

Pharmacology and Pharmaceutical Sciences D92
The Leader of the Doctoral School: Dr. Pintér, Erika

A-148/1993

**The isolation and examination of
Biologically active compounds**

Program leader: Dr. Deli, József

Dr. Agócs, Attila attila.agocs@aok.pte.hu	Department of Biochemistry and Medical Chemistry	Synthesis and pharmacological investigation of carotenoid dendrimers and water soluble carotenoids
Starting mainly from hydroxy carotenoids, derivatives with potential biological activity are synthesised. The main focus lies on the synthesis of water soluble carotenoids and carotenoid glycosides that can be important also in human medicine. The synthesis of carotenoid dimers and trimers are important in aggregation studies. The carotenoids are isolated or obtained semisynthetically. Antioxidant activity and pharmacology of the new products are compared with those of the native carotenoids.		

Dr. Horváth, Györgyi Dr. Kocsis, Béla gyorgyi.horvath@aok.pte.hu kocsis.bela@pte.hu	Department of Pharmacognosy & Department of Medical Microbiology and Immunology	Investigation of biologically active metabolites from medicinal plants using in vitro and in vivo techniques
Plants can produce several chemically different compounds during their metabolism. Appearance of multidrug resistant bacteria and growing antibiotic resistance is leading to a continuous need for discovering new drugs and alternative treatments against infections. The investigation of the antibacterial effect of essential oils (EOs), which are commonly used nowadays in cosmetics, health care, traditional medicine and food industry, could be one of the promising solutions for this worldwide problem. The main aims of this topic include the isolation of EOs from medicinal plant, investigation of EO composition by gas chromatography – mass spectrometry (GC-MS), determination of antimicrobial activity of EOs and their main components using agar dilution, direct bioautography and vapour phase techniques. We would like to study the effect of EOs on the outer membrane protein composition of Gram negative bacteria. Based on the in vitro results, we plant to investigate the anti-inflammatory effect of EOs in in vivo (mouse) models. The present results might open new perspectives for drug and product development purposes as well.		

Dr. Horváth, Györgyi Dr. Krisch, Judit gyorgyi.horvath@aok.pte.hu krisch@mk.u-szeged.hu	Department of Pharmacognosy	The investigation of antimicrobial activity of essential oils in in vitro test systems
The application of secondary plant metabolites in medication is particularly important in several countries. The antibiotic-resistance denotes a significant problem in health care. Several publications have been demonstrated that essential oils possess antimicrobial effect but the mode of action has not been fully		

understood. The discovering of these mechanisms may provide valuable data for development of new pharmaceutical formulas. The main aims of this PhD topic: isolation of essential oils from different plant sources, analysis of chemical composition of essential oil samples by GC-FID and GC-MS techniques, investigation of antimicrobial activity of essential oils (e.g. inhibition of biofilm production, anti-quorum sensing activity). The results may offer new data for the development of antibacterial and antifungal products containing natural products, e.g. essential oils.

