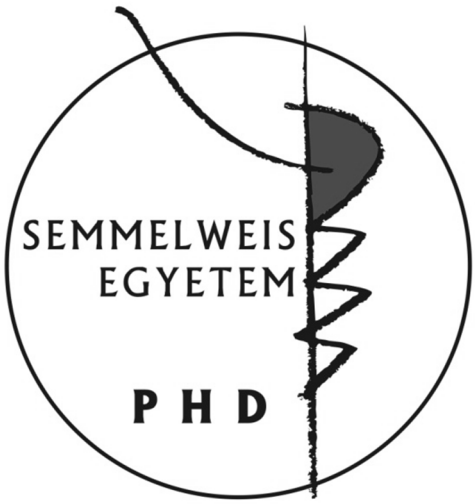

PHD SCIENTIFIC DAYS
2014

10-11 APRIL 2014
Semmelweis University
NET Building

INTRODUCTION

It is a great pleasure for me to welcome participants of the *PhD Scientific Days 2014 Conference*. This event provides an opportunity for PhD students from each of the eight Doctoral Schools of Semmelweis University to network and present their latest research and clinical findings during the 7 oral presentation and 4 poster sessions. The primary objective of the conference is that PhD students and candidates should present and discuss their doctoral research in a professional enviroment. It is expected that participants will benefit from questions and intellectual advice related to their presentations and they will widen and strengthen professional relationships.

In the frame of the program of the *PhD Scientific Days 2014 Conference*, professors György Kéri and Zsolt Radák, holders of "*Excellent PhD Supervisor Award*" have been invited to give plenary lectures.

The event is open to graduate and postgaduate students, peers, junior and senior faculty members from Semmelweis University and from other universities.

I eagerly look forward to welcoming you at the *PhD Scientific Days 2014 Conference* and promise you a pleasant and professionally rewarding time.

Dr. Károly Rácz
Head of the Doctoral Council

SCIENTIFIC PROGRAM

10. April 2014. Thursday

09.00 - 09.30	**Opening Ceremony:** Dr. Ágoston Szél, rector of Semmelweis University Dr. Károly Rácz, head of the Doctoral Council, Semmelweis University
09.30 - 09.50	"Excellent PhD supervisor" Award recipient: Dr. György Kéri, professor: *Jelátviteli és egyénre szabott terápia, driver gének gátlása -a tumor terápia új irányai* Signal transduction and personalized therapy, blocking the driver genes - new perspectives for cancer therapy
09.50 - 10.10	"Excellent PhD supervisor"Award recipient: Dr. Zsolt Radák, professor: *A testedzés hatása az agyműködésre* The impact of physical training on brain function
10.10 – 10.30	*Coffee break*
10.30 - 12.30	Oral presentations: E-I/1 – E-I/12
10.30 - 12.30	Poster presentations: P-I/1 – P-I/13
12.30 - 13.30	*Lunch*
13.30 - 16.00	Oral Presentations: E-II/1 – E-II/15
14.00 – 16.00	Poster presentations: P-II/1 – P-II/9
16.00 - 16.30	*Coffee break*
16.30 – 18:30	Oral presentations: E-III/1 – E-III/12

11. April 2014. Friday

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10.30 - 12.40	Poster presentations: P-III/1 – P-III/13
12.30 – 13.30	*Lunch*
13.30 – 16.00	Oral presentations: E-VI/1 – E-VI/16
13.30 – 14.30	Poster presentations: P-IV/1 – P-IV/6
16.00 – 16.30	*Coffee break*
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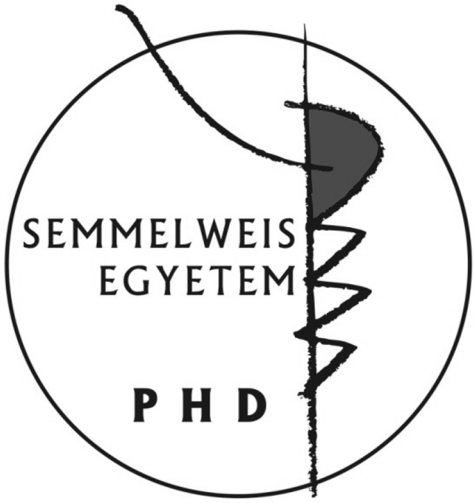

E/I
ORAL PRESENTATIONS

Chairman:
Prof. Dr. Károly Cseh

E/I-1
CYCLODEXTRIN-BASED CAPILLARY ELECTROPHORETIC ENANTIOSEPARATION OF TAPENTADOL STEREOISOMERS

Ida Fejős, Szabolcs Béni

Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary

R,R-tapentadol (Nucynta®) is a novel centrally acting drug that combines mu-opioid receptor agonism and noradrenaline reuptake inhibition, producing analgesic effects in various painful conditions. This analgesic agent exists in four stereoisomeric forms, among which the *R,R* enantiomer is approved for clinical use.

The complete physico-chemical characterization of the single enantiomer drug *R,R*-tapentadol was quantitated in terms of protonation macro- and microconstants and octanol-water partition coefficient using pH-potentiometry, UV-pH and ^{1}H NMR-pH titrations.

As the control of enantiomeric contamination is required by Pharmacopoeias and regulatory agencies, for routine analysis it is necessary to have high throughput, low cost analytical methods with simple sample preparation and small sample consumption. Cyclodextrin-modified capillary electrophoresis was applied to study the analyte-cyclodextrin interaction and the separation of tapentadol enantiomers. Over 15 cyclodextrins were investigated in terms of apparent complex stability and enantioresolution.

In the case of non-charged hydroxypropylated-cyclodetrins the beta derivative was able to discriminate the *S,R*- and *R,S*-, while the gamma the *S,S*- and *R,R*-tapentadol isomers, respectively. Using acidic background electrolyte at pH 2.5, a dual cyclodextrin system was optimized to separate all four isomers.

Among the negatively charged hosts, sulfated-alpha-cyclodextrin was found to resolve the enantiomers with excellent resolution (Rs = 16.2 and 9.1) at pH 4.75 and pH 9.0, respectively. The system containing sulfated-alpha-cyclodextrin was capable to separate all the isomers with optimal enantiomer migration order and the optimized method was amenable to detect *S,S*-tapentadol potential optical impurity at 0.1% concentration level.

Supported by OTKA PD 109373. Sz. B. thanks the Hungarian Academy of Sciences for the financial support under the János Bolyai Research Scholarship.

Doctoral School: *Pharmaceutical Sciences*
Program: *Modern trends in pharmaceutical scientific research*
Supervisor: *Szabolcs Béni*
E-mail: *ida.fejos@gmail.com*

E/I-2
SYNTESIS OF 6A- AND B-ACYLAMINO MORPHINAN DERIVATIVES AND PHARMACOLOGICAL CHARACTERIZATION

Ákos Urai, Péter Horváth, Sándor Hosztafi, Béla Noszál

Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary

Treatment of chronic pain is still an important area of pharmaceutical research. Researchers are trying to develop more potent analgesics with less side effects. In our research project 6β-amino derivatives of morphine were synthesized with Mitsunobu reaction then acylated with cinnamoyl chloride or substituted benzoyl chlorides. We synthesized more than 24 substance, in vitro and in vivo testes were carried out in the Memorial Sloan-Kettering Cancer Center. These new compounds bind strongly to the μ morphine receptor, thus they are selective, and this also means these might have less side effect. The 6α-amino derivatives can be synthesized with reductive aminations, in order to obtain these derivatives with higher yield and selectivity. Several reducing agents were examined. O-Methyl oximes were synthesized form oxycodone, naltrexone and naloxone. Reduction of the oxime-ethers resulted in epimeric mixtures of hydroxylamines, these were acylated with benzoyl chloride. Separation of the epimers was successful in some cases. For structure determination mass spectroscopy, nuclear magnetic resonance spectroscopy and combination of circular dichroism spectroscopy and quantum chemical computations were utilized.

Doctoral School: *Pharmaceutical Sciences*
Program: *Modern trends in pharmaceutical scientific research*
Supervisor: *Sándor Hosztafi*
E-mail: *urai.akos@pharma.semmelweis-univ.hu*

E/I-3
EXPLORATION OF AN UNEXPECTED SIDE REACTION IN DAPOXETINE SYNTHESIS

András Darcsi, Szabolcs Béni

Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary

Dapoxetine (Dpx), (*S*)-*N*,*N*-dimethyl[3-(naphthalen-1-yloxy)-1-phenylpropyl]amine hydrochloride, Priligy®) is a novel short acting selective serotonin reuptake inhibitor (SSRI) that is being developed specifically as an on-demand oral treatment of premature ejaculation with a unique pharmacokinetic profile. The eutomer (*S*)-Dpx is 3.5 times more potent SSRI than (*R*)-Dpx, that is why Dpx is marketed as a single enantiomer drug. A wide range of synthetic procedures were developed to synthesize racemic and enantiopure Dpx. The slight modification of a literature synthetic route of dapoxetine resulted in the formation of an unexpected compound. The structure of this by-product was elucidated using 2D NMR and MS-TOF techniques. The new tricyclic compound: 4-phenyl-2H,3H,4H-naphtho[1,2-b]pyran, is a potential impurity of dapoxetine and it has never been reported previously.

Aims *:* Our aim was to explore the mechanism of the impurity formation and extend the route for the synthesis of various heterocyclic compounds.

Results*:* The mechanism was clarified and this intramolecular alkylation and cyclization reaction was successfully applied for the synthesis of divergent tricyclic compounds as shown in *Figure 1*.

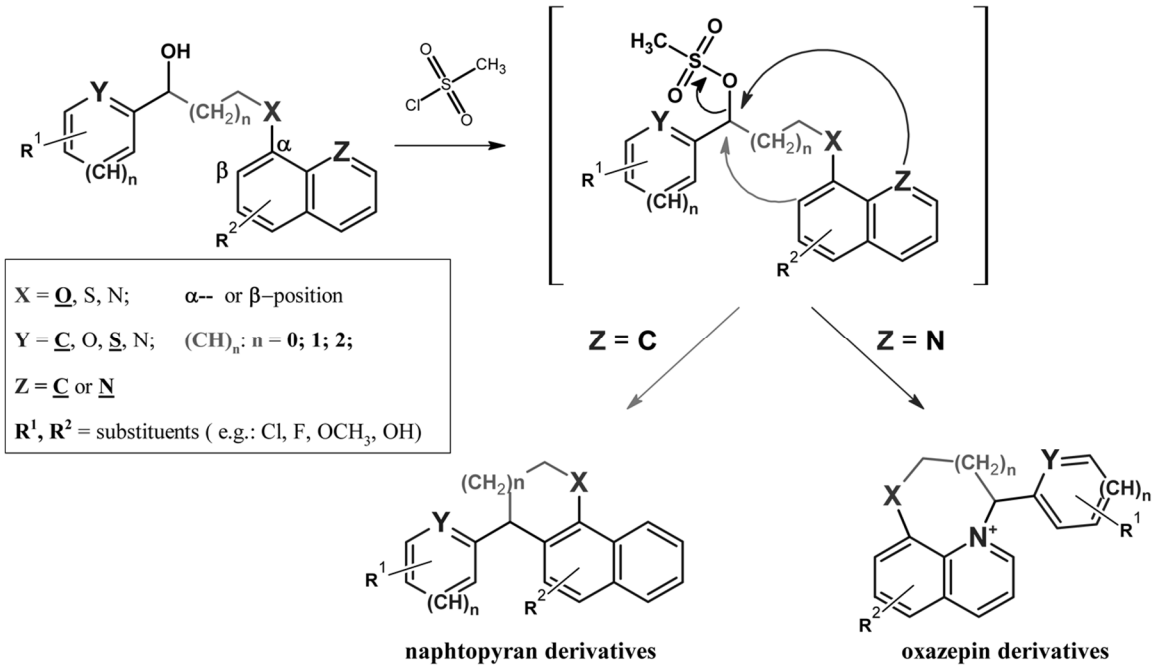

Figure 1. Synthetic applications of the intramolecular ring closure reaction

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Doctoral School: *Pharmaceutical Sciences*
Program: *Modern trends in pharmaceutical scientific research*
Supervisor: *Szabolcs Béni*
E-mail: *darcsi.andrew@gmail.com*

E/I-4
CHARACTERIZATION AND QUANTITATION OF ISOMERIC DISACCHARIDES: N-ACETYLLACTOSAMINE AND LACTO-N-BIOSE IN HUMAN MILK

Réka Balogh[1], Péter Jankovics[2], Szabolcs Béni[1]

[1] Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary
[2] National Institute for Quality- and Organizational Development in Healthcare and Medicines, Budapest, Hungary

The structurally diverse non-conjugated oligosaccharides found at high concentrations in the human milk possess complex biological effects. Besides shaping the microbiota (known as prebiotic effect) and the composition of the bowel system, these oligosaccharides can influence the development of brain and can act as immunmodulators. To determine further structure-activity relationships and to produce more complex infant formulas, it is essential to isolate, characterize and quantify new structures from the colostrum and the human milk.

The aim of our work was to detect and quantify the two major constituents of oligosaccharides: N-acetyllactosamine (LacNAc) and lacto-N-biose (LNB) in colostrum samples. For the isolation of LacNAc and LNB, the samples were defatted and the proteins were removed. The lyophilized samples were subjected to size-exclusion separation.

For the challenging separation of disaccharides, high-performance liquid chromatography was applied using a porous graphite stationary phase with gradient elution. Methanol and water (containing 0.1 v/v % formic acid) served as eluents. To eliminate the anomeric splitting (and concomitant gain in signal-to-noise ratio) a borohydride reduction step was applied prior separation. For chromatographic detection, a triple quadrupole mass-spectrometer was used, and baseline separation was achieved. The fractions containing the isomeric structures were repeatedly lyophilized, hence higher concentrations were achieved. The previously developed LC-qqqMS method was used to determine the concentration of LacNAc in human milk samples collected on the first days of lactation.

LNB was detectable but under the quantification limit. The concentration of LacNAc similarly to the oligosaccharides decreased (from 6.7 μg/mL to 2.3 μg/mL) in the first month of lactation.

Doctoral School: *Pharmaceutical Sciences*
Program: *Experimental and clinical Pharmacology*
Supervisor: *Szabolcs Béni*
E-mail: *rekac13@gmail.com*

E/I-5
CHARACTERIZATION OF A NOVEL INFLAMMATORY PATHWAY INHIBITOR USING DIFFERENT INFLAMMATORY CELL MODELS

Attila Varga[1], Pál Gyulavári[1], Zoltán Greff[2], Tamás Németh[3], Krisztina Kerekes[4], Diána Brauswetter[1], Márton Kokas[1], Anna Erdei[4], Attila Mócsai[3], György Kéri[1, 2], Tibor Vántus[5]

[1] HAS-SU Pathobiochemistry Research Group, Department of Medical Chemistry, Semmelweis University Budapest, Hungary
[2] Vichem Chemie Research Ltd., Budapest, Hungary
[3] Department of Physiology, Semmelweis University, Budapest, Hungary
[4] Department of Immunology, Eötvös Lóránd University, Budapest, Hungary
[5] Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, Hungary

Inflammatory diseases have severe effects on healthcare worldwide. Despite all efforts, currently available therapeutic interventions are limited. Therefore, development of novel inflammatory pathway-specific inhibitors would be of great value. Protein kinase D1 (PKD1) is involved in various inflammatory pathways and has become recently a validated anti-inflammatory target.

First we screened a kinase specific molecule library against PKD1 using recombinant kinase assay and identified VCC251801. In the latter, we recognized vascular endothelial growth factor receptor 2 (VEGFR2) as a co-target kinase of VCC251801 besides PKD1 inhibition. Then we tested the effect of this inhibitor on different cellular assays.

In endothelial cells (EA.hy926) PKD1 is a member of VEGFR2 signaling pathway, which has a critical role in angiogenesis and related inflammatory diseases. Treatment with VCC251801 effectively inhibited the intracellular activation of PKD1 and VEGFR2 and the proliferation of EA.hy926 cells. Our compound was also an efficient inhibitor in *in vitro* angiogenesis assays interfering with endothelial cell wound healing and tube formation processes.

Inflammatory cellular models such as neutrophils, mast cells and basophils were also applied to prove the anti-inflammatory effect of VCC251801. The neutrophil study showed that VCC251801 could specifically diminish the tumor necrosis factor-α (TNF-α)-fibrinogen and the immune-complex stimulated neutrophil activation. In addition, similar inhibitory results were found after VCC251801 treatment in the mast cell (RBL 2H3) degranulation assay and in the basophil test.

In the present study, we have identified and characterized a small molecular inhibitor of PKD1 and VEGFR2, which could efficiently inhibit pathological inflammatory pathways involving these kinases.

Doctoral School: *Pharmaceutical Sciences*
Program: *Modern trends in pharmaceutical scientific research*
Supervisor: *Tibor Vántus*
E-mail: *varga.attila@med.semmelweis-univ.hu*

E/I-6
THE BURDEN OF CLOSTRIDIUM DIFFICILE INFECTION BETWEEN 2010 AND 2013: TRENDS AND OUTCOMES FROM AN ACADEMIC CENTER IN EAST EUROPE

Barbara Dorottya Lovász[1], Petra Anna Golovics[1]

I. Department of Medicine, Semmelweis University, Budapest, Hungary

Background and aims*:* Clostridium difficile infection (CDI) is one of the most important healthcare associated infections (HAI). Increasing incidence of CDI was reported. Our aim was to analyze incidence and possible risk factors in inpatients treated with CDI between 1 January 2010 and 1 May 2013 at 1st Department of Medicine, Semmelweis University, Budapest, Hungary.

Patients and methods*:* A total of 11751 inpatients were treated in our clinic in the follow-up period. 247 inpatients were diagnosed with a CDI infection. For the risk analysis a 1:3 matching was used. Data of 732 matched for age, gender, inpatient care period and unit were compared to the CDI population. Inpatient records were collected and comprehensively reviewed.

Results*:* The incidence of CDI infection was 21.0/1000 admissions **(**2.1% of all cause-hospitalizations and 4.45% of total inpatient days). The incidence of severe CDI was 12.55% (2.63/1000 of all cause hospitalisations). Distribution of CDI cases was different according to the unit type, with highest incidence rates in hematology, gastroenterology and nephrology units (32.9, 25 and 24.6/1000 admissions) and lowest rates in 1.4% (33/2312) in endocrinology and general internal medicine (14.2 and 16.9/1000 admissions) units. Recurrence of CDI infection was 11.3%/12 week after discharge. Duration of hospital stay was longer (17.66 (SD: 10.78) vs. 12.4 (SD: 7.71) days) in patients with CDI infection. CDI accounted for 6.3% of all-inpatient deaths, 30 day mortality rate was 21.86% (54/247 cases). Risk factors for CDI infection were: antibiotic therapy (including 3rd generational cephalosporins or fluoroquinolons, OR:4.559 ,$p<0.001$), use of proton pump inhibitors (OR:2.082, $p<0.001$), previous hospitalization within 12 months (OR:3.167, $p<0.001$), previous CDI infection (OR:15.32, $p<0.001$), while presence of diabetes mellitus was identified as a protective factor against CDI (OR:0.484 , $p<0.001$). 30-days mortality rate was high (21.9%).

Conclusions*:* Incidence of CDI was high and CDI accounted for a significant burden with longer hospital stay and adverse outcomes. Antibiotic therapy, proton pump inhibitor therapy and previous hospitalization/CDI infection were identified as risk factors for CDI

Doctoral School: *Clinical Medicine*
Program: *Molecular genetics, pathomechanism and clinical aspects of metabolic disorders*
Supervisor: *Peter Laszlo Lakatos*
E-mail: *barbi.lovasz@gmail.com*

E/I-7
HOSPITALIZATION RATE BEFORE AND AFTER ANTI-TNF THERAPY, RESULTS FROM TWO REFERRAL CENTERS

Petra Anna Golovics, Barbara Dorottya Lovász

I. Department of Medicine, Semmelweis University, Budapest, Hungary

Background and aims: Hospitalization is an important outcome measure and a major driver of costs in patients with IBD. Our aim was to analyze prospectively the prevalence and predictors of hospitalization and re-hospitalization before and after anti-TNF therapy.

Patients and methods: Data of 194 consecutive IBD (152 CD, 42 UC) patients were analyzed (male/female: 88/106, median age at diagnosis: 24.0, IQR: 19-30 years, duration: 8, IQR: 8-12.5 years) in whom anti-TNF therapy was started after January 1, 2009. Total follow-up was 1874 patient-years and 474 patient-years with anti-TNF exposure. Both in- and outpatient records were collected and comprehensively reviewed.

Results: The hospitalization rate in the 2 years preceding anti-TNF therapy was significantly higher compared to the hospitalization rate during anti-TNF therapy (61.6/100 patient-years vs. 43.2/100 anti-TNF exposed patient-years, OR: 0.64, 95%CI 0.43-0.95, p=0.03) in the total cohort. The risk for hospitalization decreased only in CD (OR: 0.57, 95%CI 0.36-0.90, p=0.02), but not UC and in univariate analysis it was associated with female gender (p=0.02), previous surgery (p=0.03) and smoking (p=0.03). The same tendency was observed for complicated behavior (p=0.06) and lack of perianal disease (p=0.08).

Conclusion: Hospitalization rates decreased significantly in this referral CD but not UC cohort after the introduction of anti-TNF therapy. The decrease in hospitalization rates after the introduction of anti-TNF therapy was associated to gender, previous surgery and smoking habits.

Doctoral School: *Clinical Medicine*
Program: *Gastroenterology*
Supervisor: *Peter Laszlo Lakatos*
E-mail: *golovics.petra@gmail.com*

E/I-8
MESENCHYMAL STEM CELLS INDUCE THE ALTERNATIVE PATHWAY OF MACROPHAGE ACTIVATION

Gyöngyi Kudlik

Stem Cell Biology Unit, National Blood Service, Budapest, Hungary

In recent years it has become clear that the therapeutic potential of mesenchymal stem or stromal cells (MSC) is related not only to their multilineage differentiation capacity but also to their ability to suppress inflammatory and immune responses. Therefore, we studied the influence of mouse bone marrow-derived MSCs on peritoneal (Pe-) and bone marrow-differentiated (BM) macrophage (MΦ) polarization in the presence or absence of certain inductors: bacterial lipopolysaccharide (LPS), interferon gamma, IL-4 and heat-aggregated IgG. Using C57Bl/6 mice as cell source, we either differentiated MΦs from the BM or isolated Pe-MΦs and co-cultured these cells with MSCs. We found that Pe-MΦs co-cultured with MSCs consistently showed a higher level of phagocytic activity, increased expression of mannose receptor, and markedly elevated IL-10, but reduced or unchanged IL-1 and TNF-α levels in the culture supernatants compared to the controls as measured by commercial ELISA assays. Even in the presence of high amounts of LPS, stromal cells were able to attenuate classical (M1) polarization of Pe-MΦs. On the other hand, the MSC-induced (M2b-like) MΦ polarization appears to correlate with their enhanced ability to induce proliferation of in vivo antigen-primed T cells. Transwell co-culture system revealed that the cross-talk between MSCs and Pe-MΦs was primarily but not exclusively mediated by soluble factors that include prostaglandin E2. BM-MΦs react similarly to the presence of MSCs as Pe-MΦs shifting towards an M2b-like functional profile. Furthermore, we proved that BM-MΦs are able to switch polarization states – to an extent – several times between M1, M2a and M2b phenotypes in the presence of the appropriate inductors. These results demonstrate that MSCs switch MΦs into regulatory cells characterized by low pro-inflammatory and high anti-inflammatory cytokine production, high ability to ingest pathogens and apoptotic cells, and a marked increase in their antigen-presenting potential probably aiming to control hyper-inflammation and tissue regeneration.

Doctoral School: *Clinical Medicine*
Program: *Clinical Haematology*
Supervisor: *Ferenc Uher*
E-mail: *gyongyi0888@gmail.com*

E/I-9
DIFFERENT CALCIUM INFLUX CHARACTERISTICS UPON KV1.3 AND IKCA1 POTASSIUM CHANNEL INHIBITION IN T HELPER SUBSETS

Csaba Orbán[1,3], Enikő Biró[1], Anna Bajnok[1], Barna Vásárhelyi[2], Tivadar Tulassay[1], Gergely Toldi[1]

[1] I. Department of Pediatrics, Semmelweis University, Budapest, Hungary
[2] Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary
[3] Department of Dietetics and Nutritional Sciences, Semmelweis University, Budapest, Hungary

Balance between T helper subsets has crucial role in the normal immune function. Transient increase of cytoplasmic calcium level, and sustention of negative membrane potential by voltage sensitive Kv1.3 and calcium-dependent IKCa1 potassium channels are essential for short-term lymphocyte activation.

Aims: We aimed to investigate the Kv 1.3 expression, and calcium influx characteristic of Th1, Th2, Th17 and Treg cells, and their sensitivity to the inhibition of IKCa1 and Kv1.3 channels.

Results*:* Highest cytoplasmic calcium concentration was observed in stimulated Th1 cells, while the lowest level was measured in Treg cells. In Th1 and Th17 cells, inhibition of both investigated potassium channels decreased calcium influx. In Th2 cells only the inhibitor of Kv1.3 channels, while in Treg cells none of the inhibitors had significant effect. Upon the inhibition of IKCa1 channels, short-term activation of pro-inflammatory cells was specifically decreased without affecting anti-inflammatory subsets. Fitting function proved to be appropriate method to distinguish the kinetic of different T helper subsets calcium influx.

Doctoral School: *Clinical Medicine*
Program: *Clinical application of basic science results*
Supervisor: *Gergely Toldi*
E-mail: *orbancsaba1988@gmail.com*

E/I-10
THE EFFECT OF CALCINEURIN-INHIBITION ON THE RENAL RENIN-ANGIOTENSIN SYSTEM. A NEW PLACE FOR RENIN EXCRETION

Rózsa Csohány, Ágnes Prókai, Domonkos Pap, Leonóra Balicza-Himer, Ádám Vannay, Andrea Fekete, János Peti-Peterdi, Attila J. Szabó

I. Department of Pediatrics and Laboratory for Pediatrics and Nephrology, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary

Introduction Tacrolimus (Tac) and Cyclosporin A (CyA) are two effective immunosuppressant which are essential therapeutic solutions of the prevention of the allograft rejection. However, it is well known that both of them possess nephrotoxic potential. The precise effect how these drugs act as nephrotoxic agents are still not fully revealed. In this study we investigated *in-vivo* the effect of calcineurin-inhibitors on the renal renin-angiotensin system.

