Basic Medical Sciences (D95)
The Leader of the Doctoral School: Dr. Szekeres, Júlia

A-138/1993 Immunological aspects of reproduction — Program leader: Dr. Szekeres, Júlia

Dr. Barakonyi, Alíz barakonyi.aliz@pte.hu	Department of Medical Microbiology and Immunology	**Immunoregulatory mechanisms during healthy and pathological pregnancies**
How the fetal 'allograft' avoids rejection during pregnancy remains a major unresolved immunological paradox. The complex anatomical nature of the feto-maternal interface, the involvement of multiple types of cellular immunbiological functions, as well as the wide variety of mediator cytokines, are employed in this highly adaptive, dynamically regulated system. Members of the natural immune system play a crucial role in this immunoadaptation. Here we investigate maternal gamma/delta T and NK cell populations focusing on their exact function during healthy pregnancy and on the disturbances of this precise immunoregulation.		

B-139/1993 Essentials of immunology — Program leader: Dr. Németh, Péter

Dr. Balogh, Péter balogh.peter@pte.hu	Department of Immunology and Biotechnology	**Role of Nkx2-3 transcription factor in the regulation of innate lymphoid cell homeostasis in visceral lymphoid organs and the onset of inflammatory bowel diseases**
Lymphoid tissues formed in the intestines play important roles in the simultaneous defence against gut microbiota and establishment of tolerance towards the polysaccharide and protein components of food. In chronic inflammatory bowel diseases (IBD) induced by altered enteral microbes innate lymphoid cells (ILC) and innate-like lymphocytes (ILC) may have important contribution. Although IBD is frequently associated with enhanced expression of Nkx2-3 homeodomain transcription factor, currently there are no suitable in vivo experimental models which could be used to investigate its involvement in the homeostasis and mucosal function of ILL/ILC cells. The aim of this work is to clarify the role of Nkx2-3 in the (1) maturation of gut-associated lymphoid tissues, (2) splenic and intestinal homeostasis of ILC/ILL cells and (3) their recirculation using transgenic and chimera animal models, including cellular and molecular assays and in vivo imaging.		

Dr. Balogh, Péter balogh.peter@pte.hu	Department of Immunology and Biotechnology	**Regulation and differentiation of the myelopoietic stroma of spleen**
In addition to its various immunological activities, the murine spleen also exerts myelopoietic activity. It is not yet known whether the splenic development of erythroid, monocytoid and megakaryocytic cells is guided by the same stromal elements and hematopoietic factors that are present in the adult bone marrow. The aim of this project is to isolate various splenic stromal constituents and their functional and transcriptome analysis, and the identification of network of interacting myeloid cells by their selective depletion.		

Dr. Balogh, Péter balogh.peter@pte.hu	Department of Immunology and Biotechnology	**Role of serosal lymphoid tissues in the peritoneal dissemination of B-cell lymphoma**
A spontaneous high-grade B-cell lymphoma has been found to show a tissue-specific accumulation and retention in the mesenteric lymph nodes and spleen		

following intraperitoneal injection; however, the cellular and molecular components contributing to this restricted spreading are unknown. The aim of this study is to determine those stromal factors (cellular and molecular) that promote the lymphatic spreading and target tissue accumulation of this lymphoma by using combined cellular immunological and imaging procedures.

Dr. Balogh, Péter balogh.peter@pte.hu	Department of Immunology and Biotechnology	**Organization and lymphoid homeostasis of serosal lymphoid tissues**
The knowledge of the immunological protection of serosal surface of the intraabdiminal organs is very scarce, despite its clear medical significance. The aim of this project is the analysis of the connection between the peritoneal lymphoid structures and the intestinal lymphoid tissues, their developmental relationship using cellular immunological and molecular biological approaches in various animal models.		

Dr. Engelmann, Péter engelmann.peter@pte.hu	Department of Immunology and Biotechnology	**Unravelling the mechanisms of nanoparticle toxicity to invertebrate and human cells: an integrative in vitro and in vivo parallel approach**
Nanotechnology is a dynamically developing field producing large amounts of nanoparticles that are applied in industry, daily life and health care. During production, use, and waste these materials (e.g. silver nanoparticles) could end up in water or soil. Large scale contaminations of our environment are a threat to public health. There is a general lack of detailed assessment of how nanoparticles affect human health and environment. Metallic pollution can have harmful effects on the immune system, as revealed by numerous studies in humans and other vertebrates. The relative simplicity of invertebrate immune functions offers potentially sensitive and accessible means of monitoring the effects and complex interactions of metal nanoparticles which ultimately affect host resistance. Among terrestrial invertebrates, earthworms are the “keystone” species to evaluate the health of soil ecosystems. The aim of this project is to understand and compare the conserved toxic mechanism of metal nanoparticles on the innate immune responses of invertebrate and vertebrate immune systems. With the aid of our complex *in vitro* and *in vivo* experimental system the obtained knowledge can provide exciting insights into the conserved molecular and cellular mechanisms of NP toxicity between invertebrates and vertebrates. Understanding the unique characteristics of engineered nanoproducts and their interactions with biological systems in our environment is essential to the safe realization of these materials in novel biomedical applications.		

