

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
<p>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.</p>		
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
<p>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.</p>		
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
<p>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</p>		

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. 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
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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.

Dr. Papp, Nóra Dr. Ambus, Tünde nora4595@gamma.ttk.pte.hu ambrust@vfu.cz	Department of Pharmacognosy	Medicinal plants in the pharmaceutical therapy and the history of pharmaceutical culture
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Several data have been published on the use of medicinal plants from the Ancient Times. First uses were based on empiric knowledge, but according to the development of pharmaceutical sciences, these records realized in institutional forms later times. Several medicinal plants and remedies are described in herbal books, in the monastery medicinal period, ethnobotanical works, and the official medicinal and pharmaceutical practice at all historical periods. The research involves the ethnopharmacobotanical, terminological, linguistical, historical, artistical and medicinal evaluation of works related to the history of pharmaceutical, medical and scientific fields.

A-143/1993

Optimization of pharmacotherapy

Program leader: Dr. Botz, Lajos

Dr. Kőszegi, Tamás koszegi.tamas@pte.hu	Department of Laboratory Medicine	In vitro testing of extracts of antidiabetic herbs using tissue culture models
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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.

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

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.		

A-292/1994**Neurofarmacology****Program leader: Dr. Pintér, Erika**

Dr. Bölskei, Kata kata.bolskei@aok.pte.hu	Department of Pharmacology and Pharmacotherapy	Investigation of transcriptional alterations after trigeminovascular activation with a translational approach
The project focuses on investigating the transcriptome of blood samples collected from migraine patients during headache and in headache-free periods. RNA will be isolated from samples and next-generation RNA sequencing will be performed to find differentially expressed genes between healthy controls and patients, and in patients between headache and headache-free conditions. An experimental headache model and an orofacial pain model will also be investigated in rats and samples collected from the animals will also be subjected to a similar transcriptome analysis. Investigation of patient samples can reveal the involvement of yet unknown activation mechanisms and may lead to the discovery of new drug targets. The comparison of human results with the experimental animal samples can help us to evaluate the translational value of the headache and facial pain model and help us optimize the experimental approach for future drug development projects.		

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. 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
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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 pongacz.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
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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. PEPT1 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 pongacz.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
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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
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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

<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-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</p>		

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 biotelemetry (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
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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 biotelemetry (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
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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 biotelemetry 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
<p>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.</p>		
Dr. Czimmer, József czimmer.jozsef@pte.hu	1 st Department of Internal Medicine	Epidemiology of gastro-oesophageal reflux disease and functional esophageal disorders in Eastern Europe
<p>Gastro-esophageal reflux disease (GERD) is one of the most common gastroenterological disorders affecting quality of life and leading to disorders like Barrett metaplasia and esophageal adenocarcinoma, asthma or upper gastrointestinal bleeding lesions. Anti-acid secretory treatment dependency of GERD also leads to chronic complications in certain patient populations highlighting the importance of research of novel therapeutical approaches. This requires detailed diagnostic and epidemiological approach. We have very few epidemiological data in this field from Hungary and Eastern Europe, we planned our project to study it.</p>		
Dr. Czimmer, József czimmer.jozsef@pte.hu	1 st Department of Internal Medicine	Role of carbohydrate maldigestion and malabsorption in clinical aspects of irritable bowel syndrome
<p>Irritable bowel syndrome (IBS) is one of the most frequently diagnosed disorders on the field of gastroenterology, which can lead to significant impairment of quality of life (e.g. social isolation or stigmatization), decreased work productivity and an increase of health care and societal costs. Its pathogenesis remained unknown, but probably among many others, altered gut microbiota plays a significant role. Intolerance to dairy products (mainly to lactose) and other foods is more frequent among patients with IBS than among healthy subjects. In our preliminary meta-analysis we proved the beneficial effect of low-FODMAP diet compared to standard IBS diet with high-FODMAP content, but the efficacy of a lactose restricted diet is still unclear in IBS. Data about lactase enzyme replacement is also controversial. In this project we evaluate correlation of carbohydrate maldigestion and malabsorption to IBS in different aspects by running prospective, multicentre, randomized, double-blind, controlled trial.</p>		
Dr. Czimmer, József czimmer.jozsef@pte.hu	1 st Department of Internal Medicine	Epidemiology the functional bowel disorders in Eastern Europe
<p>The functional gastrointestinal disorders (FGID's) are among the most frequently diagnosed disorders on the field of gastroenterology, which can lead to significant impairment of quality of life (e.g. social isolation or stigmatization), decreased work productivity and an increase of health care and societal costs. Its pathogenesis remained unknown, but probably among many others, altered gut microbiota plays a significant role. Rome-IV criteria redefined the FGID's leading to different prevalence data and clinical significance. We have very few epidemiological data in this field from Hungary and Eastern Europe, we planned our project to study it.</p>		