Methods Three week old, male C57 black 6 mice (n=15) were divided into five groups: mice treated with vehicle (C) or with 0.075 mg/kg/day of Tac or with 2mg/kg/day of CyA or with 0.075 mg/kg/day of Tac + 25mg/kg/day Aliskiren or with 2mg/kg/day of CyA + 25mg/kg/day Aliskiren. After three weeks of administration, renin content in the collecting duct (CD) was evaluated applying FACS and multi-foton microscopy. The contraction of the vessels was assessed and the consequent fibrosis was determined by Masson staining. Eventually, serum creatinine was measured.

Results Serum creatinine was significantly elevated in both Tac and CyA groups. The CD renin content increased four times higher following the administration with calcineurin inhibitors, which was further supported by multi-photon microscopy, the renin granulation increased remarkably in both localizations. As a result of the local activation vasoconstriction was present in both treated groups and as early as the third week of the treatment with immunosuppressants fibrotic islands were found in the kidney.

Conclusion In summary, our studies revealed first that calcineurin inhibitors possess nephrotoxic effect on the kidney parenchyma due to the enhanced renin activity not only in JGA but in the CD segment as well. Therefore, the inhibition of renin-angiotensin system could be beneficial in prevention of nephrotoxic effect of the calcineurin inhibitors. However, further studies are needed to reveal what kind of inhibitors and in which combination could provide the most efficient treatment?

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Doctoral School: *Clinical Medicine*
Program: *Prevention of chronic diseases in childhood*
Supervisor: *Attila J. Szabó*
E-mail: *csohany.rozsa@gmail.com*

E/I-11
ELECTROSPUN POLY(AMINO ACID) BASED FIBROUS MATRIX FOR TISSUE ENGINEERING

Kristóf Molnár, Angéla Jedlovszky-Hajdú, Miklós Zrínyi

Department of Biophysics and Radiation Biology, Nanochemistry Research Group, Semmelweis University, Budapest, Hungary

The interest in the development of biocompatible and biodegradable polymer matrices has increased with their usability in a wide range of medical fields. The goal of tissue engineering is the cellular based regeneration of damaged soft or hard tissue where regeneration without any external help would not be possible. By copying the backbone of the connective tissue, the extracellular matrix (ECM), one can obtain a scaffold, which can help cell attachment and regulate cell growth at the damaged area. Electrospinning (ES) is a versatile and robust technique for creating nanofibers in the diameter range of 10 nanometre and 1-2 micrometres. In ES an electrically charged polymer jet is ejected from a metal needle to a grounded collector placed at a well-defined distance. The non-woven meshes created by ES could have the texture of the network similar to the collagen fibres creating the ECM. Poly(amino acid)-based polymers that have desirable chemical, mechanical and biological properties have recently emerged as a promising new class of biomaterials.

In our work we have utilized a modified poly(succinimide) (PSI) (anhydrous form of poly(aspartic acid), PASP), the thiol side-chain containing poly(succinimide) (PSI-CYS) as base polymer. In order to imitate the structure of the backbone of the connective tissue, reactive electro-spinning technique was applied to prepare artificial extracellular matrix. During the ES process the thiol side-chains create cross-links between the polymer chains preventing the fibrous network from dissolution. The crosslinking reaction took place during the electro-spinning process at 10 kV (0.8 ml/h flow rate and 15 cm target distance). The mean value and distribution of the fibre diameter were determined by Atomic Force Microscopy after sample preparation. The first *in vitro* studies with human fibrosarcoma (HT1080) and human fibroblast cells were performed. Our novel biocompatible and biodegradable artificial scaffold seems to be a promising poly(amino acid) based fiber matrix for tissue replacement.

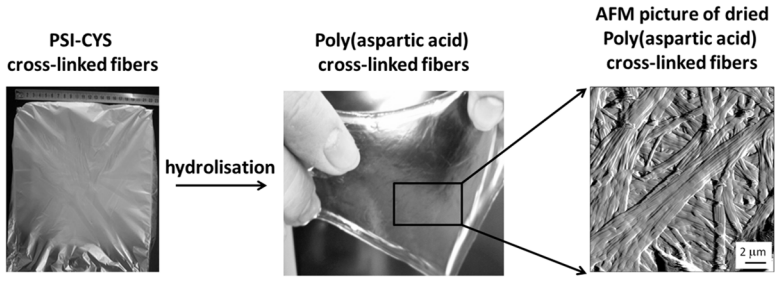


Figure 1. The picture from left to right shows the dry PSI based matrix after preparation, the poly(aspartic acid) based system in wet state after preparation and the AFM image of the dried PASP based fibers.

Doctoral School: *Basic Medicine*
Program: *Cellular and molecular biophysics*
Supervisor: *Angéla Jedlovszky-Hajdú*
E-mail: *molnar.kristof@med.semmelweis-univ.hu*

E/I-12
THE ROLE OF STATE-DEPENDENT AFFINITY AND ACCESSIBILITY IN SODIUM CHANNEL INHIBITOR EFFECTS

Anett Szabó[1] Róbert Károly[1], Nóra Lenkey[2], Árpád Mike[1]

[1] Department of Pharmacology, Institute of Experimental Medicine, Budapest, Hungary
[2] Department of Cellular and Network Neurobiology, Institute of Experimental Medicine, Budapest, Hungary

Sodium channel inhibitors (e.g. local anesthetics, class I antiarrhythmics, and certain anticonvulsants) share some essential properties of inhibition: it is voltage-dependent, frequency-dependent, and is accompanied by a shift of the "steady-state" availability curve. The two main theories explaining drug-induced behavior of the channel are the modulated receptor hypothesis (MRH), which is based on state-dependent affinity; and the guarded receptor hypothesis (GRH), which supposes state-dependent accessibility.

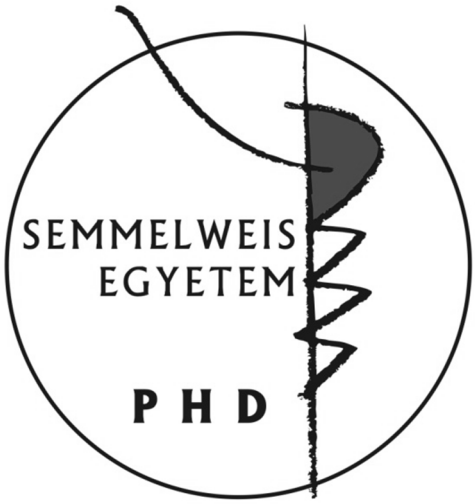
Aims*:* We intended to test the contribution of the two hypotheses. We reasoned that affinity is primarily reflected by the equilibrium of inhibition, while accessibility is expected to determine the rates of onset and offset. We tested five sodium channel inhibitor drugs: the local anesthetic lidocaine and bupivacaine, the class Ic antiarrhythmic flecainide, the antiepileptic phenytoin, and the neuroprotective agent riluzole.

Results*:* We described both hypotheses in terms of free-energy changes, and showed that the two hypotheses are not mutually exclusive, but they overlap. We also showed that the contribution of the two hypotheses ("modulatedness" and "guardedness") to the mechanism of action for specific drugs could in theory be quantified.

A simple HH-type phenomenological model of channel gating (activation and inactivation) was used to test hypotheses regarding the mechanisms of inhibition and to quantify the changes in affinity and accessibility.

The effect of lidocaine and bupivacaine could be well described by roughly equal changes in affinity and accessibility upon inactivation. For phenytoin the state-dependence of affinity was more prominent. In the case of flecainide inactivated-state dependence was negligible, but extremely high open state accessibility was required to reproduce its effects. For riluzole the effect seemed to require a change in accessibility to both open and inactivated states, as well as a change in affinity to inactivated state. Its pattern of inhibition suggests the involvement of other conformational states as well.

Doctoral School: *„János Szentágothai" Neurosciences*
Program: *Functional Neurosciences*
Supervisor: *Árpád Mike*
E-mail: *szabo.anett@koki.mta.hu*



E/II
ORAL PRESENTATIONS

Chairman:
Prof. Dr. Gábor Bánhegyi

E/II-1
HEART RATE VARIABILITY IS SEVERELY IMPAIRED AMONG TYPE 2 DIABETIC PATIENTS WITH HYPERTENSION

Anna Erzsébet Körei[1], Ildikó Istenes[1], Zsuzsanna Putz[1], Nóra Németh[1], Tímea Martos[1], Katalin Keresztes[1], Miklós Soma Kempler[1], Orsolya Erzsébet Vági[1], Péter Vargha[2], Péter Kempler[1]

[1] I. Department of Medicine, Semmelweis University, Budapest, Hungary
[2] Cardiovascular Centre, Semmelweis University, Budapest, Hungary

Cardiovascular autonomic neuropathy is a common complication of diabetes, but may occur in essential hypertension as well. Heart rate variability has negative prognostic value regarding future cardiovascular morbidity and mortality. Our aim was to evaluate the relative impact of diabetes and hypertension on heart rate variability.

Methods: Four age-matched groups were studied, including 62 Type 2 diabetic patients with (mean age: 55,2±6,6 years; median diabetes duration: 3 years; median duration of hypertension: 7 years) and 40 Type 2 diabetic patients without hypertension (mean age: 52,8±8,1 years; median diabetes duration: 3 years), 74 non-diabetic patients with essential hypertension (mean age: 53,0±12,3 years; median duration of hypertension: 5 years) and 25 healthy control subjects (mean age: 52,2±9,1 years). Autonomic function was evaluated by the standard cardiovascular reflex tests (CVRT) and 24-hour heart rate variability (HRV) measurement. HRV was characterized by the triangular index (HRVti) and by the spectral components of the frequency domain analysis.

Results*:* All HRV parameters were influenced negatively by diabetes (HRVti: $p<0,001$, low frequency component: $p<0,0001$, high frequency component: $p<0,001$, total power: $p<0,0001$), while hypertension had negative effect only on the low frequency component ($p<0,05$). The interaction between hypertension and diabetes was not significant, meaning that their effects on the HRV parameters are additive. Regarding spectral parameters and the parasympathetic CVRTs, the lowest values were observed among patients with diabetes and hypertension. Beat-to-beat variation to deep breathing, the most sensitive cardiovascular reflex test was also negatively influenced by both diabetes ($p<0,001$) and hypertension ($p<0,05$), and their effects were additive (no interaction, $p=0,357$).

Conclusions: Diabetes seems to have a greater impact on autonomic dysfunction compared to hypertension. Patients suffering from both diabetes and hypertension are at the highest risk of reduced heart rate variability. Early assessment of the autonomic nerve function is suggested being performed among diabetic patients with hypertension.

Doctoral School: *Basic Medicine*
Program: *The mechanisms of normal and pathologic functions of the circulatory system*
Supervisor: *Peter Kempler*
E-mail: *anna.korei@yahoo.com*

E/II-2
ENDOTHELIAL DERIVATIVES OF HUMAN PLURIPOTENT STEM CELLS: WAY TOWARD VASCULAR TISSUE ENGINEERING

Edit Gara[1], Judit Skopál[1], Annamária Kosztin[1], Éva Szigetfű[1], Béla Merkely[1], Gábor Földes[1, 2]

[1] Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[2] National Heart and Lung Institute, Imperial College, London, UK

Purpose: Endothelial derivatives of human pluripotent stem cells are promising for therapeutic angiogenesis. Our aim was to investigate the effect of differentiation protocols on the development of arterial and venous endothelial cells and to study the arterial and venous gene expression pattern after in vivo engraftment of endothelial cells.

Methods: H7 human embryonic stem cells (hESC, from Wicell) were differentiated via embryoid body (EB) formation method in normoxygenic (20%) and hypoxic (5%) conditions as well as via monolayer method in the presence of vascular-endothelial growth factor (VEGF, 1ng/ml). Human induced pluripotent stem cells (hIPSC, from ReproCell) were differentiated under normoxygenic condition via EB formation. CD31-positive endothelial cells (EC) were sorted by FACS. For engineering 3D constructs, human aortic wall samples were decellularised with detergent solution (2% sodium dodecyl sulfate) and hESC-EC and hIPSC-EC were seeded onto this extracellular matrix. Human ESC-EC and hIPSC-EC were transplanted into three months old athymic nude rats using Matrigel as an extracellular matrix carrier.

Results: The mRNA levels of angiopoietin2 showed an increase in hESC-EC when differentiated with EB method (EB normoxia 353.17±86.29; EB hypoxia 323.89±86.63, $p<0.001$, $n=3$, mRNA levels normalized to those in undifferentiated hESC). As shown by immunocytochemistry, differentiated hESC-EC and hIPSC-EC were stained positive for anti-CD31, von Willebrand factor and ve-cadherin; cells formed capillary-like tubules on Matrigel and took up acetylated-LDL. Quantitative PCR showed abundant expressions of both arterial (EphrinB2, Notch1-2) and venous (EphB4) endothelial markers; however, lymphatic endothelial cells were not detectable. Human ESC-EC and hIPSC-EC seeded onto decellularised human extracellular matrix remained viable as shown by calcein AM staining. Cells remained viable also upon in vivo engraftment; marked increase was found in mRNA levels of all arterial and venous marker genes in re-isolated cells (EphrinB2, EphB4, Notch 1-2, CD31, $n=3$).

Conclusions: EB-based differentiation protocol of endothelial cells from human pluripotent stem cells has the highest angiogenic potency in vitro. After in vivo conditioning, expression of endothelial markers increased, suggesting the functional role of engrafted endothelial cells and possibly supporting future therapeutic purposes with specific angiogenic cells.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular Disorders: Physiology and medicine of ischaemic circulatory diseases*
Supervisor: *Gábor Földes*
E-mail: *gara.editgara@gmail.com*

E/II-3
THE ROLE OF FRACTALKINE IN THE RESYNCHRONIZATION THERAPY OF HEART FAILURE

András Boros[1], Péter Perge[1], Szabolcs Szilágyi[1], István Osztheimer[1], Endre Zima[1], László Gellér[1], Levente Molnár[1], Béla Merkely[1], Gábor Széplaki[1]

[1] Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Fractalkine (CX3CL1) promotes inflammation. Previous studies have revealed that fractalkine is a predictor of mortality in heart failure, while new evidence suggests its specific role in endothelial dysfunction. Statins and aspirin improve endothelial function. We aimed to investigate whether fractalkine predicts the 2-year survival of heart failure patients with cardiac resynchronization therapy (CRT) and how medical therapy influences this survival.

We measured plasma fractalkine levels in 136 heart failure patients before CRT implantation. 62% were on optimal medication with beta blocker, ACE inhibitor/angiotensin receptor blocker and aldosterone antagonist. 26% took aspirin (overall 46%) and 36% statin (overall 61%) additionally. For comparative statistics we used ANOVA or t-test and the log rank test for survival analysis.

The baseline fractalkine level was 0.55 [0.42-0.7] ng/ml and the highest tercile of fractalkine predicted the 2-year survival of patients (0.64 ng/ml, p=0.01, HR=2.21; 95%CI=1.23-5.04).

Those who were on aspirin or statin treatment had lower fractalkine (0.49 [0.38-0.60] vs 0.61 [0.46-0.77] ng/ml, p=0.02 and 0.51 [0.40-0.66] vs 0.61 [0.47-0.77] ng/ml, p=0.04. Optimal medication with additional aspirin or statins decreased the levels of fractalkine (0.49 [0.39-0.58] vs 0.68 [0.56-0.81] ng/ml, p=0.03 and 0.49 [0.40-0.63] vs 0.68 [0.48-0.79] ng/ml, p=0.07).

Optimal medication alone did not influence the survival of patients (p=0.11), but those who had additional aspirin or statins lived longer (p=0.01, HR=0.32, 95%CI=0.11-0.77 and p=0.02, HR=0.35, 95%CI=0.08-0.81). We adjusted the lower terciles of fractalkine to the models and the power of survival analysis increased (aspirin: p=0.02, HR=0.3, 95%CI=0.05-0.76; statins: p=0.001, HR=0.21, 95%CI=0.019-0.39).

In conclusion, fractalkine is predictive for mortality in the resynchronization therapy of heart failure. Optimal medication combined with aspirin or statins are crucial in heart failure and fractalkine amplifies their predictive value in survival. Aspirin and statins lowers the level of fractalkine, which might be in relation with the improvement of endothelial function.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders: Physiology and medicine of ischaemic circulatory diseases*
Supervisor: *Gábor Széplaki*
E-mail: *borosandrasmihaly@gmail.com*

E/II-4
ASSOCATION BETWEEN SUBCLINICAL ATHEROSCLEROSIS AND RISK FOR TYPE 2 DIABETES IN PARTICIPANTS OF A CARDIOVASCULAR SCREENING PROGRAM

Loretta Kiss, Zsolt Bagyura, Réka Vadas, Lívia Polgár, Pál Soós, Zsolt Szelid, Béla Merkely

Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Ankle-brachial index (ABI) and carotid intima-media thickness (CIMT) measurements are non-invasive methods of revealing subclinical atherosclerosis that also play role in cardiovascular risk assessment of patients with type 2 diabetes mellitus (DMT2). Our aim was to study signs of cardiovascular disease in patients with elevated risk for DMT2. By 2013 December, health questionnaire, physical examination and risk assessment of 2420 participants (30.4% of adult population) in a voluntary screening program, Budakalasz Health Survey, was performed. Risk for DMT2 was estimated by the Findrisc scoring system (FR). A score above 11 implies increased risk. Pre-diabetes was indicated by HbA1c% level between 5.7-6.4%. ABI in the range of 0.9-1.3 and CIMT ≤ 0.9 mm was considered normal. Patients with manifest DMT2 (10.9%) or HbA1c% level above 6.4 (3.2%) were excluded. CIMT measurement of 1134 participants was analysed, mean age 53.8+/-14.6 years, 39.9% male. FR > 11 was found in 23.8%. CIMT was pathological in 5.1%, ABI in 11.2%. In those at increased risk for DMT2 (FR>11) frequency of a CIMT (3.2% vs. 9.0%, p=0.001) or ABI (10.1% vs. 14.4%, p=0.014) out of the normal range was significantly higher. Proportion of participants with pre-diabetes (HbA1c% level > 5.6) was 38.3%. HbA1c% level increases gradually by FR risk category (low: 5.42, slightly increased: 5.67, increased: 5.75, high: 5.79, substantial: 5.93). Frequency of pathological CIMT (3.2 vs. 7.8%, p=0.002) or ABI (8.9% vs. 13.8% p=0.001) values was significantly higher among patients with HbA1c% level above 5.6. CIMT showed a positive correlation with HbA1c% level (r=0.346, p<0.001) Among patients with increased risk for DMT2 and with pre-diabetes CIMT and ABI values were more frequently out of the normal range, that draws attention to the presence of subclinical atherosclerosis in that group. Evaluation of Findrisc score may facilitate early recognition of pre-diabetic state and increased cardiovascular risk.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases*
Supervisor: *Zsolt Szelid*
E-mail: *kisslotti@gmail.com*

E/II-5
REMODELING OF CORONARY ARTERY NETWORK DURING QUERCETIN SUPPLEMENTATION

Anna Monori-Kiss, Gréta Pásti, György L. Nádasy

Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary

Aims: Polyphenols, including quercetin, present in human diet, have various physiological effects. Short term vasodilatory actions on coronary arterioles have been demonstrated in our laboratory, but no information is available concerning their long term effects on microvascular networks.

Methods: Male Wistar rats were divided into two groups. In group Q, animals were treated with 30 mg/kg quercetin per os (n=9), while group C was kept in parallel (n=10) for 8 weeks. Animals were sacrificed, and left desceding coronary artery was prepared in a standard manner with its ramifications, down to 30-50 μm inner diameters. Orifice was cannulated, and continuous saline flow, and pressure was maintained during recording. Pictures of the network were digitally analyzed.

Results: Quercetin treatment reduced hemodynamically disadvantageous components in the network: branching angles under 45° or over 105° were less frequent in group Q (9% vs. 24%), like multiple branching (1/13 vs. 1/10). Segmental tortuosity decreased (2.0±0.3% vs. 3.5±0.4%, $p<0.05$), similar to the frequency of broken courses (1.0±0.5 vs. 3.1±0.4 pc, $p<0.05$). At bifurcations, symmetry of daughter branches increased (1.69±0.08 vs. 2.26±0.24, $p<0.05$). Overall vascularization of exposed network slightly increased (23.4±3.1 mm vs. 28.3±4.1 mm, ns.) due to a significant lengthening in 50-100 μm and in 150-300 μm inner diameter range. Wall was thickened in 0-400 μm arterioles ($p<0.05$), but not above 400 μm.

Conclusions: Chronic administration of quercetin resulted in reduced number of hemodynamically disadvantageous sections of coronary networks. We assume that it can delay non-benefitial remodelling caused by e.g. long term hemodynamic stress, or ageing.

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Doctoral School: *Basic Medicine*
Program: *Mechanism of normal and pathological functions of the circulatory system*
Supervisor: *György Nádasy, Emil Monos*
E-mail: *monorikiss.anna@med.semmelweis-univ.hu*

E/II-6
DEVICE MEASURED PHYSICAL ACTIVITY AS A PREDICTOR OF REVERSE REMODELING AND CLINICAL OUTCOME

Eszter M. Végh[1,2], Jagdesh Kandala[2], Gaurav Upadhyay[2], Béla Merkely[1], Jagmeet P. Singh[2]

[1] Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[2] Massachusetts General Hospital, Boston, MA, USA

Implanted devices can provide objective assessment of physical activity over prolonged periods of time. The purpose of this study was to investigate the prognostic value of device-measured physical activity data as compared to a six-minute walk test (6MWT) in predicting clinical response to cardiac resynchronization therapy (CRT).

This was a single-center study in which patients undergoing CRT for standard indications were evaluated. Daily physical activity and 6MWT was evaluated post-implant at 1-, 3- and 6-months. The primary end-point was a composite of heart failure (HF) hospitalization, transplant, left ventricular (LV) assist device, and all-cause death at 3 years. Echocardiographic response, as defined as a ≥10 % improvement in LV ejection fraction (EF), at 6 months was the secondary endpoint.

164 patients were included: average age was 67.3 ± 12.9 years, 77% were men, baseline LVEF was 25±7%. Kaplan-Meier curves showed superior freedom from the composite endpoint in the highest tertile of both 6MWT and physical activity when compared to the lowest tertile (41 vs. 23 cases ($p<0.001$) for 6MWT and 22 vs. 7 cases for activity ($p=0.001$)). In an adjusted multivariate model, independent predictors of improved clinical outcome included 1-month physical activity (HR 0.546 [95% CI 0.361-0.824], *p=0.004*) and 6MWT (HR 0.581 [95% CI 0.425-0.795], *p=0.001*). An additional hour of higher activity at 1 month translated to a 1.38 times (95% CI: 1.075-1.753, $p=0.011$) higher likelihood of improved echocardiographic response.

In conclusion device-based measures of physical activity may be useful in predicting echocardiographic reverse remodeling and long-term clinical outcome in patients receiving CRT.

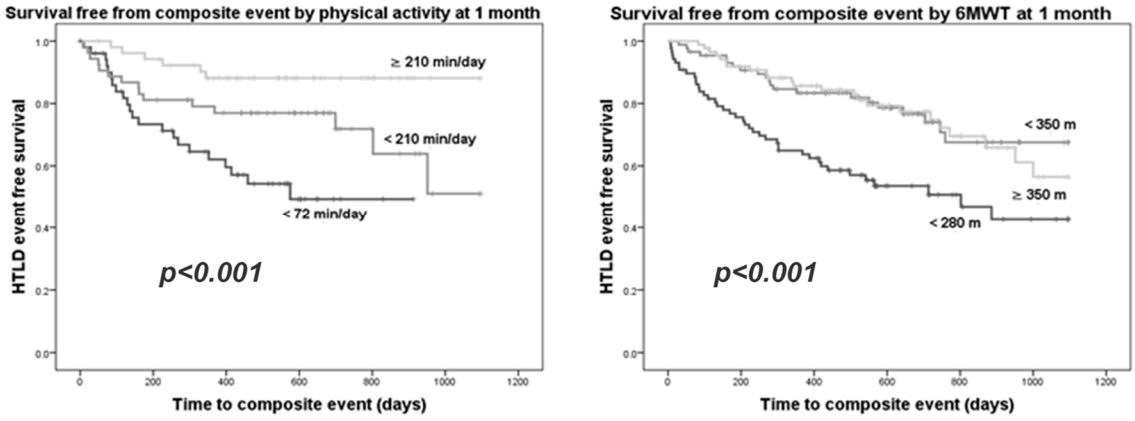

Figure 1. Survival analysis by daily physical activity

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases*
Supervisor: *László Gellér*
E-mail: *vegh.eszter.m@gmail.com*

E/II-7
FEASIBILITY OF SEMIAUTOMATIC TRANSLUMINAL ATTENUATION GRADIENT ASSESSMENT IN THE DETECTION OF HEMODYNAMICALLY SIGNIFICANT STENOSIS IN CORONARY CT ANGIOGRAPHY

Csilla Celeng

Heart and Vascular Center, Semmelweis University, Budapest, Hungary
HAS-SU "Lendület" Cardiovascular Imaging Research Group, Budapest, Hungary

Background: To date, coronary computed tomography angiography (CCTA) is the only diagnostic imaging technique that allows non-invasive visualization and robust assessment of coronary artery plaque and stenoses. However, the assessment of hemodynamic relevance of a coronary luminal narrowing with CCTA remains challenging.

Purpose: The aim of this study was to assess the feasibility of semiautomated transluminal attenuation gradient (TAG) measurements in CCTA in order to determine the lesion specific ischaemia.

Methods: CCTA scans were performed with a 256-slice CT-scanner. CCTA images of left anterior descending coronary artery (LAD) were analyzed in eight patients (age: 37-70). Four patients with significant LAD stenosis were compared with four patients with normal coronary arteries (controls). The CCTA diagnosis of significant stenosis was confirmed by cardiac catheterization. The coronary lumen was segmented and the TAG was measured with semiautomatic method using a dedicated software. The mean luminal HU values were recorded in 0.5 mm increments. The HU values were smoothed over 20 cross-sections using a moving average filter. The distal thirds of the LADs were excluded. Linear least square regression line was fitted to the TAG. Trendline slopes were compared between the stenosis group and controls.

