HABILITATION THESIS

INTERDISCIPLINARY PERSPECTIVES ON INFECTIOUS DISEASES

Dr. Anca Meda Georgescu

ABSTRACT

The present Habilitation thesis highlights the professional and scientific achievements obtained in 2007, after sustaining my PhD thesis.

I am the author of 214 scientific papers, publishing up to now 13 articles in ISI journals with IF, 4 articles in ISI journals without IF, 17 articles in BDI journals and 180 abstracts. I have also written and published 8 speciality books and 15 chapters in edited volumes. Through the grants that I submitted I won 3 research projects as project manager and I was also member in an international and a national project.

My interest in this period was extended to the following fields of study:

- The study of biomarkers involved in sepsis diagnosis and prognosis – I have studied the suPAR level (soluble urokinase-type Plasminogen Activator Receptor) as a biomarker in sepsis, assessing its predictive ability of bacteremia and mortality prognosis. I have also studied the role of Angiopoietin-2 and Tyrosine kinase 2 as biomarkers in sepsis discovering the usefulness of Ang-2 determination in combination with PCT in patients with SIRS criteria and excluding the usefulness of Tie-2 in diagnosing sepsis.
- The study of genetic variability of mediators involved in sepsis development was aimed to assess the role of IL-6 gene polymorphism on the susceptibility, severity and prognosis of patients with sepsis and assess their association with plasma levels. I have revealed the association between GG genotype and the severity of sepsis and that the C allele has a protective role in the development of severe sepsis while IL 174G / C does not have a significant contribution neither in assessing risk for sepsis nor in its management. I have also demonstrated the role of IL-6 572G / C as a prognostic marker in sepsis and reconfirmed the role of IL-6 as a biomarker in patients with severe sepsis.
- The experimental studies performed regarding the cellular mechanisms in the evolution of sepsis confirmed by clinical, laboratory and histological data a model of producing sepsis by administration of lipopolysaccharide, the effect being observed at the level of the lungs as alveolar-capillary membrane lesions. I have also identified an association between Soluble receptor of advanced glycation end-products (RAGE) and pulmonary reperfusion injury, showing that ischemic preconditioning prevents local and systemic consequences of ischemia-reperfusion injury and the amplitude of systemic inflammatory response syndrome. At the same time, I have revealed that apoptosis is increased in case of endotoxin-induced lung injury and is likely to contribute to lung injury. High levels of caspase-3 expression in rat lung after exposure to LPS have been linked to the

morphologies observed in the affected lung. The administration of LPS to rats resulted in a significant dose-dependent increase in the levels of plasma FasL. These levels correlated with all the studied markers of lung injury, thus FasL could play a central role in the expansion of apoptotic epithelial injury.

- By continuing the studies regarding HIV-related heart failure, I have demonstrated that cardiac damage during pediatric HIV infection is significantly different depending on the mode the virus is transmitted, the acquisition of the infection through horizontal transmission being responsible for a lower prevalence of this pathology. Echocardiographic examinations together with histopathological ones can significantly enhance the overall picture of the disease. I also determined that pulmonary hypertension syndrome in children with HIV infection acquired through horizontal transmission is frequent and evolves as a seemingly primitive condition of mild severity without being influenced by the clinical and immunological stages of HIV infection.

The professional, scientific and academic development plans highlight, from a didactic point of view, my involvement in the process of curriculum reform initiated by the University. In terms of research, my intention is to address the following topics:

- Continue to study biomarkers used for sepsis diagnosis by expanding the range of studied biomarkers.
- Study of genetic variability in the development of sepsis – this project currently represents my main scientific concern which pursues the study of clinical relevance of cytokine gene polymorphism (IL-6, IL-10, TNF-alpha), cellular receptors (CD14, TREM-1, TLR4) and PAI- 1 in sepsis. The overall objective of this project is to improved early diagnosis and prognosis of severe sepsis by establishing a serological BM profile in septic patients correlated with the severity of clinical forms (sepsis, severe sepsis, septic shock) and the role of genetic variation of certain serum proteins with a BM value sepsis susceptibility and its evolution.
- Studying the molecular and cellular mechanisms of HIV infection - I intend to study the importance of p17 protein and its variants by investigating the mechanisms involved in protein blocking in order to remove it from circulation/tissues and the manner in which its biological actions can be changed.
- Evaluation of bacterial resistance in patients with severe infections - I propose to obtain high-quality observational data useful for designing randomized clinical trials for specific infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenem resistant *A. baumannii* (CRAB) and providing cohort data that could be used as „controls" for future comparisons with novel drugs used for the treatment of CRE.

The accumulation of additional experience in the coordination of interdisciplinary research projects and the publication of new research studies in the areas mentioned above will create the framework to train PhD students to conduct PhD thesis of high scientific value.