Dr. Kvell, Krisztián kvell.krisztian@pte.hu	Department of Pharmaceutical Biotechnology	**The biochemical role of PPARgamma as a transcription factor of thymic senescence**
Thymic senescence is defined by the degeneration or adipose involution of the thymic epithelium. The process begins rather early in life, right after puberty. The process leads to decreased naive T-cell production with severe immunological consequences (increased incidence of infections, autoimmune diseases and cancers). PPARgamma has a key role in the process and its biochemical role and partners are currently being discovered. These challenging discoveries have significant medical relevance.		

Dr. Kvell, Krisztián kvell.krisztian@pte.hu	Department of Pharmaceutical Biotechnology	**Establishment of personalised 3D thymus from peripheral blood**
Thymic aging begins early, accelerates with puberty and continues at an individual pace. If the thymus shows accelerated aging, its biological age is ahead of chronological age. Thymic aging may be accelerated by various factors including toxic substances, steroid hormones, infections. These can significantly decrease fresh naive T-cell output leading to increased incidence of infections, cancers and autoimmune diseases. Our long-term goal is to establish artificial		

personalised 3D thymus tissue from peripheral blood that is suitable for both immunology research and medical autologous reimplantation to support immune functions. For this first 3D PCL scaffold is printed then colonised by thymic epithelial cells trans-differentiated from peripheral blood monocytes. This is then seeded with peripheral blood hemopoetic stem cells (CD34+ HSC) differentiated towards T-lineage thus constructing a thymus lobe.

Dr. Kvell, Krisztián kvell.krisztian@pte.hu	Department of Pharmaceutical Biotechnology	**Differences in tissue senescence: lessons from thymic and pulmonary contexts**
Different organs reach their functional apex at various ages, following which their senescence begins, although with various pace and mechanism. For example the thymus begins to age right following puberty, while the central nervous system begins to decline after approx. 24 years of age and the skeletal system begins to degenerate after approx. 30 years of age. For other organs (i. e. the lungs) the time-point of functional peak is more challenging to define. However, deciphering the relevant molecular mechanisms may shed light on such macroscopic differences. Our research group (with the supervision of Prof. Judit Pongracz and Dr. Krisztian Kvell) aims to discover molecular differences responsible for desynchronized organ senescence through comparing senescence in two rather different tissues: the thymic and the pulmonary context.		

Dr. Kvell, Krisztián kvell.krisztian@pte.hu	Department of Pharmaceutical Biotechnology	**Changes in miRNA profile of human thymic epithelial exosomes with age**
Exosome research has seen breakthrough in the past years: several physiological changes (development, aging) and diseases (inflammation, cancer) have been linked to exosomes. The thymic epithelium is an unusually rich source of exosomes compared to other tissues. Also their special characteristics (lack of surface CD63 molecule) allow for their specific enrichment from human serum samples. Thymocytes develop in the thymus to become naive T-cells of the peripheral blood once fully mature where they provide protection from infection and cancer. So-called regulatory T-cells that regulate autoimmune disorders also develop in the thymus. With age the incidence of infections, cancer and autoimmune disorders increases. Our research aims to determine changes in miRNA profile of human thymic epithelial exosomes with age and to clarify their role in the development of infections, cancer and autoimmune disorders.		

Dr. Pongrácz, Judit pongracz.e.judit@pte.hu	Department of Pharmaceutical Biotechnology	**Investigation of PKC isoenzymes in Wnt signal transduction**
There are 19 Wnt genes in vertebrates coding proteins homologous to Drosophila wingless genes. Wnt-s are important in cellular proliferation, differentiation, migration and polarity. There is two main signaling pathway: the beta-catenin dependent or canonical and the beta-catenin independent or non-canonical pathways. One of the non-canonical pathways require PKC-s for signal transduction. This pathway is still poorly understood.		

Dr. Pongrácz, Judit pongracz.e.judit@pte.hu	Department of Pharmaceutical Biotechnology	**Chronic inflammatory diseases in the lung and the role of Wnt molecules in the inflammatory process**
Millions succomb to chronic inflammatory lung diseases yearly. Both the inflammatory process and fibrosis are regulated by the evolutionarily conserved Wnt molecules. The role of Wnt-s in chronic inflammation will be studied.		

Dr. Pongrácz, Judit pongracz.e.judit@pte.hu	Department of Pharmaceutical Biotechnology	**Investigation of Wnt-s in non-small cell lung cancer (NSCLC)**
Chronic inflammatory mechanisms in the lung are tightly linked to cancer development. One of the main lung cancer types is NSCLC that causes millions of		

deaths each year. The Wnt family of glyco-lipoproteins regulate several mechanisms important in carcinogenesis. Wnts and their role in NSCLC development will be studied on primary human lung resections and using molecular studies.

Dr. Pongrácz, Judit pongracz.e.judit@pte.hu	Department of Pharmaceutical Biotechnology	**Molecular background and epigenetic regulation of the aging mechanisms in the human lung**
Healthy aging is centrally important problem as the population ages in the developed world. Aging is regulated genetically as well as epigenetically. Identification of the epigenetic mechanisms in the human lung can aid development of drugs and mechanisms for tissue regneration.		