Results: The average length of the analyzed coronary segments was 158.8±42.5 mm and 164.0±14.5 mm for the stenosis and for the control groups, respectively. The stenosis group showed a greater attenuation gradient (-7.8 HU/10mm) compared to the control group (+2.0 HU/10mm), $p<0.05$.

Conclusion: The semi-automated measurement of TAG is feasible. The assessment of TAG with 256-slice CT-scanner may add a functional aspect to the evaluation of the coronary artery stenosis.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases*
Supervisor: *Pál Maurovich-Horvat*
E-mail: *celengcsilla@gmail.com*

E/II-8
POSITIVE INOTROPIC SUPPORT IN ACUTE CARDIAC DECOMPENSATION - HAEMODYNAMIC AND ARRHYTHMOGENIC EFFECTS OF COMBINED TREATMENT WITH LEVOSIMENDAN AND CATECHOLAMINES: EXPERIMENTAL STUDIES

Vivien Klaudia Nagy, Eszter Mária Végh, Balázs Sax, Annamária Kosztin, Gábor Szűcs, Endre Zima, Nóra Túri-Kováts, Violetta Kékesi, Béla Merkely

Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Background: Ca^{2+}-sensitiser levosimendan became first-line treatment in acute systolic dysfunction besides catecholamines (CAs). We aimed to evaluate haemodynamics and arrhythmogenic effects of levosimendan (LEV) administered together with catecholamines (dobutamine, DOB; dopamine, DA; norepinephrine, NE) in a canine heart failure (HF) model.

Methods: HF (n=12) was induced by chronic right ventricular tachy-pacing (240/min), continued until acute cardiac decompensation. Two groups of anesthetized (ketamine-midazolam) animals were constituted: *Group I.* - continuous infusion of LEV (0.1 g/kg/min iv.) combined with 10-10 minutes infusion of different CA doses: $DOB_{3\text{-}6\text{-}12}$, $DA_{4\text{-}8\text{-}16}$ és $NE_{0.04\text{-}0.08\text{-}0.16}$ (μg/kg/min, iv.); *Group II.* – CAs were given in same doses without LEV. Measured variables: systemic blood pressure (BP), left ventricular end-diastolic pressure (LVEDP), contractility ($dP/dt_{min\text{-}max}$), duration of monophasic action potential at 50%, 90% of repolarisation ($MAPD_{50}$, $MAPD_{90}$). Ventricular premature beats (VES), ventricular tachycardias were counted.

Results: In Group I. LEV alone did not alter mean BP (105±13 mmHg) and LVEDP (28±5 mmHg). However, dP/dt_{max}, dP/dt_{min} (1779±313 and -1967±322 mmHg/s) were increased by 56±15, 49±15 Δ% ($p<0.001$). There was further increase in dP/dt_{max} with combination of LEVO and CAs, maximal effect was observed with $LEV+DA_{16}$ (+73±19 Δ%, $p<0.001$). LVEDP tended to decrease during $LEV+DOB_{12}$ and to increase at $LEV+NE_{0.16}$ (ns). In the CAs-only group (II.) basal haemodynamic parameters (BP, LVEDP, dP/dt_{max}, dP/dt_{min}) did not differ from Group I. Moreover, CAs without LEV exerted cardiovascular responses similar to those in LEV+CA group.

Malignant ventricular arrhythmias or increase in VES occurrence were not observed in both groups. During LEV infusion left ventricular $MAPD_{50}$ decreased significantly (214±8 vs 242±9 msec, $p<0.01$), which was further shortened by $LEV+NA_{0.16}$ (204±20 msec, $p<0.02$).

Conclusion: Co-administration of levosimendan and catecholamines elicited similar improvement in cardiac contractility to catecholamines given separately. This beneficial effect was not accompanied by malignant arrhythmias, despite of $MAPD_{50}$ shortening during LEV infusion.

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Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases*
Supervisor: *Béla Merkely*
E-mail: *nagyklaudiavivien@gmail.com*

E/II-9
DEVELOPMENT AND COMPLETE MORPHOLOGICAL AND FUNCTIONAL REVERSIBILITY OF ATHLETE'S HEART IN A RAT MODEL

Attila Oláh, Árpád Lux, Balázs Tamás Németh, Csaba Mátyás, Ede Birtalan, Dalma Kellermayer, Mihály Ruppert, Lilla Szabó, Gergő Merkely, Béla Merkely, Tamás Radovits

Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Background*:* Long-term exercise training is associated with characteristic structural and functional cardiac adaptation termed athlete's heart. However the effect of discontuniation of the training (detraining) on left ventricular (LV) function is unclear. Our aim was to evaluate the development characteristics of athlete's heart and the reversibility of morphological and functional changes during detraining.

Methods: Rats were divided into trained (n=15) and control (n=17) groups. Trained rats swam 200 min/day for 12 weeks. Detrained rats remained sedentary for 8 weeks after completion of the training protocol. We regularly performed echocardiographic measurements to investigate the development and regression of exercise-induced cardiac changes. LV pressure-volume analysis was performed to calculate cardiac functional parameters. LV samples were harvested for histological examination and myocardial gene expression analysis was performed using qRT-PCR.

Results: Echocardiographic examinations showed rapidly developing LV hypertrophy in the trained group according to wall thickness values. This adaptation regressed after detraining, which was confirmed by post-mortem measured heart weight and histological morphometry. Unchanged myocardial expression of TGF-β and β-MHC and unaltered amount of LV collagen confirmed the physiologic nature of the observed cardiac hypertrophy. Hemodynamic measurements indicated decreased LV end-systolic volume (LVESV) along with increased stroke volume (SV), improved systolic function (ejection fraction) and contractility (end-systolic pressure-volume relationship), ameliorated active relaxation and mechanoenergetics (mechanical efficiency, ventriculo-arterial coupling) after long-term exercise training. After the detraining period regression of exercise-induced cardiac functional changes were observed: LVESV, SV, LV contractility, active relaxation and mechanoenergetic enhancement reverted completely to control values. Training and detraining did not affect myocardial stiffness.

Conclusions: Our results confirm that the morphological and functional adaptation of exercise-induced physiologic LV hypertrophy completely regressed after 8 weeks of detraining.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases*
Supervisor: *Tamás Radovits*
E-mail: *o.attilio@gmail.com*

E/II-10
PHARMACOLOGICAL ACTIVATION OF THE SOLUBLE GUANYLATE CYCLASE INHIBITS PRESSURE OVERLOAD-INDUCED CARDIAC HYPERTROPHY

Balázs Tamás Németh, Csaba Mátyás, Attila Oláh László Hidi, Mihály Ruppert, Árpád Lux, Dalma Kellermayer, Ede Birtalan, Gergő Merkely, Béla Merkely, Tamás Radovits

Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Pathological cardiac hypertrophy is observed in pressure overload of the left ventricle. Elevated intracellular cGMP-levels have been reported to prevent the development of pathological myocardial hypertrophy. We investigated the effects of chronic activation of the cGMP producing enzyme, soluble guanylate cyclase (sGC) by cinaciguat in a rat model of pressure overload-induced cardiac hypertrophy.

We performed aortic banding (AB) to evoke pressure overload-induced cardiac hypertrophy in our rats. Sham operated animals served as controls. Experimental and control groups were treated with 10 mg/kg/day cinaciguat (Cin) or placebo (Co) p.o., respectively. Development of cardiac hypertrophy was investigated by echocardiography. We performed left ventricular (LV) pressure-volume analysis with a pressure-conductance microcatheter to assess cardiac function. In addition to our functional experiments, histological and molecular biological measurements were carried out.

Echocardiography showed marked myocardial hypertrophy in the AB-Co group (left ventricular mass index (LVMi): 3.15±0.09 AB-Co vs. 2.13±0.04g/ttkg Sham-Co) which was verified by post mortem investigation of the hearts (heart weight/tibial length ratio (HW/TL): 0.384±0.015 AB-Co vs. 0.293±0.008g/cm Sham-Co) and by histology (cardiomyocyte diameter (CD): 17.37±0.04 AB-Co vs. 14.55±0.12μm Sham-Co). Increased left ventricular dimensions (left ventricular end-diastolic volume: 414±19 AB-Co vs. 341±19μl Sham-Co) were observed while ejection fraction and fractional shortening remained unchanged. Cinaciguat did not alter blood pressure (182.27±7.86 AB-Co vs. 174.63±4.53mmHg AB-Cin, p=n.s.) but effectively attenuated left ventricular hypertrophy (LVMi: 2.64±0.06g/ttkg, HW/TL: 0.339±0.009g/cm, CD: 15.08±0.10μm, $p < 0.05$ vs. AB-Co).

Our results demonstrate that chronic stimulation of the NO-cGMP signaling pathway by pharmacological activation of the soluble guanylate cyclase might be a novel therapeutic approach in the prevention of pathological myocardial hypertrophy.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases*
Supervisor: *Tamás Radovits*
E-mail: *nemethbl@gmail.com*

E/II-11
CINACIGUAT PREVENTS DIABETES MELLITUS RELATED CARDIAC ALTERATIONS IN RATS

Csaba Mátyás[1], Attila Oláh[1], Balázs Tamás Németh[1], László Hidi[1], Ede Birtalan[1], Mihály Ruppert[1], Marianna Török[1], Gábor Kökény[3], Gábor Szabó[2], Béla Merkely[1], Tamás Radovits[1]

[1] Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[2] Department of Cardiac Surgery, University of Heidelberg, Germany
[3] Institute of Pathophysiology, Semmelweis University, Budapest, Hungary

Diabetes mellitus (DM) is associated with severely impaired nitric oxide (NO) signallig which leads to development of diabetic cardiomyopathy. Improvement of NO – cGMP signalling have been reported to have cardioprotective effects. We investigated the effects of chronic activation of soluble guanylate cyclase (sGC) by cinaciguat in diabetic cardiomyopathy in a rat model of type-1 DM.

Methods: DM was induced by a single i.p. injection of streptozotocin in our rats. Rats were treated with 10 mg/kg/day cinaciguat (treatment groups) or with placebo (control groups) orally for 8 weeks. Left ventricular (LV) function was assessed using a pressure-volume (PV) conductance microcatheter system. Additionally to our functional experiments, gene expression (by qRT-PCR) and protein expression analysis (by Western blotting (WB)) were performed. Apoptosis was investigated by TUNEL assay. Cardiac remodelling and fibrosis were examined by histology and immunohistochemistry.

Results*:* DM was associated with significantly elevated endothelial nitric oxide synthase myocardial expressions while WB proved elevated phosphodiesterase-5 and protein kinase G levels (PKG) and decreased PKG activity (p-VASP/VASP ratio). We observed increased atrial natriuretic factor, transforming growth factor-β and matrix metalloproteinase-9 levels and fibrotic remodelling of the diabetic hearts. TUNEL assay showed increased apoptosis in DM. Impaired LV contractility (preload recruitable stroke work (PRSW): 49.5±3.3 vs. 83.0±5.5mmHg, $p<0.05$) and diastolic function (time constant of LV pressure decay (τ): 17.3±0.8 vs. 10.3±0.3msec, $p<0.05$) were found in the untreated DM group. Cinaciguat treatment prevented DM associated molecular changes and cardiac remodelling and significantly improved systolic (PRSW: 66.8±3.6 vs. 49.5±3.3mmHg, $p<0.05$) and diastolic function (τ: 14.9±0.6 vs. 17.3±0.8msec, $p<0.05$) compared to untreated DM. It had no effect in non-diabetic control animals.

Conclusions: Our results demonstrate that cinaciguat prevents myocardial alterations and improves cardiac dysfunction in diabetic rats. Pharmacological activation of sGC might be a novel therapeutic approach for diabetic cardiomyopathy. (Supported by the grant OTKA PD100245)

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders: Physiology and medicine of ischaemic circulatory diseases*
Supervisor: *Tamás Radovits*
E-mail: *csaba.matyas@gmail.com*

E/II-12
HEPATOCYTE GROWTH FACTOR IS A PREDICTOR OF 2-YEARS MORTALITY RISK FOLLOWING CARDIAC RESYNCHRONIZATION THERAPY

Péter Perge, András Boros, Szabolcs Szilágyi, István Osztheimer, Levente Molnár, Endre Zima, László Gellér, Béla Merkely, Gábor Széplaki

Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Hepatocyte growth factor (HGF) has mitogenic, angiogenic, antiapoptic and antifibrotic effects on various cells. The levels of HGF were found elevated during acute myocardial infarction and in heart failure. Notable cardioprotective effect were observed in diverse animal models. In humans HGF is a strong and independent predictor of all-cause mortality in patients with advanced heart failure. The object of the present study was to determine the association between plasma levels of HGF and clinical outcomes after CRT implantation.

We enrolled 137 HF patients who underwent CRT. Clinical controls were done at baseline, six months and two years after implantation. Primary end point was mortality, secondary end point was responder status at 6 months defined as more than 10% improvement in ejection fraction or more than 25% improvement in 6 minute walking test. Plasma HGF levels were analysed by ELISA from venous blood samples.

The median age of our patients were 67,9 years, the proportion of males were 80%. After six months 94 patients met the previously definced responsiveness criteria. Baseline HGF level was 1931±162,2 pg/ml, it decreases significantly after six months to 1160±49,02 pg/ml (p=0,005). The reduction was signficant both in responders and non-responders (p=0,0003 and p<0,0001). There was no statistically significant difference between responders and non-responders neither at baseline, nor after six months (p=0,1947 and p=0,2). We compared the survival of patients in the highest tertile of baseline HGF (1611-10692 pg/ml) with the lower two tertiles (492-1611 pg/ml). Two year mortality was significantly increased in patients with higher plasma HGF levels, with a hazard ratio of 3,237 (p=0,00002; 95%CI of HR=1,913-7,465).

Our results showed that elevated plasma HGF levels before CRT implantation predict significantly worse outcome, with a notably increased mortality after two years of follow-up. HGF might be an important marker to assess clinical outcome following CRT.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of circulatory diseases*
Supervisor: *Gábor Széplaki*
E-mail: *peter.perge@gmail.com*

E/II-13
DECREASED CAROTID DISTENSIBILITY IS PRESENT BUT DOES NOT EXPLAIN THE IMPAIRMENT OF BAROREFLEX-FUNCTION IN SCHIZOPHRENIC PATIENTS

Adrienn Sárközi[1], Beatrix Mersich[2], Domonkos Cseh[1], Márk Kollai[1], Alexandra Pintér[1]

[1] Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary
[2] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

Background: Increased cardiovascular mortality was reported in schizophrenic patients, most frequently due to arrhythmia-related sudden cardiac death (SCD). It was shown that impaired short-term blood pressure regulation, indicated by reduced baroreflex-sensitivity (BRS), was a risk factor for SCD in various diseased states. Reduced BRS was found in schizophrenic patients, but the underlying mechanism was not clarified. Stiffening of baroreceptor vessel wall may result in decreased activity of the baroreceptors and blunt the baroreflex. We investigated the distensibility of a baroreceptor vessel wall – such as the common carotid artery (CCA) – and tested the hypothesis that reduced BRS is associated with increased carotid artery stiffness in schizophrenic patients.

Subjects, methods*:* 25 first-episode schizophrenic patients (28±5 years) and 28 healthy, age- and gender-matched controls were examined. Diastolic diameter and pulsatile distension of the CCA were measured by echo wall-tracking, carotid pulse pressure was registered by tonometry. Based on these data, distensibility coefficient (DC) was calculated. ECG and beat-to-beat blood pressure recordings were used to determine BRS (BRSsp).

Results (mean±SD): DC showed marked reduction in schizophrenic patients compared to controls (4.0±1.3† vs. 5.2±1.3 10-3/mmHg). As expected, BRSsp was significantly decreased in patients (9.8±6.9† vs. 22.9±7.9 ms/mmHg). No relation was found between the DC and the BRSsp in patients, whereas the two parameters showed significant positive correlation in controls ($r=0.55^{\dagger}$). († $p<0.01$)

Discussion: In schizophrenic patients, carotid artery distensibility was markedly reduced but it was not related to diminished baroreflex-sensitivity. The underlying mechanism for increased carotid artery stiffness is yet unclear. In schizophrenic patients, elevated plasma homocysteine level and increased oxidative stress may contribute to the decrement of carotid distensibility. Our results suggest that decreased carotid elasticity does not contribute to the impairment of baroreflex-function substantially. We presume that reduced BRS may be related to a neuronal damage within the baroreflex arch.

Doctoral School: *Basic Medicine*
Program: *The mechanisms of normal and pathologic funcions of the circulatory system*
Supervisor: *Márk Kollai*
E-mail: *sarkozi.adrienn@med.semmelweis-univ.hu*

E/II-14
MEASUREMENT OF THE EFFECT OF DECELLULARIZED PORCINE HEART SCAFFOLD ON THE ADHESION OF HUMAN CARDIOVASCULAR CELL LINES USING IMPEDIMETRIC TECHNIQUE

Lívia Polgár[1,2]

[1] Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[2] Chemotaxis Research Group, Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary

Heart failure has high mortality rates despite development in medical and device therapy. Heart transplantation still seems to be the most effective therapy, however organ deficiency is a worldwide leading problem. Tissue engineered bioartificial hearts may solve this problem in Athe future. To produce an immune-neutral organ scaffold the heart has to be decellularized. In this work we examined the effect of cell-adhesion as a possible way of recellularization using impedimetric technique.

Human fibrosarcoma (HT-1080), endothelial (HMEC-1) and cardiomyocyte (HCM) cell lines were investigated. Adhesion was measured by xCELLigence SP system which allows real-time recording of impedance changes caused by cells adhering to golden electrodes placed at the bottom of the array. Adhesion was measured in the presence of different coatings: decellularized porcine heart scaffold homogenizate, fibronectin and fibronectin-homogenizate combination. Adhesion was calculated as the slope of the curves, normalized to control (DS).

Significant changes in adhesion were measured with all three cell lines. Decellularized porcine heart scaffold homogenizate did not decrease adhesion in any cell type. Fibronectin highly increased adhesion compared to control in all cells – especially in endothelial cells (DS 2.044+0.010 vs. 0.968+0.005). This positive effect of fibronectin was maintained even when mixed with homogenizate (DS 2.154+0.013), and was enhanced by homogenizate in cardiomyocytes (fibronectin-homogenizate combination vs. fibronectin alone, DS 2.128+0.013 vs. 1.069+0.003). These effects did not show significant decrease even in long term (72 hrs). In case of endothelial cell coating cardiomyocytes showed good adhesion to this cell layer (DS 3.121+0.077), positive effect of fibronectin incubation (DS 6.981+0.088) was measured here as well.

Based on these results, decellularized porcine heart scaffolds may be a good basis for adhesive recellularization by cardiovascular cells. This may be an important step in the development of tissue engineered whole heart and providing a curative therapy of heart failure.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischaemic circulatory diseases*
Supervisors: *Pál Soós, László Kőhidai*
E-mail: *gorlicze@gmail.com*

E/II-15
CORONARY CT ANGIOGRAPHY WITH MINIMAL TRAINING: DOES ITERATIVE RECONSTRUCTION HELP?

Mihály Károlyi, Ildikó Kocsmár, Márton Kolossváry, Béla Merkely, Pál Maurovich-Horvat

Heart and Vascular Center, Semmelweis University, Budapest, Hungary
HAS-SU "Lendület" Cardiovascular Imaging Research Group, Budapest, Hungary

Purpose: To evaluate the effect of experience with coronary computed tomography angiography (CCTA) on the plaque quantification using a semiautomatic software tool and different image reconstruction algorithms.

Methods: In total 25 patients with significant coronary artery disease on CCTA were randomly selected. All CCTA images were acquired on a 256-slice scanner. Images were reconstructed with standard filtered-back projection (FBP) and iterative reconstruction (iDOSE) techniques. Proximal 40 mm of the left anterior descending (LAD) artery of all patients were analyzed by two readers: Reader 1 (R1) with 5 years of experience in CCTA, Reader 2 (R2) a medical student with minimal experience in CCTA. The plaque quantification was performed by using a semiautomatic software tool. Coronary segmentation, lumen and vessel wall delineation was performed automatically, and corrected manually, if necessary. Time for automated segmentation of the coronaries and segmented length of the LAD was registered. Plaque burden and plaque components (fibrous tissue, dense calcium) were quantified using an adaptive threshold setting.

Results: Coronary segmentation was faster with iDOSE as compared to FBP (54.9 vs. 58.6 sec, $p<0.0001$). Importantly, automatic segmentation could not be performed in 5/25 cases with FBP and in 1/25 case using iDOSE. Longer path of the LAD was segmented automatically with iDOSE, than with FBP (144.7 vs. 121.9 mm, $p<0.05$). The mean plaque burden by Reader 1 versus Reader 2 in FBR were: 0.40 vs. 0.44 ($p<0.005$; bias 10.0%); in iDOSE: 0.39 vs. 0.40 ($p=0.15$; bias 4.0%). Whereas, corresponding plaque volumes were 193.4 vs. 214.6 mm^3 ($p<0.005$; bias 19.7%) and

193.5 vs. 196.3 mm^3 ($p=0.11$; bias 1.4%), respectively. The fibrous tissue volumes by R1 versus R2 in FBR were: 64.9 vs. 76.6 mm^3 ($p<0.05$; bias 16.5%); in iDOSE: 59.6 vs. 63.9 mm^3 ($p=0.06$; bias 7.1%). The mean dense calcium volumes by R1 versus R2 in FBR were: 33.4 vs. 47.3 mm^3 ($p<0.0001$; bias 34.5%); in iDOSE: 36.0 vs. 40.8 mm^3 ($p<0.05$; bias 12.5%).

Conclusions: Coronary segmentation was more robust using iDOSE, than with FBP. The medical student with no experience in CCTA was able to perform coronary plaque analysis after minimal training. However, she has systematically overestimated the plaque burden and plaque components. Importantly, the overestimation was smaller using iDOSE as compared to FBR.

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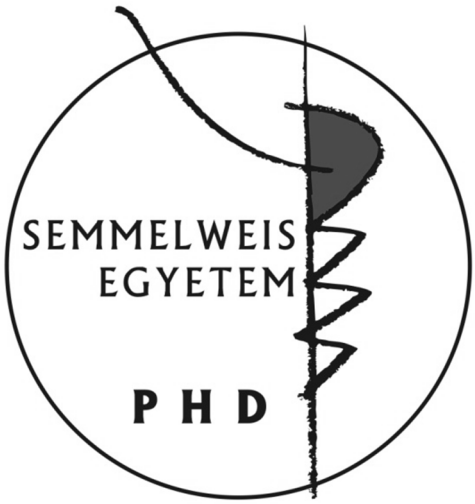
Doctoral School: *Basic Medicine*
Program: *Cardiovascular disorders, Physiology and medicine of ischaemic circulatory diseases*
Supervisor: *Béla Merkely*
E-mail: *karolyidr@gmail.com*



E/III
ORAL PRESENTATIONS

Chairman:
Prof. Dr. László Kopper

E/III-1
NEW ONSET DIABETES MELLITUS AND THE ANALYSIS OF DIPEPTYDIL-PEPTIDASE-4 AFTER LIVER TRANSPLANTATION

György Gámán

Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary

Introduction: New onset diabetes mellitus after transplantation (NODAT) is a common complication after orthotopic liver transplantatoin (OLT). Diabetogenic effect of Hepatitis C Vírus (HCV) infection is well known.

The aim of this study was to analyze the glucose homeostasis before and after OLT. Oral glucose tolerance test (OGTT) was carried out, and dipeptydil-peptidase-4 (DPP-4) activity was measured. Method: The study period was: 2012 to 2014. We enrolled 49 non-diabetic patients from the waiting list (Group-A) and 21 patients after OLT (Group-B). Seven patients were monitored continuously both before and after OLT. According to our preoperative OGTT results, 13 patients in group-A had newly diagnosed diabetes mellitus (group-A/DM) and 11 had impaired glucose tolerance (group-A/IGT). In 25 cases normal glucose tolerance was diagnosed (group-A/NGT). The calculated homeostasis model assessment insulin resistance (HOMA2-IR) values were both in group-A/DM and-IGT higher compared to group-A/NGT (2,42±0,81 vs 2±0,98 vs 1,28±0,67; p=0,001). In case of HCV infection (n=14; 29%) DM and IGT were more frequent. Postoperative results (group-B): Six patients in group-B had NODAT. In 9 cases IGT and in 6 cases NGT was detected. In case of HCV infection (n=9; 43%) DPP-4 levels were higher compared to patients with all other indications for OLT (15,5±5,2 vs 8,7±3,5; p=0,008). Evaluated the same individuals before and after OLT (n=7), decrease in beta-cell function was more charcterizing.

Conclusions: Preoperative OGTT is an important and easy investigation to rule out glucose imbalance prior to OLT. The HOMA2 calculation can also be useful both in preoperative and postoperative risk assessment. In our results DPP-4 activity is not specific for the type of glucose homeostasis imbalance, but in HCV infection it is higher. Refer to this study DPP-4 inhibitors can be effective in the therapy of NODAT, especially in HCV infected patients.

Doctoral School: *Pathological Sciences*
Program: *Clinical and experimental transplantation*
Supervisor: *Balázs Nemes*
E-mail: *gaman.gyorgy@med.semmelweis-univ.hu*

E/III-2
DIFFERENTIAL RESPONSE TO BRAF INHIBITION IN TUMOR CELLS WITH ONCOGENIC BRAF MUTATION

Eszter Molnár[1], Tamás Garay[1,2], Walter Berger[3], Balázs Döme [2,5], József Tímár[1,4], Balázs Hegedűs[4,5]

[1] *II. Department of Pathology, Semmelweis University, Budapest, Hungary*
[2] *National Korányi Institute of TB and Pulmonology, Budapest, Hungary*
[3] *Institute of Cancer Research, Medical University of Vienna, Vienna, Austria*
[4] *HAS-SU Molecular Oncology Research Group, Budapest, Hungary*
[5] *Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria*

Background and aim: BRAF is a key component in the RAS/RAF/MEK/ERK signaling cascade. Despite the fact that oncogenic BRAF mutation can be a driver in various malignancies not all BRAF mutant tumors show similar sensitivity to BRAF inhibition. Accordingly, we evaluated the *in vitro* effect of BRAF inhibitors as single agent or in combination with other inhibitors targeting relevant activating mutations in BRAF mutant melanoma, colorectal and non-small lung cancer cell.