Dr. Molnár, Péter peter.molnar@aok.pte.hu	Department of Pharmacognosy	Carotenoid analysis of inflorescences and fruits of medicinal plants
<p>Connected to our earlier plant analytical investigations [1], as a main research direction of our department, we are involved in the exact determination of the carotenoid composition of numerous medicinal plants. One of the main objectives of these investigations is the isolation and identification of new carotenoids with unknown structures [2, 3]. The separation of the components will be carried out by chromatographic methods (CC, HPLC). The identification of the components will be achieved on the basis of their chromatographic properties, UV/VIS spectroscopic data, by co-chromatography with authentic reference samples and on the basis of their simple chemical reactions [(E/Z)-isomerization, furanoid-oxide reaction, NaBH₄ reduction]. Recently the carotenoid analysis of the inflorescence of <i>Tanacetum vulgare</i> L. and of the fruits of <i>Cornus mas</i> L., <i>Tamus communis</i> L. and of <i>Taxus baccata</i> L. [4, 5] was performed. Our future plans for carotenoid analysis include the inflorescences of <i>Helianthus tuberosus</i> L., <i>H. rigidus</i> L., <i>Solidago canadensis</i> L., <i>Chelidonium majus</i> L., <i>Linaria vulgaris</i> Mill., various <i>Euphorbiaceae species</i>, as well as the fruits of <i>Sorbus aucuparia</i> L., <i>Berberis vulgaris</i> L., <i>Arum maculatum</i> L., <i>Ruscus aculeatus</i> L. and <i>R. hypoglossum</i> L.. The carotenoid composition of the two <i>Ruscus species</i> will be compared, too. According to our preliminary investigations the appearance of new carotenoids was observed in the fruits of <i>Arum maculatum</i> L.</p> <p>[1] Péter Molnár: The (E/Z)-Isomerization of the polyene chain of carotenoids; plant biochemical investigations; occurrence, isolation and identification of carotenoid-isomers. <i>Doctoral (D.Sc.) Theses, Pécs, 2004</i>. [2] J. Deli, P. Molnár, E. Ósz, G. Tóth: Capsoneoxanthin, a New Carotenoid Isolated From the Fruits of <i>Asparagus falcatus</i> L., <i>Tetrahedron Lett.</i> 41, 9153-9155 (2000). [3] P. Molnár, J. Deli, G. Tóth, A Häberli, H. Pfander, K. Bernhard: (9Z)-Capsanthin-5,6-Epoxyde, a New Carotenoids From the Fruits of <i>Asparagus falcatus</i> L., <i>J. Nat. Prod.</i> 64, 1254-1255 (2001). [4] Gy. Horváth, E. Turcsi, P. Molnár, L. Gy. Szabó, J. Deli: Isolation and Identification of Carotenoids in the Fruits of Cornelian Cherry (<i>Cornus mas</i> L.), 55th International Congress and Annual Meeting of the Society for Medicinal Plant Research, Graz, Austria, September 02-06, 2007. <i>Planta Medica</i> 73, 912 (2007); P 286. [5] Gy. Horváth, E. Turcsi, P. Molnár, L. Gy. Szabó, J. Deli: Carotenoid Content of the Flower of Tansy (<i>Tanacetum vulgare</i> L.), 55th International Congress and Annual Meeting of the society for Medicinal Plant research, Graz, Austria, September 02-06, 2007. <i>Planta Medica</i> 73, 911 (2007); P 284.</p>		

Dr. Nagy, Veronika vera.nagy@aok.pte.hu	Department of Biochemistry and Medical Chemistry	Synthetic modification of naturally occurring carotenoids, and pharmacological investigation of the products
<p>Carotenoids are natural antioxidants and their biological activity can be enhanced by chemical modifications. So-called kappa-carotenoids, which are mainly responsible for the red colour of paprika species, are among the best antioxidants, however, their synthetic modifications have not been studied yet. We focusing on the covalent coupling of carbohydrates, fullerenes, or antibiotics to carotenoids with kappa-end group, and other naturally occurring carotenoids. The synthesised products will be studied as antioxidants in vitro and in vivo.</p>		

A-143/1993**Optimization of pharmacotherapy****Program leader: Dr. Botz, Lajos**

Dr. Kószegi, Tamás koszegi.tamas@pte.hu	Department of Laboratory Medicine	In vitro testing of extracts of antidiabetic herbs using tissue culture models
<p>Type 2 diabetes mellitus affects hundreds of millions of people worldwide. There is a wide choice of antidiabetic herbs used in complementary treatment on the basis of ethnobotanical observations. The majority of the applied herbs are rich in antioxidants but to our latest knowledge solely the antioxidant feature is not selective and is also not effective in decreasing the symptoms of diabetes mellitus. A potential tool for solving the problem is to reduce insulin resistance at the initial stage of the disease. Intracellular glucose content and/or uptake can easily be measured in tissue culture models by luminescent glucose determination and fluorescent glucose analogues by fluorescent microscopy, flow cytometry and spectroscopic techniques. Anchorage dependent cells (e.g. HepG-2, liver origin) and suspension cultures will be used. Effects of aqueous and apolar extracts of test herbs on the cells will be studied by multiparametric viability-cytotoxicity assays, antioxidant capacity tests and total intracellular glucose/glucose uptake determinations. Plant extracts might affect cell signaling pathways as well, these will be analyzed by immune fluorescence and/or western blotting.</p>		

