

Clinical Medical Sciences D94
The Leader of the Doctoral School: Dr. Kovács, L. Gábor

A - 319 Nephrology

Program leader: Dr. Wittmann, István

Dr. Wittmann, István istvan.wittmann@aok.pte.hu	2 nd Department of Medicine and Nephrological Center	Accumulation of hydroxyl free radical products ortho- and meta-tyrosine is the cause of chronic hormone resistance
As described in our patent 'Hormone resistance', it has been discovered that accumulation of hydroxyl free radical products takes place in the blood vessel wall exposed to oxidative stress. These results are planned to be extended: we plan to investigate the insulin- and erythropoietin resistance developed in fat cells and the acetyl-choline resistance developed in the vessels due to the accumulation of ortho- and meta-tyrosine. We further plan to study the accumulation of abnormal tyrosine isoforms and their effects in renal failure.		

Dr. Wittmann, István istvan.wittmann@aok.pte.hu	2 nd Department of Medicine and Nephrological Center	The effect of oxidative stress on the efficacy of insulin and erythropoietin
We plan the investigation of following hypotheses: 1. Phosphorylation of eNOS changes upon cigarette smoke in 3T3-L1 adipocytes. Western blot studies. 2. Examination of phosphorylation of Akt using Western blot in 3T3-L1 adipocytes due to oxidative stress. 3. Examination of phosphorylation of Erk in 3T3-L1 adipocytes due to oxidative stress using Western blot. 4. To study the effect of antioxidant resveratrol on the signaling pathways of insulin and erythropoietin using Western blot. 5. To study the connection between carbohydrate metabolism and oxidative stress using continuous interstitial glucose monitoring (CGMS) and measurement of oxidative stress. 6. Measurement of hydrogen-peroxide in vivo with a sensor in development.		

A-146/1993

Significance of molecular pathological and laboratory studies in medical diagnostics and therapy

Program leader: Dr. Miseta, Attila

Dr. Czéh, Boldizsár czeh.boldizsar@pte.hu	Department of Laboratory Medicine	Investigating potential biomarkers for neuropsychiatric disorders using novel diagnostic tools
Description: Neuropsychiatric disorders are common and often chronic illnesses imposing severe social and economic burden on our civilized societies. A further complicating issue is that often there are no valid biomarkers that could help us to make the proper diagnosis and to monitor the progression of the disease and the therapeutic response. However, it is important to search for novel, potential biomarkers and this is a field of intense clinical research. The applicant would join to a team of researches doing such clinical research and by that would also get familiar with the current diagnostic tools.		

Dr. Faust, Zsuzsanna Dr. Nagy, Tamás faust.zsuzsanna@pte.hu tamasnagy01@gmail.com	Department of Laboratory Medicine	Investigation of O-GlcNAcylation in packed red blood cells (RBC), and its role in storage-associated RBC deterioration
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O-GlcNAcylation (O-GlcNAc) is a reversible, posttranslational modification of proteins, in which a single N-acetyl-glucosamine is attached to serine and/or threonine residues of proteins. It is known that high glucose intake increases the ratio of O-GlcNAc-associated proteins. The involvement of O-GlcNAcylation is recognized in many physiological and pathological processes, most notably in diabetes. In RBC concentrates the relative high glucose concentration of the additive solution provides energy source for the erythrocytes during storage, up to 35 days. A series of biochemical and biomechanical changes might occur in red blood cells during this time. These changes reduce the half-life and function of the red blood cells once transfused to patients. We plan to assess the effect of high glucose concentration of the additive solution on O-GlcNAcylation and its relationship with RBC damage and functionality.

Dr. Kőszegi, Tamás koszegi.tamas@pte.hu	Department of Laboratory Medicine	Analysis of mode of action of ochratoxin A in cultured cells
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Ochratoxin A (OTA) is a widely known and worldwide occurring mycotoxin playing an important role in the development of the so called Endemic Balkan Nephropathy. The major target of OTA is the kidneys especially the tubular cells. In spite of the numerous data found in the literature the mode of action of OTA is still not understood in every detail and unfortunately other organs than the kidneys (e.g. the liver) might also be involved. Most probably the major actions of OTA comprise genotoxicity, inhibition of protein synthesis, induction of oxidative damage finally resulting in apoptotic and necrotic processes in the target cells. The aim of the planned research is to analyze the mode of action of OTA toxicity at the molecular level using in vitro tissue culture models. We plan to develop new cytotoxicity assays and to follow the changes in the transcription rate of intracellular proteins. The morphological changes of the cytoskeleton will be also studied by fluorescence microscopy (actin-phalloidin). It is of utmost importance to get new data on OTA-cell interactions by fluorescence spectroscopy and flow cytometry. A better understanding of the mode of action of OTA toxicity may be a good basis for finding and testing of cytoprotective molecules. In this context we plan to study naturally occurring molecules primarily of plant origin (antioxidants, competitors). In our investigation we plan to use anchorage dependent cells and also cells grown in suspension. The toxin-cell interaction will also be studied in 3 dimensional tissue cultures.

Dr. Kőszegi, Tamás koszegi.tamas@pte.hu	Department of Laboratory Medicine	Detection and characterization of circulating tumor cells in malignant
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The most frequent cause of mortality in malignant diseases is metastasis formation by hematogenic or lymphogenic routes. A small part of tumor cells that somehow get into the peripheral circulation are similar to the normal stem cells therefore they are called cancer stem cells (CSCs). CSCs may be isolated or cultured from peripheral blood and they form characteristic spheroid colonies. To our present knowledge, CSCs are responsible for tumor invasivity, metastasis formation and late relapse. During the planned research, blood samples of patients suffering from epithelial malignancies will be cultured under special circumstances which enable CSCs to outgrow normal cells and to form colonies. We try to find correlation between the number of colonies and the grade of the tumors. Viability of the cultured CSCs will be studied by luminescent methods and cell surface markers analyzed by flow cytometry. Growth

properties of the cells will be followed by 3D cell culturing technique, co-culturing them with fibroblasts. Diffusion characteristics in the 3D cultures will be examined by fluorescent probes and by application of fluorescent doxorubicin, uptake and cytotoxicity of the drug will be measured. We plan to characterize the diagnostic potential of CSCs and also to assess the predictive value of the method in regard of metastasis formation.

Dr. Kőszegi, Tamás Dr. Bártai, István koszegi.tamas@pte.hu ibatai@freemail.hu	Department of Laboratory Medicine, Department of Anaesthesiology and Intensive Therapy	Effects of preconditioning in surgical treatments
<p>Preconditioning means when the human body exerts a defense mechanism due to exposure of short-term ischemia or to low dose of chemical compounds in order to avoid further tissue injury. Early preconditioning results in the response of the body within a few minutes and it lasts for 3 hours. Effects of late preconditioning begin 8 hours later after exposure to provoking agents reaching the maximum effect at 24 h and the total duration is at about 96 h. Protective effect of ischemia is realized not only in local processes but it has a beneficial effect in distant organs that will be exposed later to ischemic events. This is called remote ischaemic preconditioning (RIP). Besides a large body of evidences (in vitro and animal models) human studies also support the protective effects of chemical preconditioning in heart and liver surgery. After pursuing in vitro and animal models preliminary studies in humans also support that anesthetic preconditioning reduces postoperative stress response. In the proposed project we plan to study the effects of early and late preconditioning in the surgical groups and also those of distant ischemic preconditioning groups by measuring oxidative stress markers and total antioxidant capacity with luminescent techniques. The obtained results will be compared to classical lab data that might have influence on antioxidant parameters and also with classical stress markers.</p>		

Dr. Kőszegi, Tamás Dr. Mühl, Diána koszegi.tamas@pte.hu diana.muhl@aok.pte.hu	Department of Laboratory Medicine, Department of Anaesthesiology and Intensive Therapy	Different approaches for studying inflammatory mediators in septic patients
<p>Sepsis is still one of the leading causes of mortality at intensive care units. To date 178 biochemical markers have been identified for the diagnosis and follow up of septic patients. This group consists of many biologically active molecules including pro-inflammatory mediators and classic acute phase proteins. Interestingly, besides the laboratory analysis of blood the investigation of urine and other body fluids has been of minor importance. In our earlier studies we demonstrated that orosomucoid (or otherwise called acidic alpha-1-glycoprotein, AGP) known as an acute phase protein could be detected even in healthy individuals by the method developed in our laboratory. On the other hand, we also showed that AGP in the urine of septic patients was present at extremely high concentrations. Therefore, AGP might be considered as a potential sepsis marker in urine. The main goal of the proposed research is to find any types of relationship between urinary AGP levels and changes of serum inflammatory mediator concentrations based on daily monitoring of the patients. A further aim is to decide if urinary AGP determination could possess a predictive value in the studied patient group. As a methodological development we plan to work out a quantitative measurement test of urinary AGP suitable for routine automated analysis.</p>		