Methods: We performed short-term viability and long-term clonogenic assays on 3 melanoma (V600E), 2 colorectal (V600E) and 2 non-small-cell lung cancer (L597V and G466V) BRAF mutant cell lines to assess effect of BRAF (vemurafenib, PLX4720 and dabrafenib) inhibition as single therapy or in combination with EGFR (erlotinib) and RAS prenylation (zoledronic acid) inhibitors. The effect on the signal transduction was measured by Erk1/2 activation via immunoblot assay.

Results: Cell lines with L597V and G466V BRAF mutation demonstrated the lowest sensitivity to vemurafenib and PLX4720 since these agents are highly specific for V600E mutation. Nevertheless all cell lines showed sensitivity to dabrafenib a less mutation specific BRAF inhibitor. Combination with erlotinib resulted in increased inhibition in cells that expressed high levels of EGFR or carried alterations in the EGFR signaling. Interestingly, while vemurafenib or zoledronic acid alone was ineffective in NRAS/BRAF double mutant cells, the combination treatment led to a robust synergism.

Conclusion: BRAF mutant tumor cells display distinct response to BRAF inhibition. Our data suggests that to achieve effective treatment of BRAF mutant tumors combination treatments should be developed that target complementary pathways or additional oncogenic alterations concurrently.

Doctorial School: *Pathological Sciences*
Program: *Oncology*
Supervisor: *Balázs Hegedűs*
E-mail: *molnar.eszter@med.semmelweis-univ.hu*

E/III-3
POLYMYXIN-RESISTANCE IN KLEBSIELLA PNEUMONIAE AND ENTEROBACTER ASBURIAE

Béla Kádár, Béla Kocsis, Károly Nagy, Dóra Szabó

Institute of Medical Microbiology, Semmelweis University, Budapest, Hungary

Polymyxins are polypeptide antibiotics that are bactericidal against several Gram-negative bacteria, affecting the outer membrane of these microbes. After their discovery in the late 1940s they were disregarded from clinical practice because of their toxic side effects. However, as multidrug resistant Gram-negative pathogens became more frequent, polymyxins were reintroduced into therapy. Since then, resistance to polymyxins has appeared. In Hungary, the first polymyxin-resistant *Klebsiella pneumoniae* strains, were detected among KPC-2 producing ST258 clone in 2008. We investigated one polymyxin-susceptible and five polymyxin-resistant *K. pneumoniae* ST258 strains, as well as *Enterobacter asburiae* strains from sporadic cases. Checkerboard test was implemented on two *K. pneumoniae* strains originating from that outbreak to find possibly efficient antibiotic combinations. Combinations of imipenem-tobramycin and imipenem-ciprofloxacin were found synergistic against both strains, despite their carbapenemase-production. Rifampicin-imipenem and rifampicin-ciprofloxacin were proved to be partially synergistic, whereas colistin-rifampicin and polymyxin B-rifampicin combinations were found synergistic too.

Outer membrane proteins from each strain were separated by two-dimensional electrophoresis and were analysed by MALDI-TOF mass spectrometry. The protein sequences were determined based on Swiss-Prot database. In the resistant strains a 16 kDa protein fraction loss was detected and the missing proteins were LysM/BON domain superfamily and DNA starvation proteins. The relative gene expression of *phoP-pmrD-arn* regulatory system was investigated by real-time PCR, and overexpression was confirmed in the polymyxin-resistant *K. pneumoniae* strains. We performed assays to analyse the susceptibility of the strains to antimicrobial polypeptides protamine, lactoferrin and lysozyme. The polymyxin-resistant strains showed significantly higher bacterial cell counts than the susceptible counterparts, indicating association between resistance to polymyxins and tolerance to antimicrobial peptides. To the best of our knowledge our investigations were the first ones to detect outer membrane protein change in polymyxin-resistant Enterobacteriaceae strains.

Doctoral School: *Pathological Sciences*
Program: *Study of the immunbiological effects of microorganisms and of their components at molecular and cellular level and in the microorganisms*
Supervisor: *Dóra Szabó*
E-mail: *kadar.bela@gmail.com*

E/III-4
UNUSUAL HOST RANGE OF THE FELINE ADENOVIRUS

Balázs Stercz

Department of Medical Microbiology, Semmelweis University, Budapest, Hungary

Adenoviruses are important pathogens in humans and animals. Their major pathogen effects are latency in immune cells, immunosuppression and transactivation of retroviruses beside the acute infections. Although feline AIDS would be ideal to study interaction of FIV and adenoviruses, so far no adenovirus has been known in the members of Felidae family. The first isolate (feline adenovirus, FeAdV) obtained from a Hungarian cat shows very unusually wide host range on the contrary of other adenovirus species.

Aims*:* We studied the permissivity of feline, human, simian, porcine, hamster and mouse cells of different histological types. FeAdV was purified and concentrated by using a chromatography based system and the infectious viral particles were quantitated. Cytopathic effect (CPE) of the adenovirus replication and latent infection without visible CPE were verified by direct immunofluorescence (IFA) and immunochemical staining (ICS) using anti-hexon monoclonal antibodies.

Results*:* Visible cytopathic effect and IFA/ICS positivity was detected in non-tumours (e.g. HEK-293, M426) and tumorous (HeLa, MCF-7, U-87, A-172) cells. Human epithelial cell line (MEWO), deficient in integrin expression, did not show CPE. Human freshly isolated PBMC, B- (Bjab) and T- (MOLT-3, HSB-2, Sup-T1, E6.1) lymphocytes, U937 myeloid cells were IFA+ without CPE. Simian (Vero, OMK, COS-7), porcine (PD-5, PK-15) cells showed CPE and IFA/ICS positivity. Interestingly, hamster CHO and mouse 3T3-LI cells were resistant to FeAdV infection.

Conclusions*:* Possible configural alteration, due to the known fiber knob mutations, result in the unusual wide host range that suggest zoonotic infection and interspecies spread. Lately, FeAdV with 100% hexon homology was detected by PCR in Japan and Brazil. Human and feline immunocompromised individuals might be at higher risk of infections.

Doctoral School: *Pathological Sciences*
Program: *Alterations of cells, fibres and extracellular matrix and diagnostic pathomorphological studies in the course of heart and vascular diseases and in certain tumours. Experimental and diagnostic pathomorphological studies*
Supervisor: *József Ongrádi*
E-mail: *stercz.balazs@med.semmelweis-univ.hu*

E/III-5
CELL CYCLE ANALYSIS CAN DIFFERENTIATE THIN MELANOMAS FROM DYSPLASTIC NEVI AND REVEALS ACCELERATED REPLICATION IN THICK MELANOMAS

Gergő Kiszner

I. Department of Pathology and Experimental Cancer Research & HAS-SU Tumor Progression Research Group, Semmelweis University, Budapest, Hungary

The overlapping clinical presentation and histopathology of dysplastic nevi and thin melanomas and the lack of proper biomarkers in borderline lesions carry the risk of misdiagnosing melanomas. Cell replication integrates aberrations of cell cycle regulation and diverse upstream pathways which all can contribute to melanoma development and progression. In this study, cell cycle regulatory proteins were detected *in situ* in cutaneous benign and malignant melanocytic tumors for correlating major cell cycle fractions (G1, S-G2 and G2-M) with melanoma evolution.

Dysplastic nevi expressed early cell cycle markers (cyclin D1 and Cdk2) significantly more ($p<0.05$) than common nevi. Post-G1 phase markers such as cyclin A, geminin, topoisomerase IIα (peaking at S-G2) and aurora kinase B (peaking at G2-M) were expressed in thin (≤1 mm) melanomas but not in dysplastic nevi suggesting that dysplastic melanocytes engaged in the cell cycle do not complete replication and remain arrested in G1 phase. In malignant melanomas the expression of general and post-G1 phase markers correlated well with each other implying a negligible cell cycle arrest. All post-G1 phase markers as well as Ki67 but none of the early markers cyclin D1, Cdk2 or Mcm6 were significantly more frequent in thick (>1 mm) compared to thin melanomas. Except an elevated aurora kinase A expression, metastatic melanomas did not differ significantly from thick melanomas. Combined detection of the post-G1 phase cyclin A, the replication licensing Mcm6, and Ki67 correctly classified thin melanomas and dysplastic nevi in 95.9% of the original samples and in 93.2% of cross-validated grouped cases at 89.5% sensitivity and 92.6% specificity.

In conclusion, the combined detection of post-G1 phase and general cell cycle markers may provide significant information on malignancy in doubtful cases for preventing false negative diagnosis and support the concept of an accelerated cell cycle progression associated with vertical melanoma growth.

Doctoral School: *Pathological Sciences*
Program: *Experimental Oncology*
Supervisor: *Tibor Krenács*
E-mail: *kiszner@mail.korb1.sote.hu*

E/III-6
EFFECT OF IONIZING RADIATION ON BBB ENDOTHELIAL DISRUPTION AND RECOVERY. AN IN VIVO STUDY

Boglárka Schilling-Tóth[1], Nikolett Sándor[1], Violetta Léner[2]

[1] Frédéric Joliot-Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary
[2] Department of Morphology and Physiology, College of Health Care, Semmelweis University, Budapest, Hungary

Aims: The aim of the study was to detect the harmful effect of radiation in young and adult mice therefor we have investigated impairment in BBB integrity induced by low (0.02 – 0.5Gy) and high (1-10 Gy) doses of X-ray exposure. Dividing the early acute impairment and late side effect the mice were harvested at different time points. Nevertheless we measured the type of cell death of endothelial cells. Furthermore detecting the endothelial progenitor cells (EPC) was to pursue the recovery of endothelial disruption.

Methods: The effect of local cranial irradiation on the permeability of BBB was investigated in Bl/6 mice at 10 days old age, 10 week's old age and *in utero* exposed animals. Following in time the brain extravasation was assessed with Evan's Blue (EB) at one day, one week, one and six month after X-ray exposure. Brain edema was evaluated using the wet/dry method. Senescence was measured by SA-β-Gal assay. EPCs were investigated using colony assay (CFU-EPC). The numbers of peripheral mononuclear cells (PMNC) also was measured.

Results: Our data suggest an age-dependent decline in the radio-sensitivity of mice, because in the 10 weeks of age irradiated group significant increase of the permeability was observed at one week, in 10 days old age irradiated mice at one month, *in utero* treated mice at 6 months after X-ray exposure.

In senescence of endothelial cells a significant elevated level was noticed after higher doses.

Circulating EPC outgrowth colonies were reduced at higher dose at 24 hours, which did not reached the control level even later. At low dose the decline of colony- number was observable just at 24 hours. Although we performed local head irradiation a PMNC lessening was noticed in early time after irradiation. Our results suggest that mice exposed up to 2 Gy irradiation have decreased numbers of circulating EPCs, what remained at the later time points at the higher doses.

Conclusion: Our in vivo experimental data demonstrated that impairment of permeability was delayed in the immature brains. A better understanding and awareness of this phenomenon are essential for designing appropriate treatment modality in brain radiotherapy or in diagnostic radiology.

Doctoral School: *Pathological Sciences*
Program: *Experimental Oncology*
Supervisor: *Hargita Hegyesi, Géza Sáfrány*
E-mail: *schtboge@gmail.com, nikisan@osski.hu*

E/III-7
CONNEXIN 43 EXPRESSION AND CELL COUPLING IN GIANT CELL TUMOR OF BONE (GCTB)

Péter Balla, Máté Előd Maros, Nóra Meggyesházi, Gergő Kiszner, Tibor Krenács

I. Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

Intercellular communication mediated by connexins (Cx) plays a critical role in the control of cell proliferation and differentiation. Gap junctions permit the transfer of ions, and regulatory molecules of <1.8 kDa including morphogens, metabolites and secondary messengers i.e. cAMP, IP3 between coupled cells. Connexins can also mediate interactions both with the extracellular microenvironment through hemichannels and with intracytopasmic signaling proteins. Gap junctions are involved in the regulation of osteoblast development and survival through promoting signals and nutrients between osteoblasts (bone marrow stromal cells) and osteocytes. Mutations of Cx43 gene can lead to skeletal malformations i.e. oculodentodigital dysplasia (ODDD). Giant cell tumour of bone (GCTB) is an aggressive osteolytic lesion, in which neoplastic stromal cells drive osteoclastogenesis.

Cx43 expression in GCTB was tested with immunoperoxidase staining in tissue microarrays using digital slides including image quantitation. Subcellular localization, mRNA and protein expression of Cx43 and dye transfer charaterizing cell coupling were compared between primary GCTB stromal cells and HDFa fibroblasts.

Cx43 protein was mainly localized to the cell membranes in HDFa fibroblasts, while it was stack in the endoplasmic reticulum network in neoplastic GCTB stromal cells. Both in tissue sections and in immunoblots Cx43 protein and mRNA levels were significantly reduced in primary GCTB stromal cells compared to HDFa fibroblast. Furthermore, and extra protein band consistent with Cx43 phosphorylation was exclusively seen in HDFa extracts but not in neoplastic stromal cells. Flow cytometry revealed a six-fold cell coupling in fibroblasts cultures compared to primary GCTB stromal cells.

Connexin 43 can be detected at a significanlty reduced level in primary GCTB stromal cells compared to fibroblasts. This and the delocalization of Cx43 to the endoplasmic reticulum are responsible for the reduced cell coupling in neoplastic cells, which may contribute to their osteoclastogenic phenotype of GCTB.

Doctoral School: *Pathological Sciences*
Program: *Experimental Oncology*
Supervisor: *Tibor Krenács*
E-mail: *ballapeti81@gmail.com*

E/III-8
PROGRAMMED CELL DEATH AND IMMUNOGENIC CELL DEATH SIGNALS INDUCED BY MODULATED ELECTROHYPERTHERMIA IN COLORECTAL ADENOCARCINOMA MODEL

Nóra Meggyesházi[1], Gábor Andócs[2]

[1] I. Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
[2] Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan

Objective: Electric field and the concomitant heat (modulated electrohyperthermia, - mEHT) can synergistically provoke cell death in tumor tissue, due to elevated glycolysis (Warburg effect), ion concentration and permittivity in cancer compared to non-malignant tissues.

Here we studied the molecular mechanism of cell death and if damage associated molecular patterns (DAMP) required for professional antigen presenting cells for inducing immunogenic cell death (ICD) can be detected upon mEHT treatment *in vivo* in colorectal cancer.

Methods: HT29 colorectal adenocarcinoma cell lines implanted into the femoral region of Balb/c (nu/nu) mice were subjected to a single shot of 30 min 13.56MHz mEHT. Contra-lateral untreated and the treated samples were collected at 0, 1, 4, 8, 14, 24, 48, 72, 120, 168 and 216h post-treatment. Whole genome mRNA expression, apoptosis protein arrays, tissue microarrays, immunofluorescence and digital microscopy were used.

Results: mEHT treatment induced significant tumor cell death linked with DNA fragmentation (24-48h) using TUNEL assay, in line with the mitochondrial translocation of Bax (8-14h), cytochrome c release from mitochondria to the cytoplasm (8-14h) and concomitant nuclear translocation of apoptosis inducing factor AIF (14-24h). Activated caspase-3 was not detected in tumor cells. In mRNA assay at 4h, significant differential expression of 48 genes including heat shock proteins was seen upon mEHT treatment. Immunohistochemistry and apoptosis protein array confirmed elevated hsp70 expression (14-24h) in the morphologically intact peripheral parts of treated tumors. Furthermore, an early (4h) cytoplasmic to cell membrane exposure of carleticulin and later (24-48h) the release HMGB1 protein from cell nuclei was also revealed in the treated samples.

Conclusion: In HT29 xenograft mEHT caused a dominantly caspase independent programmed cell death involving AIF activation along with the spatiotemporal appearance of DAMP signals relevant to ICD. As opposed to systemic ICD inducers, local mEHT treatment does not cause general damage of immune cells.

Doctoral School: *Pathological Sciences*
Program: *Experimental Oncology*
Supervisor: *Tibor Krenács*
E-mail: *meggyeshazinora@gmail.com*

E/III-9
DECORIN DEFICIENCY PROMOTES HEPATIC CARCINOGENESIS

Zsolt Horváth, Ilona Kovalszky, Alexandra Fullár, Katalin Kiss, Kornélia Baghy

I. Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

Hepatocellular carcinoma represents one of the most-rapidly spreading cancers in the world. In the majority of cases, an inflammation-driven fibrosis or cirrhosis precedes the development of the tumor. During malignant transformation, the tumor microenvironment undergoes qualitative and quantitative changes that modulate the behavior of the malignant cells. A key constituent for the hepatic microenvironment is the small leucine-rich proteoglycan decorin, known to interfere with cellular events of tumorigenesis mainly by blocking various receptor tyrosine kinases (RTK) such as EGFR, Met, IGF-IR, PDGFR and VEGFR2. In this study, we characterized cell signaling events evoked by decorin deficiency in two experimental models of hepatocarcinogenesis using thioacetamide or diethyl nitrosamine as carcinogens. Genetic ablation of decorin led to enhanced tumor occurrence as compared to wild-type animals. These findings correlated with decreased levels of the cyclin-dependent kinase inhibitor $p21^{WAF1/CIP1}$ and a concurrent elevation in retinoblastoma protein phosphorylation via cyclin dependent kinase 4. Decreased steady state $p21^{Waf1/Cip1}$ levels correlated with enhanced expression of transcription factor AP4, a known transcriptional repressor of $p21^{Waf1/Cip1}$, and enhanced c-Myc protein levels. In addition, translocation of β-catenin was a typical event in diethyl nitrosamine-evoked tumors. In parallel, decreased phosphorylation of both c-Myc and β-catenin was observed in $Dcn^{-/-}$ livers likely due to the hindered GSK3β-mediated targeting of these proteins to proteasomal degradation. We discovered that in a genetic background lacking decorin, four RTKs were constitutively activated (phosphorylated), including three known targets of decorin such as PDGFRα, EGFR, IGF-IR, and a novel RTK MSPR/RON. Our findings provide powerful genetic evidence for a crucial in vivo role of decorin during hepatocarcinogenesis as lack of decorin in the liver and hepatic stroma facilitates experimental carcinogenesis by providing an environment devoid of this potent pan-RTK inhibitor. Thus, our results support future utilization of decorin as an antitumor agent in liver cancer.

Doctoral School: *Pathological Sciences*
Program: *Oncology*
Supervisor: *Kornélia Baghy*
E-mail: *hzsolt@korb1.sote.hu*

E/III-10
MECHANICAL INJURY INCREASES NORADRENALINE RELEASE IN THE RAT SPINAL CORD

Zoltán Borbély, Krisztián Benedek Csomó

Department of Oral Biology, Semmelweis University, Budapest, Hungary

In this study we measured the changes in the release of noradrenaline during the acute phase of spinal cord injury. By this we aimed to observe the uptake and liberation of this neurotransmitter that is most closely related to neuroimmune responses and to develop a method to test possible therapeutic methods for the treatment of spinal cord injury.

Methods: Wistar rats were divided into three groups: control, 1 day after hemisection, 3 days after hemisection. In the hemisection groups the spinal cord was cut unilaterally with a blade at the L4 segment. The release of noradrenaline was measured 1 or 3 days later from spinal cord segments L5 to S1. Shortly, measurements were performed as follows: The tissue was cut into slices and incubated in a medium containing ^{3}H-noradrenaline for 45 minutes to incorporate the radioactively labelled neurotransmitter. Slices were put into superfusion chambers and effluents were collected in 19 fractions of 200 seconds. Electric field stimuli were applied at the beginning of the 3rd and 13th fractions. In one half of each group the selective noradrenaline-reuptake inhibitor nisoxetine was added beginning from the 8th fraction. The ^{3}H-noradrenaline content of each fraction was determined using a scintillation counter.

Results*:* Hemisection caused a significant increase in the release of noradrenaline from the spinal cord. When compared to the control group the transmitter release increased 1 day after the injury with a further increase on the 3rd day. Nisoxetine increased the measured release of the transmitter by inhibiting its reuptake. This effect however was diminished by the spinal cord injury in the hemisection groups.

Conclusion: The changes in transmitter uptake and release and the overall increase in noradrenaline levels near the injury may play a role in the inflammatory process and consequential loss of function in spinal cord injuries.

Doctoral School: *Clinical Medicine*
Program: *Dental research*
Supervisor: *Gábor Varga*
E-mail: *zoltan@drborbely.hu*

E/III-11
GENES EXHIBITING CELL CYCLE-DEPENDENT EXPRESSION PROFILE REFLECT THE MALIGNANCY SIGNATURE OF ADRENOCORTICAL CANCER

Vince Kornél Grolmusz[1], Eszter Tóth[2], István Likó[3], Péter Igaz[1], János Matkó[2], Károly Rácz[1,4], Attila Patócs[4,5,6]

[1] II. Department of Medicine, Semmelweis University, Budapest, Hungary
[2] Department of Immunology, Eötvös Loránd University, Budapest, Hungary
[3] Richter Gedeon Ltd, Budapest, Hungary
[4] Molecular Medicine Research Group, Semmelweis University – Hungarian Academy of Sciences, Budapest, Hungary
[5] Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary
[6] "Lendület" Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences, Budapest, Hungary

Background: Adrenocortical cancer is a rare neoplasm with poor prognosis. Recent studies have implicated several molecular pathways, including cell cycle alterations in its formation.

Aims To analyze the gene expression profile in human adrenocortical cancer cell line, H295R in a cell cycle dependent manner, and to correlate with those measured in human cancerous tissues.

Materials and Methods: Cultured H295R cells were sorted according to their cell cycle phase. Genomic DNA was stained using Vybrant DyeCycle Orange stain. Viable cells were sorted according to the DNA content into three groups representative to their phase: G1, S, G2 using BD FACS Aria III Cell Sorter. Total RNA was isolated from sorted cells and whole genome gene expression profile was assessed by Agilent 44k cDNA microarray. Nine differentially expressed genes were validated by quantitative real time PCR (qPCR) using individual Taqman assays. Expressions of detected genes were compared with the malignancy signature of adrenocortical cancer. For statistical analysis ANOVA, Tukey post-hoc test, Benjamini-Hochberg correction and Student's paired T-test was used.

Results: 23 genes were differently expressed between cells sorted by cell cycle phases. All genes chosen for qPCR were validated successfully. Comparison with former adrenocortical cancer expression data showed that genes upregulated in S phase compared to G1 phase were upregulated in cancer tissues, while a gene downregulated in S phase compared to G1 phase was also dowregulated in cancer tissues.

Conclusions: DNA-content based flow cytometry sorting is a useful method to obtain enough cells in different cell cycle phases for further whole genome analyses. Gene expression changes between G1 and S phases reflect the malignancy signature of adrenocortical cancer, underlining the exceptional importance of cell cycle alterations in the pathogenesis of adrenocortical cancer.

The authors acknowledge the financial support from Hungarian Resarch Fund (OTKA PD100648) and from National Development Agency (KTIA_AIK-2-2012-0010).

Doctoral School: *Clinical Medicine*
Programme: *Hormonal regulations*
Supervisor: *Attila Patócs*
E-mail: *grolmusz.vince@med.semmelweis-univ.hu*

E/III-12
PRIMARY SPINAL TUMOR MORTALITY SCORE (PSTMS): A NOVEL SCORING SYSTEM FOR PREDICTING POOR SURVIVAL

Zsolt Szövérfi, Áron Lazáry , Péter Pál Varga

National Center for Spinal Disorders, Budapest, Hungary

Introduction: Although, surgical and oncological therapy of primary spinal tumors (PST) has changed significantly over the last few decades, the prognosis is still poor.

Aims: The objective of the present study was to investigate pre-operative factors associated with PST mortality, and to develop a predictive scoring system of poor survival.

Methods: The study included 323 consecutive patients with PST, treated surgically over an 18 year period at the National Center for Spinal Disorders. Patients were randomly divided into a training cohort (TC; n=273) and a validation cohort (VC; n=50). In the TC twelve pre-operative factors were investigated using Cox regression. Based on the mortality related variables, a simple scoring system of mortality was created, and three groups of patients were identified. Kaplan-Maier and log-rank analyses were used to compare the survival in the three groups. The model performance was assessed by measuring the discriminative ability (c-index) of the model and by applying a pseudo R-squared goodness-of-fit test (Nagelkerke's R_N^2). Internal validation was performed using bootstrapping in the TC and assessing the discrimination and explained variation of the model in the VC.

Results: Patient age, spinal region, tumor grade, spinal pain, motor deficit and myelopathy/cauda syndrome were significantly associated with poor survival in the multivariate analysis ($p<0.001$, $R_N^2=0.799$). Based on these variables, we developed the Primary Spinal Tumor Mortality Score (PSTMS), where an eight-point scale was divided into three categories (low, medium and high mortality). The three PSTMS categories were significantly associated with the overall survival ($p<0.001$, $R_N^2=0.811$, c=0.82). The models performance remained similarly high in the VC ($R_N^2=0.831$, c=0.81).

Conclusion: The present study identifies six predictive variables for mortality in PST. Using these six variables, an easy-to-use scoring system was developed which can be applied to estimate the postoperative survival in all types of PST patients.