A-137/1993 Theoretical and practical guidance for the multidisciplinary research of the central neural and humoral regulation

Program leader: Dr. Karádi, Zoltán

Dr. Ábrahám, István istvan.abraham@aok.pte.hu	Institute of Physiology	**Investigating of non-classical estrogen action in the brain**
Estrogen secreted from the ovary alters the function of several neuronal phenotypes. Cholinergic neurons degenerate in Alzheimer's disease and estrogen plays a role in determining the vulnerability of cholinergic neurons in this condition. The estrogen also acts a feedback manner to alter the function of gonadotropin releasing hormone (GnRH) neurons, the central "processor unit" of the fertility. Although estrogen primarily alters the neuronal activity by modulating gene expression directly it also exerts "non-classical" effects on neurons by altering signal transduction pathways. In our laboratory, we are systematically characterizing the mechanism and role of estrogen-induced "non-classical" effect on signalling molecules in cholinergic and GnRH neurons using immunohistochemistry, calcium imaging, single cell electrophysiology, single molecule detection, bahavioural tests and transgenic technology.		

Dr. Buzás, Péter peter.buzas@aok.pte.hu	Institute of Physiology	**Investigations on mechanisms and brain pathways of colour vision in non-primate mammals**
Our research is concerned with the biological basis of colour vision. In most mammals, except for trichromatic primates, colour vision is based on two types of photoreceptors: the "blue" and "green" cones. The neural pathway transmitting colour information has, however, not been identified in these animals. We have recently discovered a neurone population in the deep layers of the lateral geniculate nucleus of cats that show receptive field properties typical of colour processing cells, such as cone opponency and low sensitivity to achromatic contrast. Aims of the current research are (1) to characterise these cells further and (2) to follow the course of the putative colour vision pathway towards the retina as well as visual cortex. To this end, we use electrophysiological methods well established in our lab. Here we characterise the receptive fields of neurones on the basis of their responses to computer-generated, cone-specific visual stimuli. As part of their PhD project, students can also learn and use immunocytochemical, functional imaging (optical imaging) and computer simulation methods. Our research contributes to understanding the phylogenetic basis of primate colour vision and the mechanisms of colour processing in the cerebral cortex.		

Dr. Buzás, Péter **Dr. Jandó, Gábor** peter.buzas@aok.pte.hu gabor.jando@aok.pte.hu	Institute of Physiology	**Neurophysiology of parallel mechanisms in stereopsis**
The project is concerned with the neural mechanisms of stereopsis. Recent literature indicates that binocular information is processed by two parallel channels with a common origin in primary visual cortex. Cortical areas belonging to the dorsal stream evaluate disparity information for controlling eye movements and perception of 3D motion. By contrast, the ventral stream utilises depth information for image segmentation and object recognition. The two systems process the binocular stimulus by fundamentally different mechanisms, but their division is likely gradual. Also, the two mechanisms may occur concurrently and they may contribute to specific behavioural or neural responses to varying degrees. Based on our recent results, we aim to demonstrate and characterise these two mechanisms in electrophysiological (EEG, LFP, multi-electrode single unit) and functional imaging (optical imaging, fMRI) responses evoked by random dot stereograms. The measurements will be carried out mainly in experimental animals whereas parallel experiments in humans will supplement the study.		

Dr. Buzás, Péter **Dr. Jandó, Gábor** peter.buzas@aok.pte.hu gabor.jando@aok.pte.hu	Institute of Physiology	**Binocular stimuli in Amblyopia screening**
The objective of this project is a feasibility study of using Julesz's binocular cyclopean stimuli as a potential tool to detect amblyopia. Student will learn the methodological principles of binocular visual stimulation, i.e. Dynamic Random Dot Correlograms (DRDCs), Dynamic Random Dot Stereograms (DRDSs), and the effects of stimulus parameters (e.g. dot density, disparity, frame rate and noise) on the phsychophysiologic responses. Results, compared with data collected under different stimulation conditions, may help to understand how these binocular stimuli are processed in the human brain and provide further evidences how these techniques could be used in the clinical practice. Successful accomplishment of the program will provide valuable data to answer basic scientific questions and have clinical utility too. Implementation of these powerful methods can be used in screening for amblyopia, the leading cause of vision loss under the age of 40, and contribute to the understanding of early postnatal visual development.		

Dr. Gálosi, Rita rita.galosi@aok.pte.hu	Institute of Physiology	**The role of forebrain monoamines in the regulation of behavior**
Our main question is to determine the role of monoamine in reinforcement learning including ingestive and avoidance behavior. It is known that the mesolimbic and mesocortical dopamine systems are involved in the regulation of reinforcement. Other monoamine as the forebrain noradrenergic system has an influence on the activity of dopamine system, but in the reinforcement processes the role of this interaction is not known. The main component of incentive learning together incentive salience, reward prediction and prediction error will be examined during operant as well as pavlovian condition. The aim of these studies to map the neuronal network involving in regulation of reinforcement learning using rodent models and to detect the changes in dopamine and noradrenaline levels with description of the interactions between these systems. The effects of pharmacologic or pharmacogenetic manipulations of dopamine and adrenergic receptors will be examined. Automatic behavioral conditional system will be used in the experiments. Monoamines and their		

metabolites in vivo and from in vitro samples will be detected with HPLC system and electrochemical detection. The results of these experiments may contribute to understand the psychophysiology of reinforcement and by this way the learning mechanisms.