Dr. Kőszegi, Tamás Dr. Papp, Nóra koszegi.tamas@pte.hu nora4595@gamma.ttk.pte.hu	Department of Laboratory Medicine Department of Pharmacognosy	Analysis of cytoprotective effects of ethnopharmaco-botanically important medicinal plants originating from Transylvania using in vitro tissue culture models
<p>Regions in Transylvania without permanently available medical and pharmaceutical services are still rich sources of many new or already known medicinal plant taxons with potentially new medical indications. Our research focuses on the antioxidant or other cytoprotective effects of the active compounds isolated from the recorded plant species. The task of the Ph.D. candidate is to analyze the biological activity of selected taxons and their extracts obtained from the fieldwork done in Transylvanian regions in tissue culture models. Medicinal plant derived carotenoids, flavonoids, polyphenols and many other molecules – primarily antioxidants – exert a significant effect in prevention of chronic degenerative diseases (malignancies, autoimmune processes, cardiovascular diseases, etc). In spite of the large body of evidences obtained from epidemiological studies, from in vitro models and animal experiments the mechanism of cytoprotection is not completely understood. It may be postulated – and experimentally it is already partially verified – that the major cytoprotective factor lies in the antioxidant feature of the studied molecules. On the other hand, the interpretation of the data is often difficult because most authors use only single, purified factors while most probably the favorable effects depend on the synergistic action of a combination of many molecules. The proposed research focuses partly on the already known antioxidants and partly tries to characterize the combined effects of a mixture of protective factors. An in vitro tissue culture model will be established using adherent cell types (e.g. fibroblast, HepG-2, MDCK, etc) and also cells in suspension (e.g. Jurkat, K-562). Cytoprotection will be studied after induction of oxidative stress (e.g. by addition of menadione) by viability testing (ATP/protein ratio), chemiluminescence and fluorescence spectroscopic methods where cells are labeled with oxidant-sensitive dyes. The fluorescence technique will be adapted to flow cytometric analysis. Another part of the experiments is monitoring of the changes in the protein pattern of the treated cells using SDS-PAGE and chemiluminescent Western blotting.</p>		
Dr. Miseta, Attila attila.miseta@aok.pte.hu	Department of Laboratory Medicine	The role of phosphoglucomutase in the therapeutic action of lithium
<p>The bipolar, (BP) or maniac depressive condition is second in occurrence among psychotic illnesses after the unipolar depression. It is particularly frequent in our country, but its occurrence is in excess of 1% in most other countries. According to our discovery the decreased activity of phosphoglucomutase (PGM) results in significantly elevated (6-9-fold) calcium storage in the presence of galactose in <i>S. cerevisiae</i>. The modification of calcium homeostasis and signaling affects the post-translational modifications of proteins in mammalian cells too. The mechanism may play significant role in the therapeutic action of lithium, and may present a clue to the phenomenon why some of the patients are lithium responders while others are non-responders.</p>		
Dr. Mühl, Diána diana.muhl@aok.pte.hu	Department of Anaesthesiology and Intensive Therapy	Haemostatic management of vascular surgical procedures associated with high bleeding risk
<p>Aim: Comparative study on efficacy of haemostatic therapy guided either by standard laboratory parameters or point-of-care testing in patients undergoing vascular surgical procedures. The bleeding risk associated with surgical procedures is increased by the fact that the majority of patients affected are on a single or in some cases on double antiplatelet therapy, and/or receive prolonged anticoagulation treatment. Discontinuation of the treatments is expensive and, in case of indication for acute surgery, may not always be carried out. In the European guidelines, the application of transfusion algorithms and protocols incorporating predefined intervention triggers to guide haemostatic intervention during preoperative bleeding are recommended, as well as viscoelastic point-</p>		

of-care tests (POCT). The first step for optimal restoration of the function of haemostasis system has to be the regulation of the concentration of fibrinogen in the blood plasma, using either conventional laboratory tests or point-of-care testi. It is essential that besides erythrocyte (RBC) concentrate fresh frozen plasma (FFP) has also to be given (RBC:FFP=2:1) in a timely manner, in a fixed proportion. In case of excessive blood loss and transfusion, administration of thrombocyte concentrate is also necessary.

Dr. Tornóczy, Tamás tornoczki.tamas@pte.hu	Department of Pathology	The histopathological lesions of minor salivary glands in systemic autoimmune diseases
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It is not widely known, that the minor salivary glands show different, variable degree of histopathological changes in systemic autoimmune diseases. We have hundreds of archived samples of many years back to study. We plan to examine inflammation, fibrosis, acinic atrophy and fatty infiltration using standard HE, specific histochemical and immunohistochemical stainings completed with modern image analysis methods to have the chance of quantifying some of them. The final aim is to examine not only the quantity, but also the quality of the inflammation and above all the fibrosis. All of the changes will be evaluated in relation to the clinical data and diagnosis. We also plan to study the inflammatory changes of the major salivary glands with special interest to the IgG4-related cases.

B-145/1993

Molecular pathomorphology

Program leader: Dr. Pajor, László

Dr. Alpár, Donát alpar.donat@med.semmelweis-univ.hu	Department of Pathology	Genetic abnormalities in plasma cell myeloma
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Myeloma is a genetically and clinically heterogeneous, incurable malignancy occurring through the clonal proliferation of terminally differentiated B-cells. The various disease-associated, recurrent genetic aberrations and their combinations allow the determination of biologically and clinically relevant subgroups. In this study, we aim to investigate (i) the evolution of biologically and/or prognostically important cytogenetic aberrations in plasma cell myeloma; (ii) the applicability of various cytogenetic and molecular genetic techniques in the pathological diagnostics of myeloma, and (iii) the correlation between clinical features and genetic alterations detectable using novel methods with potential utilization in diagnostics.

Dr. Lákós, Pál jakso.pal@pte.hu	Department of Pathology	Analysis of CD20 positive T cells in hematological malignancies
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Introduction. CD20 positive T cells represent 3% of the whole lymphocyte population in normal blood and bone marrow. These cells have been described almost twenty years ago. The function of these cells is still unknown. According to early studies this population carries the most T cell surface markers but do not express any B cell marker except the CD20. They have mostly CD8+ cytotoxic phenotype in contrast to CD20 negative T cells in which the ratio of CD4+ T helper cells is much higher. No other specific phenotype is described. According to our results these cells may accumulate in malignancies like multiple myeloma and myelodysplasia. This observation raises the possibility that these cells may play a role in the antitumor immune response however very few data are published regarding this theory. Aim of the study. To study the function of CD20 positive cells in samples of patients with malignancies. 1. Multicolor flow cytometric analysis of receptors and other molecules which are important in antitumor immune response (e.g. CD314 (NKG2D), CD28,

CD279 (PD-1 receptor), perforin). 2. Isolation of CD20+ T cells for functional studies (e.g. apoptosis induction, T cell activation). 3. Investigation of the ratio of CD20+ T cells in diagnostic and treated patient samples. 4. Analysis of the possible correlations with prognosis.

Dr. Pajor, László pajor.laszlo@pte.hu	Department of Pathology	Investigation of the cytogenetics of hyperdiploid childhood acute lymphoblastic leukemia
Acute lymphoblastic leukemia (ALL) is the most frequent malignancy in childhood. The optimal therapeutical decision-making devoid of under- or overtreatments relies on the international classification of the disease and is based on the presence or absence of various specific, non-random genetic aberrations. The two most common subtypes are defined by the ETV6/RUNX1 translocation and hyperdiploidy with 51-66 modal chromosome number making up altogether appr. 55% of all pediatric ALL (pALL) and appr. 80% of patients between 2 and 7 years of age. The goal of this study is the identification of the 4 or 5 chromosomal abnormalities most important for the diagnosis and treatment of hyperdiploid all arising presumably in utero. The fluorescence in situ hybridization performed on non-dividing, interphase cells (i-FISH) and the automated evaluation of i-FISH signals are the most efficient approaches to identify these chromosomal aberrations and clonal evolution processes. The investigation of large number of samples archived in the Department of Pathology forms the basis of this study.		

**B-2/2004 The clinical and molecular research
of the new mechanisms, diagnostics
and therapy of cardiovascular diseases**

Program leader: Dr. Szokodi, István

Dr. Faludi, Réka gaszner.balazs@pte.hu	Heart Institute	Modern echocardiographic techniques and biomarkers in the diagnosis of heart failure
In addition to the classical, widely used echocardiographic methods more new, special techniques (tissue Doppler imaging, strain, strain rate) have been developed. Systolic or diastolic functions of both the left and right ventricles as well as the atria are investigated by applying these new techniques in cardiomyopathies and in some special diseases complicated with heart failure (systemic sclerosis, COPD, etc.). In addition to the echocardiographic methods, serum levels of some biomarkers (e.g. NT-proBNP, galectin-3, VEGF) as well as estimation of the functional capacity (6 minute walk test, cardiopulmonary exercise test) are also used.		