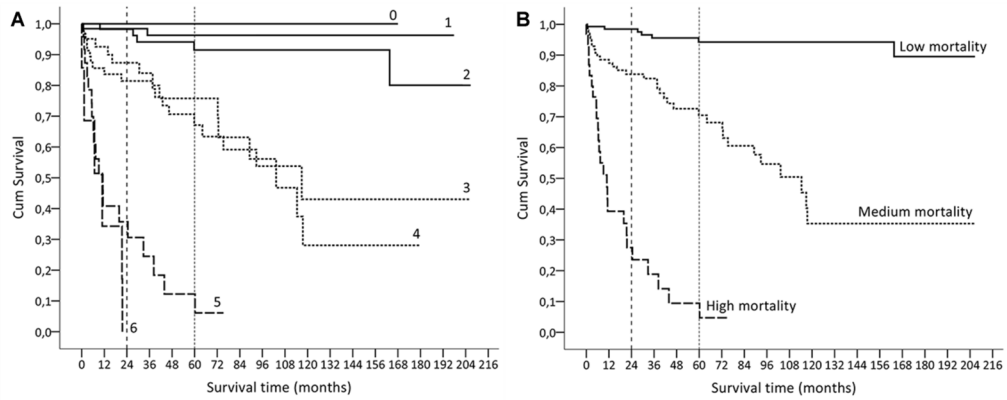
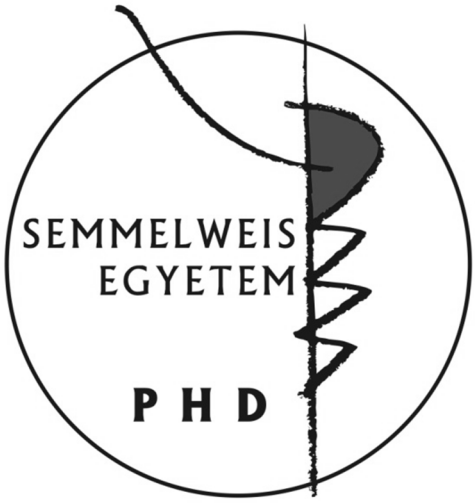


Figure 1. – Estimated Kaplan–Meier survival based on the PSTMS. ***A.*** *Cumulative survival plots based on the total scores of the PSTMS (p<0.001).* ***B.*** *Cumulative survival plots based on the three categories of the PSTMS (p<0.001).*

Doctoral School: *Clinical Medicine*
Program: *Physiology and pathology of the musculoskeletal system*
Supervisor: *Áron Lazáry*
E-mail: *zsolt.szoverfi@bhc.hu*



E/IV
ORAL PRESENTATIONS

Chairman:
Prof. Dr. Barna Vásárhelyi

E/IV-1
YAP1 IN THE HIPPO PATHWAY INFLUENCES THE RISK OF ASTHMA

Lili E. Fodor[1], Ildikó Ungvári[1], Ágnes F. Semsei[1], Orsolya Lautner-Csorba[1], András Bikov[3] Csaba Szalai[1,2]

[1] Department of Genetics, Cell-and Immunobiology, Semmelweis University, Budapest, Hungary
[2] Heim Pal Children's Hospital, Budapest, Hungary
[3] Department of Pulmonology, Semmelweis University, Budapest, Hungary

Asthma is an inflammatory disorder of the lungs. The main aim of this study was to identify new asthma susceptibility genes within the Hippo pathway. The Hippo pathway is responsible for organ size control, and is an important pathway that mediates survival and apoptosis of immune cells that play a role in asthma.

The expression of seven genes in the Hippo pathway was studied on RNA isolated from induced sputum of twenty asthmatics and twelve non-asthmatics. TaqMan gene expression assays were used in order to find a new gene to play a role in asthma. Furthermore, fifteen, single nucleotide polymorphisms (SNPs) in the promoter region of *YAP1* were genotyped on 525 asthmatics and 710 controls using KASPar genotyping, in order to find a susceptibility allele within this gene.

As a result, *YAP1* gene expression levels were found to be significantly different between the two groups studied ($p=0.044$), hence indicating *YAP1* as a novel gene in the Hippo pathway to play a role in asthma susceptibility. Additionally, correlation studies showed a significant positive correlation between *YAP1* mRNA level and sputum macrophage percentages ($p=0.034$), which confirms that *YAP1* gene expression increases in asthmatic progress, as well as the macrophage count increasing, leading to inflammation of the lungs in asthma. Additionally, *YAP1* mRNA level also showed significant differences between the control, the mild asthmatic and the moderate to severe asthmatic groups ($p=0.035$). On the other hand, the data acquired from KASPar genotyping is still under evaluation.

To conclude, in this study a new gene was identified within the Hippo pathway that may play a role in asthma contributing to the existing knowledge on the pathogenesis of asthma.

Doctoral School: *Molecular Medicine*
Program: *Basis of human molecular genetics and gene diagnostics*
Supervisor: *Csaba Szalai*
Email: *fodorlilierika@hotmail.com*

E/IV-2
THE DIFFERENT REGULATION OF IL-17 AND IL-22 PRODUCTION DURING THE HUMAN IN VITRO TH17 CELL DIFFERENTIATION

Eszter Baricza[1], Barbara Érsek-Molnár[1], Edit I. Buzás[1], György Nagy[2]

[1] Department of Genetic-, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary
[2] Department of Rheumatology, Semmelweis University, Budapest, Hungary

Background: Th17 cells produce several inflammatory cytokines, such as interleukin (IL)-17A, -17F, -21, -22, and tumor necrosis factor-α). In the present study we investigated the human Th17 cell differentiation in vitro.

Materials and methods: CD4 positive T cells were negatively separated by magnetic method from peripheral blood mononuclear cells (PBMC) of healthy volunteers. The cells were treated for 5-10 days with anti-CD3 and anti-CD28 antibodies and with TGFβ (2.5ng/ml), IL-6 (25ng/ml) and IL-1 (10ng/ml) cytokines, furthermore with anti-IL-4 (10μg/ml) and anti-IFNγ (10μg/ml) blocking antibodies. The IL-17 and IL-22 production were measured by ELISPOT and ELISA, the RORγt expression was measured by real-time PCR and by Western blot methods. Cell viability was monitored by Trypan blue staining and by Annexin V binding.

Results: Anti-CD3/CD28 treatment increased the IL-17 production, but did not alter the RORγt expression. The anti-IL-4 and anti-IFNγ antibody treatment significantly increased the anti-CD3/CD28, TGFβ, IL-6, and IL-1 induced RORγt expression. The IL-17 production was similar in the fifth and tenth day of the treatments by contrast the IL-22 production was greatly reduced by TGFβ, IL-6, IL-1, cytokines, anti-IL-4 and anti-IFNγ blocking antibodies. The applied treatments did not change the viability of the cells.

Conclusion: Our results suggest that IL-17 and IL-22 production are regulated in different ways during CD4 T cell activation and Th17 differentiation.

Doctoral School: *Molecular Medicine*
Program: *Basis of human molecular genetics and gene diagnostics*
Supervisor: *György Nagy*
E-mail: *bekyca86@gmail.com*

E/IV-3
ONTOGENESIS OF HEMOPOIETIC CELLS OF YOLK SAC ORIGIN

Dávid Dóra

Institute of Human Morphology and Developmental Biology, Semmelweis University, Budapest, Hungary

Introduction*:* Studies on bird embryos showed it first, that in the advanced vertebrates, therefore in human embryo, the embryonal haematopoiesis begins in the blood islands of the extraembryonic yolk sac, and it continues with the formation of intraembryonal hemopoietic organs. During the immunologic characterization of the haemopoetic cells of early chick embryos, we observed two types of CD45+ cells: a round one, and one with a stellate - like morphology . The round shaped CD45+ cells appear in the blood islands of the 2-day old embryo's yolk sac. After 24 hours, by the emerge of the embryo's own circulation, and its intraembryonic hematopoiesis, round-shaped CD45+ cells appear in the lumen of the embryonal vessels. At the same time with the appearance of the round CD45+ cell clusters, a stellate-like CD45+ cell population shows up scattered throughout the embryonal mesenchyma, which one will populate the settlement of nearly all organ rudiments in the subsequent development stages.

Aims: Our current researches' goal was, to find out the ontogenetic connection between the round and the stellate CD45+ cell populations, and to determine the stellate CD45+ cells' origin, by seperating the yolk sac, and the embryo itself. In order to respond our questions we applied in vitro and in ovo embryonal cell cultures.

Results*:* Between sterile circumstances we excised the 2-day chick embryos before the beginning of circulation, and we incubated the safely preserved yolk sacs for 48 hours. After the procedure, we incubated the isolated chick embryos in an organ culture of collagenmatrix basis till 2 days, before their cross section's were stained by different immunologic markers. The immuncitochemical stainings indicated, that in the isolated embryo cultures only cells with round morphology were growing. On the contrary, in the in ovo yolk sac cultures both the round one, and the one with the ramified morphology cell groups evolved equally. Our results so bring up the hypothesis, that the stellate - like CD45+ cells derive from the yolk sac, which ones will later colonize the embryonal organ rudiments, and will differentiate organ - specifically to cells, with dentritic morphology.

Doctoral School: *Molecular Medicine*
Program: *Embryology, theoretical, experimental and clinical developmental Biology*
Supervisor: *Nándor Nagy*
E-mail: *doradavid11@gmail.com*

E/IV-4
IMPACTS OF O-GLCNAC ON ENDOTHELIAL NITRIC OXIDE SYNTHASE IN DIABETIC NEPHROPATHY

Renáta Gellai[1,2], Judit Hodrea[1,4], Lilla Lénárt[1,4], Sándor Kőszegi[1,4], Ágota Vér[2], Nóra Fanni Bánki[1,4], László Wagner[5], Norbert Fülöp[6], Ágnes Molnár[1], Ádám Vannay[3,4], Attila J. Szabó[4], Andrea Fekete[1,4]

[1] HAS-SU „Lendület" Diabetes Research Group, Budapest, Hungary
[2] Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, Hungary
[3] HAS-SU Pediatrics and Nephrology Research Group, Budapest, Hungary
[4] I.Department of Pediatrics, Semmelweis University Budapest, Hungary
[5] Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary
[6] Kaposi Mór Hospital, Kaposvár, Hungary

Introduction: O-linked ß-N-acetylglucosamine (O-GlcNAc) glycosylation is a posttranslational modification on the serine and treonine residues of proteins which is in competition with phosphorylation due to the identical sites of modification. It is already accepted that O-GlcNAcylation plays an important role in the development of diabetic cardiomyopathy, but little is known about it's role concerning diabetic nephropathy (DNP).

Aims: We examined O-GlcNAcylation and the effect of renin-angiotensin-aldosterone

system (RAAS) inhibitors in a rat model of DNP and in human proximal tubular cells (HK2). O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA), which are responsible for the addition and removal of the single O-GlcNAc moiety were investigated. Since decreased expression of endothelial nitric oxide synthase (eNOS) plays a pivotal role in the progression of DNP, we also measured alterations in phosphorylated eNOS and Akt levels.

Methods*:* Five weeks after streptozotocin (65 mg/bwkg, ***i.p.***) induced diabetes (DM) male Wistar rats were treated for two weeks pe ***os*** with enalapril, losartane, spironolactone or eplerenone. Vehicle-treated healthy or DM animals served as controls (n=6/group). Systemic blood pressure was measured, renal functional and structural damage was evaluated, OGlcNAcylation, OGT, OGA, phospho-Akt and phospho-eNOS protein levels were measured. HK2 cells were cultured in high glucose (35 mM) medium for 24 (HG24) or 48 (HG48) hours and then treated with the drugs mentioned above for 72 hours. Untreated and mannitol treated cells were used as controls.

Results*:* Blood pressure was not altered by DM or various RAAS-blocker treatments. Renal functional and structural damage represented the development of DNP that was ameliorated by all RAAS-blockers. Renal O-GlcNAcylation was elevated in DM and in HG48 cells, which was decreased by RAAS-blockers. HG induced rapid elevation of OGT in HG24 cells, while both HG48 and in the kidney OGT was decreased. In diabetic kidney OGA was decreased. While pAkt levels remained unaltered in the kidney and in cultured cells, peNOS levels decreased in DM and in HG48 cells. This decrease was mitigated by RAAS-blockers. No alterations were found in HG24 cells.

Discussion: The time-dependent increase of renal O-GlcNAcylation by inhibiting eNOS phosphorylation and decreasing enzyme activity may contribute to the progression of nephropathy in DM. The reduction of O-GlcNAcylation suggests a new effect of RAASblockers.

Grants: LP008/2011, OTKA- NK84087/2010, - K100909, -K108688, KMR12-1-2012-007. Ádám Vannay is a holder of the János Bolyai research grant; this work was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

Doctoral School: *Molecular Medicine*
Program: *Pathobiochemistry*
Supervisor: *Ágota Vér*
E-mail: *renata.gellai@gmail.com*

E/IV-5
GAIN OF COPY NUMBER OF PIK3CA IN HEAD AND NECK CANCERS (HNSCCS)

Diána Brauswetter[1], Kornél Dános[2]

[1] HAS-SU Pathobiochemisrty Research Group, Semmelweis University, Budapest, Hungary
[2] Department of Oto-Rhino-Laryngology, Head-Neck Surgery, Semmelweis University, Budapest, Hungary

Mutations and copy number gains resulting an increased activity of the PI3K/Akt/mTOR pathway have a known and important role in the pathogenesis of head and neck cancers. However, the importance of this pathway in the different subtypes of HNSCCs and its relation to HPV-positivity is still unclear. The use of target therapies is currently increasing, therefore predictive biomarkers of sensitivity are becoming more important and nessesary. The PI3K is a remarkable target in cancer cells, accordingly, examination of its catalytic subunit, PIK3CA is up-to-date and relevant.

Aims*:* Our aim was to investigate the copy number gain of PIK3CA in head and neck cancers. Tumor samples of 133 patients were examined with fluorescence in situ hybridisation method (FISH). Four major groups were distinguished: negative (gene/CEN <1,5) weak copy number gain (gene/CEN ≥1,5) amplified (gene/CEN ≥ 2), polysomy (median of CEN≥ 3) These three positive groups were considered as „enhanced activity". Subsequently, we looked for correlations with clinical parameters, localization and previously studied biomarkers (Ki67, p53, p16, 9G2, EGFR).

Results: 10.5% of the studied tumors met the criteria of amplification, while 24% of polysomy was established. Weak copy number gain was found in 27% of the tumors, thus „enhanced activity" was found in 44% of the cases. Comparing the patients' survival according to the PIK3CA copy number gain, we found that patients with „enhanced activity" had singificantly worse survival rate than those with normal copy number of the gene. Significant correlation was revealed between tumor size (T) or lymph node metastasis status (N) and the „enhanced activity" (p = 0.018, p=0.002, respectively): higher T and N status was associated with „enhanced activity". In addition, we found correlations between p16-positivity and copy number gain. The rate of enhanced activity was significantly higher in the p16-negative cases (p=0.000).

Doctoral School: *Molecular Medicine*
Program: *Pathobiochemistry*
Supervisor: *István Peták*
E-mail: *brauswetter.diana@med.semmelweis-univ.hu*

E/IV-6
IMPROVED CHARACTERIZATION OF EXTRACELLULAR VESICLE PREPARATIONS BASED ON PROTEIN/LIPID RATIO AND LIPID PROPERTIES

Xabier Osteikoetxea[1], Andrea Balogh[2], János Matkó[2], Krisztina Pálóczi[1], Dániel Vértessy[1], Andrea Németh[1], Bence György[1], Ágnes Kittel[3], Tamás G. Szabó[1], Katalin Szabó-Taylor[1], Barbara Sódar[1], Maria Pásztói[1], Edit I. Buzás[1]

[1] Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary
[2] Department of Immunology, Eötvös Loránd University, Budapest, Hungary
[3] Department of Pharmacology, Institute of Experimental Medicine, Budapest, Hungary

In the rapidly growing field of extracellular vesicles (EV) there is much debate about classification of these structures. Furthermore, standardization and quantification solely based on particle enumeration or determination of protein content is inconclusive.

Aims: The goals of the present study were to identify novel parameters that enable improved characterization of EV preparation subtype and quality.

Results: We found characteristic protein/lipid ratios for different subpopulations of EVs. Importantly, damaged or poor quality EV preparations (as confirmed by tEM) had significantly altered protein/lipid ratios. Furthermore, different lipid membrane orders (based on spectroratiometric fluorescence) allowed for the distinction of the different EV populations in fluorescent microscopy and flow cytometry. These results suggest that vesicle composition and quality can be better characterized by determining protein/lipid ratio and lipid properties.

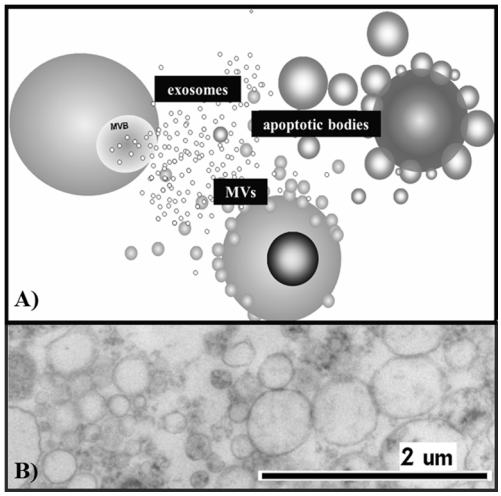


Figure 1. – Extracellular vesicles. A) Schematic representation. B) Transmission electron micrograph.

Doctoral School: *Molecular Medicine*
Program: *Basis of human molecular genetics and gene diagnostics*
Supervisor: *Edit I. Buzás*
E-mail: *xabieruf@gmail.com*

E/IV-7
TRAINING-INDUCED DIFFERENCES IN MITOCHONDRIAL BIOGENESIS IN RAT TESTICULAR TISSUE

Melitta Pajk[1], Orsolya Marton[1], Enikő Nagy[1], Lauren Gerard Koch[2], Steven Britton[2], Zsolt Radák[1]

[1] Faculty of Physical Education and Sport Sciences, Semmelweis University, Budapest, Hungary
[2] University of Michigan, Ann Arbor, MI, USA

Introduction: The incidence of civilization diseases is increasing worldwide with inactive lifestyle and low fitness level (VO2max). We know that VO2max is largely dependent on genetics, but regular physical activity also plays a role in the body's adaptation via mitochondriogenesis. We hypothesized, animal groups with low running capacity can reach the level of high running capacity animals. In addition,we assumed that due to physical activity or resveratrol the difference in mitochondriogenesis between animals of different running capacity would be attenuated.

Methods: In our study, 22nd generation male rats,which were selected by their running capacity, low (LRC) and high capacity (HRC), were divided into 8 groups: control LRC (Clow), LRC trained (Tlow), resveratrol treated (RSVlow),trained and resveratrol treated (T+RSVlow),control HRC (Chigh), trained HRC (Thigh),resveratrol treated (RSVhigh),trained and resveratrol treated (T+RSVhigh). A motor-driven treadmill was used for endurance training 5 times a week for 12 weeks at 60% of VO2max. Protein analysis was carried out by Western blotting of testicular tissues.

Results: Training significantly increased VO2max values in the RSVlow group, while resveratrol had moderate effect. The levels of SIRT1 increased significantly in the RSVlow group while it is increased moderatly in case of T+RSVlow compared to the control group. The PGC-1α increased in groups of T.low and RSVhigh compared to the control group. In the case of the NRF-1,we observed an increas in the RSVhigh animals compared to Chigh, while in TFAM a significant difference between trained animals and those receiving resveratrol and combination therapy was observed.

Discussion: We examined a new area because to date research is only available on other tissues (heart,muscle,liver). We could only assume that in spite of the difference in testicular tissue we would experience similar changes as found in previous studies. We can conclude that resveratrol administration and physical activity had beneficial effects on mitochondriogenesis.

Doctoral School: *Sport Sciences*
Program: *Physical training, regulation, metabolism*
Supervisor: *Zsolt Radák*
E-mail: *pajkmelitta89@gmail.com*

E/IV-8
CHANGES IN THE FUNCTIONAL CHARACTERISTICS OF THE ATHLETE'S HEART WITH THE TRAINING SEASON IN ELITE YOUNG ENDURANCE ATHLETES

Eszter Csajági[1], Péter Horváth[2], Zsuzsanna Major[1], Gábor Pavlik[1]

[1] Department of Health Science and Sports Medicine, Semmelweis University, Budapest, Hungary
[2] Hungarian Swimming Team, Budapest, Hungary

Introduction: Little is known of the changes that occur in the cardiac adaptation with the training season in athletes. Most data refer either to the morphological adaptation or the effect of the detraining period. Also the findigs in the training adaptation of the heart in younger ages are controversial.

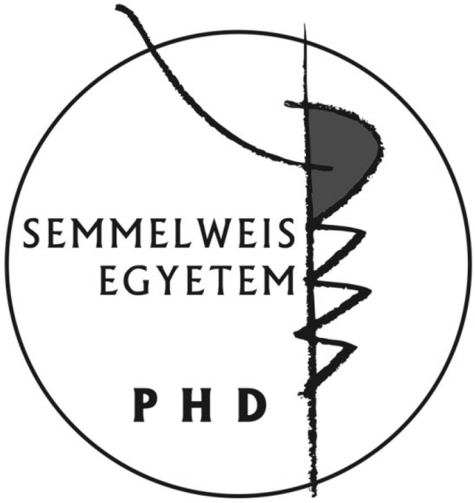
Aim of Study: The aim of our study was to followup the changes that occur in the cardiac adaptation to specific training methods and maturation during a 1,5 year training period in young elite endurance athletes.

Methods: 15 elite young swimmers took part in our study, 7 girls (g) and 8 boys (b) (age: g: 13,8±0,89 ys, b: 13,75±0,70 ys), intensive training for at least 4 years (g: 5,9±1,73 ys, b: 6,37±1,41ys) with approximatly 20-23 training hours a week. Sport medical examination with 12-lead ECG took part every 6 months, an echocardiographic examination (2D, Doppler, TDI) every 3 months following the macro- and microcyclic changes in training: groundtraining one (GT1)- end of groundtraining one (GT1E)- competition period one (C1)- after 1 month detraining (DT)- end of groundtraining two (GT2E)- competition period two (C2),. Technical evaluation was carried out offline. Repeated measurement ANOVA was used for the staitistical analysis (Statistica for Windows 11.0).

Results: There was no change in the resting heart rate with the training period, no training bradycardia was to be observed. Diastolic function of the left and the right ventricle was characterized with the lateral annular velocties acquired with TDI. But no changes in the diastolic function was to be observed. The left ventricular ejection fraction was getting significantly better in both genders (b: C2 from GT1 and GT1E, g: GT1 from GTE2 and C2).

Conclusion: The most important changes with the training season appear in the morphology of the left ventricle, without impairment of the diastolic function with the increasing training load. In addition to this the systolic function of the left venrticle seems to improve with the combination of maturation and endurance training.

Doctoral School: *Sport Sciences*
Program: *Training and adaptation*
Supervisor: *Gábor Pavlik*
E-mail: *eszter.csajagi@gmail.com*



E/V
ORAL PRESENTATIONS

Chairman:
Prof. Dr. Zoltán Benyó

E/V-1
ACCURACY OF OCTOPUS CLUSTER TREND ANALYSIS SOFTWARE TO EARLY DETECT GLAUCOMATOUS PROGRESSION

Farzaneh Naghizadeh[1], Péter Vargha[2], Gábor Holló[1]

[1] Department of Ophthalmology, Semmelweis University, Budapest, Hungary
[2] Cardiovascular Center, Semmelweis University, Budapest, Hungary

Purpose: To compare the ability of Corrected Cluster Trend Analysis (CCTA) and Cluster. Trend Analysis (CTA) with event analysis of Octopus visual field series to detect early glaucomatous progression.

Methods: One eye of 15 healthy, 19 ocular hypertensive (OHT), 20 preperimetric and 51 perimetric glaucoma (PG) patients were investigated with Octopus normal G2 test at 6-month intervals for 1.5 to 3 years. Progression was defined with significant worsening in any of the 10 Octopus clusters with CCTA, and event analysis criteria, respectively.

Results: With event analysis, 9 PG eyes showed localized progression and 1 diffuse MD worsening. With CCTA, progression was indicated in 1 normal, 1 OHT and 1 preperimetric glaucoma eyes due to vitreous floaters, and 28 PG eyes including all 9 eyes with localized progression with event analysis. The locations of CCTA progression matched those found with event analysis in all 9 cases. In 17 of the remaining 19 eyes, progressing clusters matched the locations that were suspicious but not definitive for progression with event analysis. In the eye with diffuse MD worsening CTA found significant progression for 7 clusters. For global MD progression rate, eyes worsened with CCTA only did not differ from the stable eyes but had significantly smaller progression rates than the eyes progressed with event analysis (p=0.0002).

Conclusions: In perimetric glaucoma, Octopus CCTA and CTA are clinically useful to identify early progression and areas suspicious for early progression. However, in some eyes with no glaucomatous visual field damage vitreous floaters may cause progression artifacts.

Doctoral School: *Clinical Medicine*
Program: *Imaging methods in glaucoma diagnosis and follow-up*
Supervisor: *Gábor Holló*
E-mail : *farzaneh_n2001@yahoo.com*

E/V-2
REGULATORY T-CELL DYSFUNCTION IN TYPE 1 DIABETES

András Zóka[1], Anikó Somogyi[1], Gábor Barna[2], Ágnes Oláh[1], Gábor Firneisz[1]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] I. Department of Pathology and Experimental Cancer Research, Semmelweis University Budapest, Hungary

Introduction: Type 1 diabetes mellitus (T1DM) develops as a result of the autoimmune damage of pancreatic ß-cells. Regulatory T-cells (T_{reg}) have a crucial role in limiting the naturally occuring autoreactivity. Foxp3 is a master regulator transcription factor of T_{reg} differentiation. Active T_{reg} cells express high levels of IL-2 receptor α-chain (CD25) and CTLA4 (Cytotoxic T-Lymphocyte Antigen 4). The aim of our study was to clarify certain details of the immunological dysregulation and T_{reg} dysfunction.

Patients and methods: Fourtyone patients with T1DM (M/F= 19/22; 34.5±10.9 years) and fourty age-matched non-diabetic control subjects (M/F= 16/24; 33.1±11.6 years) were involved. The mean disease duration was 16.3(±7) years. Fasting, EDTA-anticoagulated blood samples were collected. CD3, CD4, CD8, and CD25 surface proteins, intracellular CTLA4 and intranuclear Foxp3 were stained with specific fluorescent antibodies. A Beckman Coulter Navios flow cytometer and Kaluza software were used for quantitative analysis. Fluorescence intensity was described as median fluorescence intensity (MFI). Shapiro-Wilks normality test, Mann-Whitney-U-test, T-test and the Statsoft Statistica software were used.

Results: The proportion of Foxp3+ cells among CD4+ lymphocytes was not different in T1DM patients and control subjects. The proportion of CD25+ cells among CD4+Foxp3+ lymphocytes was lower in T1DM patients (63.19% vs. 73.01%, $p<0.0001$). CD25 and CTLA4 expression of the helper T-lymphocytes was significantly lower in T1DM patients (CD25: 0.74±0.44 vs. 1.12±0.38, $p<0.001$; CTLA4: 1.63±0.40 vs. 1.87±0.44, $p<0.05$). A weak positive correlation was observed between the CD25 and the CTLA4 expression of CD4+ lymphocytes ($p=0.01$. $r=0.31$).

Conclusions: Altough the CD4+Foxp3+ T_{reg} cell population was not quantitatively different, the higher proportion of CD4+Foxp3+CD25-cells and lower CTLA4 expression in CD4+ lymphocytes may reflect an increased proportion of inactive T_{reg} cell subpopulation. This might contribute to the impaired immune regulation. To overcome the impaired T_{reg} cell activation in T1DM might be an attractive therapeutic approach in the future.