Dr. Hernádi, István hernadi@ttk.pte.hu	Institute of Physiology	**Behavioral pharmacology of attention and learning: development of new test batteries for translational research**
The main purpose of the research is to decide whether and how non-invasive magnetic stimulation of cortical areas may result in increase or decresase of cognitive performance in humans and non-human primates. We will also test the effects of combination of novel cognitive enhancer pharmacological agents and the stimulation technique. In favourable condition, the combined therapies will open new avenues in the treatment of various neurological conditions, especially in the therapy of dementias. Technical background: computer-controlled non-verbal cognitive test batteries, high performance electroencephalography (EEG), repetitive transcranial magnetic stimulation (rTMS), eye movement monitoring.		

Dr. Hernádi, István hernadi@ttk.pte.hu	Institute of Physiology	**Investigation of cognitive enhancer pharmacological targets in preclinical research of aging**
Neurocognitive impairments, such as Alzheimer's disease (AD), are among the most serious health issues in the world. Cholinesterase inhibitors (e.g., donepezil) and the glutamatergic antagonist memantine are used to attenuate the progression of cognitive deficits in AD. Due to their low efficacy and serious limitations, there is no effective therapy which can reverse or stop the progression of neurodegeneration. Thus, the development of new therapeutical avenues is needed. Recently alpha7 nicotinic acetylcholine receptors (nAChR) were intensively studied as new therapeutic targets, suggesting that combinational or multi-target therapies may further increase the efficacy of treatments and decrease side-effects. As action on alpha7 nAChRs may have a primary role in the procognitive effects of memantine, activators of the alpha7 nAChRs may act as potential amplifiers of the effects of memantine. In the current research our aim is to investigate the nature of such interactions and their consequences regarding the effectiveness of the combined treatments. We will explore two behavioral models: 1) transient pharmacological dementia using mAChR antagonist scopolamine, 2) aging animals showing memory impairment verified by functional neuroanatomy (MRI). We hypothesize that the synergistic activation of alpha7 nAChRs on hippocampal pyramidal neurons are in the background of the observed procognitive effects. Routine histology (labeling degenerating neurons or counting dendritic spine, alpha7nAChR-immunohistochemistry) will also reveal the putative structural alterations in the background of behavioral dysfunctions and the reversal capacity of the treatments.		

Dr. Karádi, Zoltán zoltan.karadi@aok.pte.hu	Institute of Physiology	**Investigation of functional attributes of forebrain glucose-monitoring neurons intimately involved in the regulation of homeostasis**
The research program summarizes our multiple neurophysiological experimental plans that aim to provide functional characterization of the glucose-monitoring (GM) neuronal network involved in the closely interrelated regulation of feeding, metabolism and the maintenance of body weight. To realize these plans, extracellular single neuron recording, neurochemical-biochemical and behavioral experiments will be conducted in laboratory rats and rhesus monkeys that are phylogenetically close to the human being. The project targets directly and indirectly interconnected structures of the limbic forebrain. By employment of the multibarreled microelectrophoretic technique as well as by local intracerebral microinjection of chemicals influencing or destroying the GM neurons, it is possible, on the one hand, to achieve a broad functional characterization of the GM neurons, on the other hand, to elucidate the homeostatic significance of these chemosensory cells. Successful accomplishment of the program serves the better understanding of the central regulation of feeding and metabolism. It is also expected to learn more about related diseases (e.g. obesity, diabetes mellitus) which are supposed to develop on the basis of pathological alteration of the above processes, and which cause increasing problem in the modern societies.		

Dr. Kertes, Erika erika.kertes@aok.pte.hu	Institute of Physiology	**The role of tachykinins and the neuropeptide interactions in the mechanisms of learning, reinforcement, memory and in the regulation of addictive behavior.**
The limbic system has a substantial role in the control of learning and memory processes, in motivation and reinforcement, and also in emotional processes. In the regulation of these mechanisms the dopaminergic (DA) system is essentially involved. The main goal of the project is, however, to unravel the functional role of DA - neuropeptide interactions and the investigation of the modulatory effects of neuropeptides. The role of substance P (SP) is confirmed in learning and memory processes, in the positive reinforcement, as well as in fear and anxiety. Electrophysiological, neurochemical and behavioral methods will be applied to investigate the effects of tachykinins, included SP, and its antagonists in the aforementioned processes, on the function of the limbic neurons and on the DA interactions in the terminal fields of the mesolimbic DA system. The effects of different doses of tachykinins and their antagonists will be investigated in behavioral tests (open field, rotarod, place preference, elevated maze, Morris water maze tests), and in electrophysiological experiments (single unit, multibarrel technique). Immunohistological examinations will be performed to detect SP immunoreactivity in limbic structures. After immunological lesions we will examine the behavior of Wistar rats in the former tests. Our results may contribute to unravel the still unknown peptidergic processes of learning, reinforcement and drug addiction.		

Dr. László, Kristóf kristof.laszlo@aok.pte.hu	Institute of Physiology	**Effects of neuropeptides on learning, memory and reinforcement and their role in the function of limbic neural networks**
The role of neuropeptides (neurotensin, oxytocin, substance-P, RFRP-1 and RFRP-3) - microinjected into the limbic system- are investigated on reinforcement, learning and memory processes in male wistar rats. The possible rewarding-reinforcing effects of drugs are studied by means of conditioned place preference test. The relevance of neuropeptides on spatial learning is investigated in Morris water maze test. Elevated plus maze test is used to study the possible anxiogenic or anxiolytic effects of the microinjected drug. Memory processes are investigated by means of passive avoidance test. Open field test is used to examine the effects of neuropeptides on spontaneous motor activity. The role of these drugs on the limbic neural activity is studied by means of multibarelled microelectrophoretic technique. The relevance of dopamine – neuropeptide interactions is studied in different behavioral paradigms and by electrophysiological methods. In order to achieve this goal, combined intracerebral injection of dopamine D1 and –D2 agonists and antagonists, neuropeptides and their antagonist are studied. Results may give better understanding of neural processes of learning, memory and drug addiction.		