Dr. Gasz, Balázs balazs.gasz@gmail.com	Heart Institute	Potential genetic background of ischaemia-reperfusion injury of myocardium in cardiac surgery
Cardiac surgery is associated with activation of harmful events resulting in increased risk of postoperative complications. Aortic cross clamping causes myocardial ischaemia and reperfusion with cellular mechanisms of oxidative injury, deterioration of antioxidant batteries. Furthermore, cardiopulmonary bypass and surgical stress are known to trigger whole body inflammatory response which may lead to activation of leukocytes and endothelial initiating. There are inter-individual differences between patients regarding susceptibility of damaging effects during and following cardiac surgery. Individual differences of antioxidant enzymes activity may exert influence on systemic inflammatory response and myocardial damage upon ischaemia-reperfusion.		

These differences can also control how the mechanisms at cellular level can be manifested clinically. Present PhD program is aimed to investigate the genetic polymorphisms of given antioxidant enzymes and proteins involved in endogen adaptation. Polymorphisms of these proteins are suggested to influence the severity of systemic inflammatory response and myocardial damage.

Dr. Gaszner, Balázs gaszner.balazs@pte.hu	Heart Institute	Non-invasive measurement of arterial stiffness parameters in assessment of cardiovascular risk
<p>Large amount of evidence is now available on the crucial role of preclinical organ damage in determining the cardiovascular risk of individuals. Arterial stiffness parameters are commonly used for this purpose, to identify structural and functional changes of the arteries in the development of atherosclerotic disease. Recent European guidelines (ESC/ESH) recommended the assessment of arterial stiffness, as an evidence of target organ damage. However, measuring arterial stiffness parameters is currently not sufficiently widespread, and thus the information it provides remains desirable but difficult to obtain. According to the same guidelines “it might be more widely recommended if its availability were greater”. Novel developments offer different non-invasive, user friendly examination methods, which could solve this controversy. To overcome these limitations we compare two recently validated, time-saving, low expense systems: the carotid Doppler echo-tracking system (Aloka SSD-5500) and oscillometric TensioClinic Arteriograph equipment. The aim of our study is to obtain local, regional and systemic arterial functional parameters by means of these non-invasive examination methods. Among the stiffness parameters the aortic Pulse Wave Velocity (PWV), and the wave reflection, measured as Augmentation Index (AIx) are expected to determine. For the assessment of clinical applications the arterial stiffness parameters are specified in healthy volunteers, in patients with either clinical or preclinical organ damage: patients with known ischemic heart disease (IHD) and with type II diabetes mellitus (DM).</p>		

Dr. Hejmel, László hejmel.laszlo@pte.hu	Heart Institute	The measurement technique and possible applications of heart rate variability analysis
<p>Heart rate variability (HRV) analysis is a non-invasive functional study of autonomic nervous system. Rising number of publications during the recent years in this topic reflects its importance in both research and clinical fields. It is considered as an independent prognostic factor in several cardiovascular and other diseases, it also might forecast the occurrence of certain events (e.g.: arrhythmias, fetal hypoxia) earlier than the usual parameters. HRV analysis – together with other physiological parameters – can be applied in wearable monitors assuring continuous surveillance or even telemonitoring of high-risk patients, professional sportsmen or the healthy population. HRV analysis needs special measurement and technical conditions; those are the subject of intensive research nowadays. Potential applications of HRV measurement in basic and clinical sciences are almost unlimited: deeper understanding of cardiovascular control mechanisms, investigating stress actions on the human body, effects of drugs or operations, disease follow-up, predicting arrhythmias. The project covers the possible development of both hardware and software sides as well as methodical improvement of HRV analysis, additionally to its potential applications.</p>		

Dr. Hejmel, László hejmel.laszlo@pte.hu	Heart Institute	Investigation of conduction disturbances by non-invasive His-electrocardiography following valve surgery
<p>One of the most frequent cardiac operations is the valve implantation due to valvular dysfunction. Since the close vicinity of the annulus and the conduction system, approximately 3-12% of operated patient needs permanent pacemaker implantation postoperatively. Signal-averaged technique facilitates the high-resolution surface-ECG registration, and the improved signal-to-noise ratio makes possible capturing ventricular late potentials or His-electrogram. By the invasive His-ECG benign (proximal) and malignant (distal) AV-block can be differentiated, which latter one indicates permanent pacemaker implantation. The aim of present investigation is the analysis of pre- and early postoperative non-invasive electrophysiological examination focused on the conduction</p>		

system, especially the His-potential. The non-invasive electrophysiological parameters and their borderline values will be defined after the follow-up, which expectedly supports the prediction of reversibility of the perioperative conduction disturbance, facilitating the correct indication of permanent pacemaker implantation.

Dr. Hejmel, László hejmel.laszlo@pte.hu	Heart Institute	Cardiovascular actions of natural therapies and the role of the autonomic nervous system
The BEMER (Bio Electro Magnetic Energy Regulation) therapy is a treatment on a special mattress emitting low-energy electromagnetic radiation, which improves the microcirculation of the body by its unique signal shape according to scientific research. At dry carbon-dioxide treatment the patient lies waist-high in a nylon sack, and it increases the tissue-oxygenation due to the induced vasodilation in the lower and upper body parts. The efficacy of both methods has been proved by several studies; however, their mechanism of action is less clear. We investigate the cardiovascular effects mediated by the autonomic nervous system in both naturopathies by heart rate variability analysis in cardiac outpatients.		

Dr. Hejmel, László hejmel.laszlo@pte.hu	Heart Institute	Applied biomedical signal processing
In the last decades there was an enormous change in biological signal processing, thanked to recent developments in microelectronics and computer sciences. The biological system can be assessed from a new aspect through high-resolution simultaneous multichannel data acquisition and computer aided processing. This can be translated in the clinical practice as less invasive, earlier and more accurate diagnosis and more sensitive follow-up. Principally, the topic includes monitoring of cardiovascular and cardiorespiratory system, such as special ECG, photoplethysmography, impedance measurement, flow-metrics, furthermore covers the computerized analysis of their relationship from the methodological, hardware and software level development to the experimental-clinical applications. The student can join to on-going projects or the topic can be adapted to own research area following pre-arrangement.		

Dr. Komócsi, András komocsi.andras@pte.hu	Heart Institute	Immunological and haematological aspects of progression of atherosclerosis and in-stent restenosis
Several immunological mechanisms play crucial role in the evolution of the atherosclerosis involving induction, progression, plaque destabilization, positive and negative remodeling. The percutaneous coronary intervention plays an increasing role in the treatment of coronary heart disease. With development of stent technology and primary success of stent placement this type of intervention became predominant. However, in a considerable proportion of cases the lumen of the stented segment shows restenosis that eventually may lead to occlusion. Pathomechanism of in-stent restenosis is not fully understood, local cytokin response provoking proliferation and immunoreactivity to the metal content may play role. Investigation of these possible mechanisms may have important health care impact.		

Dr. Komócsi, András komocsi.andras@pte.hu	Heart Institute	Exercise induced dynamics changes in pulmonary arterial hypertension
The pulmonary arterial hypertension is a disease with poor prognosis and with no curative treatment available. One important contributor of this bad prognosis that due to uncharacteristic symptoms and the limits of the non-invasive testing the diagnosis is typically established at already advanced disease stage. The aim of the program is to ameliorate the diagnostic algorithms of PAH with investigation of the haemodynamic changes in the pulmonary arterial tree during exercise supplemented right heart catheterization, and characterization of the right ventricular load via echocardiographic testing and investigation of humoral markers.		