Doctoral School: *Clinical Medicine*
Program: *Investigation of the etiology and genetic background of diabetes mellitus, its complications and hepatic disorders*
Supervisor: *Gábor Firneisz*
E-mail: *zoka.andras@yahoo.com*

E/V-3
ELEVATED SERUM ACYLATED (BIOLOGICALLY ACTIVE) GHRELIN AND RESISTIN LEVELS ASSOCIATE WITH PREGNANCY-INDUCED WEIGHT GAIN, INSULIN RESISTANCE AND ANTROPOMETRIC DATA IN THE FETUS

Dorina Supák

II. Department of Obstetrics and Gynaecology, Semmelweis University, Budapest, Hungary

The recently discovered peptide hormone, ghrelin may serve as an endogenous ligand for the growth hormone secretagogue receptor and has a profound orexigenic effect, too. Resistin, an other newly discovered circulating cytokine is produced to a lesser extent in adipocytes, and expressed abundantly in monocytes and macrophages. Increased serum resistin levels were found in obesity, but some controversies exist concerning its role in type II diabetes, insulin resistance and hypertension in humans. Based on the aforementioned observations concerning the effects of acylated ghrelin and resistin on weight gain and insulin resistance, we studied the association of these proteins with pregnancy-induced obesity and insulin resistance in a cross-sectional study carried out in patients with GDM, healthy pregnant women and in non-pregnant control women with similar age. The diagnosis of GDM was based on 75 g oral glucose tolerance testing (OGTT) according to the WHO classification. Statistical analysis was carried out by Prism 3 and SPSS 10 programs.

Pregnancy comes with progressive insulin resistance, which begins at the middle third of pregnancy, and evolves at the third trimester to type two diabetes insulin resistance. We did not observe any differences neither in serum ghrelin nor in resistin or other cytokine levels measured before and after 2 weeks of insulin treatment in GDM patients. Adiponectin proved to be the most significant predictor of fasting C-peptide concentration in all groups. In the GDM group resistin also remained significant.

The pathophysiological role of ghrelin and resistin in pregnancy-induced insulin resistance has not yet been revealed. On one hand, orexigenic effect of ghrelin may contribute to weight gain in pregnant women, and on the other hand, however, the increased amount of adipose tissue may inversely affect ghrelin production. This observation may hypothesize the contribution of this orexigenic hormone in the appetite change and weight gain of pregnant women during the course of their pregnancy. The inflammatory cytokines, TNF-α and resistin negatively correlate with serum ghrelin levels, also supporting the existence of the aforementioned negative regulatory feed-back mechanism between adipose tissue and appetite regulation through ghrelin production.

Doctoral School: *Clinical Medicine*
Program: *Hormonal regulations*
Supervisor: *Zsolt Melczer*
E-mail: *supakdorina@gmail.com*

E/V-4
THE ANTIDEPRESSANT FLUVOXAMINE IS PROTECTIVE AGAINST RENAL ISCHEMIA/REPERFUSION INJURY

Ádám Hosszú [1,2], Zsuzsa Antal[1,2], Judit Hodrea[1,2], Sándor Kőszegi[1,2], Nóra Fanni Bánki[2], László Wagner[3], Lilla Lénárt[1,2], Ádám Vannay[4], Attila J. Szabó[2], Andrea Fekete[1,2]

[1] HAS-SU „Lendület" Diabetes Research Group, Budapest, Hungary
[2] I.Department of Pediatrics, Semmelweis University, Budapest, Hungary
[3] Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary
[4] HAS-SU Pediatrics and Nephrology Research Group, Budapest, Hungary

Introduction: Previously we showed that pretreatment with the Sigma-1 receptor (S1R) agonist fluvoxamine (FLU) improved postischemic survival and resulted in milder deterioration of renal function and kidney damage. Here we studied the effect of FLU on the S1R-Akt-NOS signaling pathway and on intrarenal vasoregulation.

Methods: Male Wistar rats were subjected to unilateral renal ischemia followed by 24 hours of reperfusion (T24). 30 min prior to the ischemia (I/R) groups were treated *i.p.* either with vehiculum (VEH); FLU; FLU+S1R antagonist NE-100 (FN); FLU+non-selective NOS blocker L-NAME; FLU+endothelial (e)NOS blocker L-NIO or FLU+neuronal (n)NOS blocker 7-NI. Controls were sham-operated animals. Renal S1R, pAkt, peNOS and nNOS protein levels were measured at different time-points. Alteration of intrarenal capillary diameters was determined *in vivo* using multiphoton microscopy. *In vitro* experiments were performed on HK2 human proximal tubular epithelial cells treated with 10μM FLU.

Results: In controls FLU had an acute vasodilatative effect which was suspended by L-NAME and 7-NI and reversed by L-NIO (FLU+L-NAME Δd=0.23 μm; FLU+7-NI Δd=0.86 μm; FLU+L-NIO Δd=-0.57 μm vs. FLU Δd=2.18 μm). S1R, pAkt and peNOS protein levels were elevated 30min after FLU treatment, while nNOS expression was minimal. At T24 I/R induced renal vasoconstriction was ameliorated by FLU (C: 9.86 ± 1.23 μm; VEH: 8.29 ± 1.29 μm; FLU: 10.64 ± 2.53 μm; FN: 7.88 ± 1.67 μm). This increase was neutralized by all NOS blockers. S1R; pAkt; peNOS and nNOS levels were more elevated in the FLU group compared to VEH and FN. S1R expression of HK2 cells was elevated after 30 min, 2 hours and 12 hours of FLU treatment. FLU induced a slight increase in eNOS phosphorylation after 30 min, that became more robust after 2 and 12 hours

Conclusions: FLU pretreatment directly acts on proxmimal tubular cells through the activation of S1R – NOS system in a time and NOS isoform specific manner. Thereby FLU – used in the long-term treatment of depression without notable side-effects – improves postischemic renal perfusion and is renoprotective in I/R. Based on this data one can hope to find a new therapeutic target in the treatment of renal I/R damage through the modulation of the S1R.

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Doctoral School: *Clinical Medicine*
Program: *Prevention of chronic diseases in childhood*
Supervisor: *Andrea Fekete*
E-mail: *hosszu.adam@gmail.com*

E/V-5
ASSOCIATION OF A VOLTAGE-GATED SODIUM CHANNEL GENE INTRONIC POLYMORPHISM WITH CARDIAC DEATH

Boglárka Marcsa, Krisztina Vörös

Department of Medical Chemistry, Molecular Biology and Pathobiochemistry Semmelweis University, Budapest, Hungary

Cardiovascular diseases are leading causes of mortality worldwide and despite up-to-date therapeutic methods their death toll has not decreased adequately over the past few years. Recent research has shed light on pathophysiological mechanisms underlying heart diseases, and several novel candidate gene polymorphisms have been identified as risk factors. Their effect, however, might be modified by epigenetic factors such as DNA methylation that is known to depend on environmental and lifestyle factors as well.

Aims: The aim of the present study was to find associations between cardiac death cases and genetic polymorphisms occurring in candidate genes of cardiovascular diseases selected a priori from the literature. To this end, case-control studies were performed by genotyping single nucleotide polymorphisms (SNPs) of the following genes: SCN5A, RyR2, NOS1AP, ADRB2 and TGFBR2.

Methods: We isolated DNA from buccal swabs of natural, heterogenous cardiovascular death cases (n=360, 66.6 % male). The age-matched control group comprised 300 healthy individuals (39.4 % males). SNPs were genotyped with a 7300 Real-Time PCR using sequence-specific TaqMan probes. Statistical analyses were carried out using SPSS 20.0 for Windows.

Results: The CC homozygote genotype of the rs11720524 intronic G/C SNP of the SCN5A gene encoding a subunit of the cardiac voltage-gated sodium channel was more frequent in the cardiac death cohort compared to the control population (Fig. 1; p=0.0052). This result was significant following the Bonferroni multiple testing as well, highlighting the role of the SCN5A marker gene in cardiovascular mortality.

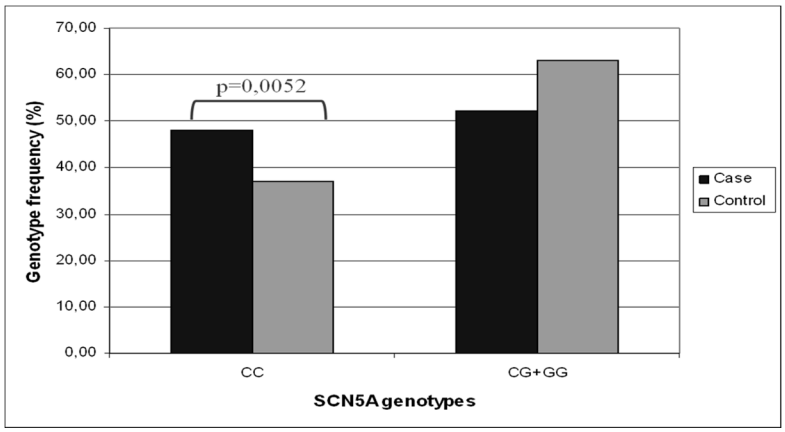

Figure 1. – SCN5A SNP(rs11720524) genotype distribution

Doctoral School: *Clinical Medicine*
Program: *Dermatology and Venerology*
Supervisor: *Klara Törő*
E-mail: *marcsa.boglarka@med.semmelweis-univ.hu*

E/V-6
ASSESSMENT OF BIOMARKERS OF BONE METABOLISM, BONE MINERAL DENSITY, AND VITAMIN D LEVEL DURING ONE YEAR INFLIXIMAB THERAPY IN PEDIATRIC PATIENTS WITH CROHN'S DISEASE

Dolóresz Szabó, Antal Dezsőfi, András Arató, Gábor Veres

I. Department of Pediatrics, Semmelweis University, Budapest, Hungary

Introduction: As it is known from the open literature low bone mineral density (BMD) is an occurrent complication in patients with inflammatory bowel disease (IBD) both in children and adults. Normal Vitamin D level is essential for normal bone mineralization. Recent studies revealed higher prevalence of lower vitamin D levels among adult and children with IBD.

Aim: Changes of bone mineralization, and seasonal variability of vitamin D status was analyzed during one year IFX treatment period.

Methods: Thirty-nine subjects (mean age 14.9 years) with moderate to severe CD received IFX induction (5 mg/kg/dose) at weeks 0, 2, and 6. Maintenance therapy was given at every 8 weeks. Serum osteocalcin/OC, beta-crosslaps/bCL, and vitamin D were determined at baseline, at week 6, 30 and 54. BMD was assessed at baseline and week 54 by DEXA. Seasonal variability of vitamin D level was analyzed in another group of children with CD (39 and 36 patients during summer- and winter period, respectively).

Results: Serum levels of OC increased due to IFX treatment ($p<0.0001$), however, there was no significant improvement in the bCL and vitamin D level during long-term therapy. Mean vitamin D levels were <25 nmol/l at every examinations. The lumbal spine and total body BMD showed significant improvement of bone density, but there were no significant changes in Z-scores. Seasonal analysis showed significantly higher baseline vitamin D level in summer period compared to those who received the first IFX in winter months ($p=0.039$). This significance smeared by the end of the one year treatment period.

Conclusions: Our results suggest that IFX therapy has beneficial effect for bone health. Low vitamin D levels of patients draw attention to the importance of the monitoring, and to the adequate supplementation of that according to the actual season.

Doctoral School: *Clinical Medicine*
Program: *Prevention of chronic diseases in childhood*
Supervisor: *Gábor Veres*
E-mail: *doloresz.szabo@gmail.com*

E/V-7
DECREASED CORD BLOOD SERUM DIPEPTIDYL-PEPTIDASE 4 (DPP4) ENZYMATIC ACTIVITY IN GESTATIONAL DIABETES MELLITUS

Zahra Al-Aissa[1], Orsolya Hadarits[2], Klára Rosta[2, 3], Jürgen Harreiter[4], András Zóka[1], Dagmar Bancher-Todesca[3], Attila Patócs[5], Katalin Kiss[6], Beatrix Sármán[1], Péter Pusztai[1], István Sziller[7], János Rigó[2], Károly Rácz[1], Anikó Somogyi[1], Alexandra Kautzky-Willer[4], Gábor Firneisz[1]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] I. Department of Obstetrics and Gynaecology, Semmelweis University, Budapest, Hungary
[3] Department of Obstetrics and Fetomaternal Medicine, University Hospital Vienna, Austria
[4] Gender Medicine Unit, Internal Medicine 3, Medical University of Vienna, Austira
[5] Hungarian Academy of Sciences, Semmelweis University "Lendulet" HET Research Group, Budapest, Hungary
[6] I. Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
[7] Department of Obstetrics and Gynecology, Szent Imre Teaching Hospital, Budapest, Hungary

Objective: DPP4 is a membrane associated sialoglycoprotein with serine protease activity, but also detectable in soluble form in the human sera. Tissue-specific DPP4 dysregulation was described in adults with diabetes mellitus. Alterations of the DPP4-incretin system have not been studied in fetal life. In the present study DPP4 activity and GLP-1 levels were assessed in cord blood of neonates born to women with gestational diabetes mellitus (GDM) and non-diabetic controls.

Research Design and Methods: 568 pregnant women were enrolled to the study in Hungary and Austria after OGTT at 24-28th gestational week. Cord blood samplings with DPP4 activity and plasma GLP-1 level measurements were possible in 270 (DPP4: 159 control, 111 GDM) and 112 (GLP-1: 72 control, 40 GDM) cases at delivery. Cord serum DPP4 activity was determined in a continuous monitoring microplate-based kinetic assay, cord plasma GLP-1 was measured using a fluorescence ELISA method. For statistical analysis Shapiro-Wilks, Mann-Whitney-U, Kruskal-Wallis and independent T-tests were used.

Findings: Cord serum DPP4 activity was lower in GDM [Mean (95%CI)= 28.07U/L (26.32-29.82 U/L)] than in controls [31.67U/L (29.93-33.29 U/L), MWU p=0.0015]. Kruskal-Wallis test (H=10,53, p=0.0052) was significant when insulin therapy was used as the independent grouping variable (LnDPP4: GDM-on Insulin group: mean=3.245, GDM managed with dietary measures only group: mean= 3.32, non-diabetic control group: mean=3.41).

Cord plasma active GLP-1 levels were close to the lower detection limit and were not altered in GDM (Control: Mean=3.43pmol/L, 95%CI:3.04-3.82pmol/L, GDM: Mean=3.61pmol/L, 95%CI:2.96-4.28pmol/L – MWU-test p=0.6).

Conclusions: Decreased cord serum DPP4 activity in GDM might be the result of an adaptive fetal response or an early dysregulation in the entero-insular axis with consequences beyond the incretin system. Cord plasma GLP-1 levels may reflect the missing oral intake with a limited glucose sensing of L-Cells via the circulation in fetal life.

Doctoral School: *Clinical Medicine*
Program: *Oxidative stress and immunological reaction in liver diseases*
Supervisor: *Gábor Firneisz*
E-mail: *alaissazahra@yahoo.com*

E/V-8
COPY NUMBER DETERMINATION OF CYP21A2 GENE SUPPLEMENTS THE MOLECULAR BIOLOGICAL ANALYSIS OF HUNGARIAN PATIENTS WITH 21-HYDROXYLASE DEFICIENCY

Klára Koncz[1], Márton Doleschall[2], Andrea Luczay[3], Júlia Pázmándi[1], Miklós Tóth[1], Nikolett Szücs[1], Károly Rácz[1,2], Attila Patócs[2,4,5]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] Molecular Medicine Research Group, Semmelweis University, Hungarian Academy of Sciences, Budapest, Hungary
[3] II. Department of Pediatrics, Semmelweis University, Budapest, Hungary
[4] Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary
[5] Lendület" Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences, Budapest, Hungary

Background: Congenital adrenal hyperplasia is a rare (prevalence 1:15000), autosomal recessiv disorder caused by 21-hydroxylase deficiency in 95% of all cases. This disorder is related to the mutation of CYP21A2 gene, that is located in a multiallelic, complex and tandem copy number variation, called RCCX module. Recent studies suggest a need of a complex molecular analysis of CAH suspected patients for accurate diagnosis and for understanding the phenotype/genotype associations.

Objective: Our aim was to analyze the mutations of the CYP21A2 gene and copy number of CYP21A1P and A2 genes in our patients.

Patients and Methods: We studied 111 clinically diagnosed CAH patients (45 salt wasting, 25 simple virilising and 41 non classical/late onset). The most frequent mutations (Δ8bpE3, P30L, IVS2-13A/C>G, I172N, R356W, Q318X) were detected by allele-specific PCR. For the direct gene copy number determination of CYP21A1P and CYP21A2 a CYP21-type specific real-time quantitative PCR was used.

Results: Using complex molecular biological analysis 94 (57; 81 % classical and 37; 90% non-classical) of 111 cases were resolved. The most frequent mutations in classical forms were IVS2-13A/C>G; I172N, R356W, and Δ8bpE3 while in the non-classical patients V281L, R356W, P30L and I172N. 52,8% of classical and 40,9% of non classical CAH patients had only one copy of the CYP21A2.

Conclusion: Determination of copy number variations is an accurate and helpful method in molecular diagnosis of CAH. It may lead to a faster diagnosis for CAH suspected patients. The lacking mutations especial in classical forms suggest that other methods including whole sequencing of the CYP21A2 gene and analysis of large deletions by MLPA should also be included into the molecular biological workup.

Doctoral School: *Clinical Medicine*
Program: *Hormonal regulations*
Supervisor: *Attila Patócs*
E-mail: *koncz.klara@med.semmelweis-univ.hu*

E/V-9
CIRCADIAN CLOCK SYSTEM CAN BE INDUCED IN H295R CELL LINE

Zsolt Nagy[1], Henriett Butz[2], István Likó[3], Péter Igaz[1], Károly Récz[1,2], Attila Patócs[2, 4]

[1] II.Department of Medicine, Faculty of Medicine, Semmelweis University, Budapest, Hungary
[2] HAS-SU Molecular Medicine Research Group, Budapest, Hungary
[3] Richter Gedeon Ltd, Budapest, Hungary
[4] HAS-SU "Lendület" Hereditary Endocrine Tumors Research Group, Budapest, Hungary

Background: The light-dark cycle governs many physiological and behavioral functions in most of the living organisms. It was thought that the central circadian clock located in the hypothalamus is responsible for these changes. There is increasing number of evidence that almost every organ possess an intrinsic peripheral circadian clock, synchronized by the central circadian system. However we know little about the hormonal regulation of the peripheral circadian clock.

Objective: In vivo primate adrenal gland clock genes show periodic expression pattern. We aimed to assess the rhythmic changes in peripheral clock genes in human adrenocortical cell line (H295R). We examined the potential effects of serum shock and dexamethasone treatment on the peripheral circadian system.

Method: We synchronized H295R cells with 24h serum starvation and with serum shock for 2 hours and treated them parallel either with 100 nmol dexamethasone or vehicle alone. Cells were harvested at certain time points for 48 hours. The expression of circadian genes was measured using TaqMan assays on quantitative Real-Time PCR.

Result: We recorded after serum shock the rhythmic oscillation of four circadian clock genes: PER1, PER2, NR1D1 and ARNTL. NR1D1 and ARNTL expression showed anti-phase pattern in accordance with previous studies. The dexamethasone treatment resulted in a more robust change of NR1D1 and ARNTL levels compared to the serum shock alone.

Conclusion: Peripheral circadian clock system can be induced in H295R human adrenocortical cell line with serum shock treatment. Dexamethasone treatment may modify the expression of peripheral circadian clock genes; therefore we may hypothesize that at least part of the clock genes are under glucocorticoid regulation. This system is a promising model for the further evaluation of hormonal adjustment on peripheral circadian system.

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Doctoral School: *Clinical Medicine*
Program: *Hormonal regulations*
Supervisor: *Attila Patócs*
E-mail: *zsolt.nagy.unise@gmail.com*

E/V-10
INVESTIGATION OF GLUCOCORTICOID RECEPTOR POLYMORPHISM IN ADDISON'S DISEASE PATIENTS

Ágnes Molnár[1], Dániel Vas[1], Klára Koncz[1], Miklós Tóth[1], Nikolette Szücs[1], Péter Igaz[1], Edit Gláz[1], Károly Rácz[1,2], Attila Patócs [2,3,4]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] Molecular Medicine Research Group, Semmelweis University, Hungarian Academy of Sciences, Budapest, Hungary
[3] Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary
[4] Lendület" Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences, Budapest, Hungary

Background: The glucocorticoid receptor polymorphisms affect glucocorticoid sensitivity, consequently, it may alter the dosage during glucocorticoid supplementation.

The aim of this study was to investigate the prevalence and the effects on glucocorticoid supplementation of three well-characterized glucocorticoid receptor polymorphisms (N363S, BclI and A3669G or 9ß polymorphism) in patients with Addison's disease.

Material and method: We studied 52 patients with Addison's disease, diagnosed and treated at the 2nd Department of Medicine, Semmelweis University. DNA was isolated from peripherial blood samples. The BclI and N363S polymorphisms were examined with allele-specific PCR, the amplified DNA sequences were separated in agarose gel electrophoresis. The A3669G polymorphism was examined with Taqman assay on Real Time PCR. The genotype distribution was compared to those observed in the general Hungarian population (n=160) using Chi square or Fischer exact t-test. ANOVA was used for evaluation of the effects of polymorphisms on glucocorticoid dosage.

Results: The allele frequency of N363S polymorphism was higher in patients compared to the control group (9.1% vs. 3.1%; $p<0,05$). For polymorphisms BclI. and A3669G the allele distribution did not differe between patients and controls (BclI 25% vs 35 %, and for A3669G 20.1% vs. 22%). The need of glucocorticoid supplementation was significantly lower for the homozygous carriers of BclI (13,3 mg vs. 24,6 mg in wild type carriers or 28 mg in heterozygous carriers). No significant association between N363S and A3669G polymorphisms and glucocorticoid dosage was detected.

Conclusion: Based on our study, in Addison's disease patients the N363S glucocorticoid receptor polymorphism occurs three times more often than the control group. The BclI. polymorphism affects the need of glucorticoid supplementation which may be important for individualized therapy.

Doctoral School: *Clinical Medicine*
Program: *Hormonal regulations*
Supervisor: *Attila Patócs*
E-mail: *agimolnar88@gmail.com*

E/V-11
THE ROLE OF *BRAIN-DERIVED NEUROTROPHIC FACTOR* (BDNF) IN THE DEVELOPMENT OF DIABETES AND COMORBID DEPRESSION

Lilla Lénárt[1,6], Judit Hodrea[1,6], Sándor Kőszegi[1,6], Renáta Gellai[1,3], Adrienn Bárczi[1], Dóra Zelena[4], Ádám Vannay[2,6], László Wagner[5], Tivadar Tulassay[2,6], Attila J. Szabó[6], Andrea Fekete[1,6]

[1] HAS-SU „Lendület" Diabetes Research Group, Budapest, Hungary
[2] HAS-SU Pediatrics and Nephrology Research Group, Budapest, Hungary
[3] Department of Medical Chemistry, Molecular Biology and Pathobiochemistry,Semmelweis University, Budapest, Hungary
[4] Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary
[5] Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary
[6] I. Department of Pediatrics, Semmelweis University, Budapest, Hungary

Introduction: The decreased level of the *brain-derived neurotrophic factor* (BDNF) plays a substantial role in the patomechanism of diabetes (DM) associated depression. Beside its serotonine reuptake inhibitory effect fluvoxamine (FLU) has been shown to be a potent Sigma-1 receptor (Sigma-1R) agonist is. We hypothesize that FLU could have a beneficial effect in depression by activating the Sigma-1R and thus increasing BDNF expression, therefore here we examined in FLU treated diabetic rats the development of depression and the alterations of Sigma-1R and BDNF axis.

Methods: Five weeks after streptozotocin (65 mg/bwkg, *i.p.*) induced DM male Wistar rats were treated for two weeks *per os* with either FLU (2 mg/bwkg/day or 20 mg/bwkg/day), or FLU + Sigma-1R antagonist NE100 (1 mg/bwkg/day). Vehicle-treated healthy or DM animals served as controls (n=8/group). The development of depression was evaluated by forced swimming test, locomotor activity was assessed using open-field test. Western blot was used to measure BDNF and Sigma-1R protein levels in various regions of the brain.

Results: The larger dose of FLU moderated depression in DM rats, while locomotor activity was not affected by any of the treatments. The DM-induced increase in the level of precursor BDNF in the hippocampus and prefrontal region were prevented by FLU. Mature BDNF levels were decreased in DM in the hippocampus, but were elevated by FLU. On the contrary, in the prefrontal region mature BDNF levels were elevated in DM, but were decreased by FLU treatment. NE100 suspended the effect of FLU in all cases. Sigma-1R expression showed no alterations in the examined regions of the brain.

Discussion*:* In DM rats significant depression develops, but it is ameliorated by large-dose of FLU. The Sigma-1R – BDNF signaling pathway in the brain plays an important role in the development of depression. The manipulation of this pathway contributes to the antidepressant effect of FLU.

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Doctoral School: *Clinical Medicine*
Program: *Prevention of chronic diseases in childhood*
Supervisor: *Andrea Fekete*
E-mail: *lenart.lillaa@gmail.com*

E/V-12
INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN DIABETIC NEPHROPATHY: FOCUSING ON RENAL FIBROSIS

Sándor Kőszegi[1,4], Judit Hodrea[1,4], Lilla Lénárt[1,4], Ádám Hosszú[1,4], Ádám Vannay[2,4], László Wagner[3], Tivadar Tulassay[2,4], Attila J. Szabó[4], Andrea Fekete[1,4]

[1] HAS-SU „Lendület" Diabetes Research Group, Budapest, Hungary
[2] HAS-SU Pediatrics and Nephrology Research Group, Budapest, Hungary
[3] Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary
[4] I. Department of Pediatrics, Semmelweis University, Budapest, Hungary

Introduction*:* Diabetic nephropathy (DN) is the leading cause of chronic renal failure in adults, however its treatment is unsolved and the exact pathomechanism is yet unknown. In diabetes the the increased renin-angiotensin-aldosterone system (RAAS) activity contributes to the development of renal fibrosis. Platelet-derived growth factor (PDGF) is one of the key molecules of fibrosis, but its signal transduction pathway DN is still not clarified.