Dr. Lénárd, László laszlo.lenard@aok.pte.hu	Institute of Physiology	**The role of neuropeptides and peptide interactions in the regulation of hunger, satiety and body weight**
The incidence of feeding related disorders (obesity, bulimia and anorexia nervosa) and appearance of related secondary diseases (arteriosclerosis, diabetes mellitus, and stroke) have increased dramatically world-wide. Utilization of experimental animal models studying central regulatory processes of feeding may contribute to the better understanding of these diseases and can result in the elaboration of new treatment strategies. The main goal of the experiments is to study the role of orexigenic and anorexigenic neuropeptides (orexins, bombesin like peptides, ghrelin, galanin and others) in the limbic system. By means of multibarreled microelectrophoretic method effects of orexigenic and anorexigenic peptides and their antagonists will be examined on neuronal activity and on the activity of the so called glucose monitoring neurons. After intracerebral microinjections body weight, food and water intake, as well as the		

microstructure of feeding, development of satiation and the level of metabolic parameters will be studied. Reinforcing effects of neuropeptides will be studied during food rewarded alimentary conditioning, and also in different rewarding and punishing paradigms. Results may cast light on the complex peptidergic central regulatory processes of feeding.

Dr. Lénárd, László laszlo.lenard@aok.pte.hu	Institute of Physiology	**The role of dopamine- neuropeptide interactions in the regulation of learning, reinforcement and addictive behavior**
It is well known that during rewarding learning processes and after intracerebral amphetamine microinjections dopamine is released. The rewarding reinforcing effects of endogenous opioids and cannabinoids have also been verified. Based on recent data it can be supposed that other neuropeptides (substance P, neurotensin, oxytocin) being released in the central nervous system can also play essential roles in the rewarding-reinforcing processes. Less is known about the importance of dopamine-neuropeptide interactions in learning and reinforcement. Effects of dopamine, dopamine receptor agonists and antagonists, as well as neuropeptides and their antagonists on single neurons will be studied in the limbic system by means of multibarreled microelectrophoretic method. After intracerebral microinjections dopamine and metabolite levels will be examined by HPLC microdialysis method. In different behavioral paradigms (conditioned place preference, Morris water maze, elevated plus maze, passive avoidance) after combined intracerebral microinjections of dopamine D1 and D2 receptor agonists and antagonists, neuropeptides and their antagonists behavior of wistar rats will be studied. Results may contribute to the better understanding of neurochemical processes of learning and drug addiction.		

Dr. Lénárd, László laszlo.lenard@aok.pte.hu	Institute of Physiology	**Importance of hedonic evaluation of food reward: animal experiments and human examinations**
The hunger motivated behavior is based on the integration of homeostatic endogenous humoral and neural information and of exogenous food related cues signaling the availability of food reward. In case of feeding disorders (obesity, anorexia, bulimia) effects of hedonic evaluation of foods and liquids, evaluation of the smell, taste, texture and sight of different foods, as well as the effects of social factors (ideal body shape) are extremely important. In animal experiments learning mechanisms of taste preference and conditioned taste aversion will be examined by means of neurochemical, electrophysiological and behavioral methods. In acute and chronic experiments single neuronal activity will be examined in the limbic system and prefrontal cortex during neophobia, application of different taste solutions and during changes of reward quality of foods. Ingestive and rejective mimetic responses will be examined by means of behavioral methods. In the second part of the project human examinations will be executed in patients with obesity and anorexia nervosa. After completing appropriate neuropsychological tests fMRI examinations will be made.		

Dr. Péczely, László laszlo.peczely@aok.pte.hu	Institute of Physiology	**The role of limbic structures and the innervating mesolimbic dopaminergic system in learning processes**
The aim of our research is to clarify the role of limbic structures and the innervating mesolimbic dopaminergic system in learning processes. The structures investigated in our experiments are the prefrontal cortex, hippocampus, nucleus accumbens, amygdala and the ventral pallidum, as well as the ventral tegmental area providing dopaminergic innervation of these structures. We have multilevel approach: on the one hand, the effects of dopamine receptor activation or inhibition in various brain regions will be investigated, on the other hand, the interaction of mesolimbic dopaminergic system with other neurotransmitter systems, as well as the interaction among the different brain regions will be studied. In our experiments, combining electrophysiological and neuropharmacological techniques in anaesthetised, as well as in awake freely moving rats, the effects of various neuropharmacons, primarily dopamine agonists and antagonists are investigated in the aforementioned brain areas, applying various learning-behavioural paradigms. These latter include the Morris		

water maze test used to examine spatial learning, the various avoidance paradigms to test punishment learning and the place preference paradigm, which is applied to investigate the potential rewarding or punishing effect of the administered drugs, etc. This study will be accomplished with male Wistar rats, the cannulae and the electrodes will be implanted to the target area by means of the stereotaxic technique. In this research program, the adequate combination and mathematical analysis of behavioural and electrophysiological data are in the focus of our attention allowing deeper interpretation of the experimental results. Findings of these experiments may contribute to the better understanding of the exact role of D2 dopamine receptor antagonists used in antipsychotic medication, therefore, the results may have therapeutical relevance.