Dr. Komócsi, András komocsi.andras@pte.hu	Heart Institute	Investigation of clinical and genetical factors influencing residual platelet reactivity after coronary stent implantation. An individualised antiplatelet strategy
<p>Dual antiplatelet therapy (AT) is essential in preventing recurrent thrombotic events after coronary interventions. However, substantial interindividual differences were described in the degree of residual platelet reactivity (RPR) despite aspirin and clopidogrel administration. High RPR is an independent predictor of death, myocardial infarction and stent thrombosis after PCI; thus, optimized AT in high-risk patients would be of great importance. We aim to establish a diagnostic system involving genetic and clinical parameters that predicts and monitors AT efficacy. With identification and better insight into the underlying mechanisms we aim to set up a tailored AT algorithm for patient with high RPR.</p>		
Dr. Simor, Tamás Dr. Faludi, Réka simor.tamas@pte.hu faludi.reka@pte.hu	Heart Institute	Correlations between CMR-derived and echocardiographic parameters of the atria in different forms of heart failure
<p>The roles of the atria are more complicated than we expected before and far from being a simple passive transport to the chambers. They are responding to pressure and stretch with the secretion of atrial natriuretic peptides (ANP) to counterbalance the sympathetic and renin-angiotensin-aldosterone systems allowing partial restoration of fluid and haemodynamic balance. Enlargement of the atria have been shown to be a reliable predictor of adverse cardiovascular outcomes, such as atrial fibrillation and remodelling. Our understanding of atrial function is rapidly evolving, and data are accumulating to suggest that this is a powerful biomarker for atrial fibrillation and heart failure. There have been huge advances in terms of our ability to characterize and quantitate atrial function using non-invasive imaging. MRI is the gold standard to evaluate the atrial function, but as an advantage to the echocardiography, it is widely used and more easily performed in the clinical practice. There are several methods in echocardiography, such as volumetric measurements which is the closest to the technique of the MRI assessments and the speckle tracking based strain. We have to find out which method of atrial function assessment is essential to its clinical and research applications. Thus we aimed to investigate the correlation between echocardiographic and valid CMR-derived parameters. Understanding the former questions will enable the development of more effective strategies for the treatment and prevention of atrial fibrillation, heart failure, and stroke.</p>		
Dr. Szokodi, István szokodi.istvan@pte.hu	Heart Institute	Regulation of cardiac contractility by protein kinases
<p>Congestive heart failure is a major cause of morbidity and mortality despite recent advances in medical therapy. The most commonly used positive inotropes, β-adrenergic agonists and phosphodiesterase inhibitors, exert their positive inotropic effects by stimulating the cAMP-protein kinase A pathway in the myocardium. These agents provide rapid and dramatic improvements in cardiac performance, producing immediate relief of heart failure symptoms. However, the prolonged use of these agents may lead to serious adverse cardiac effects. We aim to identify novel pathways in the heart that confer protection against stress-induced myocyte apoptosis, while improving contractile function. We will characterize the role of extracellular signal-regulated kinase 1/2 (ERK1/2), p38 mitogen-activated protein kinase (p38-MAPK), c-Jun N-terminal kinase (JNK), glycogen synthase kinase 3β (GSK-3β), and protein kinase C-α (PKCα) in the regulation of cardiac contractility. A signaling pathway that promotes cardiomyocyte survival while improving contractility may offer an attractive approach for treating patients with heart failure.</p>		

Dr. Szokodi, István szokodi.istvan@pte.hu	Heart Institute	Non-coding RNAs in pathological cardiac remodeling
<p>The development of cardiac remodeling is associated with fundamental changes in the molecular programs of the heart including the reactivation of fetal gene programs, deregulation of neurohormonal systems as well as the activation of senescence and various forms of cell death. It has long been considered that these gene programs are primarily under the control of protein-based regulatory systems (i.e. transcription factors and chromatin modifiers). It turned out that ~75% of the human genome is actively transcribed into RNA but only ~2% is translated into proteins. Understanding the functional significance of these non-coding RNA transcripts in versatile cellular processes is the subject of intense investigation. According to the most recent estimates, the human genome encodes for ~2000 different microRNAs and ~56000 long non-coding RNAs. Our main goal is to identify novel cell-type and context-specific interactions between, microRNAs, long non-coding RNAs, and mRNAs in regulating cardiac remodeling using the combination of in silico predictions, in vitro cell culture experiments, and animal models.</p>		

Dr. Szokodi, István szokodi.istvan@pte.hu	Heart Institute	Functional significance of apela in regulating cardiac fibrosis
<p>Recently, non-muscle cells, especially cardiac fibroblasts have emerged as crucial regulators in the process of cardiac remodeling. In the stressed myocardium, growth factors stimulate fibroblast proliferation and fibroblast-to-myofibroblast transition; however, our current knowledge regarding potential antifibrotic mechanisms is very limited. The endogenous peptide apelin and its cognate G protein-coupled apelin receptor are emerging as important regulators of the cardiovascular system. Recently, a short secretory peptide, called apela, was discovered, through mining of long non-coding RNA transcripts, which turned out to be another ligand for apelin receptor. Initially, apela was considered as an exclusively early embryonic signal crucial in cardiac development. Most recently, we reported an initial characterization of apela-apelin receptor signaling in the adult mammalian heart. We showed that apela is expressed in the adult rodent heart, predominantly in the non-cardiomyocyte fraction (i.e. cardiac fibroblasts). Moreover, we reported that the expression of both apela and apelin receptor is induced in failing mouse hearts and correlate with left ventricular ejection fraction. Our main goal is to uncover the functional significance of apela in cardiomyocytes and cardiac fibroblasts. Manipulation of the activity of fibroblasts may offer an attractive approach to effectively treat cardiac fibrosis and improve the outcome of heart failure.</p>		

B-1/2008

Surgery and its border fields

Program leader: Dr. Horváth, Örs Péter

Dr. Battyáni, István udvaracz.veronika@pte.hu	Department of Radiology	The clinical value and critical analysis of non-vascular interventional radiology techniques
<p>Non vascular interventions in radiology are increasingly used in the clinical practice. The potential applications of minimally invasive interventions are increasing. This programme provides critical scientific analysis, and evaluation of these techniques. The main area of the topic involves the critical analysis of personalised selective tumor therapies, thermoablation techniques (RFA, MWA, laser ablation, HIFU, cryoablation), the different types of tissue sampling techniques, clinical comparison of percutaneous chemotherapeutic procedures, and provides a new approach to imaging guided therapeutic interventions. Registration to this scientific topic is possible in the fields of therapeutic interventions used in the treatment of hepatic, biliary, pulmonary, musculoskeletal, pancreatic, and other diseases that affect body cavities.</p>		

Dr. Bártai, István ibatai@gmail.com	Department of Anaesthesia and Intensive Care	Effect of anaesthesia on postoperative infections
Infection is still a feared complication of surgery. It is known that anaesthesia inhibits the immune system but there are other steps how it may contribute to postoperative infection. An important issue in the protective process against invading bacteria is our normal skin and gut flora that may be disturbed by anaesthesia as well. We examine the impact of anaesthesia on normal flora and the effect of medications used in anaesthesia on bacterial growth. We also examine the interaction of medications used in anaesthesia with antibiotics.		
Dr. Bártai, István ibatai@gmail.com	Department of Anaesthesia and Intensive Care	Preconditional effect of anaesthetics and other stressors
The human body may be exposed to ischaemia and other stressors during surgery. Inhalational anaesthetics provide protection against these damages or can reduce the harm. This is called preconditioning. There are differences in the protective effect according to the inhalational agent and the stressor. We will examine the protective effect of inhalational agents in patients scheduled for liver, vessel, eye or lung surgery. We use biochemical markers and postoperative morbidity data to evaluate the possible protective effect.		
Dr. Boronkai, Árpád arpad.boronkai@gmail.com	Department of Oncotherapy	Modern options for the radiotherapy of chest malignancies
Our aim is to examine the efficacy of up to date radiotherapy and chemoradiotherapy practice in case of locally advanced and metastatic chest cancers, particularly in lung cancers. We investigate the advantages of the application of intensity modulated radiotherapy and image guided radiotherapy both in curative and palliative setting, possessing the availability of a linear accelerator with a capacity for high quality treatment. We also perform experiments involving the in vitro and in vivo examination of the poly(ADP-ribose) polimerase /PARP/ enzyme inhibition related radiosensitisation effect in a collaboration with the Department of Biochemistry and Medical Chemistry.		
Dr. Gődény, Mária m.kasler@oncol.hu	Department of Surgery - National Institute of Oncology	New opportunities, MRI biomarkers in the evaluation of head and neck cancer
Magnetic Resonance Imaging (MRI) has developed rapidly during the past few years, which according to the needs of therapy, has opened new perspectives in oncologic head and neck imaging with better realization of the latest technological advances. New therapeutic methods (improvement of radiation therapy and chemotherapy) need better tumor characterization and prognostic information along with the most accurate anatomical information. Multiparametric and multimodal anatomical and functional MR imaging (MM-MRI) using high magnetic field strength (3Tesla) are useful in determining tumour-specific MRI biomarkers and in evaluating the qualitative and quantitative changes in these parameters during therapy to provide assessment of the therapeutic response. Diffusion-weighted MRI (DW-MRI) – provides information at the cellular level about the cell density and the integrity of the plasma membrane. Dynamic contrast-enhanced MRI (DCE-MRI), as a marker of angiogenesis – provides information about vascularisation at the tissue level. Magnetic resonance spectroscopic imaging (MRSI) – provides biochemical analysis at the molecular level.		

