HABILITATION THESIS

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ABSTRACT

In the postdoctoral period, the mainstream of my professional, scientific and academic work has been performed in the fields of biochemistry, clinical biochemistry and immunology.

Educational career

Concerning my educational activity, I became assistant professor at the Department of Pharmaceutical Biochemistry in 2002; I was appointed a lecturer in 2003 and promoted to associate professor in 2009. Through this period, I have kept lectures of: Pharmaceutical Biochemistry, Environmental Chemistry, Immunology, Clinical Biochemistry, Biological medicines along with practicals of Pharmaceutical Biochemistry and Environmental Chemistry. From 2011 I am the head of the department, and from 2016 the head of the united Biochemistry-Environmental Chemistry department. In this authority, I am actively involved in curricular reform and development, surveyor of continuous educational improvement. Together with the staff of the department, I have elaborated 7 practical guides for students, and 6 scientific books, out of which 5 as the first-author.

Scientific achievements

As my personal research hotspot, the search for reliable diagnostic and prognostic biomarkers, the analysis of their clinical correlations can be appointed. My scientific activity in the post-doctoral period focuses on 4 main topics:

1. the study of biochemical pathways involved in cardiovascular atherosclerotic diseases,
2. exploration of complex regulatory pathways, signaling molecules and cellular interactions in experimental and human osteoarthritis and osteoporosis,
3. tissue expression studies for cell surface receptors and intracellular proteins, their relationships with grading and staging, biological behavior and prognosis in tumoral diseases,
4. investigation of inflammatory mechanisms in organ-specific and systemic disease.

Between 2003-2008, we intensively studied the variations of some plasma proteins (Von Willebrand Factor-VWF, osteoprotegerin-OPG, fibrinogen, C-reactive protein-CRP, cystatin C), aminoacids (homocysteine), serum lipids (total and HDL-cholesterol, triglycerids and lipoprotein (a)), hormones (testosterone, dehydroepiandrosterone) in different stages of peripheral arterial disease (PAD), an illness supposed to have a three- or four-fold real incidence compared to that believed. In the first study, SPI4, we showed that VWF is significantly higher in the plasma of PAD patients, than in those with thrombangiitis. We also could show the rise of total circulating peroxides in those with advanced stage of the disease and in the presence of diabetes. The second study was motivated by the incomplete conclusions of SPI4, and, partially, by the intriguing results of an australian group (Zanettino AC et al, 2005) who demonstrated the co-localization in, and co-secretion from the Weibel-Palade bodies of human endothelial cells of VWF and OPG.

In the second clinical study (TET), performed in collaboration with colleagues from the Clinical Research Center, University of Debrecen, on a cohort of 115 PAD patients and 109 controls we provided important new results:

a.) the linkage between the nature of AB0 blood groups and the plasma levels of osteoprotegerin, this being significantly higher in patients with non-0 groups than in those with 0 Group,
b.) the significant positive correlation between the levels of VWF antigen (VWF:Ag), VWF collagen binding activity (VWF:CB) and OPG,
c.) significant elevation of OPG and VWF:CB in patients compared to controls and in patients with critical limb ischemia compared to those with early disease stages.
In satellite studies, we described that PAD is characterized by the significant elevation of serum cystatin C and Lp (a) in comparison with controls, while in critical limb ischemia cystatin C increases in parallel with the decrease of Lp (a).
From 2009, we gradually became involved in osteoarthritis and osteoporosis research. We studied the relationships of some proinflammatory cytokines (IL-6 and TNF-α) and extracellular matrix degrading enzymes (MMP-8) with disease activity scores (IKDC) in human and found that patients suffering of osteoarthritis and trauma-induced meniscal lesions have significantly elevated MMP-8 levels in sera, but these do not correlate with the synovial quantities of the enzyme. However, synovial MMP-8 correlated negatively with the IKDC disease activity score. In another human study, serum osteocalcin, but not synovial osteocalcin, nor OPG was found to be significantly higher in early, than in advanced disease stages.
In an experimental model featuring Wistar rats, we provoked osteoarthritis with mono-iodoacetate (MIA) injection. We studied the biochemical and tissue-level effects of a potentially disease-modifying drug: the preferential cyclooxygenase-2 (Cox-2) inhibitor, meloxicam (MXC). Two doses of MXC were applied (0.2 mg/kg bw vs. 1 mg/kg bw.) along with a placebo-solution (vehicle). Control animals receiving only saline injection showed no or only minimal lesions, while animals receiving MIA, but only placebo treatment developed the classical signs of disease. At the high-dose meloxicam group, we observed the significant decrease of the collagen type II-specific degradation product, CTX-II ; the Osteoarthritis Research Society International (OARSI) histological scores referring to the depth and width of the cartilage lesions were significantly lower in both MXC groups, than in the placebo-treated Group. Moreover, the high-dose protected also against the subchondral bone and bone marrow lesions. Both low- and high-dose MXC suppressed efficiently the expression of Cox-2 at the level of cartilage and subchondral bone. Thus, we could show that both MXC doses ameliorate significantly the lesions of cartilage, and, that high-dose MXC has a stronger effect, protecting also the subchoodral bone compartment in experimental osteoarthritis.
Currently, we are exploring the expression of representatives of the Wnt-signalling pathway (DKK-1, SOST-sclerostin, Wnt 5a ş.a.) in two ongoing research projects, focused on triggered human osteoblast cell culture and various biological fluids in order to establish relationships with the lung maturation in pre-mature newborn.
In tissue expression studies, we showed that the expression of the neoangiogenesis marker CD34 and the tumor suppressor gene product p53 protein, can predict the disease course and leukemic transformation in myelodysplastic syndrome (MDS). The expression level of these molecules can define new risk classification schedules in MDS.
A successfull diagnosis and our case-presentation of an unusual form of neuroborreliosis can be perceived apparently as a scientific outlier. We described an acute psychosis-like syndrome complicated with severe catatonia and epileptic seizure, caused by a chronic Borrelia infection, successfully treated by prolonged antibiotic treatment. However, in the field of immunology we

become increasingly involved in Borrelia-infection related research. The pursuit for reliable, new biomarkers for tissue tropism is an important target in this field.
As a main output of our scientific achievements, it is to mention that in the post-doctoral period we published 10 papers in ISI-indexed journals with impact factor, out of which 5 with first-authorship and 21 articles in journals with international database indexation. Meanwhile, I was granted with directorship or membership of 6 national, international and regional research projects.

Scientific and academic development plans

Concerning didactic activity, I plan to introduce new topics of molecular biochemistry and pathobiochemistry in the course curriculum. The curricular reform is dedicated to improve the students' overall performance and comprehension. In the field of research activities, we aim to continue the exploration of the main issues presented, with a special emphasis on osteoarthritis and osteoporosis biochemical pathways. We are currently engaged in 3 important ongoing research projects, planning to publish at least 1-2 scientific papers related to these topics.
With reference to scientific and international recognition, we plan to be more involved in mainstream research topics, to establish new scientific relationships and to apply successfully for international industrial partnerships.