B-1/2004**Visceral function and pharmacology of autonomic and sensory nerves****Program leader: Dr. Barthó, Loránd**

Dr. Barthó, Loránd lorand.bartho@aok.pte.hu	Department of Pharmacology and Pharmacotherapy	Identification of sensory neurotransmitters and studying the modulation of their release in isolated renal pelvis and main bronhus preparations
<p>Renal pelvis and main bronchi hardly possess autonomic efferent nerves, but are supplied by sensory nerves. Thus, electrical „field” stimulation of their nerves elicits mechanical responses <i>via</i> releasing sensory neurotransmitters. Our aim is to influence the release of sensory transmitters with known and putative neuromodulators. Smooth muscle activity of the substances tested can be excluded in preparations possessing spontaneous myogenic activity. Wherever it has not been fully clarified, we intend to identify the sensory transmitters themselves. For this, we shall use specific antagonists. Influencing sensory neurotransmitters may have relevance as to modulating pain and hyperalgesia.</p>		

Dr. Barthó, Loránd lorand.bartho@aok.pte.hu	Department of Pharmacology and Pharmacotherapy	The pharmacology and possible roles of nitric oxide, carbon-monoxide, ATP and other non-classical neurotransmitters in motor responses of visceral organs
<p>In addition to „classical” cholinergic and monoaminergic transmitters newer „non-adrenergic, non-cholinergic” (NANC) transmitters are being identified. New members of the neuropeptide family of transmitters are appearing. Moreover, well-known peptide transmitters can be antagonized with recently-discovered drugs only, antagonists that often act at recently-identified receptor subtypes. Our aim is to clarify the physiological/pathophysiological roles of peptide and non-peptide transmitters and modulators in motor responses of intestinal and other visceral preparations. The discovery of roles and therapeutic applications of NO has stimulated research concerning other „gasotransmitters”. There are recent data of the literature indicating motor effects of endogenous CO (produced by hem-oxygenase) on visceral motor responses. We plan to study this problem with inhibitors of hem-oxygenase and guanylate cyclase on</p>		

responses evoked by nerve stimulation or selectively-activating drugs (such as the sensory neuron stimulant capsaicin; see Barthó et al., 2004, Eur. J. Pharmac. 500: 143-157). A more recent member of the gasotransmitter family is H₂S. This substance can be formed in nerves and other types of cells and has both excitatory and inhibitory effects on innervated smooth muscles (e.g., by stimulating capsaicin-sensitive receptors). We plan to analyse the effect of exogenous H₂S but, on the long term, also the roles of endogenous H₂S. Antagonists of purine (e.g., ATP) receptors have also become available and make it possible to detect the roles of endogenous purinergic transmission. Whenever possible, we check the human relevance of our results seen on animal preparations; human visceral tissue is obtained from the operation theatre.

A-292/1994

Neurofarmacology

Program leader: Dr. Pintér, Erika

<p>Dr. Balaskó, Márta marta.balasko@aok.pte.hu</p>	<p>Institute for Translational Medicine</p>	<p>The effects of perinatal environment on the regulation of energy homeostasis and on the development of body weight and body composition</p>
<p>Intrauterine and early perinatal development (with special emphasis on the nutritional status of the mother and offspring and such environmental factors as physical exercise) exert a significant influence on regulatory systems of energy homeostasis (hormonal imprinting). Such alterations in the peripheral and central mediator systems may contribute to the development of early onset (childhood) obesity and the appearance of severe forms of metabolic syndrome later in life. In the PhD program in addition to the effects of malnutrition and excess caloric intake of the mother (intrauterine) and offspring (perinatal), the influence of physical activity of young individuals and those of perinatal capsaicin desensitization (to determine the role of capsaicin-sensitive neural afferents) on the development and abnormal alterations of the peripheral and central regulatory systems of energy balance will be analyzed. To achieve these objectives, the body weight, food intake development of rats will be followed continuously. To test the development and alterations of the regulatory systems, responsiveness of central catabolic (e.g. melanocortin, corticotropin) and anabolic (e.g. neuropeptide Y, agouti related peptide, orexin) systems will be tested in different age-groups of rats. Food intake is to be recorded in an automated FeedScale system, circadian rhythm of core temperature, heart rate, spontaneous locomotor activity in a biotelemetric (MiniMitter system). These measurements will be complemented by the registration of oxygen consumption, core and tail skin temperature (the latter indicates heat loss) in an Oxymax system for indirect calorimetry.</p>		