Dr. Kásler, Miklós m.kasler@oncol.hu	Department of Surgery - National Institute of Oncology	Extended surgeries of head and neck cancers, and their surgical reconstructions
<p>Head and neck cancer is a locoregionally aggressive disease, therefore its treatment needs effective methods of local therapy. None of the currently known non-surgical treatments could overcome the results of radical surgery. However in cases of chemo- and radiosensitive tumors, results of non-surgical treatments are comparable with results of surgery. <u>Proposed fields of research:</u> Comparison of survival and quality of life of patients treated with radical surgery or postoperative radiotherapy, and patients treated by chemoradiation which is the standard non-surgical treatment modality currently. Assessment of oncological and functional results of flap reconstruction following radical surgery of head and neck cancer. Development of new reconstructive methods, and/or modifications of the known flaps. More extended use of surgical implants. Oncological surgery of the mandible; possibilities of mandibular reconstruction; role of dental rehabilitation</p>		
Dr. Kásler, Miklós m.kasler@oncol.hu	Department of Surgery - National Institute of Oncology	Radiochemotherapy of head and neck cancer
<p>Currently, chemoradiation is the standard non-surgical treatment of locally advanced head and neck squamous cell cancer. In Hungary, traditional treatment of these cancers was radical surgery and postoperative radiotherapy. The introduction of the non-surgical treatment of advanced head and neck cancers delayed approximately a decade compared to Western-Europe and the United States. There is still need for increasing the efficacy of radiotherapy by the use of more effective drugs and alternative fractionation schemes. The increase of the efficacy of chemoradiation is limited by the severe late side effects of radiochemotherapy. <u>Proposed fields of research:</u> Creation of a database of patients treated either by radiochemotherapy or primary non-surgical methods, and assess and compare the efficacy, safety and overall survival of both treatments. Development of new radiation fractionation techniques or combination of radiotherapy with new drugs, and compare them with the standard therapy in prospective clinical studies. Search for new biological markers of chemo- and radiosensitivity, and increased sensitivity of the normal tissues. Development of new methods of radiotherapy in order to decrease the severity of late side effects. Investigations of the effect of radiotherapy on the quality of life of head and neck cancer patients using internationally validated questionnaires.</p>		
Dr. Kásler, Miklós m.kasler@oncol.hu	Department of Surgery - National Institute of Oncology	Laser surgery of head and neck cancer
<p>The role of lasers in surgery has a 30-year tradition in Hungary. They largely contributed to the use and effectiveness of minimally invasive surgery. Development of new types of lasers and photosensitizing agents are under continuous research <u>Proposed fields of research:</u> Interaction of the laser beam and the living tissues, comparison of different types of lasers. Results of the use of lasers in diagnostic surgery of different benign and malignant diseases. History and molecular basis of the use of light in medicine. Results of the use of traditional and newly developed lasers. Experimental in vivo or clinical use of new photosensitizing drugs.</p>		
Dr. Kelemen, Dezső kelemende@gmail.com	Department of Surgery -	Investigation of new perspectives for the early recognition of pancreatic cancer
<p>The aggressive behaviour and dismal prognosis of pancreatic cancer is well-known. However more advantageous survival can be achieved by the early diagnosis. Such supporting screening method would be of especially great importance. Promising researches are going on in the field of micro-RNS</p>		

expression and K-ras gene mutation analysis, which may have pathognomic value. However their clinical relevance and applicability as biomarker are still unsolved. In this setting examination of pancreatic tumor tissue and blood samples would supply useful data. The researches would be performed in collaboration with the Department of Public Health Medicine.

Dr. Kelemen, Dezső kelemende@gmail.com	Department of Surgery	Innovations in pancreatic surgery and their influences for the postoperative results
The morbidity rate following pancreatic resections is still high, 30-40%, and the prognosis of pancreatic cancer is bad, despite of oncological therapy. These stimulate pancreatic surgeons to work out better methods. In the last decade there were several technical innovations in pancreatic surgery, like antegrade reconstruction during Whipple procedure, rutine portal vein resection in order to achieve R0 resction, retrograde pancreatic head dissection, etc. Moreover several new methods were introduced in the field of pancreatodigestive anastomoses to decrease the rate of the most frequent and important surgical complication, namely pancreatic fistula. The literary background, then the own results of the surgical department should be surveyed and analysed. Further purpose is to investigate their influence for the postoperative results (morbidity, mortality, reoperation, survival, quality of life, etc.).		

Dr. Ladányi, Andrea ladanyi@oncol.hu	Department of Surgery - National Institute of Oncology	Role of tumor-infiltrating immune cells in influencing tumor progression and the effectiveness of anticancer treatment
Recent studies have demonstrated that, besides providing valuable prognostic information concerning tumor progression and the outcome of the disease, investigations on immune cell infiltration in tumors may also contribute to predicting the efficiency of certain cancer treatment modalities. Based on these discoveries, we propose investigation of immune markers in oncologic patients treated with chemo-, radio- or targeted therapy as well as immunotherapy, and assess their applicability in predicting treatment response and the outcome of the disease. We plan to apply immunohistochemical staining for the detection of immune cell types that were proved of prognostic importance in previous studies, including dendritic cell and T-cell subtypes and B lymphocytes. Associations of the infiltrating cell densities of each cell types in pre- and posttreatment samples, as well as of their changes during therapy (when applicable) with response to treatment and survival would be evaluated, primarily in patients with melanoma, head and neck cancer and rectal cancer.		

Dr. Menyhei, Gábor menyhei.gabor@pte.hu	Department of Vascular Surgery	Computational fluid dynamics for the diagnosis of vascular diseases and follow ups of open and endovascular interventions
Advances in imaging technologies (CT, MRI, DSA) enable creating and analyzing three dimension images. The encouraging method of computational fluid dynamics (CFD) creates a possibility to simulate flow dynamics in the vessels. CFD can provide information about the flow dynamics of aneurysms, the nature of endoleak and about the causes of restenosis following carotid and peripheral vascular procedures. Information about the flow dynamics can be an important tool for making indications of open and endovascular procedures and may assist in the decision making for further therapeutic tasks.		

Dr. Papp, András papp.andras@pte.hu	Department of Surgery	Evaluation of prognostic factors in the surgical treatment of colorectal liver metastases
Colorectal cancer (CRC) are on the second place in cancer related death in Hungary. It means about 8500 new cases annually, with an estimated 5000 annual death. About 50 % of the CRC patients have liver metastases during their life and mostly it is the cause of death. Also well known that only 25 % of colorectal liver metastases (CRLM) are primary resectable, and about 20% would be resectable with the help of oncological treatment. Our aim is to analyse the previously clinical data to clear what kind of prognostic factors have role in the survival after a successful hepatic resection of CRLM. We would like to		

find a clinically useable factor, which is able to predict the prognosis, especially to clear the usability of the „heat-shock proteins” (HSP), which were earlier established as a good prognostic factor in other malignancies. In addition we would like to evaluate the correlation between the oncological quality of the surgical resection and the survival, especially at R1 surgical resections.

Dr. Polgár, Csaba polgar@oncol.hu	Department of Surgery - National Institute of Oncology	Intensity modulated and image guided radiotherapy (IMRT and IGRT)
<p>The goal of radiotherapy (RT) in the management of malignant tumours is selective killing of cancer cells and avoiding surrounding normal tissues from radiation damage. CT based, three-dimensional (3D) conformal treatment planning is a standard technique both in teletherapy and brachytherapy. Further optimisation of dose distribution is possible using intensity modulated radiotherapy (IMRT). Image guided radiotherapy (IGRT) is a new technique to overcome daily set-up errors and internal organ movements during the delivery of RT. Using different imaging modalities (e.g. digitally reconstructed radiographs, US, megavoltage and kilovoltage cone-beam CT) the additional margin around the clinical target volume (CTV) can be decreased resulting a significantly smaller planning target volume (PTV). Consequently, dose to critical structures can be decreased and/or total tumour dose can be increased resulting better clinical results – including lower incidence of radiation side-effects and higher rate of local tumour control. The task of the candidate is to work-out, implement, and prove the clinical efficacy of intensity modulated and/or image guided teletherapy and/or brachytherapy techniques for the management of different tumour sites.</p>		

Dr. Pytel, József pytelj@t-online.hu	Department of Otorhinolaryngology	Reconstructive possibilities in the head-neck surgery
<p>One of the difficulties in the head & neck surgery are the reconstruction of the big defects after the radical oncological surgery. Numerous locale flaps and micro vascular flaps are used in the head & neck oncological surgery such as pectoral maior miocutan flap, latissimus dorsi miocutan flap or forearm free flap. The task is to analyze these techniques and to develop new or modified flap techniques. Further on the task is to analyze the blood supply of these flaps.</p>		

