction mentioned above and in a larger cohort that includes more than 1000 patients with acute coronary conditions, recruited between 2014-2023 within LundHeartGene-MR, a study initiated by me at Malmö and Lund University Hospitals. We will analyse large panels of protein and metabolic biomarkers in blood samples collected up to 24h after the acute event and after 6-8 weeks, and we will study the associations with cardiac function measured by echocardiography acute and at 6 months, and with subsequent adverse clinical events (new coronary events, heart failure and mortality). These studies will be financed by grants obtained by me in Sweden and Romania as project director, worth approximately 500 000 EUR per year. I will continue my activity as the main supervisor for the doctorates in progress in Sweden, but I intend to supervise doctoral students in Romania as well, within the projects initiated by me at UMFST Tg-Mureş and at ICBP N. Simionescu Bucharest.

In parallel with the research activity, but in a much smaller percentage of my total activity, I will also continue my clinical and teaching activity as coordinator of the clinical education of students from the Faculty of Medicine of Lund University and leader of the course of "Applied biomedical research" of UMFST Tg-Mureş.