<p>Dr. Balaskó, Márta marta.balasko@aok.pte.hu</p>	<p>Institute for Translational Medicine</p>	<p>The role of peptide mediators and peripheral neural afferents in the development of fever, sickness behavior and in the adaptation to fasting: age-related alterations</p>
<p>The anorexia, somnolence, apathy, allodynia frequently associated with fever, form a syndrome that is called sickness behavior (SB). The SB syndrome that is regarded as a defence mechanism of the infected host, also presents a significant population-wide health-related problem, especially in older populations. In these age-groups the efficacy of the SB in the defence against infections is diminished, the capacity to develop fever is reduced, while anorexia becomes exaggerated, further aggravating age-related loss of body weight (cachexia) leading to sarcopenia (a 20-40% loss of skeletal muscle mass). Peripheral (e.g. capsaicin-sensitive neural afferents) and central regulatory mechanisms (e.g. central neuropeptide systems) contribute to the development of various members of SB that involve the collaboration of several organ systems. These regulatory systems show characteristic age-related alterations. The aim of the program is to uncover age-related alterations in the pyrogenic and anorexigenic mechanisms of SB. We aim to clarify the role of peripheral neural afferents [capsaicin-</p>		

sensitive neural afferents, transient receptor potential vanilloid 1 (TRPV1 receptors)] **and that of peptide mediators** (e.g. corticotropin-releasing factor, cholecystokinin, somatostatin) in endotoxin- or inflammatory cytokine-induced SB and in the adaptation to fasting. These mechanisms and their age-related alterations will be investigated in different age-groups of Wistar rats and those of knock-out (KO) mouse strains (TRPV1KO, somatostatin type 4 receptor KO, etc.). In order to analyze the above mentioned mechanisms, oxygen consumption, thermoregulatory responses (core and tail skin temperatures) will be recorded. Additionally, circadian rhythm of core temperature, heart rate and spontaneous locomotor activity will be registered in a biotelemetric (MiniMitter) system.

Dr. Balaskó, Márta Dr. Garai, János marta.balasko@aok.pte.hu janos.garai@aok.pte.hu	Institute for Translational Medicine	The effects of estrogen-mimetic endocrine disruptors on the regulation of energy homeostasis
--	---	---

Complex peripheral and central regulatory alterations may be assumed in the background of long-term tendencies of energy homeostasis regarding obesity of the middle-aged and the weight loss and cachexia of old age-groups, since these phenomena are not only observed in humans but also in mammals. Based on characteristic gender differences in these age-related changes of body weight and body composition, a potential role of sex hormones in these regulatory alterations emerges. Beneficial effects of alpha estrogen receptors on energy homeostasis were described, but their contribution to age-related alterations are still obscure. The role of beta estrogen receptors in energy homeostasis and its age-related alterations is also largely unexplored. The importance of the field is further enhanced by the fact that our food and drinking water may contain such pollutants that may negatively affect estrogen receptor functions, i.e. endocrine disruptors. In the PhD program we aim to compare data obtained from male and female, ovariectomized and intact female laboratory rodents concerning the effects of estrogen on the development and age-related peripheral and central regulatory alterations of energy homeostasis. In addition to the regular measurements of body weight and food intake, responsiveness of catabolic (e.g. melanocortins, corticotropins) and anabolic (e.g. neuropeptide Y, agouti-related peptide, orexin) regulatory systems will be tested in different age-groups. Food intake will be recorded in an automated FeedScale system, core temperature, heart rate and spontaneous locomotor activity will be registered in a biotelemetric (MiniMitter) system. These studies will be complemented by measurements of oxygen consumption (metabolic rate/heat production) using indirect calorimetry (Oxymax) and simultaneous measurements of core and tail skin (heat loss) temperatures for complete thermoregulatory analysis.