Dr. Pytel, József pytelj@t-online.hu	Department of Otorhinolaryngology	Long term follow up of hearing improvement operative techniques
<p>The modern therapy of the chronic suppurative otitis is the surgery, the tympanoplasty. The tympanoplasty consists of two parts: the sanation and the improvement or preservation of the hearing. The treatment of the conductive hearing loss of the otosclerosis is also the surgery, the replacement of the fixed part of the ossicular chain with a mobile system of the sound conduction. There is a big debate on the materials of the ossicular chain reconstructions. There are newer and newer methods for ossicular chain reconstructions, for this reason it is very important to exam of the long term follow up results.. Our aim of elaborating a database proper for langterm analyzis, containing all the important details regarding the audiological results and the results of the sanations. We would like to compare methods as much as possible.</p>		

Dr. Pytel, József pytelj@t-online.hu	Department of Otorhinolaryngology	Objective audiometrical techniques
<p>It is obvious, that we objective information need on the hearing capacity of the newborn babies, school- age children, working adults and elderly. In Hungary will be ratified the law upon the objective universal newborn baby hearing screening, but the method of the objective screening is controversial. Further on there are subjective components in the objective methods, e.g. the evaluation depends on the experience of the operators or audiologists. Our aim is to</p>		

minimize these subjective components by elaborating of expert programs. Beyond the examination of the peripheral parts of the hearing pathway such as Otoacoustic emissions (OAEs), Electrocochleography(ECog), Brainstem electric responses (ABR, BERA, MLR, ASSR) we pay special attention to the objective measurements of the cortical hearing processes (CERA, CNV, Cognitive potentials)

Dr. Vajda, Péter vajda.peter@pte.hu	Department of Paediatrics	Evaluation of Complications Following Surgical Correction of Complex Developmental Disorder in Children and Adolescents
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The aim of research is to evaluate surgical, metabolic and histological complications after complex reconstructive surgery in children and adolescents with developmental disorders. Complications are investigated by clinical and experimental studies during a medium and long-term follow-up along different and international working groups. Studies cover wide spectrum analysis from the molecular changes to the patient's body functions, symptoms, overall health, psychological and social well-being, quality of life and satisfaction with the healthcare.

B-322/1996 Experimental cardiology

Program leader: Dr. Tóth, Kálmán

Dr. Kenyeres, Péter kenyeres.peter@pte.hu	1st Department of Internal Medicine	Erythrocyte deformability measurements with ektacytometry. Methodical pitfalls.
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Hemorheology concerns both the global flow properties of blood and the unique properties of certain components. Ektacytometry is used to describe erythrocyte deformability. It measures the extent of deformation that various known stresses cause to cells. Results are not only affected by the physical properties of the intact cells but may be biased by changes due to manipulation with the cells and measurement circumstances as well. The study aims to uncover methodical pitfalls. We aim to set up measurement standards where bias of results is minimal. We also seek transformation methods to make results of measurements performed among different circumstances comparable.

Dr. Kenyeres, Péter kenyeres.peter@aok.pte.hu	1st Department of Internal Medicine	Hemorheological aspects of hematological malignancies
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Hematological malignancies are accompanied with the clonal over-proliferation of a blood component and the suppression of others. The composition of blood may be drastically different from that of the healthy one that may lead to macro- and microcirculatory consequences. Therapeutic methods aim to reduce pathologically high cell numbers and substitute scarce ones. We aim to study the hemorheological consequences of the diseases and applied therapies. We investigate what support hemorheological methods may provide in the assessment of risk for certain complications, in the evaluation of the effectiveness of therapy or in scheduling therapy.

Dr. Késmárky, Gábor kesmarky.gabor@pte.hu	1st Department of Internal Medicine	Investigation of variables affecting blood and oxygen supplementation in peripheral arterial diseases
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A significant part of the population suffers from peripheral arterial diseases but the awareness of these diseases is much lower, the secondary prevention and even the symptomatic treatment are inappropriate frequently compared to the vascular disorders. Therefore we are aiming to investigate those factors which

can affect the blood and oxygen supplementation of the extremities performing cardiological, angiological, haemorheological and tissue oxygen tension examinations in order to be able to salvage the limbs and improve life quality. We examine the effects of the various pharmacological and non-pharmacological therapies on these variables and limb survival.

Dr. Koltai, Katalin koltai.katalin@pte.hu	1st Department of Medicine	Effects of impaired glucose metabolism on hemorheological parameters and platelet aggregation
<p>Rheological factors and increased platelet aggregation are convincingly implicated in the development of micro- and macrovascular diseases associated with diabetes mellitus. Glycemic control seems to be a major factor to determine the hemorheological consequences of diabetes. Positive associations have been found between parameters of glycemic control, fibrinogen levels and red blood cell aggregation; fibrinogen levels are also correlated to insulin resistance. The binding of fibrinogen to the GP IIb-IIIa receptor is increased in diabetic patients, and they also have a higher ratio of platelets expressing activation-dependent adhesion molecules such as activated GPIIb-IIIa, lysosomal Gp53, thrombospondin and P-selectin; plasma fibrinogen levels are also increased in diabetes. Platelets may interact with glycosylated low density lipoproteins, von Willebrand factor or immune complexes, and platelet turnover may be shortened in diabetes, thereby contributing to the observation that antiplatelet agents such as aspirin and clopidogrel have a diminished effect in these patients. We aim to study the effects of impaired glucose metabolism on hemorheological parameters, platelet activation and aggregation in patients treated with different antidiabetic regimens.</p>		

Dr. Tóth, Kálmán Dr. Battyáni, István toth.kalman@pte.hu udvaracz.veronika@pte.hu	1st Department of Internal Medicine; Department of Radiology	Development of super-paramagnetic drug delivery platform
<p>Develop and optimizing a nanocarrier platform which is suitable for targeted delivery of tPA and other potential thrombolytic drugs using iron oxide core. Developing an alternative protocol for synthesizing labeled nanoparticles to follow up the thrombus lysis at in vitro and in vivo environment Performing the sufficient physical-chemical characterizations such as measuring size, shape, Zeta-potential, stability, calculating the loaded amount of drug into the particles Testing the NPs in in vitro environment with and without flow. Developing a method for making identical thrombus (mouse, pig, human) in ex vivo environment Introducing the NPS into an alternative magnetic field for testing their behavior, measuring the lysis efficiency and time with heating effect. Developing a mouse and pig ferric chloride arterial injury model and testing the NPs in in vivo environment using intravital microscopy technique. Performing the remote guidance of NPs via external magnetic fields.</p>		

Dr. Tóth, Kálmán Dr. Késmárky, Gábor toth.kalman@pte.hu kesmarky.gabor@pte.hu	1st Department of Internal Medicine	Hemorheological variables in various diseases. Diagnostic and prognostic implications
<p>Blood flow properties and blood cell characteristics can be altered in several diseases: they can provoke symptoms in a part of diseases or they can be co-factors in other ones. The haemorheological parameters could be valuable in risk stratification and diagnostics. In our laboratory haemorheological investigations are performed at various patient populations: plasma and whole blood viscosity, red blood cell aggregation and deformability, platelet</p>		

aggregation are measured and they are analysed in respect of clinical parameters. The clinical usefulness of a novel variable, haematocrit and blood viscosity ratio characterising the oxygen carrying capacity of blood is evaluated.