Methods: Five weeks after streptozotocin (65 mg/bwkg, i.p.) induced diabetes male Wistar rats were treated for two weeks per os with enalapril (40 mg/bwkg/day), ramipril (10 μg/bwkg/day), losartan (20 mg/bwkg/day), spironolactone or eplerenone (50 mg/bwkg/day). Vehicle-treated healthy or diabetic animals served as controls (n=6/group). Mesangial matrix expansion and renal fibrosis were evaluated on PAS, Masson and fibronectin stained sections. PDGF and αSMA protein level were measured in the kidney. Human proximal tubular cells (HK2) were cultured in normal (5.5 mM) or high (35 mM) glucose medium. Isosmotic controls were cultured in a mannitol (35 mM). First, we measured the glucose-induced PDGF production of HK2 cells. Then to verify the effect of PDGF, normal rat kidney (NRK-49F) fibroblasts were treated with PDGF (10 ng/mL) and αSMA protein level was detected.

Results*:* Impaired renal function and metabolic parameters confirmed the development of DN. The decline in GFR was ameliorated by RAAS blockers. Increased mesangial matrix expansion and interstitial fibrosis in DN were reduced by all RAAS inhibitors, while the amount of fibronectin was only decreased by ACE inhibitors and eplerenone. In high glucose PDGF production of tubular cells was increased, but not in mannitol. PDGF- treated fibroblasts produced more αSMA. Diabetes induced elevation of renal PDGF and αSMA protein was decreased by RAAS blockers.

Discussion: High glucose increases the PDGF production of proximal tubular cells, that in turn induces the αSMA production in renal fibroblast. , This mechanism also contributes to the development of renal fibrosis seen in DNP. RAAS blockers ameliorates this process by directly acting on renal fibroblasts which could serve as a new therapeutic potential in the treatment of renal fibrosis.

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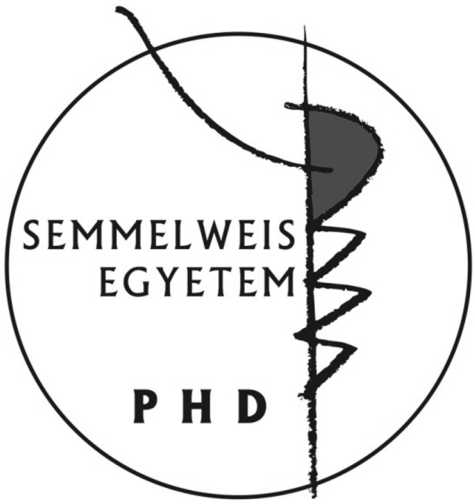
Doctorial school: *Clinical Medicine*
Program: *Prevention of chronic diseases in childhood*
Supervisor: *Fekete Andrea*
E-mail: *koszegi.sanyi@gmail.com*



E/VI
ORAL PRESENTATIONS

Chairpersons:
Dr. Pál Czobor
Dr. Róbert Bódizs
Dr. Beáta Dávid (Pethesné)

E/VI-1
THE BODY MASS INDEX AND ITS CONNECTIONS WITH RELATIONSHIP QUALITY AND SEXUALITY AMONG HUNGARIAN YOUTH

Tamás Dömötör Szalai

Institute of Behavioral Sciences, Semmelweis University, Budapest, Hungary

Body mass index (BMI) classifies underweight and overweight individuals and distinguishes endangered populations, specially in terms of eating disorders. It also influences body image, personal appeal and general self-esteem. Through sexuality, this pervades the intimate relationship. Although severe thinness is often associated with sexual aversion and negative self-esteem, stereotypes suggest that personal and sexual success are attainable through low body weight.

Aims*:* To explore the connections of BMI with relationship quality and sexuality, among 15-29-year-old Hungarian males/females.

Method: Study was based on the nationally representative sample called „Magyar Ifjúság 2012". 7605 subjects were classified into five WHO recommended BMI categories (Onnis and Habicht, 1996). Effects were measured with MANOVA filtering the impact of age and gender.

Results: Subjects with severe thinness had the smallest possibility to have a companion, while overweight ones had the biggest. More overweight subjects had a permanent sexual relationship and 50% more partners during lifetime, than ones with moderate or severe thinness. Three times as many form the thin subjects have not experienced sexuality yet, than overweight ones. Neither the requited love, nor the frequency of sexual intercourse were dependent on body weight. Severe thinness and obesity were both associated with lower relationship satisfaction.

Conclusions: The effect of BMI on relationship and sexuality is explicit. While severe thinness has consequent negative relationship, overweight has less or no negative effects on several factors. Results highlight, that attitude towards own weight has a bigger impact on relationship, than the weight itself.

Doctoral School: *Mental Health Sciences*
Program name: *Mental health sciences*
Supervisor: *Ferenc Túry*
E-mail: *szalai.domotor@gmail.com, szalai.tamas@med.semmelweis-univ.hu*

E/VI-2
MENTAL WELL-BEING, HEALTH RISK BEHAVIORS AND SOCIOECONOMIC STATUS AMONG HIGH SCHOOL STUDENTS

Szabolcs Varga[1], Bettina F. Piko[2]

[1] Institute of Behavioral Sciences, Semmelweis University, Budapest, Hungary
[2] Department of Behavioral Sciences, University of Szeged, Szeged, Hungary

Previous health related studies established that adults' mortality and morbidity are in a gradient relationship with socioeconomic status (SES). On the other hand, this relationship is not consistent across the life course. Several studies found a relative 'equalization' in adolescents' health status compared to adults and children. Despite these findings there may be differences in other aspects of health related issues among this age group, such as mental health status and health risk behaviours, which may have a long term effect on health in later adulthood.

Aims: The goal of our study was to determine whether SES is associated with mental health status (including self-esteem, loneliness, psychosomatic symptoms, need to belong and shyness) and risk behaviors (alcohol use and smoking) of Hungarian adolescents, based on a sample from three high schools of Debrecen (N=501, 14-22 years old).

Results: According to our results there is a positive association between adolescents' SES and mental well-being. Among SES variables self-assessment of SES was the best predictor of students' mental health. Parents' occupational status also proved to be good determinants. On the other hand, relationship between risk behaviours and SES was only partial. In the case of smoking only mother's occupational status was found to be a significant predictor. The likelihood of smoking is higher among students with unemployed mother or mother with manual occupation. Our results did not support any relationship between SES and alcohol use. Accordingly, professionals of health prevention programmes should consider students, whose parents are unemployed or have manual occupational status, as a high risk group in terms of mental well-being and smoking.

Doctoral School: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Piko F. Bettina*
E-mail: *varga.szabolcs85@gmail.com*

E/VI-3
SEX DIFFERENCES IN SLEEP EEG CORRELATES OF INTELLIGENCE

Péter P. Ujma[1], Boris Konrad[2], Péter Simor[3], Adrián Pótári[1], János Körmendi[1], Ferenc Gombos[1], Martin Dresler[2,4], Axel Steiger[2], Róbert Bódizs[1]

[1] Institute of Behavioral Science, Semmelweis University, Budapest, Hungary
[2] Max Planck Institute of Psychiatry, Munich, Germany
[3] Institute of Cognitive Science, Budapest University of Technology and Economics, Budapest, Hungary
[4] Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands

Previous has reported an association between sleep EEG features – most prominently sleep spindles and the corresponding sigma spectral band – and IQ.

We collected all-night EEG from 160 subjects (72 females, 88 males, ages 17-69 years, IQ 81-150), and we administered standardized nonverbal intelligence tests to measure IQ. A composite raw score was computed for all available raw test scores. Sleep spindles were detected using the Individual Adjustment Method, using individually determined slow and fast sleep spindle frequencies and computing the density, mean duration, median and maximum amplitude of slow and fast spindles, respectively. Power spectral analysis was performed on REM and NREM sleep EEG. We computed partial correlation coefficients (controlling for age) between sleep spindle parameters, power spectral density of NREM and REM sleep, and composite raw intelligence scores.

Striking sex differences are revealed in the correlations between sleep spindle parameters, sleep EEG spectra and IQ. In females, a positive association between fast spindle amplitude and NREM sigma power in central derivations and slow spindle durations in all derivations was found. A positive association between NREM alpha, REM beta power and intelligence and a negative association between REM delta power and intelligence was also found in females. In males, only a negative association between occipital fast spindle density and IQ was found.

The positive association between sleep spindle amplitude, NREM sigma power and intelligence in females are in line with previous research about the correlation between white matter density and both sleep spindle amplitudes and IQ in females (but not males). Longer spindles in more intelligent females may reflect higher spindle elicitability, which has been shown to correlate with intelligence. It is currently unclear whether higher NREM alpha and REM beta power in more intelligent females is the sign of functionally important activation or sleep disturbing arousal. The reason for the correlations found in males cannot be thoroughly tested with the available data, but we speculate that a negative relationship between occipital spindle density and IQ is due to greater neural efficiency in the lower-level visual cortex.

Doctoral school: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Róbert Bódizs*
E-mail: : *peteru88@gmail.com*

E/VI-4
THE ROLE OF SOCIAL SUPPORT DURING LOW-DOSE INTERFERON TREATMENT IN MELANOMA PATIENTS

Péter Kovács[1,2], Gitta Pánczél[1], Gabriella Liszkay[1], György Bagdy[2,3], Gabriella Juhász[2,3.4]

[1] National Institute of Oncology, Budapest, Hungary
[2] Department of Pharmacodynamics, Semmelweis University, Budapest, Hungary
[3] HAS-SU Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Budapest, Hungary
[4] Neuroscience and Psychiatry Unit, University of Manchester, UK

The most frequent serious psychological side effect of immune therapies is depression. In the present study, we tested whether social support, as a positive environmental effect, is able to moderate depression or anxiety symptoms in melanoma patients during adjuvant low-dose interferon treatment.

Hundred and twenty-seven melanoma patients with negative psychiatric history were included in our longitudinal study and followed up for one year. Depression (Beck Depression Inventory, BDI) and anxiety (State-Trait Anxiety Inventory, STAI) symptoms were measured six times during the treatment: at baseline, at 1st, 3rd, 6th, 9th and 12th month of the interferon therapy. In addition, social support was investigated with the Social Dimension Scale.

As it were expected, depressive symptoms significantly increased during the 12 months follow-up period ($p<0.001$). However, social support significantly moderated the depressogenic effect of low-dose interferon treatment ($p<0.001$). Patients with better social support showed attenuated increase of depression. Anxiety showed no significant changes during the low-dose interferon therapy ($p=0.230$) suggesting that this therapy has less anxiogenic than depressogenic effect. Furthermore, social support had no moderating effect on anxiety symptoms ($p=0.745$) during the follow up.

In summary, our results demonstrated that social support effectively decreased the depressogenic effect of low-dose interferon treatment. Our data provide further evidence that environmental and biological factors, namely social support and the proinflammatory cytokine pathway, significantly interact in the development of depression. Thus, the interdisciplinary management of patients during adjuvant interferon treatment is essential to decrease psychological side effects.

Doctoral School: *Mental Health Sciences*
Program: *Clinical Psychology and Psychiatry*
Supervisor: *Gabriella Juhász*
E-mail: *kope.kope@gmail.com*

E/VI-5
POTENTIAL INTERACTIONS BETWEEN MEDIA USE (MAGAZINE, TELEVISION, INTERNET) AND EATING DISORDER SYMPTOMATOLOGY

Kornélia Szabó, Irena Szumska, Edit Czeglédi, Ferenc Túry

Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary

Introduction According to the bio-psycho-social model of eating disorders in the development and maintenance of these disorders many contributing factors are participating. The model suggests that complex interactions are between social, environmental, psychological, and biological factors. In western societies a great emphasis is placed on shape, weight and more generally on bodily appearance. The sociocultural factors manifest on different levels and influence body weight regulation indirectly. Media has utmost importance in shaping values and norms.

Objective In this pilot study the aim was to investigate the relationship between media (magazines, internet and television) consumption and eating disorder symptomatology, with special focus on body dissatisfaction, self-esteem and social comparison.

Methods We implemented a cross sectional design. Self-administered instruments, anthropometric and demographic data were collected via single online assessment among Hungarian college and university students. Instruments measured media use, eating disorder symptomatology, body image satisfaction, social and appearance comparison.

Results The first results showed that there are gender differences among participants (n=217; 40 male and 177 female; mean age = 26.4 , SD=4.6) in media use and ED symptomatology. Female participants who spend more time reading appearance related magazines or spend more time browsing similar content on the Internet are more dissatisfied with their bodies ($r=.27$; $p<.01$) and have lower self-esteem ($r=-.19$; $p<.05$). Those who are at higher risk for developing an ED tend to use more appearance related media content ($t_{(175)}=3.105$, $p<.01$). Mediating factors such as appearance comparison will be discussed.

Conclusion The sociocultural theory underlines the importance of media in shaping values and norms. The study explored potential associations between eating disorder symptomatology and media (magazine - TV - internet) use. Preliminary results show that media effects females and males differently. However media use is in connection with lower self-esteem, negative body attitudes and higher risk for eating disorders.

Doctoral School: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Irena Szumska*
E-mail: *szabo.kornelia@med.semmelweis-univ.hu*

E/VI-6
PSYCHOSOCIAL WORK CONDITINONS AMONG HEALTHCARE WORKERS: A COMPARATIVE STUDY

Katalin Nistor, Anikó Nistor, Szilvia Ádám, Adrienne Stauder

Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary

Objectives: The assessment of the impact of the psychosocial work environment in case of the Hungarian healthcare workers and the active working population (control group).

Methods: A voluntary sample of 3894 employees (healthcare N=1949, randomized national sample N=1949) completed an online Work Stress Questionnaire. Occupations were coded according to the classification of Hungarian Central Statistical Office. The COPSOQ II scales and the outcome variables were analyzed using descriptive statistics, the independent sample t-test method, the effect size being measured trough *Cohen's d* indicator. Gender distribution and age: healthcare sample: 15% male, 85% female, age = 41,9 years respectively control group: 40% male, 60% female, age = 36,4 years.

Results: This study found that the healthcare participants are exposed to statistically significantly higher levels of Emotional demands, Role conflicts and experience more Threats of violence, Bullying, Physical violence and Sleeping troubles in comparison to the control group. Also the healthcare workers have more Possibilities for development and experience a more Meaningful work. The healthcare workers showed significantly lower scores in comparison with the active working population regarding the following psychosocial factors at work: Quantitative demands, Influence at work, Predictability, Reward, Quality of leadership, Social support from supervisor, Mutual trust between employees, Job satisfaction, Trust regarding management, Justice and respect, and lower Self rated health.

Conclusions: According to the present study, not only the demands at work, the work organization and the offensive behavior but also the horizontal and vertical interpersonal relations among the health care workers require special attention from the employers in order to improve the psychosocial working conditions.

Doctoral School: *Menthal Health Science*
Program: *Mental health sciences*
Supervisor: *Stauder Adrienne*
E- mail: *nistorkata@yahoo.com*

E/VI-7
THE DIFFERENCES AMONG PILS IN DESCRIPTIONS OF CURATIVE EFFECTS CAN INFLUENCE PEOPLE'S CHOICES AMONG OTC-MEDICINES WITH THE SAME EFFECT

Ildikó Komsa[1,2]

[1] *Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary*
[2] *Institute of Health Promotion and Sport Sciences, Eötvös Lóránd University, Budapest, Hungary*

In the past few years self-medication in the case of minor, self-limiting conditions is more and more increasing and nowadays it is an important part of health care. According to consumers it is a fast and simply way of healing and sparing time.

Package information leaflets (PIL's) which are important tools of patient education need to contain high-quality source of understandable information about medication because for those people who choose self-medication, the PIL's can be the main or the only information source to prevent from disadvantageous effects of medication errors such as misuse and abuse.

There are many factors that can influence patients' choices among OTC-medicines with the same effect such as family and cultural traditions, previous personal experiences, perceptual characteristics of pills, ads, financial factors, and content of PILs.

In researches about PILs, mainly readability, understandability and enumerated side-effects has been regarded as highly important factors and not much attention has been paid to the effects of the description of curative effects.

The aim of our study is to analize these effects helping to create better PILs which can help consumers to become responsible partners and conscious decision-makers in their self-care and to limit the potential risks involved in inappropriate self-medication.

According to our results, significant differences among perceived understandability and attractivity of the selected parts of PILs exist and these differences can influence patients' preferences and choice. The most important features of highly rated descriptions are understandability, the length of the description and the amount of beneficial effects and symptoms to be treated.

The technical and experimental knowledge regarding how to create more effective PILs is increasing but it is not surprising that the patients' viewpoints are in the very last place - though a really consumer-oriented policy would be much more ideal.

The importance of the patients' participation in PILs making have already been recognized – increasing the efficacy of PILs by using colours, larger print size, better design and more detailed form - and it is hoped that our results can bring a little bit closer that the patients can be provided with better designed and understandable PILs which contain more positive suggestions as well.

Doctoral School: *Menthal Health Science*
Program: *Mental health sciences*
Supervisor: *József Kovács*
E- mail: *komsa.ildi@gmail.com*

E/VI-8
BEHAVIOURAL-EPIDEMIOLOGICAL ANALYSIS OF ADOLESCENTS' PROBLEM BEHAVIOURS IN A POPULATION OF A SMALL TOWN AND ITS AREA BETWEEN 2008 AND 2013

Mate A. Balazs, Bettina F. Piko

University of Szeged, Faculty of General Medicine, Department of Behavioural Sciences, Szeged, Hungary

Problem behaviours are one of the most severe public health concerns all over the world. It is especially true in case of Hungary and other Eastern European countries where the different problem behaviours for instance smoking and alcohol drinking among adolescents are among the highest in Europe. In case of adolescents' substance use there is a tendency to extreme and abused consumption, for example binge drinking. Substance uses in this life period are able to increase the chance of use in the future. The study was performed in all of the elementary and high schools of Mako and the villages in its area in Hungary. The pupils of grade from 7 to 13 were questioned anonymously. The study of 2013 consisted of 2011 pupils. The sample of 2010 is consisted of 2072 pupils, in 2008 546 adolescents were involved in the study. Self-administered questionnaires were applied. The survey included sociodemographic variables, lifetime and monthly prevalence of smoking and alcohol drinking, different influencing factors, beliefs and attitudes related to substance use. Descriptive statistics, cross-tabulations and chi–square tests were used to test these interrelationships with SPSS MS 19.0 statistical program.

Aims: The purpose of the present study was to measure and compare the prevalences and other factors in terms of adolescents' health and risk behaviours. It was the third study in this region which performed by our research group after 2008 and 2010.

Results*:* According to comparison the worsening tendency, increasing substance use is present in case of both smoking and alcohol drinking. Significant risk factors were detected, especially in case of problem drinking and extreme substance user habits.

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Doctoral School: *Menthal Health Science*
Program: *Mental health sciences*
Supervisor: *Bettina F. Piko*
E-mail: *balazsmateadam@hotmail.com*

E/VI-9
HIGH FREQUENCY EEG ACTIVITY DURING SLEEP IS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN KIDNEY TRANSPLANT RECIPIENTS

Katalin Z. Rónai[1], András Szentkirályi[1,2], Alpár S. Lázár[1,3], Ákos Ujszászi[1], Anett Lindner[1,4], Katalin Fornadi[1,4], Mária E. Czira[1], Rezső Zoller[1,5], Csilla Z. Turányi[1], Zsolt I. Lázár[6], István Papp[6], István Mucsi[1,7,8], Róbert Bódizs[1], Miklós Z. Molnár[9,10,11], Márta Novák[1,12]

[1] Institute of Behavioral Sciences, Semmelweis University, Budapest, Hungary
[2] Westfälische Wilhelms-University, Inst. of Epidemiology and Socialmedicine, Münster, Germany
[3] Centre for Brain Repair, Department of Clinical Neurosciences University of Cambridge, Cambridge, UK
[4] Department of Neurology, Semmelweis University, Budapest, Hungary
[5] I. Department. of Internal Medicine, Semmelweis University, Budapest, Hungary
[6] Department of Physics, Babes-Bolyai University, Cluj-Napoca, Romania
[7] Institute of Pathophysiology, Semmelweis University, Budapest, Hungary
[8] Department of Medicine, Division of Nephrology, McGill University Health Centre, Montreal, Quebec, Canada
[9] Division of Nephrology & Hypertension, University of California Irvine Medical Center, Orange, CA, USA
[10] Harold Simmons Center for Chronic Disease Research & Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA
[11] Department of Medicine, Division of Nephrology, University Health Network, University of Toronto, Toronto, Canada
[12] Neuropsychiatry Program, University Health Network, University of Toronto, Toronto, Canada

Background and objectives: Depression is frequent among kidney transplant recipients and is associated with reduced adherence, impaired quality of life and also with increased morbidity, graft loss and mortality. Furthermore, a bidirectional association between depression and sleep disorders has been thoroughly documented. Despite its significance, the association between objective markers of sleep quality and subjective symptoms of depression has not been studied. In this study we aimed to document the characteristics of sleep architecture and EEG activity in kidney transplant recipients related to their subjective measures of depression.

Design, setting, participants and measurements: Patients were selected from all prevalent adult transplant recipients (n=1,214) followed at the Department of Transplantation and Surgery of the Semmelweis University, Budapest. Standard overnight polysomnography and consequent power spectral analysis on sleep EEG was performed in 56 kidney transplant recipients. Subjective symptoms of depression were assessed by the CESD (Center for Epidemiologic Scale) questionnaire.

Results: The severity of depressive symptoms was not associated significantly with parameters of sleep architecture, there was only a tendency towards a positive correlation with the amount of Stage2 sleep ($r=0.24$; $p=0.07$). In univariate analysis high frequency EEG activity during NREM and REM sleep showed a positive, significant association with CESD score (NREM gamma: $\beta=0.35$; $p<0.001$, beta: $\beta=0.34$; REM gamma: $\beta=0.276$; beta: $\beta=0.27$; $p<0.05$). In multivariate analyses the association between the CESD score and beta ($\beta=0.24$; $p<0.05$) and gamma ($\beta=0.28$; $p<0.05$) bands during NREM sleep remained significant after controlling for covariables.

Conclusions: Self-reported severity of depression is independently associated with increased wake-like EEG activity during NREM sleep, despite the lack of depression-specific markers in sleep architecture. Our results suggest that the quality of sleep could be a modifying factor between depression severity and clinical outcomes. Furthermore, treatment should also consider altered sleep in kidney transplant recipients with depression.

Doctoral school: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Márta Novák*
E-mail: *ronaikatalin.fmc@gmail.com*

E/VI-10
THE ONTOGENY OF DREAMING IN THE MIRROR OF COGNITIVE AND AFFECTIVE DEVELOPMENT

Piroska Sándor[1], Sára Szakadát[1,2], Katinka Kertész[1], Róbert Bódizs[1,2]

[1] Institute of Behavioral Sciences, Semmelweis University Budapest, Hungary
[2] Department of General Psychology, Pázmány Péter Catholic University, Budapest, Hungary

Inspired by Foulkes' longitudinal laboratory based studies the mainstream of developmental dream research considers preschooler's dreams to be strikingly simple and barren, and depicts dreaming solely as a cognitive performance. In contrast, the current neurocognitive approaches of adult dreaming see the function of REM sleep and dreams in the consolidation of emotional memories and in affective regulation.

Our aim was to re-evaluate the development of dreaming in the broader context of emotional and cognitive development and to bridge the gap between the theoretical approaches of the adult and developmental literature.

Children's dreams (n=30, age = 3.5-8.5 years, mean= 6.1 years) were collected in a home setting by pre-trained parents in the form of tape-recorded dream diaries over the course of six weeks. Dream reports were examined by our content analysis system based on those of Foulkes and of Hall and Van de Castle.

Cognitive abilities were assessed by the Wechsler Intelligence Scale for Children (WISC), the Raven's Coloured Progressive Matrices Test, the Attention Network Test (ANT) and the Stroop Test for children. For measuring emotional maturation we administered the Emotional Stroop Test for children and the Manchester Child Attachment Story Test (MCAST).

The results confirmed our expectations regarding the emotional nature of children's dreams. Emotions were already present in 46% of the dream reports of the youngest children. Age correlated positively with verbs reflecting cognition ($p=0.033$, Kendall's $tau=0.284$) as well as emotions appearing in dreams ($p=0.063$, Kendall's $tau=0.244$). Maturation of emotional processing was shown to be positively related to the length of dream reports as measure of dream activity when age was held constant ($p=0.006$, $r=0.49$).

Our results show significant connections of dream activity with emotional maturation and could serve as the first step towards an integration with contemporary neurocognitive dream theories based on adult dream reports.

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Doctoral School: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Róbert Bódizs*
E-mail: *sandorpiros@gmail.com*

E/VI-11
EXAMINING DYSKINESIA IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH AND WITHOUT ONGOING METHYLPHENIDATE TREATMENT

Ágnes Keresztény[1,2], Judit Balázs[2,3]

[1] *Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary*
[2] *Institute of Psychology, Eötvös Loránd University, Budapest, Hungary*
[3] *Vadaskert Child Psychiatry Hospital and Outpatient Clinic, Budapest, Hungary*

Background/Aims: Several studies proved that methylphenidate is a safe and effective treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). Some case studies presented that methylphenidate can trigger dyskinesia in children with ADHD, however it is scarcely investigated. The aim of our study was to investigate weather it is true.

Method: We investigated three groups (aged 6-18 years): 1) treatment-naïve children with ADHD 2) children with ADHD who were under methylphenidate treatment before the study 3) healthy control children. The Mini International Neuropsychiatric Interview Kid and the Abnormal Involuntary Movements Scale were used for evaluation. Methylphenidate administration of the children was in accordance with the dose prescribed by their therapist.

Results: There were significant difference in the level of dyskinesia between the groups both before ($F(2)=8.74$; $p<0.05$) and after ($F(2)=7.94$; $p<0.05$) methylphenidate administration. In the post hoc test, the ADHD group under methylphenidate treatment reported significantly higher level of dyskinesia symptoms than the treatment-naïve ADHD group and the control group; however, there was no difference between the control group and the treatment-naïve ADHD group.

Discussion: Our results suggest that methylphenidate enhance the level of dyskinesia in children with ADHD, so clinicians should pay attention to dyskinesia as a possible adverse effect of methylphenidate in the treatment of ADHD.