Dr. Csupor, Dezső csupor.dezso@pharm.u-szeged.hu	Institute for Translational Medicine	Assessment of safety of safety and interactions of food supplements with medicines
<p>In self-medication, patients are prone to use products that do not belong to the category of medicines but to the category of food supplements. However, the use of food supplements is usually not proposed or controlled by physicians, hence there is limited information available on their utilization patterns and safety. Several prospective and retrospective studies have analysed the use and the impact of certain products in different pathologies; however, in most of the cases, the body of evidence on the safety and efficacy is insufficient. The aim of the proposed PhD research is to collect data on the use of food supplements in different patients groups by registries and to assess the efficacy and the safety of various products used in self-medication by meta-analyses as well. The primary goal of the registries is to map the pattern of use, possible interactions and adverse effects, in addition to the long-term impact on quality of life, morbidity and mortality.</p>		

Dr. Faluhelyi, Nándor faluhelyi.nandor@pte.hu	Department of Medical Imaging	Imaging in pancreatic disease: methodology, protocols, follow-up
<p>Early recognition of pancreatic disease, determination of the severity of either acute or chronic pancreatitis and identification of the different complications of these conditions are all challenging. Although a broad spectrum of pancreatic imaging is available, the exact parameters of these methods are still highly variable. There is only limited evidence-based data on the required optimal imaging parameters, just like on the timing and follow-up schedule of these investigations. The application of the existing recommendations in the clinical practice is also ambiguous. Imaging and incidental recognition of cystic pancreas lesions also meets all the above-mentioned problems. In our research, we plan to investigate the imaging methods of inflammatory and cystic pancreatic diseases from ultrasound to MRCP. With retrospective data and image analysis of large number of cases, we try to determine for each mentioned disease group the advantages and disadvantages of the applied methodological parameters. Also, we plan to specify the effects of timing of imaging and follow-ups on the clinical outcome. Based on our findings, we plan to develop optimized imaging protocols for each investigated pancreas disease and/or symptom-groups and to integrate them to clinical practice. In addition, we plan to check efficiency of our recommendations in prospective study(ies).</p>		

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

Dr. Gombos, Katalin katalin_gombos@yahoo.com	Department of Laboratory Medicine	Molecular diagnostic approach for the identification of SARS-CoV-2 and COVID-19 related pathogenetic markers
<p><i>Severe acute respiratory syndrome coronavirus 2</i> (SARS-CoV-2), is a novel human pathogene that causes coronavirus disease 2019 (COVID-19). The clinical presentation of COVID-19 is non-specific, and symptoms overlap with other seasonal respiratory infections concurrently circulating in the population. To support infection control measures, there is an urgent need for accurate molecular diagnostics to identify COVID-19 positive individuals and uncover pathogenic risk factors related to the development of the symptomatic disease. The recent topic is focusing on highly sensitive and specific molecular diagnostic techniques targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), envelope (E) and nucleocapsid (N) genes of SARS-CoV-2 and predisposing genetic and epigenetic factors that prone individuals to severe disease progression. Methods enroll high throughput molecular techniques including fluorescent quantitative real-time PCR, droplet digital PCR and next generation sequencing.</p>		

Dr. Hamar, Péter hampet@net.sote.hu	Institute for Translational Medicine	Pathophysiology of renal allograft rejection – the role of micro RNAs
<p>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.</p>		