Dr. Varga, Csaba csaba.varga@aok.pte.hu	Institute of Physiology	**The electrophysiological and morphological examination of neuronal networks in the entorhinal cortex**
The temporal lobe of the cortex plays a critical role both in memory formation and spatial navigation. Disfunction of this brain area can cause debilitating illnesses (epilepsy, Alzheimer-disease) which are accompanied by severe cognitive deficits. Multiple level of information from other brain areas is being processed within the so-called “entorhino-hippocampal loop” in the temporal cortex during formation and consolidation of memory traces. Growing body of studies investigated the circuitry within the hippocampus, meanwhile our knowledge about the entorhinal cortical microcircuits are limited mostly due to technical limitations. Current models of microcircuit functions in the entorhinal cortex are largely based on knowledge gained in other cortical areas, however, the cytoarchitecture and firing properties of the neurons in entorhinal cortex predict unique information processing motifs in this brain area. Recently, we have shown the specific division of labor between inhibitory circuits (Varga et al. 2010 Nature Neurosci) which largely contributes to the salient features of entorhinal cortical microcircuits. In our laboratory, we interrogate the effect of several inhibitory systems on the computational power of the entorhinal cortex. We use in vivo electrophysiology, optogenetics, immunohistochemistry, light and electron microscopy in order to understand the normal and diseased activities within the entorhinal cortex.		

A-141/1993 Molecular pathogenesis of bacterial infections Program leader: Dr. Kerényi, Mónika

Dr. Kerényi, Mónika kerenyi.monika@pte.hu	Department of Medical Microbiology and Immunology	**Investigation of nosocomial infection**
Patients treated on intensive care units frequently suffer from nosocomial infections. It is known that both the environment and staff are also responsible for the colonisation of hospitalised patients. It may be difficult, especially in the case of multidrug resistant bacteria whether they only colonise or infect the patient. Our aim is to study which host and microbial properties contribute to bacterial colonisation and how can the multidrug resistant strains survive in hospitals for months or years. We will complete surveillances to get more knowledge. The isolated strains will be examined by molecular microbiological methods. We will also study the role of bacterial translocation in the development of postoperative infections.		

Dr. Reuter, Gábor reuter.gabor@pte.hu	Department of Medical Microbiology and Immunology	**Detection and characterization of novel, non-enveloped viruses with positive, single-stranded RNA genome**
Our knowledge about viruses is far from complete and, nowadays, it is fundamentally changing. However, the characteristic features of the genetic materials of viruses – as the fingerprint – help us for identification and classification. The aim of the study is identification and characterization of previously unknown		

non-enveloped viruses with positive, single-stranded RNA genome in different host species including humans. Using methods designed previously in our Laboratory we will identify ("take the hook") and than we will completely characterize the whole genome of the novel viruses in promising samples. In addition, the aims of the study are to determine the host species spectrum, the etiological and clinical importance, pathogenesis and the zoonotic impact of the novel viruses, too. For the research we will use classical virological as well as modern up-to-date viral metagenomic methods in close contact with leading international experts and world-class laboratories in virology.

Dr. Tigyi, Zoltán tigyi.zoltan@pte.hu	Department of Medical Microbiology and Immunology	**Characterisation of virulence factors of Klebsiella pneumoniae isolated from different clinical, commensal and environmental samples**
Which virulence factor-patterns characteristic for the different clinical (i.e. urine, blood, wound, respiratory) tract and non-clinical (i.e. commensal and sewage) isolate types. The isolates will be tested for proven and putative virulence factors as follows: iron uptake systems (siderophors), fimbrial and non-fimbrial adhesins, biofilm production, serum resistance, plasmid profile analysis, invasion adhesion to eukaryotic cells, connective tissue matrix binding capacity. Putative virulence genes: allS, (allantoin syntesis), kfuB (klebsiella feri uptake system), rmpA (regulator of mucoid phenotype),pks, (Polyketid syntas colibaktin) etc. Applied strain typing methods: random amplified polymorphic DNA (RAPD-PCR), Enterobacterial Repetitive Intergenic Consensus Sequnce (ERIC- PCR), Pulsed Field Gel Electrophoreses (PFGE). Further typing of selected strains on the basis of phylogenetic tree of PFGE by help of Multi Locus Sequence Typing (MLST) to reveal further connections among the clones or clusters.		