Dr. Balaskó, Márta marta.balasko@aok.pte.hu	Institute for Translational Medicine	Contribution of the central corticotropin system to age- and nutritional state-related regulatory alterations of energy balance
---	---	--

Age-related regulatory alterations may be assumed in the background of middle-aged obesity and aging anorexia since they also appear in other mammals. Our previous studies described such regulatory alterations of the central catabolic melanocortin system: a weak catabolic responsiveness to alpha-melanocyte stimulating hormone in middle-aged and a strong one in old age-groups. Corticotropin releasing factor (CRF) and urocortins are important catabolic peptide mediators downstream to the melanocortins. Their effects are mediated by CRF1 and CRF2 receptors. In the PhD program we aim to investigate the age- and nutritional state-associated alterations in the central corticotropin system (and those of its receptors). Animal experiments will be carried out in different age-groups (from juvenile to old) of laboratory rodents. Regarding nutritional state, we establish ad libitum fed, diet-induced obese and calorie-restricted groups within the age-groups. During the analysis of central acute and chronic corticotropin responsiveness, food intake is to be recorded in an automated FeedScale system, circadian rhythm of core temperature, heart rate, spontaneous locomotor activity in a biotelemetric system (MiniMitter, Respironics).

These measurements will be complemented by the registration of oxygen consumption, core and tail skin temperature (the latter indicates heat loss) in an Oxymax system (Columbus) for indirect calorimetry.

Dr. Balaskó, Márta Dr. Soós, Szilvia marta.balasko@aok.pte.hu szilvia.soos@aok.pte.hu	Institute for Translational Medicine	The role of central insulin in the regulation of energy balance in rats, according to age and nutritional state
--	---	--

In the CNS insulin is important in the regulation of energy balance and peripheral glucose metabolism. The central effects of insulin are anorexia, hypermetabolism, and it also suppresses glucose release from the liver. However, with aging and/or obesity insulin resistance may develop not only in the periphery, but also in the brain, what may contribute to the development of metabolic syndrome. Accordingly, rats of various age-groups will be given intracerebroventricular insulin injection or infusion to analyze the development of central resistance. Since the resistance may also depend on the nutritional state, the central insulin sensitivity is to be analyzed also in rats of similar ages but kept chronically on calorie restricted diet and in diet-induced obese rats. Glucose tolerance test will be performed in all cases.

Dr. Czéh, Boldizsár czeh.boldizsar@pte.hu	Department of Laboratory Medicine	Newborn neurons in the adult brain: Regulation and therapeutic possibilities
---	--------------------------------------	---

Adult hippocampal neurogenesis, a once unorthodox concept, has changed into one of the most rapidly growing fields in neuroscience. Numerous factors regulate adult neurogenesis including various neurotransmitters, hormones, stress, physical exercise learning and inflammation. Neurogenesis has been implicated in cognitive function and is stimulated by antidepressant drugs. A lasting reduction in neurogenesis following severe or chronic stress exposure, both in adult or early life, may represent impaired hippocampal plasticity and thus, can contribute to the cognitive symptoms of depression. Our aim is to understand the factors regulating this cellular process and to find novel approaches to stimulate this form of neural plasticity.

Dr. Garami, András andras.garami@aok.pte.hu	Institute for Translational Medicine	Investigation of the mediators of systemic inflammation in different animal models
---	---	---

Systemic inflammation constitutes a serious financial and healthcare problem even in the modern societies. Its on-target, efficient treatment would require the understanding of the involved neural, humoral, and endocrine regulatory factors as well as the effect of those factors on the progress of the disease. In small animals, systemic inflammation can be modeled in several different ways, for example with the administration of bacterial endotoxin, which evokes “aseptic” systemic inflammatory response syndrome (accompanied by fever or hypothermia) or with cecal ligation and puncture, which results in septic shock. Our goal is to investigate the role of certain receptors, neurotransmitters, humoral factors, and neural structures under the formerly mentioned and related inflammatory conditions. Our studies involve the measurement of body temperature in systemic inflammation models, as well as other in-vivo experiments (e.g., nociceptive tests), molecular biology, immunohistochemistry, and further experimental techniques.