Dr. Hegyi, Eszter eszter.hegyi@aok.pte.hu	Institute for Translational Medicine	Mechanism of genetic risk in chronic pancreatitis
<p>Chronic pancreatitis is a progressive inflammatory disease of the pancreas leading to irreversible morphological changes and impairment of both exocrine and endocrine functions. Genetic susceptibility plays an important role in the pathogenesis of chronic pancreatitis, especially in children. Over the past 20 years the role of genetic factors in the etiology of chronic pancreatitis has been extensively studied and a mechanistic model in which premature trypsinogen activation plays a central pathogenic role has been established. More recently, an alternative pathomechanism unrelated to accelerated intrapancreatic trypsinogen activation has been revealed, in which mutation-induced misfolding and consequent ER stress lead to acinar cell damage and pancreatitis. Using animal models of genetically determined chronic pancreatitis we aim to study both pathomechanisms, the trypsin-dependent and the ER stress related pathways in vivo. Moreover, we also focus on the identification of new genetic risk factors in chronic pancreatitis using candidate gene association studies.</p>		

Dr. Hegyi, Eszter eszter.hegyi@aok.pte.hu	Institute for Translational Medicine	Gene-environment interactions in chronic pancreatitis
<p>Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas leading to irreversible morphological changes and impairment of both exocrine and endocrine functions. There is no specific therapy for CP and the cost of lifelong supporting care places a significant burden on the health care systems worldwide. CP is a complex chronic inflammatory disorder which results from the interplay of genetic predisposition, environmental exposures and random stressful events. The major etiologic factor of CP in adults is excessive alcohol consumption, however growing evidence suggests a substantial contribution of genetic predisposition to pancreatitis, especially at younger age. Over the past 20 years the role of genetic factors in the etiology of CP has been extensively studied and a mechanistic model which posits that uncontrolled intrapancreatic trypsin activity is responsible for the disease onset and progression has been established. More recently, an alternative pathological pathway of pancreatitis risk unrelated to accelerated intrapancreatic trypsinogen activation that involves endoplasmic reticulum stress caused by mutation-induced misfolding of digestive enzymes has been identified. Our aim is to investigate how high-fat diet/smoking and genetic risk synergize in the development of CP. This translational approach will contribute to gain better understanding of the importance of gene-environment interactions in the pathogenesis of chronic pancreatitis.</p>		

Dr. Hegyi, Péter hegyi.peter@pte.hu	Institute for Translational Medicine	Investigation of the pathomechanism and disease course of COVID-19
<p>On the morning of March 12, 2020, the World Health Organization (WHO) announced the outbreak of the new coronavirus disease (COVID-2019). By the time this research proposal was written, more than 3,500,000 cases had been confirmed from more than 180 countries, claiming the lives of more than half a million people. This trend predicts that the epidemic is still far from peaking. As with other infectious diseases, some cases are asymptomatic or mild, so they remain undiagnosed. Thus, it is difficult to accurately estimate the true incidence and outcome of the disease. An analysis of 72,314 Chinese patients with the SARS CoV-2 epidemic found that 5% of the population required intensive care (ICU), with the most common indications being acute respiratory failure, septic shock, and / or multiple organ failure. Similar data were reported from Italy. Two days after the outbreak in Italy, 60% of the ICU beds in the Lombardy region was occupied by COVID-19 patients. The situation that has since deteriorated significantly. We are launching several research projects that study (1) the pathomechanism of the disease course, (2) the disease-aggravating comorbidities, and (3) the disease course characteristics. ETT TUKEB Ethical approval number: 20800-6/2020 EÜIG.</p>		