B-134/1993 Neuroendocrinology and neurohistology Program leader: Dr. Csernus, Valér

Dr. Csernus, Valér valer.csernus@aok.pte.hu	Department of Anatomy	**Circadian rhythmic biological functions and their cellular mechanisms**
Studies on the rhythmic biological processes and their practical utilization in the bio-medical field are a timely and relevant topic of the biological research. Among the various rhythmic biological processes of variable period length especially the one-day-long (circadian) rhythms are studied due to their profound impact on our everyday life. The goal of the course is: to introduce you to the rhythmic, first of all circadian biological processes describing their theoretical background, their cellular mechanism, as well as their practical utilization in the biological research and medical practice. The presentation of the features of the circadian biological rhythms will be based primarily on the experimental work carried out in our institute. Our experiments targeting the intracellular mechanism and the synchronizing processes of the circadian rhythmic events are carried out first of all on explanted avian pineal glands model. The pineal gland of the birds lives well also in vitro for over a week, and contains a fully functioning biological clock, which can be influenced, synchronized, also in vitro, by changing a number of physical (light, temperature, magnetic field) and biochemical (norepinephrine, VIP, etc.) environmental parameters. By extracellular analysis of melatonin, the hormone, produced by that endocrine gland, one can easily determine the momentary phase of the pineal biological oscillator without disturbing the life of the cells. Because of these, the explanted avian pineal is an excellent model for studies on the mechanism of the biological rhythms. Our experiments are carried out with a combination of various modern, state-of-the-art methods, such as in vitro bioassay (superfusion), nucleic acid (classic "molecular biology") techniques (PCR, RT-PCR, blotting, gen silencing), histological methods (immunohistochemistry at light- and electron-microscopic level, in situ hybridization), microsurgery, behavior analysis and hormone determinations. To study the ontogeny of the biological rhythms, experiments on embryos are also carried out. In collaborations with clinicians, our studies are also supplemented with human observation, and examination of human tissues.		

Dr. Gaszner, Balázs balazs.b.gaszner@aok.pte.hu	Department of Anatomy	**Development and validation of new animal models for mood disorders using functional-morphological and behavioral tools**
Depression is the most common chronic cause of disability in our community. The neurobiological background of the condition is not well understood. For instance, medication strategies targeting the monoaminergic systems seem to be ineffective in many cases, moreover, in a high proportion of patients the symptoms return. Hence, there is a clear need for new therapeutical strategies based on reliable animal models. Until now there is no equivocally accepted rodent model for mood disorders. The first aim of this program is to set up and validate the three hit theory (genetic, epigenetic, and environmental factors) by de Kloet and Mill in a mouse model. A genetically modified in-house bred mouse strain mutant for the pituitary adenylate-cyclase activating polypeptide shows depression-like behavior. Young offspring of this strain is exposed to maternal deprivation inducing epigenetic changes, and later, adult mice are subjected to stress. Using immunohistological tools we focus on the corticotropin releasing factor, urocortin1 and serotonin systems. Besides these, behavioral test are performed to assess depression and anxiety levels, moreover, the stress hormone titers are also determined. Our second aim is to set up the rat model for the novel match-mismatch hypothesis by Schmidt and co-workers. The essence of this hypothesis is, that stress systems adapted to the environment perceived in young age may fail to cope with altered environmental circumstances even if the subjective change seems to be beneficial, or harmful (mismatch), precipitating the symptoms of mood disorders. In contrast, subjects spending their whole lifespan in ideal or in very suboptimal environment do not develop the symptoms (match), because they successfully adapt to the environmental requirements by the plasticity of the neuroendocrine systems. The above listed technical approaches are available to assess the model's validity in the rat.		

Dr. Reglődi Dóra dora.reglodi@aok.pte.hu	Department of Anatomy	**Neuroprotective and general cytoprotective effects of pituitary adenylate cyclase activating polypeptide (PACAP)**
Soon after the discovery of PACAP in 1989, it was found that PACAP has neuroprotective effects. Our research group has shown these effects in animal models of several diseases of the nervous system, such as Parkinson`s disease, Huntington chorea, stroke, excitotoxic neuronal lesions and retinal degeneration. We have later described that these effects are not limited to nerve cells, but can be shown in various peripheral tissues and cells. Among others, PACAP has protective effects against oxidative stress in endothelial cells and cardiomyocytes. One of our main topics is the investigation of the cytoprotective mechanism. We are investigating the antiapoptotic and anti-inflammatory effects, using molecular biological methods. Furthermore, we study the effects of PACAP and its fragments and peptide variants on the apoptotic pathways in neuronal diseases in in vitro and in vivo models. Using peptide analogs and shorter fragments could make the in vivo use of PACAP more feasible. We also study the changes in the expression profile of PACAP and its receptors following nervous system and peripheral lesions.		

Dr. Reglődi Dóra dora.reglodi@aok.pte.hu	Department of Anatomy	**Physiological functions of pituitary adenylate cyclase activating polypeptide (PACAP) in peripheral organs**
PACAP was first isolated from the hypothalamus, however, it was later shown to be distributed not only in the entire brain but also in peripheral organs. High concentrations of PACAP can be found in the urogenital system, in endocrine glands, in the gastrointestinal and respiratory systems. PACAP plays regulatory roles in reproductive functions, influences gastrointestinal motility and secretion and peripheral inflammatory processes. A lot of biological effects are still not described, however. We are investigating the roles of PACAP in neurogenic inflammation, pain transmission, secretory processes, kidney physiology, behavioral processes and memory. All these functional studies also involve the use of PACAP deficient (KO) mice, to elucidate the endogenous effects of the		

peptide. We also investigate the occurrence of the peptide in biological samples and fluids, which can pave the path for future diagnostic use. We standardize the measurements of PACAP in human plasma and other fluids, using radioimmunoassay and mass spectrometry. Comparing normal, healthy values and samples obtained from patients will hopefully help us to elaborate a method to use PACAP as a biomarker.