Dr. Helyes, Zsuzsanna zsuzsanna.helyes@aok.pte.hu	Department of Pharmacology and Pharmacotherapy	Investigating the mechanisms of Complex Regional Pain Syndrome in a mouse model
---	---	--

Enhanced inflammation and hyperalgesia are induced in mice with passive transfer (i.p. injection) of the IgG fraction of Complex Regional Pain Syndrome (CRPS) patients after a minor injury. In this model developed, published and validated by us, we focus on the peripheral and central sensitization mechanisms

with special emphasis on the role of sensory-immune interactions, neuropeptides, cytokines, as well as glia cell activation. Our results can help to identify the key mediators and targets in this disease that can open novel perspectives for drug development.

Dr. Horváth, Györgyi Dr. Helyes, Zsuzsanna gyorgyi.horvath@aok.pte.hu zsuzsanna.helyes@aok.pte.hu	Department of Pharmacognosy, Department of Pharmacology and Pharmacotherapy	Isolation of natural compounds having anti-inflammatory activity from medicinal plants and investigation of their effect in pharmacological models
--	---	---

In the ethnomedicine, several medicinal plants are used as an anti-inflammatory agents, however their pharmacological effect has not been proven in pharmacological experiments. The main aim of this topic is the phytochemical investigation of medicinal plants and the examination of their isolated compounds in in vitro and in vivo pharmacological models. The results might open novel perspectives for development of anti-inflammatory drugs and products.

Dr. Pintér, Erika erika.pinter@aok.pte.hu	Department of Pharmacology and Pharmacotherapy	TRPA1 receptor as potential drug target in the treatment of neurodegenerative and neuroinflammatory disorders
---	---	--

Investigation of molecular mechanisms of complex neuro-immune interactions and neuroinflammation in the CNS has become a hot topic recently. The Transient Receptor Potential Ankyrin 1 (TRPA1) ion channel expressed not only on neurones, but also on glial cells, revealed a novel neurohumoral signalling mechanism in the brain. The TRPA1 channel represents a unique type of multimeric receptors, which is activated by a broad range of endogenous inflammatory agents, such as lipid mediators, reactive oxygen species, and gasotransmitters. Its involvement is relatively well-established in certain pain and peripheral inflammatory mechanisms. The pivotal role of TRPA1 receptor in the sensation of the oxidative stress and its involvement in tissue damage, degeneration and regeneration have been recently emphasised. The PhD project is a comprehensive study for characterization of the roles of TRPA1 receptors in neurodegeneration, cognitive functions and neuro-inflammation with special emphasis on neuro-immune crosstalk between glial cells and neurons using an integrative approach with gene deleted mice and pharmacological tools. Methodology: multi-directional functional investigations, in vivo optical imaging, molecular biological techniques, and microscopic morphological analysis. The results will elucidate the modulatory role of TRPA1 receptors in the glia-neuron interactions during the development of neuroinflammatory-neurodegenerative disorders. It could lead to the identification of novel therapeutic targets.

Dr. Pongrácz, Judit pongracz.e.judit@pte.hu	Department of Pharmaceutical Biotechnology	Test system development for peptide based drug delivery via the human lung using primary human lung tissue model
---	---	---

It is important to find optimized methods to deliver peptide based drugs to treat lung diseases or to administer these drugs systemically via the lung. PEPT1 and PEPT2 have been cloned from human tissues. PEPT2 is present in the human lung. PEPT2 is integrated into the cell membrane and has 12 membrane-spanning domain. PEPT2 is present in the bronchial epithelium, and the alveolar epithelium type II. Expression pattern, modulation of expression application in drug delivery will be tested using a lung model.

Dr. Pongrácz, Judit pongracz.e.judit@pte.hu	Department of Pharmaceutical Biotechnology	Modification of drug transporter expression and function in Non-small cell lung cancer (NSCLC) and their role in lung cancer therapy
---	---	---

NSCLC is the leading cause of cancer deaths worldwide. The currently available therapies are inefficient, five year survival after diagnosis is poor. Novel

therapeutic agents are constantly tested, but their efficiency depends on their ability to enter the cell via ATP-dependent drug transporters. Modification of drug transporters and their activity in NSCLC will be tested. Drug efficacy will be tested using modified drug transporters.