Dr. Hegyi, Péter hegyi.peter@pte.hu	Institute for Translational Medicine	LIFESPAN study
<p>Lifestyle, prevention and risk of acute pancreatitis (AP). The LIFESPAN[1] study is a prospective, multicentre, observational, case-control study examining the association between socioeconomic factors, dietary habits, physical activity, chronic stress, sleep quality and AP. Although there are numerous studies on the most common risk factors for AP, there are only a few articles published on the effect of lifestyle factors. This insufficient information is even more problematic since (1) there is no specific treatment for the disease, therefore prevention would be very important; and (2) 20% of all AP is recurrent so lifestyle suggestions decreasing the risk of an additional attack could be highly efficient. The data collection is based on questionnaires and medical histories. Relevant data will be prospectively collected from patients and controls. Patients enrolled into the case group have suffered from AP; the control group subjects must not have AP in their medical history. 1. Koncz B, Darvasi E, Erdősi D, et al. LIFESStyle, Prevention and Risk of Acute PaNcreatitis</p>		

(LIFESPAN): protocol of a multicentre and multinational observational case-control study. *BMJ Open* 2020;10:e029660. doi:10.1136/bmjopen-2019-029660

Dr. Hegyi, Péter hegyi.peter@pte.hu	Institute for Translational Medicine	ELEFANT study
<p>Acute pancreatitis (AP) is a life-threatening inflammatory disease. Of the various etiological factors, hypertriglyceridemia (HTG-AP) causes the most severe inflammation of the pancreas with the highest mortality rate. Its frequency is constantly increasing due to changes in eating habits and the obesity epidemics worldwide. ELEFANT is a randomized, controlled, multicentric, international study designed to investigate the effectiveness of early triglyceride lowering and to select the appropriate intervention in patients with HTG-APs. The trial is testing the concept that early elimination of triglycerides (TG) and free-fatty acids from the blood is beneficial in HTG-AP. Patients between the ages of 18-80 with HTG-AP defined by TG level over 11.3 mmol/l (1000 mg/dL) and with an abdominal pain less than 48 h prior admission are included. On admission, after laboratory and imaging examinations if the patients agree to the study, they are randomized into three groups: (1) patients who undergo plasmapheresis, (2) patients who receive insulin and heparin treatment and (3) patients with no additional specific treatment.</p>		

Dr. Hegyi, Péter hegyi.peter@pte.hu	Institute for Translational Medicine	Tools for monitoring dietary adherence in celiac disease
<p>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).</p>		

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 (<i>Gut</i>, 2008 57:1102-12 és <i>Gut</i>, 2011 60:361-9), (ii) compromised ductal fluid and bicarbonate secretion can increase patient risk to AP (<i>Am J Gastro</i>, 2010, 105:2119-20), (iii) mitochondrial injury and ATP depletion is one of the key aspects of ductal damage (<i>Gut</i>, 2010 Sept 28. [Epub ahead of print] and <i>Gut</i> 2011 60:136-8) and (iv) trypsin, the protease long recognized to be involved in the pathogenesis of</p>		

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.

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. 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.</p>		

Dr. Keszthelyi, Dániel d.keszthelyi@mumc.nl	Institute for Translational Medicine	Use of digital instruments in irritable bowel syndrome: towards understanding underlying pathophysiology
<p>Irritable bowel syndrome is one the most common gastrointestinal conditions. It is associated with decreased quality of life and increased healthcare and indirect costs. The pathophysiology IBS remains unclear but is believed to be related to a disorder in the gut-brain interaction. Stress is one of the factors contributing to the development, severity and persistence of abdominal complaints. Stress and abdominal complaints vary greatly on a day-to-day basis. In order to capture these fluctuations, assessment of symptoms on multiple occasions per day is necessary. To this end, a smartphone application has been developed on the basis of the so-called experience sampling method. Aim of this project is to validate the use of this in novel tool in a population of Hungarian IBS patients and to investigate the stress-abdominal symptom relationship in more detail.</p>		

