Title of the research project: The use of experimental and clinical models of metabolic processes, nutrition and pharmacotherapy for the advancement of knowledge, clinical practice and quality of life improvement

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Summary of 2007 results

Title of the presentation: Nutritional and pharmacological intervention on metabolic processes.

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During 2007, all planned results of the current research project were achieved; in total 18 original papers were published in journals with impact factor and another 60 in peer-reviewed journals. All individual working groups within the project team produced the aforementioned papers.

Interactions of selected signalling pathways (p53-dependent) after administration of micronutrients (selenium, zinc and inositol hexaphosphate) were studied with help of advanced morphological and molecular techniques (blotting, immunofluorescence) in colon cancer cells (HCT-116, HT-29, SW480 and SW620).

We isolated distinct mesenchymal stem cell populations from the bone marrow and the dental pulp and provided their phenotypic characterization using a panel of 22 antibodies. We also succeeded in isolation of stem cells from periodontal ligaments. The latter cells represented a homogeneous cell population with a high proliferative potential and expressed markers of mesenchymal stem cells (CD29, CD44, CD73, CD 90, CD105). The expression levels differed from markers expressed by bone marrow and dental pulp stem cells which confirms isolation of a unique and distinct cell population.

In vitro experiments performed on rat hepatocytes in suspension and/or in culture were focused on the study of possible protective effect of S-adenosylmethionine against acetaminophen-induced injury. Beside markers of cell viability also parameters of functional capacity, ROS production, reduced and oxidized glutathione content and activity of glutathione reductase were measured. Increased sensitivity of mitochondrial permeability transition pore after triiodothyronine administration in vitro was documented. Expression of uncoupling protein 2 RNA was found in the liver in various intervals after partial hepatectomy.

Study of leukaemia cells MOLT-4: Ionizing radiation initiated an ATM-kinase-dependent pathway resulting in upregulation of p53 and induction of apoptosis. Activation of p53 on serine 15 was dose-dependent up to 3 Gy. Valproic acid administered both before and after the irradiation has a radiosensitizing effect.

We found that L-carnitine administered with mitoxantrone in mice may protect against drug-induced toxicity. Furthermore, a new, syngenic mammary tumour model growing in NMRI

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mice was characterized with selected cytostatic drugs both *in vitro* and *in vivo*. We described in detail the pharmacokinetics and, for the first time, the biliary excretion of melibiose and rhamnose in healthy and cholestatic rats. Moreover, we showed that the dual-sugar permeability test can characterize the alteration of the blood–biliary barrier in acute extrahepatic cholestasis.
Study of liver myofibroblasts: Individual components of extracellular matrix in a culture medium (fibrin, collagen I) modified the cell morphology and selectively influenced gene expression. Hence, there may be a feedback between myofibroblasts and their products.
To obtain deeper insight into the role of cardiac troponins as biomarkers of anthracycline cardiotoxicity, the release kinetics of cTnT and cTnI were studied using an *in vitro* model of isolated rat neonatal ventricular cardiomyocytes (daunorubicin 0.1 – 3 μM). On the rabbit model of daunorubicin cardiotoxicity, it was revealed that novel iron chelator deferipron is unable to protect myocardium against oxidative stress and heart failure (in contrast to *in vitro* findings found in the literature).
To understand the pathogenesis and to find new treatment possibilities of muscle wasting in cachexia we studied the effect of proteasome inhibitors (PIs) and leucine metabolite β-hydroxy-β-methylbutyrate (HMB) on protein metabolism of septic rats. PIs bortezomib or belactosin significantly reduce myofibrillar proteolysis and inhibit chymotrypsin-like activity (CHTLA) of proteasome in skeletal muscle while cathepsin activity did not change. HMB treatment induced significant decrease in proteolysis, CHTLA and leucine oxidation both in red and white type of muscle.
The influence of –493G/T polymorphism of the gene promotor for microsomal triglyceride transfer protein was studied in 86 persons with metabolic syndrome and 184 controls. The T allele carriers differed from G homozygotes only in the group of men with MS by raised concentrations of insulin, nonesterified fatty acids, cholesterol, triglycerides and decreased content of polyunsaturated fatty acids in plasma phospholipids.
We developed a new modification of hemorheopheresis to treat severe atherosclerotic disease wounds. Our pilot trial confirmed the assumption that a series of hemorheopheresis treatments have a benefit for patients with macular degeneration. 2-Using Laser Doppler Line Scanner we demonstrated, that skin blood flow changes were dependent on several parameters of malnutrition inflammation syndrome. 3-The effect of hyaluronan-iodine complex was studied on 18 patients suffering from complicated foot diabetic wounds and complete healing was evident in 15 patients within 9-20 weeks after the start of treatment.
Biomarkers showed that amiodarone-treated rats exhibited 3.3-fold decrease in renal clearance of conjugated bilirubin and reduction of MTX biliary clearance of methotrexate to 72% with a significant increase in plasma concentration. In man, methamphetamine can partially impair visual processing. In a rat model of lipopolysaccharide-induced pulmonary inflammation, pentoxifylline administered intratracheally reduced nitrosative and oxidative stress as documented by exhaled nitric oxide as well as by other cellular and biochemical markers of inflammation.

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