Dr. Szőke, Éva eva.szoke@aok.pte.hu	Department of Pharmacology and Pharmacotherapy	Investigation of activation mechanisms of Transient Receptor Potential Vanilloid 1 ion channel and its role in pain conditions of different origin
Chronic persistent pain of different origin (inflammatory and degenerative joint diseases, cancer, neuropathy and migraine) are great health and social problems that decrease the quality of life of a large population. The treatment of neuropathic pain is still an unresolved problem, the presently available drug groups (anti-epileptics, opiates, anti-depressants, lidocaine) do not provide satisfactory relief in most cases. Transient Receptor Potential (TRP) cation channels as the TRP Vanilloid 1 (TRPV1) are nociceptors playing important role to trigger pain. TRPV1 serves as thermosensor and is suitable to be activated also by several exogenous and endogenous chemical ligands. Our aim was to investigate the gating of the TRPV1 receptor in sensory neurons, sensory nerve terminals or receptor-expressing cell line and its role in pain transmission in in vivo animal models.		

B-1/2016

Translational Medicine

Program leader: Dr. Hegyi, Péter

Dr. Hamar, Péter hampet@net.sote.hu	Institute for Translational Medicine	Pathophysiology of renal allograft rejection – the role of micro RNAs
Renal transplantation offers the best quality of life in renal failure patients. The development of surgical techniques, modern immunosuppression and supportive therapies improved prognosis significantly in the past decades. Thus, presently the leading cause of graft loss is a process previously called chronic rejection but recently described as interstitial fibrosis and tubular atrophy (IFTA). Several factors are involved in the development of IFTA such as early damage of the graft due to ischemia-reperfusion injury, increased work-load on the sole kidney and alloantigen dependent, subclinical rejection episodes. Furthermore, chronic processes such as chronic inflammation culminating in fibrotic, scarring tissue-remodelling and graft failure. We utilize rodent (rat, mouse) models (orthotopic kidney transplantation, ischemia-reperfusion injury, fibrosis) and human material (registry data, biobank-samples) to investigate the driving processes of renal fibrosis, focusing on small-, protein-non-coding RNAs. Exogenous short interfering RNAs (siRNA) are capable of inhibiting the synthesis of specific proteins, whereas influencing the synthesis of endogenous micro RNAs (miRNA) the role of whole signaling cascades can be investigated.		

Dr. Hegyi, Péter hegyi.peter@pte.hu	Institute for Translational Medicine	Tools for monitoring dietary adherence in celiac disease
Celiac disease (CD) is a systemic immune-mediated disorder. In addition to the genetic vulnerability (HLA-DQ2 or DQ8 alleles), the consumption of gluten-containing cereals (that is, wheat, barley, and rye) play a crucial role in the disease pathogenesis. The clinical phenotype of CD varies: intestinal (e.g., diarrhea and abdominal pain) and extraintestinal symptoms (e.g., anemia, osteoporosis, dermatitis herpetiformis, autoimmune diseases, and malignancies) can develop. The only feasible therapeutic option is the lifelong strict gluten-free diet (GFD). The introduction of the GFD is usually followed by a quick and complete remission of the symptoms: the quality of life improves, the complication rate and the mortality drop. Tools for monitoring dietary adherence are		

limited. The former gold standard was the achievement of small intestinal mucosal recovery, but recent guidelines do not recommend the invasive control biopsy in asymptomatic patients. Celiac-specific serology, i.e., the level of serum tissue-transglutaminase antibody (tTG-IgA/G) in adults, can refer to major dietary transgressions but not to the occasional intake of trace amounts of gluten. Today, dietary questionnaires, collecting self-reported data of which objective interpretation is difficult to execute, are used in the first line. The aim of this project is to examine newly emerging methods and to make a comparison between these and the earlier gold standards to facilitate stricter follow-up of CD patients. In the long run, our results might contribute to the measurement of the effects of newly emerging celiac-specific drugs (e.g., zonulin inhibitors).