Dr. Szalai, Eszter szalai.eszter@pte.hu	Department of Ophthalmology	Epidemiology, diagnosis and treatment of ocular surface neoplasias
<p>There are three types of ocular surface tumors, the epithelial, stromal and secondary, metastatic neoplasias. Since some of these tumors have a highly malignant behavior – 5 year mortality rate of conjunctival melanoma could be 30% - incidence and epidemiological features of these neoplasias are of importance. Early and precise diagnosis is crucial to perform the most suitable treatment modality and to prevent any further morbidity. The standard diagnostic method includes excision biopsy with histology. Traditionally ocular surface malignancies have been treated with surgical excision with adjuvant cryotherapy. However, recurrence rates after surgical excision can be quite high and repeated surgeries may lead to limbal stem cell deficiencies, thus medical interventions have been used increasingly. Our comprehensive research plan involves data collection on risk factors and demographic features of ocular surface malignancies. Based on these data, we plan on analysing disease process and outcome. On the other hand, in vivo diagnostics of these rare neoplasias, following up patients, recording disease process, response to treatment and surgeries are also included in the study plan. To correlate the in vivo examinations with the histology results for patients who underwent surgical excision is another aim. Our further plan to gain short and long term experience with topical chemo- and immunotherapy and to interpret these results.</p>		
Dr. Szanyi, István szanyi.istvan@pte.hu	Department of Otorhinolaryngology	Study of the epidemiology, risk factors, clinical presentation and effectiveness of treatment of HPV associated head and neck squamous cell carcinoma (oro-hypopharynx, larynx). Register for head and neck squamous cell carcinoma
<p>Head and neck squamous cell carcinoma represents the 6th most common malignant tumour worldwide. The most frequent localisation is the larynx. Smoking and alcohol consumption are important and well known risk factors. However, nowadays the HPV infection is getting more highlight as a serious risk factor in mesopharyngeal cancers, especially involving the tonsils and the base of the tongue. The incidence of the mesopharyngeal squamous cell carcinoma is rising continuously, affecting especially younger men. Although, it's role is emerging also in hypopharyngeal and laryngeal cancers. The most significant difference between the HPV associated and non-HPV associated head and neck tumours is the prognosis of the disease. It is known that the HPV associated type correlates with a better prognosis and favorable healing rate. In the treatment of both types is crucial the early diagnosis and starting an adequate treatment without delay. For this purpose, it is inevitably necessary to explore the clinical course, the predisposing factors, the common symptoms of the disease and it's response to the treatment. For this purpose we create a head and neck HPV register.</p>		
Dr. Vincze, Áron vincze.aron@pte.hu	1 st Department of Internal Medicine	Prevention and treatment of adverse events during retrograde cholangio-pancreatography
<p>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.</p>		

Dr. Vincze, Áron vincze.aron@pte.hu	1 st Department of Internal Medicine	Examination of quality parameters of gastrointestinal endoscopy
<p>A high-quality endoscopy is an examination in which patients receive an indicated procedure, correct and relevant diagnoses are recognized or excluded, any therapy provided is appropriate, and all steps that minimize risk have been taken. Universal and procedure specific quality indicators of endoscopic procedures were developed first in 2006, and were updated in 2014. Gathering data on these indicators will help to identify insufficiencies, to improve outcome and to answer clinical research questions. National database will be developed initially to conduct clinical research, to monitor patient care and to identify those parameters where changes can improve the quality of care.</p>		

Dr. Vincze, Áron Dr. Hegyi, Péter vincze.aron@pte.hu hegyi.peter@pte.hu	1 st Department of Internal Medicine	The epidemiology of precancerous pathologies and cancers in the upper gastrointestinal tract in Eastern Europe
<p>The aim of this research is to gather epidemiological data on the precancerous pathologies and cancers of the UGI tract and to better understand the geographical differences of these pathologies between Eastern Europe and the rest of the World. Recent significant technical and scientific advances resulted in the development of effective endoscopic treatment for early neoplasia in the UGI tract and there is ample data and research in this topic in Western Europe, North America, Australia and the developed countries of Asia, however there is very little known about the epidemiology of these pathologies in Eastern Europe and there is very scarce data on the treatment of these conditions. The main areas for research and work will be: The epidemiological trends of squamous cell cancer and adenocarcinoma of the oesophagus and gastric cancer in the last five decades in Eastern Europe. The epidemiology of H. pylori in Eastern Europe since its discovery. Investigation of the relationship between the above two epidemiological trends and findings. The epidemiology of precancerous pathologies in the UGI tract (Barrett's oesophagus and chronic atrophic gastritis) in Eastern Europe. Building prospective registries and databases for the above pathologies. Initiation of international cooperation in the above scientific research. This scientific project is the essential first step in organising and advancing the Hungarian endoscopic service for precancerous pathologies and early neoplasia in the UGI tract.</p>		