B-149/1993

Molecular epidemiology of tumors

Program leader: Dr. Kiss, István

Dr. Kiss, István istvan.kiss@aok.pte.hu	Department of Public Health Medicine	Role of genetic polymorphisms in cancer susceptibility
<p>The so called individual susceptibility factors play an important role in determining the risk of chronic non infectious diseases. These are typically single nucleotide polymorphisms on the area of genes related to cancer development. They are not inherited mutations, but rather normal gene variants, which, however, to a certain extent have an influence on the risk of the formation of different tumours. In the framework of this PhD topic, allelic distributions (e.g. genes of metabolizing enzymes, DNA repair genes, tumour suppressor genes) are compared between cancer patients and cancer free controls. These molecular epidemiological studies (case-control studies) can lead to the identification of genetic risk factors of certain tumours.</p>		

Dr. Kiss, István istvan.kiss@aok.pte.hu	Department of Public Health Medicine	Epigenetic factors – cancer risk and prognosis
<p>In this PhD topic role of epigenetic factors is studied in relation to risk of cancer development, and as independent prognostic biomarkers. Role of different DNA-methylation patterns and microRNA expressions will be investigated (as potential markers of cancer risk) in human molecular epidemiological studies. With the help of clinical cooperation and on archive samples the same biomarkers will be determined from cancer tissues at diagnosis, and taking the course of the disease into account, the prognostic value of these biomarkers will be analyzed. The human studies will be supplemented with animal experiments, where the effect of potentially carcinogenic environmental/lifestyle factors will be studied on the change of methylation patterns and microRNA expressions, through several generations. These studies can shed light on the mechanisms how environmental effects may cause hereditary changes even without causing mutations.</p>		

Dr. Szilárd, István istvan.szilard@aok.pte.hu	Department of Operational Medicine	Public health response and resilience during emergency: a policy analysis of the Syria crisis
<p>Migration has been recognized as one of the greatest challenges that societies are facing and will continue to face during upcoming decades. Latest global estimates by the UN Commissioner for Refugees (UNHCR) show that a record of 59.5 million people are forcibly displaced worldwide. The rising need to address public health aspects of migration in emergency situation is gaining increasing relevance since the armed conflict in Syria displaced millions of people. The response to this crisis challenges governments and international organizations, particularly with regard to the response capacity and resilience of health systems and access to health-care services. This study will take account of the operating procedures and the policies applied by different health clusters to respond to the Syria crisis. The chosen policies will be compared and evaluated in order to formulate a new enhanced policy which is able to strengthen the international capacities for responding to level three emergencies resulting from conflicts. In order to accomplish this goal, a problem-oriented Policy Analysis Framework is proposed as the methodology to be adopted.</p>		

Dr. Szilárd, István istvan.szilard@aok.pte.hu	Department of Operational Medicine	The health conditions of the inclusion of migrants in Hungary
<p>The number of migrants entering Hungary has increased rapidly and their number become higher than in any previous year. Majority of them are originated from remote geographical regions. In spite of the clear health and public health impact of this growing migrant influx, a critical analysis of these aspects is still missing. Candidate will study and critically analyze their reception related health conditions, including the occupational health conditions of the reception centers' staff and the health service infrastructure of the centers. Based on the collected and analyzed data candidate will compose advices in order to improve the migration related health/ public health security.</p>		
Dr. Szilárd, István istvan.szilard@aok.pte.hu	Department of Operational Medicine	The realized needs and conditions of the rehabilitation and reintegration of victims of trafficking in Belgium and in Hungary. A comparative study.
<p>The multi-stakeholder approach to victim assistance favoured by the European Commission is the result of a long track record in dealing with the issue of trafficking, as it is a reflection of a victim-centred approach. Based on the experience of victim assistance providers, the involvement of healthcare professionals is particularly beneficial for early identification, victims' recovery and quicker (re-)integration into the society. The EU 2011 Directive stipulates the obligation for Member States to attend to victims with special needs, such as pregnancy, disability, mental or psychological disorder or consequences of serious psychological or physical violence-an explicit call for healthcare professionals to get involved. However, to date there has not been systematic research to determine the necessary conditions for the involvement of healthcare practitioners in the identification and rehabilitation of trafficked victims, nor the impact of their participation. This research aims to fill this gap by comparing the victim assistance services and the involvement of healthcare practitioners in a country of origin and a country of destination of trafficked victims, Hungary and Belgium.</p>		
Dr. Szilárd, István istvan.szilard@aok.pte.hu	Department of Operational Medicine	Institutional background and capacity of migrants' health care in Hungary
<p>In the world of globalisation we have to face with an increasing number of migrants also in Hungary. The purpose of the researche is to investigate which are the most common imported diseases among migrants, discovered at the Hungarian departments of infectious diseases. The patient-centered health care requires specific knowledge and skills from health care professionals working in a diversified composition of patients. The mode and availability of cultural competence training beside the professional training in medical education will also be observed, just like the self assessment on their own level and skills regarding cultural competence.</p>		
Dr. Varga, Csaba istvan.kiss@aok.pte.hu	Department of Public Health Medicine	Environmental nanotoxicology
<p>Several toxicological and genotoxicological data should be collected to assess the environmental risk of nanoproducts. The aquatic environment is primarily examined. The water types which can cause human exposures (surface, drinking, thermal and mineral waters) should be studied. Laboratory experiments, that is toxicity and genotoxicity test are carried out with nanoproducts of low or without water solubility.</p>		

Dr. Varga, Csaba istvan.kiss@aok.pte.hu	Department of Public Health Medicine	Balneoprevention
This topic involves lab experiments to clarify the possible toxic and genotoxic effects of medicinal spa waters and medical muds. Animal models may also be developed to find the possible relationship between different organic components of waters and muds and prevention of a particular disease of public health concern.		

B-1/2006 Clinical aspects and pathobiochemistry of metabolic and endocrine diseases

Program leader: Dr. Kovács, L. Gábor

Dr. Bajnok László laszlo.bajnok@aok.pte.hu	1st Department of Internal Medicine	Investigation of fat cells of obese individuals
The aim of the project is to clarify if the patterns of fat cells obtained from obese subjects – e.g. cell hypertrophy, altered adipokine secretion – are reproducible in secondary adipocytes that are differentiated <i>in vitro</i> from preadipocytes. As compared to normal weight individuals, those characteristics that can be created <i>in vitro</i> by this method can be regarded as <i>intrinsic</i> ones. In the opposite case, the role of <i>extrinsic</i> , hormonal-metabolic effects are possible. This approach helps us to the better understanding of central versus peripheral cause of obesity. It is also tested whether there are correlations between the adipokine concentrations measured in sera versus cell culture supernatant.		

Dr. Bajnok László laszlo.bajnok@aok.pte.hu	1st Department of Internal Medicine	Impacts of weight loss on metabolic and vascular parameters
In case of overweight, even 7-10% of weight loss has significant impact on the global cardio-metabolic risk. The aim of the project is to clarify the processes that might be in the background of positive changes. During the follow-ups of obese patients, comparisons are made between the original and the reached lower – at least 5% less – weight states in respect of metabolic, adipokine and circulatory parameters. During the analyses of changes, the independent correlations are to be identified.		

Dr. Kovács, L. Gábor kovacs.l.gabor@pte.hu	Department of Laboratory Medicine	Modern laboratory tests for platelet dysfunctions
Platelets play a role also in the physiological and in the pathological blood coagulation (thrombosis-embolism versus haemophilia). For the examination of the so-called hormonal components (venous thrombosis-embolism and factor deficiencies) of the blood coagulation system wide-range of globally accepted classic laboratory methods are available. Contrarily the TAI (thrombocyte aggregation inhibition) test – known for the formation and therapy of the arterial thrombosis – is available only in a few laboratories. In this PhD topic laboratory tests have been set for the modern flow cytometry testing of the human thrombocytes: vasodilator stimulated phosphoprotein (VASP) and P-selectin expression measurements, HIT-diagnostics and – mostly platelet origin procoagulant activity – microparticulum measurement. There are especially numerous publications about the evolution and role of microparticles of different origin (platelet, endothel, erythrocyte, leukocyte) in the variety of diseases – e.g.: sepsis, HIT, TTP, aplastic anaemia, PNH, sickle cell anaemia,		

cardiovascular and oncological diseases. The tests are used for patients treated with platelet inhibitor Aspirin (ASA) and Clopidogrel for cardiological, serious septic, heparin induced thrombocytopenic (HIT) and for tumorous patients during clinical laboratory studies. The results of the modern flow cytometry tests for thrombocytes are compared with the classic TAG and other coagulation and laboratory results. The aim of development of the thrombocyte function laboratory tests is: the better understanding of the role of the platelets in coagulation, the more accurate monitoring of the clinical efficacy and side effects of the anti-platelet anti-thrombotic therapies.