Dr. Hegyi, Péter hegyi.peter@pte.hu	Institute for Translational Medicine	Investigation of the pathomechanism of acute pancreatitis
<p>Most studies on the cellular mechanisms of AP have focused on the acinar cells and little is known about the role of pancreatic ductal epithelial cells (PDEC) in the disease. However, recent studies, including those from our group, indicate that PDEC are intimately involved in the pathogenesis of AP: (i) bile acids, well-known imitators of AP, impair pancreatic ductal function (Gut, 2008 57:1102-12 és Gut, 2011 60:361-9), (ii) compromised ductal fluid and bicarbonate secretion can increase patient risk to AP (Am J Gastro, 2010, 105:2119-20), (iii) mitochondrial injury and ATP depletion is one of the key aspects of ductal damage (Gut, 2010 Sept 28. [Epub ahead of print] and Gut 2011 60:136-8) and (iv) trypsin, the protease long recognized to be involved in the pathogenesis of AP, inhibits bicarbonate secretion (preliminary data). These recent observations strongly suggest that restoration of pancreatic ductal bicarbonate and fluid secretion may have therapeutic benefits in AP. In this project we propose both in vitro and in vivo experiments using novel cell physiological and biochemical techniques (i) to understand the development of ductal damage in response to active trypsin and (ii) to find new therapeutic targets and treatment possibilities which may restore ductal function. In this project we propose to employ both in vitro and in vivo cutting-edge cell physiological and biochemical techniques to (i) understand the development of ductal damage, especially the inhibitory effects of trypsin at the cellular level and (ii) find new therapeutic targets and develop novel treatment possibilities to (which may) restore ductal function. Acute pancreatitis (AP) is an inflammatory disorder of the pancreas with an unacceptable high mortality (5-10%) and with no specific pharmacological treatment. Therefore, pathophysiological studies aiming to understand the development of the disease are crucially important. By the end of this project, hopefully we will announce a colloidal ATP delivery system for pancreatic energy supply that can protect the pancreatic ductal (and probably acinar) cells from cell death. The results of this project may open up the possibility of pharmacological therapy of acute pancreatitis for the first time, leading to reduced morbidity and mortality.</p>		

Dr. Hegyi, Péter hegyi.peter@pte.hu	Institute for Translational Medicine	Examination of the composition of early enteral nutrition in animal models with experimental and spontaneous pancreatitis
<p>The aim of our study is to evaluate the possible beneficial effects of early enteral feeding of high-energy diets containing different amount of fatty acids in the treatment of patients with acute pancreatitis using a spontaneous canine model of the disease. On the basis of scientific literature early enteral feeding is recommended against parenteral feeding in the treatment of acute pancreatitis. The diets used for this purpose are usually normal fat concentration. However, despite this practice, no studies have yet been performed to prove if this is beneficial or a disadvantage namely is there a difference in the kinetics of the disease in case of a diet with zero-fat or a high-fat concentration. We would like to study the problem mentioned above with the use experimental (mouse and rat) and spontaneous (canine) model. First we plan to examine the dosage and time-dependency on the experimental models, then we perform a prospective, randomised, double blinded clinical study on the effects of diets with different fat-concentration in a naturally occurred canine model of the disease. It is known that pancreatitis occurs more often in dog and especially in certain breeds of dogs (e.g. cocker spaniels, miniature schnauzers) than in humans.</p>		

Clinical picture and treatment are the same in both humans and dogs therefore dogs can serve as a valuable, spontaneous, naturally occurring model of the human pancreatitis. In the experimental models we induce pancreatitis with the use of cerulein and basic amino acids, while spontaneous pancreatitis in canines is routinely diagnosed based on clinical symptoms (acute onset vomitus, severe abdominal pain, shock) and confirmed by the examination of certain blood parameters (complete blood count, amylase, lipase, canine pancreas specific lipase, C-reactive protein) and abdominal ultrasonography.

Dr. Vincze, Áron vincze.aron@pte.hu	1 st Department of Internal Medicine	Prevention and treatment of adverse events during retrograde cholangio-pancreatography
Pancreatitis is the most frequent complication after endoscopic retrograde cholangio-pancreatography (ERCP) with an incidence of 3.5% in unselected patients. Post-ERCP pancreatitis appears unavoidable even in the hands of expert endoscopists. Consequently, attempts to reduce the rate of this complication by different cannulation techniques and/or pharmacological intervention should be pursued. A web-based registry for the procedure will be created to record multiple aspects of ERCP. Multiple national and foreign centers will be invited to participate in data collection and analysis to clarify the role of different factors which influence the outcome in the first phase. Interventional prospective multi-center trials will be initiated using the registry in the second phase of the project with the aim to improve the outcome.		