B-1/2014 Pharmaceutical chemistry

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Dr. Perjési, Pál Dr. Almási, Attila pal.perjesi@gytk.pte.hu attila.almasi@aok.pte.hu	Institute of Pharmaceutical Chemistry	The role of glutathione-conjugation in the biologic effects of chalcones and chalcone analogues
<p>In our earlier studies, several chalcones and cyclic chalcone analogues showed cancer cell cytotoxic effect. On the other hand, they showed a structure-dependent antioxidant (cytoprotective) effect as well. Cytotoxic effect of related α,β-unsaturated carbonyl compounds are frequently associated with their expected reactivity with the essential thiol groups in the living organisms. Earlier results indicated that the investigated chalcones can react with reduced glutathione (GSH) even in spontaneous reaction. In the framework of the present program, we are planning to investigate the kinetics and stereochemistry of</p>		

the addition reactions by UV-Vis and HPLC methods. The kinetics of formation and the diastomeric ratio of the chalcone-GSH adducts will be studied in the presence of GST enzyme as well.

Dr. Perjési, Pál Dr. Fischer, Emil pal.perjesi@gytk.pte.hu emil.fischer@aok.pte.hu	Institute of Pharmaceutical Chemistry	Effects of pathological conditions on elimination of xenobiotics
<p>It is known that during diseases or various pathological conditions, the functioning of individual organs can change. We have relatively little data on what changes can occur in the elimination of pharmacones in cases when conditions other than physiological appear, for example, in the case of chronic diseases. In the framework of this research, the effect of diabetes, one of the very important and widespread pathological conditions, is examined on the hepatic and the intestinal metabolism, and excretion of drugs. In animal studies, experimental diabetes is induced by streptozotocin, and its elimination activity in the experimental animals is studied by chromatographic analysis of small intestine perfuzate and bile samples. With such experiments, we can also answer the question of whether one of our organs might be able to compensate for the reduced or lost elimination function of another organ.</p>		

Dr. Perjési, Pál Dr. Rozmer, Zsuzsanna pal.perjesi@gytk.pte.hu zsuzsanna.rozmer@aok.pte.hu	Institute of Pharmaceutical Chemistry	Structure-to-activity relationship studies on cytotoxic and cytoprotective effects of chalcones and chalcone analogues
<p>In our earlier studies, several chalcones and cyclic chalcone analogues showed cancer cell cytotoxic effect. On the other hand, they showed a structure-dependent antioxidant (cytoprotective) effect as well. Among the investigated compounds it was the seven-membered ring derivatives that showed the most promising effects. In the framework of the present program, the aim of our study is to analyze how the steric, electronic and hydrophobic properties of the compounds affect their cytotoxic and cytoprotective activities. For determination of the relevant physico-chemical properties chromatographic and spectroscopic methods are applied. The antiproliferative effects are tested on different cell cultures.</p>		

Dr. Perjési, Pál pal.perjesi@gytk.pte.hu	Institute of Pharmaceutical Chemistry	Determination of drugs/drug metabolites in natural and drinking water samples
<p>Many drug active substances are excreted unchanged in a biologically active form into the environment as a result of normal physiological processes. The level of active substance detected in surface waters typically falls within the range of ng/L and µg/L. Drug residues can cause changes in the human body and in otherwise stable ecosystems. They are integrated into feeding chains, disrupting natural material flows and the natural (e.g. reproduction) behaviour of life communities and individual species. In the framework of the program, validated analytical (HPLC-MS) methods are developed for quantitation of steroid hormones, non-steroidal anti-inflammatory drugs and some other frequently detected drugs/drug in natural and drinking waters. Our inspections cover the waters around Pécs and Pécs.</p>		