Dr. Kovács, L. Gábor kovacs.l.gabor@pte.hu	Department of Laboratory Medicine	Viability assessment of in vitro fertilized embryos using biomarkers of the cell culturing medium
<p>Infertility in the developed world affects a relatively high percentage of the mature population leading to an increasing need to the use of assisted reproductive technologies, and in vitro fertilization (IVF). The rate of successful embryo implantations however is surprisingly low, not more than the 30% of the total number of IVF experiments. Worldwide huge efforts are made to select the possibly most viable embryos using morphological or more recently molecular markers to increase the success rate of IVF experiments. The issue is that the analysis should be completely non-invasive as due to ethical reasons only the cell culture medium surrounding the embryo during the first few day of its development can be experimented. The aim of the research is to find any candidate molecules in the embryo culturing media to assess viability prior the transfer.</p>		

Dr. Kovács, L. Gábor kovacs.l.gabor@pte.hu	Department of Laboratory Medicine	Analysis of circulating cell-free DNA and miRNA as pathogenetic markers in liquid biopsy
<p>Circulating cell-free DNA with both nuclear or mitochondrial origin and exosomal gene expression regulatory miRNAs get into the body fluids either by cellular destruction or active secretion. Recognition of these molecular fractions in biological fluids has generated an interest for their potential use as markers for genetic disorders or progressive human diseases. Quantitative and structural analysis of circulating cell-free DNA and exosomal miRNA from body fluid has emerging role as liquid biopsy-based markers. The study focuses on cfDNA and miRNA preparation and subsequent analysis on spent IVF embrional culture media and human liquid biopsy samples. Methods enroll high throughput molecular techniques including fluorescent quantitative real-time PCR, droplet digital PCR and next generation sequencing.</p>		

Dr. Kovács, L. Gábor kovacs.l.gabor@pte.hu	Department of Laboratory Medicine	Genetic diagnosis in the embryo culture media during in vitro fertilization
<p>The ability to noninvasively and reliably predict which embryos have the potential to healthily develop to the blastocyst stage and to reach full-term once transferred would be invaluable for human in vitro fertilization. Chromosomal defects, gene interactions, and individual genes can all contribute to developmental failure. During the past decade, small non-coding RNA molecules including the micro-RNAs (miRNA) have been recognized to be key posttranscriptional regulators of gene expression. The regulatory role of miRNAs has recently begun to be explored in the human reproductive system and have been shown to play an important role in control of reproductive functions, especially in the processes of implantation, and early embryonic development. Successful embryo implantation requires synchronous development and communication between the blastocyst and the endometrium; however</p>		

the mechanisms of communication in humans are unknown. Recent studies have revealed that miRNAs are present in bodily fluids and secreted by cells in culture. Human blastocysts differentially secrete miRs in a pattern associated with their implantation outcome. The aim of our research is to identify and confirm DNA-mRNA-miRNA functional modules from spent embryonic culture media which are specific for aneuploidy or major genetic defects of the human embryo. Methodology includes quantitative real-time PCR, bidirectional Sanger sequencing and NG sequencing techniques.

A-327/1995 The investigation of pathological conditions of the circulation in *in vivo* surgical models and in-patients

Program leader: Dr. Jancsó, Gábor

Dr. Gasz, Balázs balazs.gasz@gmail.com	Department of Surgical Research and Techniques	Application of 3D modelling and 3D printing in surgical planning
<p>Continuous development of 3D modelling, finite element analysis and rapid manufacturing based on 3D printing, furthermore the advances imaging techniques (CT, MR, 3D ultrasound) enables precise reconstruction and mechanical, stress analysis of different structures, organs. Moreover computational fluid analysis can help to evaluate the yet unknown effects of vascular and cardiac surgical procedures. These 3D analytical methods can be used for exact planning of surgeries as well as planning of instruments and implantations used in surgical procedures. A detailed concept of research project is planned to be developed according to personal interest and proposition of the candidate. Presently our team has the following research topics: 1) Mechanical modelling of heart valves and mechanical, stress analysis of valve-repair procedures; 2) Planning and manufacturing of patient-specific implants in cardiac surgery; 3) Application of computational fluid modelling in surgical planning of vascular and cardiac surgical procedures; 4) 3D modelling of orthopaedic pathologies and surgical planning of orthopaedic procedures.</p>		

Dr. Gasz, Balázs balazs.gasz@gmail.com	Department of Surgical Research and Techniques	Experimental and clinical evaluation of cardiac surgical procedures associated with myocardial ischaemia-reperfusion
<p>Cardiac surgery is associated with activation of harmful events resulting in increased risk of postoperative complications. Aortic cross clamping causes myocardial ischaemia and reperfusion with cellular mechanisms of oxidative injury, deterioration of antioxidant batteries. Furthermore, cardiopulmonary bypass and surgical stress are known to trigger whole body inflammatory response which may lead to activation of leukocytes and endothelial initiating oxidants. These processes can exacerbate the effects of myocardial ischaemia-reperfusion. These unwanted processes can be eliminated by cellular activation of endogen adaptation. It has been evidenced that given protocol of ischaemic postconditioning and controlled reperfusion can reduce tissue damage following myocardial ischemia-reperfusion. These mechanisms are not well-investigated in patients receiving cardiac surgery. During our investigation it is aimed to evaluate the cellular and subcellular mechanisms of endogen adaptation in cardiac surgical patients, which may influence the risk of complications. Students are invited to examine the cellular mechanisms of postconditioning in animal experiments, furthermore determine the effects of postconditioning and controlled reperfusion in cardiac surgical patients on blood and tissue samples.</p>		

B-2/2013 Acute and chronic injuries of parenchymal organs and the consequences: diagnostics and therapy

Program leader: Dr. Molnár, F. Tamás

Dr. Molnár, F. Tamás tfmolnar@gmail.com	Department of Operational Medicine	Diagnosis and therapy of acute and chronic injury of the parenchymatous organs
Acute and chronic injuries of the thoracic and abdominal parenchymatous organs (lung, liver, spleen, kidney) are investigated. Traumatic, non-traumatic (endogenous and exogenous alike, noxa specific) tissue damage is in the focus of the complex research. Diagnostic (from subcellular level to imaging) and therapeutic (reparation, resection) questions are aroused and investigated. Apart from the standard clinical/applied laboratory method approaches basic sciences and border-topics are also included.		

Dr. Molnár, F. Tamás tfmolnar@gmail.com	Department of Operational Medicine	Medical Humanities
Medicine, part of the hard sciences (realias) and arts&humanities (soft sciences) are forming the two pillars of the complex research of the title. Mutual benefit is expected from the active interactions taking place simultaneously on all of the three fields: medicine, arts and history. While medicine is in the focus, and plays the role of the hub, multidirectional flow of knowledge, translation of concepts and ideas is expected.		

B-1/2010 Clinical studies on locomotion

Program leader: Dr. Than, Péter

Dr. Radnai, Márta Dr. Than, Péter martaradnai@yahoo.com peter.than@aok.pte.hu	Department of Dentistry, Oral and Maxillofacial Surgery Department of Orthopaedics	Etiology and diagnostics of temporomandibular disorders
The Temporomandibular disorders or dysfunction syndrome (TMD) is a frequent musculoskeletal problem in the population. About 1/3rd of the population shows one or more signs of the symptoms, however in 40-75% of the people some signs can be detected with thorough clinical examination. There are more factors in the etiology of the TMD, but in some cases it is not possible to find the main reason for the development of the disease. The etiologic factors may be trauma, anatomical variations, psychological problems or systemic diseases. Aim of the study: The aim of the study is to find a potential connection between the TMD and the musculo-skeletal system. Questions to be answered: Have patients with temporomandibular dysfunction (TMD) more often pathologies in the spine or hip joint? Will these symptoms improve or disappear after the successful treatment of TMD? Whether the acquired or congenital disorders of the vertebral column plays a role in the etiology of TMD? Whether the inappropriate occlusal surface of the prosthetic restoration may cause orthopedic symptoms? Which are the most appropriate diagnostic tools to detect TMD? Whether with the early diagnosis of spinal problems the TMD can be prevented?		

A-442/2000 Reproductive endocrinology**Program leader: Dr. Gócze, Péter**

Dr. Koppán, Miklós mkoppan@gmail.com	Department of Obstetrics and Gynaecology	Investigation of molecular biological and endocrine aspects of different clinical forms of endometriosis
Research plan would include the use of human specimens obtained from endometriosis patients (nodules, blood, serum, etc.) for running certain tests to investigate endocrine and molecular biological parameters, thus to characterise the disease, as well as describe relationships between those parameters and clinical data including the staging of the disease, anatomical localisation, quality of life, pain scores and surgical outcomes.		

B-4/2004 Basic studies on dental and oral diseases**Program leader: Dr. Olasz, Lajos**

Dr. Szalma, József szalma.jozsef@pte.hu	Department of Dentistry, Oral and Maxillofacial Surgery	Examination of the prevention and treatment modalities of alveolitis in relation with impacted teeth surgery
In the everyday clinical practice the incidence of minor complications is approximately 15-20% of the total number of third molar removals. Alveolitis (dry socket syndrome) may arise in 30-40% of the surgical tooth removals. Several preventive approaches are known, such as the use of iodoformic gauze, zinc-oxide eugenol paste, platelet rich fibrin (PRF), different medicine containing pastes, like antibiotics containing, non-steroid pain killer containing, steroid containing, or the application of chlorhexidine gel and solutions. In the case of a manifest alveolitis these methods can be used as well. The aims of this research are: i) to identify the important pathogens which play role in the development of alveolitis (microbiological methods), ii) to analyze the in vitro effectivity of the different antiseptic materials in case of infections (inhibitory zones) iii) to compare the effectivity of different alveolitis preventive methods in a prospective clinical study, iv) to compare the different treatment options in alveolitis in a prospective clinical study.		