B-372/1996 Immunological and clinical aspects of polisystemic autoimmune conditions — Program leader: Dr. Czirják, László

Dr. Czirják, László czirjak.laszlo@pte.hu	Department of Rheumatology and Immunology	**Clinical, epidemiological and immunological characteristics of the connective tissue diseases and the imflammatory rheumatological diseases**
Our clinical-epidemiological ongoing projects involve several disorders including systemic sclerosis, imflammatory myopathies, systemic lupus erythematosus, Sjögren´s symdrome and psoriatic arthritis. Our main field of interest is the assessment of disease activity, organ damage, quality of life and outcome. We develope and validate new instruments for the investigation of these diseases described above. Our further aim is to look for new biomarkers that can be useful as prognostic markers in these particular disorders.		

Dr. Komócsi, András komocsi.andras@pte.hu	Department of Rheumatology and Immunology	**Cardiovascular involvement in autoimmune disorders**
Autoimmune disorders frequently lead to dysfunction of cardiovascular system, and early atherosclerosis. These have important impact on the prognosis. This excess in mortality is rarely can be explained by conventional risk factors. In several cases even treatment of the autoimmune mechanisms may have adverse impact on the cardiovascular system. Clarification of relations may provide important information to better prognosis assessment, early screening of high risk cases and better treatment algorithms. Diagnostic modalities already available at the Heart Centre (tissue Doppler imaging, vascular ultrasound, arterial stiffness measurement, Holter ECG system, and complete invasive haemodynamic assessment) together with cardiac MR imaging provide opportunities the use of contemporary research methods. Cooperation with the Rheumatology and Immunology Clinic helps the interdisciplinary approach. So far several publications characterizing the cardiopulmonary in systemic sclerosis have been published based on this cooperation.		

Dr. Komócsi, András komocsi.andras@pte.hu	Department of Rheumatology and Immunology	**Novel targets of medical treatment in pulmonary hypertension**
Pulmonary arterial hypertension (PAH) is a severe and currently incurable condition. The exact mechanisms leading to the pulmonary vasculature remodelling and the consequent right ventricular overload and insufficiency are still unclear. Intensive research for potential targets in the pathological mechanisms during the last decade resulted in a break-through of therapeutic modalities. However, in PAH cases even if the patient has received extensive combination therapies, disease may still progress. Altogether there is an unmet need for effective treatment interfering with the progression of the disease. Our aim is to investigate different rat models of PAH in order to explore the underlying cellular and molecular pathways and to evaluate the effects of existing and novel therapeutic approaches.		

B-372/1996 Behavioural sciences Program leader: Dr. Kállai, János

Dr. Csathó, Árpád arpad.csatho@aok.pte.hu	Department of Behavioural Sciences	**Effect of fatigue on cognitive functions**
Fatigue is a very common everyday phenomenon and a frequent symptom of a large number of medical conditions. Thus, research on fatigue in general might have substantial contribution to the understanding of basic brain functions and to the analysis of the causes of their dysfunctions. The aim of the proposed PhD study is to examine how cognitive functions in different sensory modalities are sensitive to fatigue. Study will strongly rely on experimental methodologies, on analyses of psychophysical and electrophysiological data. The series of experiments are mainly planned to test the fatigability of healthy individuals. In addition, however, an important part of the project is to investigate the underlying mechanisms of the experience with unusual or chronic fatigue in different groups of patients (e.g. in a group of patients with cardiovascular diseases). Disease related fatigue has a strong deteriorating effect on patients' everyday functionality. Therefore, in the proposed project we are also interested in the question of how the fatigue related these everyday functionality problems are modulated by the fatigability of specific cognitive processes.		

Dr. Csathó, Árpád arpad.csatho@aok.pte.hu	Department of Behavioural Sciences	**The cognitive modulation of pain perception**
Neural mechanism controls pain perception on the way that it ensures the immediate and reliable detection of pain stimuli, but also leaves the possibilities opened for the modulatory effects of many psychological mechanisms. Generally, the PhD project is proposed to examine the cognitive modulation of pain perception by using psychophysical and electrophysiological methodologies. The main aim of the project is to investigate pain perception as a function of time. More specifically, we are interested in the changes in the adaptation to repeated pain stimulation (e.g. pain habituation, and pain sensitization). We are looking for answers for questions like how pain adaptation is effected by earlier pain related experiences or by the individuals' cognitive (e.g. attentional) characteristics.		

Dr. Kállai, János janos.kallai@aok.pte.hu	Department of Behavioural Sciences	**Visual and proprioceptive disorders in healthy persons, neurological and psychiatric patients with body image and body schema dissociation**
The body image and body schema are the most two significant components of the human body, which in the case of biochemical or physical insults or psychiatric illness vulnerable to be dissociated. The human body build on a hierarchically ordered multimodal integration involving haptic, visual and proprioceptive stimuli. The place of the given modality in this hierarchy modifiable by experimentally generated task. The nature of these dissociation may be investigated psychological questionnaires, visuomotor task technics and fMRI method.		

Dr. Kállai, János janos.kallai@aok.pte.hu	Department of Behavioural Sciences	**Psychosocial care and treatment in children with chronic illness**
Children with chronic diseases (epilepsy, oncological, diabetes) depending on their age show different reaction to their illness and the related everyday life limitations. The coping strategy applied by their plays a significant role in the recovery. The family members have an active role both the weight of illness and the treatment. The security giving potential of the family, and its psychological condition essential in the efficient treatment. This psychological healing potential is investigated in frame of this research topic.		