Doctoral School: *Mental Health Sciences*
Program: *Clinical Psychology and Psychiatry*
Supervisor: *Judit Balázs*
E-mail: *agnes.kereszteny@gmail.com*

E/VI-12
OUTCOME OF MAJOR DEPRESSIVE EPISODE AND PERSONALITY TRAITS. A FOLLOW UP STUDY

Nóra Garamvölgyi[1], Erika Szádóczky[2], Edina Gauland[2], Sándor Rózsa[3], Zoltán Rihmer[4]

[1] College of Health Care, Semmelweis University, Budapest, Hungary
[2] Clinexpert Gyógycentrum, Budapest, Hungary
[3] Faculty of Education and Psychology, Eötvös Loránd University, Budapest, Hungary
[4] Department of Clinical and Theoretical Mental Health, Semmelweis University, Budapest, Hungary

Introduction: The aim of our folow-up study was to the outcome of major depressive episode (MDD) from a point of personality dimensions and temperaments, investigated at baseline.

Methods: Originally 85 (75,3% female, 24,7 % male) in- and outpatients with MDD were enrolled into the study. Three years later 54 patients were contacted for a follow up study. Two parameters were assessed at baseline and follow up. In both cases the severity of MDD was measured by Hamilton Depression Scale (HAM-D). Temperaments and personality dimensions were scalled by Temperament Evaulation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A), Temperament and Character Inventory (TCI). The relationship between severity of MDD and TEMPS-A/TCI temperaments scales were assessed by correlation analyzes.

Results: HAM-D scores at the time of follow up showed significant correlation with three temperaments scales assessed at baseline (TEMPS-A): 1, the depressive temperament scale ($r= 0.488$, $p< 0.01$), 2, the cyclothymic temperament scale ($r= 0.457$, $p< 0.01$), 3, and anxious temperament scale ($r= 0.493$, $p< 0.01$).

HAM-D scores at the time of follow up was in significant correlation with the Harm Avoidance dimension measured at baseline TCI ($r= 0.493$, $p< 0.01$) and was in significant negative correlation with Self Directness scale of the first study TCI ($r= -0.525$, $p< 0.01$).

Conclusions: Major depressives with depressive, cyclothymic and anxious affective temperaments showed more severe depressive symptomps at the time of three years follow up. In contrast to this, hyperthimic temperament showed (nonsignificant) negative correlation with the HAM-D scores, indicating that in patients with MDD hyperthymic affective temerament may be protective against recurrence of depression.

Doctoral School: *Mental Health Sciences*
Program: *Psychiatry*
Supervisor: *Zoltán Rihmer*
E-mail: *garamvolgyin@gmail.com*

E/VI-13
CHANGING IDENTITY OF CHRISTIAN ROMANIES

Gellért Gyetvai

Gypsy Methodology and Research Center, Békés, Hungary

It is well known that when Gypsies become intellectuals they highly probable loss their ethnic identity, or their two identities come into a conflict with each other generally.

In contrast, in our large sample research (N = 705) we found that in Roma Christian churches (new protestant churches) the double identity of membership will be different. They will have a new kind of double identity without conflict. And as far as we can see, change is one of the most important aspects of these Gypsy churches. This defines the membership mostly. And in addition, this defines their personal ethnic identity, too. They can see themselves and each other on this basis. This change has a very strong effect on their identity. There are exceptions though, but rarely.

The study presents some results, and in addition discusses the possible explanations and potential consequences.

Doctoral School: *Mental Health Sciences*
Program: *Sociological and mental health approaches to resources for individuals and communities*
Supervisor: *Péter Török*
E-mail: *gyetvaig@caesar.elte.hu*

E/VI-14
NATIONWIDE SURVEY ON UNSUCCESSFUL ADOPTIONS

Júlia Andrási

Department of Childcare and Guardianship, Ministry of Human Resources, Budapest, Hungary

This fundamental research is on surveying the situation of those minors, who had been adopted on early stages, but due to different reasons (behavioural problems or serious illnesses of the adopted minors, death or inaptness of the adoptive parents etc.) they had to leave their adoptive families after the legal approval of their adoption. In many cases the adoption has been resolved as well. These children have been living in the childcare system since they had to leave their adoptive families and rarely had the opportunity to be adopted for the second time.

Aims: In one hand the aim is to assess the demographical data of those adoptive parents and their adopted children whose adoption disrupted, on the other hand is to examine the background factors of the unsuccessfulness. There is a new regulation in Hungary for establishing a supporting and supervising system for adoptive families and the experiences of this research could be helpful to the development of this new adoption follow-up system.

Results: The study is based on a 7-page-long questionnaire that collects the data of all affected minors nationwide. The survey started in 2007 and six years' data have been collected by now. There are data of 183 minors and their adoptive families in hand. According to the plan the research is going to be conducted for minimum two more years.

Another purpose is to collect some qualitative data by interviewing experts who dealt with unsuccessful cases and possibly by semi-structured interviews with some of those adoptive parents and youth who suffered adoption disruptions in the past.

Doctoral School: *Mental Health Sciences*
Program: *Sociological and mental health approaches to resources for individuals and communities*
Supervisor: *Gabor Ittzes*
Email: *julia.andrasi@gmail.com*

E/VI-15
DIFFICULTIES IN MIDWIVES HELPING PREGNANT WOMEN TO QUIT SMOKING

Ágnes Szélvári[1], László Kalabay[1], Adrienne Stauder [2], Róbert Urbán[3]

[1] *Department of Family Medicine, Semmelweis University, Budapest, Hungary*
[2] *Institute of Behavioural Sciences, Semmelweis Egyetem, Budapest, Hungary*
[3] *Faculty of Education and Psychology, Eötvös Loránd University, Budapest, Hungary*

Introduction: The estimated proportion of pregnant women smoking during pregnancy is about 30 percent. Midwives should have an important role in helping pregnant women to quit. What midwives believe on their role in helping people to quit, the level of their qualification in this matter, effectiveness of their efforts in case they interact with smokers is not clear.

Methods: 203 midwives (mean age 41,6 +/- 10,2 years, average working experience 16,9 +/- 11,1 years) were recruited into the study in four counties of Hungary in 2012. A self administered questionnaire of 96 items partially based on some questionnaires published was used before they participated on a training on smoking cessation. Statistical analysis: SPSS v.14. (khi square test, Mann-whitney test, Spearmann correlation).

Results: Almost all (96%) midwife assesses smoking, drinking (97%) and eating (100%) habits at first visit, 64% repeats it on following visits. Almost all of them (100%) believe that it is an important preventive activity, meanwhile third of them has doubt that it is respected. 71% informs the pregrant women about short/long term consequences of smoking. These parameters were independent from length of consultation, place of residence and midwivfe's smoking status (current smoker 7%, ex-smoker 19%). Almost all subjects gave a positive answer on being motivated in helping smokers to quit, but only 41% offers their help. There was significant difference concerning assessment of the partner's or others smoking habits (chi square (12)=29,87, p=0,003), which showed correlation with qualification (r:0,162, p: 0,023), preventing relapses (r:0,197, p:0,005) and offering help to quit (r:0,234, p: 0,001). 41% of subjects reported lack of knowledge of helping people to quit.

Conclusions: Midwives believe that helping people to quit is an important preventive activity, but their knowledge is insufficient. Besides lack of time this can play a role in not offering help in quitting. This could explain the lack in the assessment of passive smoking circumstances and informing patients. Training on smoking cessation for midwives is needed.

Doctoral School: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Stauder Adrienne,*
E-mail: *drszelvari.agnes@gmail.com*

E/VI-16
FUNCTIONAL GENE CLUSTERS IN SCHIZOPHRENIA: RESULTS FROM THE SCHIZOBANK WHOLE EXOME SEQUENCING STUDY

Attila J. Pulay[1], Júlia Koller[2], Attila Horváth[3], Péter Balicza[2], Judit Benkovits[1], Gábor Zahuczky[4], Endre Barta[3], István Likó[5], György Németh[5], Zoltán Urbányi[5], Judit Mária Molnár[2], László Nagy[3], János M. Réthelyi[1]

[1] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary
[2] Institute of Genomic Medicine and Rare Diseases Semmelweis University, Budapest, Hungary
[3] Medical and Health Science Center, Institute of Genomic Medicine, University of Debrecen Debrecen, Hungary
[4] UD-GenoMed Ltd, Debrecen, Debrecen, Hungary
[5] Richter Gedeon Ltd, Budapest, Hungary

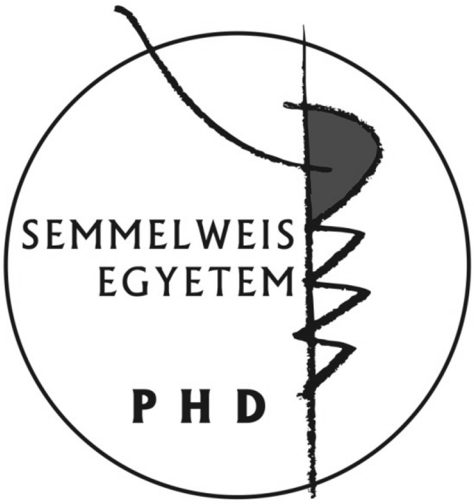
Schizophrenia is a chronic, severe and highly disabling psychiatric disorder, characterized by early onset and recurring psychotic episodes. Schizophrenia affects about 1% of the population worldwide and know to have a polygenic inheritance. Despite its high heritability and the extensive research most of its genetic variance of the disorders still remained unexplained. Possible causes of this "missing heritability" include the involvement of rare variants (SNV) that typically were not typed by previous GWAS studies. The aim of our study was to address this problem by sequencing whole exomes in schizophrenia case-parent trios.

Whole exomes of 16 case-parent trios from the SCHIZOBANK project were sequenced by using a HiScanSQ next generation sequencer, resulting in 50 M read per sample. The annotation and quality control process lead to a 241619 SNVs, of which 41903 SNVs showed recessive transmission. These SNVs were entered to a rare variant FBAT analysis with recessive inheritance model. The 535 genes (geneset1) harbouring the 689 potentially functional SNVs with $p<0.2$ were entered to the functional annotation clustering by using NCBI DAVID with high stringency. Further, the 41903 FBAT SNV p-values were also included to a gene-based association analyis by using KGG with the hybrid gene based association test (HYST). 760 genes with $p<0.2$ (geneset2) were entered to a downstream functional annotation clustering with NCBI DAVID.

The analysis of geneset1 yielded 145 clusters with the top cluster (enrichments score: 4.3) containing sensory transduction, sensory perception, cognition and neurological system process (FDRs: 6.22E-05, 0.02, 0.03 and 0.42 respectively). Top annotation cluster of geneset2 (enrichment score: 13.53) included MAGE proteins (FDR: 5.43E-12).

Processing the SNV associations to gene based functional clusters detected biologically plausible associations, and most likely fit better the polygenic inheritance model of schizophrenia. However, due to the small sample size, these results should be interpreted with caution.

Doctoral School: *Mental Health Sciences*
Program: *Clinical psychology and psychiatry*
Supervisor: *János M. Réthelyi*
E-mail: *pulay.attila@med.semmelweis-univ.hu*



E/VII
ORAL PRESENTATIONS

Chairman:
Prof. Dr. Lídia Sréter

E/VII-1
THE EFFECT OF PRIOR GESTATIONAL DIABETES ON THE SHAPE OF THE GLUCOSE RESPONSE CURVE DURING AN ORAL GLUCOSE TOLERANCE TEST 3 YEARS AFTER DELIVERY

Zsófia Szili-Janicsek, Ádám Gy. Tabák

I. Department of Medicine, Semmelweis Universitiy Faculty of Medicine, Budapest, Hungary

Background and aims: The shape of glucose response curve (sGRC) during an oral glucose tolerance test (OGTT) is an independent predictor of type 2 diabetes (T2DM). Since gestational diabetes (GDM) is associated with an increased risk of T2DM, we aimed to investigate the association between the sGRC and (1) glucose tolerance status during a pregnancy 3 years before and (2) current glucose tolerance status.

Methods: Case-control study nested in a cohort of women delivered at a single centre in 2005-2006. Participants: early GDM (n=46, diagnosed: 16-20 gestational weeks), late GDM (n=43, diagnosed: 24-28 gestational weeks), and controls (n=64, normal glucose tolerance [NGT] during pregnancy). sGRC was monophasic if it followed an inverted U-shape and biphasic if there was a second rise in plasma glucose after the first rise. Glucose tolerance was defined by WHO 1999.

Results: 20% had NGT, 5% IFG, and 15% IGT. 37% had the early GDM, 32% the late GDM, and 31% NGT during pregnancy. Women with a biphasic response had a lower hip circumference, lower triglycerides levels, higher adiponectin levels, fewer previous pregnancies, and lower early GDM frequency (all $p<0.05$). There was no difference between women with biphasic and monophasic curves in fasting and 2-hour glucose or insulin levels, or body mass index (all $p>0.1$).

Conclusion: Although the sGRC is independent of current glucose and insulin levels, it is strongly associated with 'severe' glucose intolerance during pregnancy. These may suggest that the sGRC captures abnormal glucose regulation independent of plasma glucose and may be an earlier indicator of an elevated diabetes risk than fasting or postload glucose.

Doctoral School: *Clinical Medicine*
Program: *Molecular Genetics, pathomechanism and clinical aspects of metabolic disorders*
Supervisor: *Ádám Gy. Tabák*
E-mail: *zsofi1101@gmail.com*

E/VII-2
INVESTIGATION OF EICOSANOIDS IN COPD

Orsolya Drozdovszky[1], Imre Bartha[2], Balázs Antus[2]

[1,2] Pathophisiology, Institute of National Koranyi Tbc and Pulmonology, Budapest, Hungary

Eicosanoids have been implicated in the pathophysiology of COPD. However, their levels in respiratory samples obtained by different sampling techniques could be different. In this study we investigated the levels of eicosanoids in the sputum of COPD patients hospitalized with an acute exacerbation, than compared the concentrations of prostaglandin E_2 (PGE_2), 8-isoprostane, cysteinyl-leukotrienes (cys-LTs) and leukotriene B_4 (LTB_4) in induced sputum, bronchoalveolar lavage (BAL) and exhaled breath condensate (EBC) collected from COPD patients.

We studied 25 stable COPD patients (age: 62.1±1.6 years, 48.8±4.8 pack-years) and 34 patients (age: 64.6±2.2 years, 45.8±4.1 pack-years), at hospital admission due to an exacerbation and after treatment. In the longitudinal study 23 stable, ex-smoker COPD patients (age: 63.1±1.8 years, 45.1±3.5 pack-years) were enrolled. Levels of eicosanoids were determined by enzyme-immunoassay.

Sputum PGE_2, 8-isoprostane and LTB_4 levels were increased in patients with exacerbation compared to stable subjects (PGE_2: 36.3 [13.3-81.9] vs. 3.82 [1.77-6.63] pg/ml, $p<0.001$; 8-isoprostane: 80.1 [36.4-155.4] vs. 29.7 [13.8-68.8] pg/ml, $p<0.05$; LTB_4: 581.7 [244.7-776.9] vs. 276.1 [105.4-594.7] pg/ml, $p<0.05$). After treatment only PGE_2 was decreased significantly (19.4 [4.6-52.5] pg/ml, $p<0.01$). In exacerbated patients there was a significant correlation between PGE_2 and sputum neutrophil cell counts ($r=0.68$, $p<0.005$). Concentrations of cys-LTs were significantly higher in sputum (211.9 [128.6-827.1] pg/ml) compared to BAL (122.5 [60.4-256.1] pg/ml) or EBC (33.8 [19.9-58.1] pg/ml, $p<0.01$). 8-isoprostane and LTB_4 levels were also the highest in sputum. In EBC only cys-LTs were detectable. We found correlations between the number of neutrophils and the levels of LTB_4 ($r=0.52$, $p<0.05$) and 8-isoprostane ($r=0.61$, $p<0.01$) in sputum, while lipid mediator levels in the BAL and EBC did not correlate with sputum neutrophils.

Our results suggest that PGE_2 in sputum appears to be a useful marker for monitoring exacerbation-associated inflammation within the airway of patients with COPD. Moreover, our data suggest that the highest eicosanoid levels are in the sputum and lowest in the EBC.

Doctoral School: *Clinical Medicine*
Program: *Pulmonology*
Supervisor: *Balázs Antus*
E-mail: *drozdyorsi@gmail.com*

E/VII-3
ASSESSMENT OF QUALITY OF LIFE AND DISEASE SEVERITY IN MODERATE TO SEVERE PSORIASIS: A CROSS-SECTIONAL STUDY FROM HUNGARY

Fanni Rencz[1,2], Orsolya Balogh[2], Hajnalka Jókai[3], Péter Holló[3], Sarolta Kárpáti[3], Valentin Brodszky[2]

[1] Doctoral School of Clinical Medicine, Semmelweis University, Budapest, Hungary
[2] Department of Health Economics, Corvinus University of Budapest, Budapest, Hungary
[3] Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary

Psoriasis can have a substantial negative effect on patients' quality of life, including physical, psychological and socio-economic disadvantages.

Objectives: To assess health related quality of life (HRQOL) in moderate to severe psoriasis patients, to quantify the impact of the localisation of psoriatic lesions, and to seek for new possible predictors of HRQOL in psoriasis.

Methods: A cross-sectional study of 200 consecutive adults with moderate to severe psoriasis from two Hungarian university clinics was carried out. General HRQOL was measured with EuroQol 5D (EQ-5D), disease-specific HRQOL with Dermatology Life Quality Index (DLQI), and disease severity with Psoriasis Area and Severity Index (PASI).

Results: Mean age was 51 years (SD 12.9) with male predominance (68.5%). Overall 51.5% (n=103) of the patients received biological therapy. Median EQ-5D, DLQI, and PASI scores were 0.73, 3.0, and 3.45, respectively. Compared to the age-gender matched average Hungarian population, lower EQ-5D results were observed in each 10-year age group of women between 35 and 64, and in the 18-24, 25-34, 45-54, and 55-64 age groups of men ($p<0.05$). Sample size in any other age group was very small, and no further significant difference was found. Participants treated with biologicals reported better HRQOL (EQ-5D means 0.75 vs 0.63, $p<0.05$); however, both groups had significantly lower HRQOL than the age-matched average population (0.808). Patients with visible skin lesions reported poorer HRQOL than those with non-visible lesions measured not only with DLQI, but also with EQ-5D ($p<0.05$). The neck and/or décolletage involvement was associated with the greatest HRQOL impairment. Also, palmoplantar involvement, psoriatic arthritis, GP visits due to psoriasis, hospitalisations, and necessity of home help were revealed predictors of HRQOL.

Conclusions: Several clinical and health service utilisation variables were identified as possible predictors of HRQOL that should be considered for finding the optimal disease management for each psoriasis patient.

Doctoral School: *Clinical Medicine*
Program: *Dermatology and Venereology*
Supervisor: *Valentin Brodszky*
E-mail: *fanni.rencz@uni-corvinus.hu*

E/VII-4
THE BIOMECHANICAL AND FUNCTIONAL COMPARING OF HEALTHY AND DISABLED ATHLETS IN KAYAK-CANEO

Bernadett Németh Kertészné

Orthopedic Department, Semmelweis University, Budapest, Hungary

Introduction: The body movements are intergrated either kayak-caneo required this movements and a huge efficiency. The flexion – extension and rotational movements in the spine helps the technic of upper limbs. Futhermore the trunk activity contribute in the support function of lower limbs. The effect of these elements, and aligned kinematic sport movement which means that maximal efficiency demand a special technic. The cinematic chain of disabled movements contain many compensatoric elements are conditioned by damage. It depends on the lack of function, the classicism, and the scale.

Hypothesis: As a result of the damage the moving mechanism change in a wide range.

Goal: Our goal is to demonstarte the uninjured moving mechanism of kayak-caneo with an ergometer , EMG and a 3D VICON camera system, get a modell to compare disabled moving mechanism. The biomechanical laboratory of Semmelweis University Orthopedic Clinic the center of the investigation.

Conclusion: We would get exact knowledge abot the muscle activity and the range of motion in the cases of injured athletes.

Figure 1.-Weba kayak-caneo ergometer

Doctoral School: *Clinical Medicine*
Program: *Physiology and Pathology of the musculoskeletal system*
Supervisor: *Zoltan Bejek*
E-mail: : *nemet.bernadett@gmail.com*

E/VII-5
A NOVEL METHOD FOR THE MOTION ANALYSIS OF THE GLENOHUMERAL JOINT

Eszter Kővári

Department of Orthopaedics, Semmelweis University, Budapest, Hungary

Three dimensional motion analysis provides very valuable information on the kinematics of various joints, thus objective evaluation of different musculoskeletal disorders becomes possible. Initially, 3D analysis focused mostly on the lower limb, but in recent years growing attention has been paid to the upper limb, especially to the shoulder, because altered scapular kinematics is known to play an important role in different shoulder diseases. Previous models represented the shoulder as two rigid bodies connected by one articulation, however in reality shoulder movements are the summation of total scapulothoracic and glenohumeral motion.

The aim of our present study was to develop a new biomechanical approach to describe more accurately this complex movement. Data were collected using a six-camera VICON motion analysis system. The scapula, the humerus and the thorax were defined as separate rigid bodies connected by separate joints. Scapula kinematics was calculated from a marker triplet placed on the flat surface of the acromion, where skin artefacts are minimalized. Humeral and thoracic markers were placed as recommended by the VICON native Plug-In Gait Upperbody protocol.

Results: We presumed that the sum of the movement of the humerus compared to the scapula and the movement of the scapula compared to the thorax produces the same result as the humerus compared to the thorax from the VICON Plug-In Gait protocol. With the use of the developed model a better understanding of the relationship between scapular kinematics and different shoulder disorders can be achieved.

Doctoral School: *Clinical Medicine*
Program: *Physiology and Pathology of the musculoskeletal system*
Supervisor: *Gabor Skaliczki*
E-mail: *ester.kovari@gmail.com*

E/VII-6
POSTCONDITIONING THE LOWER LIMB IMPROVES SMALL INTESTINAL MICROCIRCULATION

Zsolt Túróczi[1], András Fülöp[1], Zoltán Czigány[1], Gabriella Varga[2], Oliver Rosero[1], Tünde Tökés[2], József Kaszaki[2], Gábor Lotz[3], László Harsányi[1], Attila Szijártó[1]

[1] I. Department of Surgery, Semmelweis University, Budapest, Hungary
[2] Institute of Surgical Research, University of Szeged, Szeged, Hungary
[3] II. Department of Pathology, Semmelweis Univesity, Budapest, Hungary

Background: Major lower limb vascular surgeries may result in severe, remote injury of the gastrointestinal system, which has high mortality rates. Postconditioning is a technique with potential capability of reducing remote gastrointestinal complications. Our aim was to assess the remote macro- and micro-hemodynamic changes of the small intestine following an infrarenal aortic occlusion and to evaluate the effects of postconditioning on these alterations.

Methods: Male Wistar rats underwent 3 hours of infrarenal aortic occlusion followed by 4 hours of reperfusion. In one group, postconditioning was applied. During the experiment blood pressure, superior mesenteric artery flow and mucosal microcirculation of duodenum, jejunum and ileum were assessed. At the end of the experiment, samples were taken from each intestinal segment for histological examinations.

Results: Superior mesenteric artery flow, as well as segmental small bowel microcirculation showed significant impairment in the IR group in contrast to the sham-operated group, (flow: 3.41±1.61 vs. 9.22±2.04ml/min, p=0.012; microcirculation(duodenum): 90.42±4.73 vs. 99.83±2.55%, p=0.012; microcirculation(jejunum): 73.40±5.06 vs. 98.05±6.18%, p=0.008; microcirculation(ileum): 40.56±4.19 vs. 96.01±5.87%, p=0.002 in the IR and sham groups respectively), while histological damage was significantly elevated. Strong negative correlation was found between microcirculatory values and histological damage (r= -0.911, p<0.001). Postconditioning was able to limit flow reduction in all small bowel segments and in the superior mesenteric artery (flow: 9.0±2.14ml/min, p=0.009; microcirculation(duodenum): 102.03±4,02, p=0.009; microcirculation(jejunum): 87.36±3.13, p<0,001; microcirculation(ileum): 82.58±6.26, p<0.001), and was able to significantly reduce histological damage.

Conclusions: Microcirculatory impairment might be responsible for remote intestinal injury following infrarenal aortic occlusion. Postconditioning was able to reduce this remote intestinal damage.

Doctoral School: *Clinical Medicine*
Program: *Clinical and experimental research in Angiology*
Supervisor: *Attila Szijártó*
E-mail: *termox@freemail.hu*

E/VII-7
ROLE OF INTERLEUKIN-24 (IL-24) IN THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE (IBD)

Domonkos Pap[1], Anna Ónody[1], Erna Sziksz[2], Leonóra Himer[2], Apor Veres-Székely[1], Viktória Ruszinkó[3], Gábor Veres[1], András Arató[1], Tivadar Tulassay[1,2], Ádám Vannay[2]

[1] I. Department of Pediatrics, Semmelweis University, Budapest, Hungary
[2] Research Group for Pediatrics and Nephrology, Semmelweis University and Hungarian Academy of Sciences, Budapest, Hungary
[3] Petz Aladár Teaching Hospital, Győr, Hungary

Background: The exact pathomechanism of inflammatory bowel disease (IBD) is not fully understood; its medication is not solved. Targeted therapies to cytokines belong to interleukin (IL)-10 family came into focus and are under drug development. Our recent target molecule IL-24 is a new member of the family, which function is less known. Based literature it can be hypothesized that IL-24 may be involved in the regulation of inflammation and tissue regeneration, however its role in IBD is not clarified.

Aims: The aim of our study is to better understand the pathomechanism of IBD and to find new potential therapeutic applications. We plan to examine the expression and distribution of IL-24 and its receptor in children with Crohn's disease (CD) ulcerative colitis (UC) and investigate its effect on processes involved in the pathomechanism of IBD such as proliferation or fibrosis.

Methods: Colonic biopsy samples were collected from children with CD (n=17), UC (n=12) and controls (n=20). The mRNA expression and localization of IL-24 and a common element of its heterodimer receptor complex (IL-20RB) were determined using real-time RT-PCR and immunofluorescent staining, respectively. In vitro HT-29 colonic epithelial cells were treated with recombinant IL-24 and ERK1/2, JNK1/2 specific inhibitors. Phosphorylation of ERK1/2 and JNK1/2, and the amount of tumor growth factor (TGF-ß) and platelet-derived growth factor (PDGF-ß) were analyzed by flow cytometry.

Results: The mRNA expression of IL-24 was significantly elevated in the colonic mucosa of children with IBD (CD and UC) compared to controls ($p<0.05$). Strong immunopositivity of IL-24 and IL-20RB were detected in colonic epithelial cells and subepithelial fibroblasts in children with IBD compared to controls. Increased phosphorilation of ERK1/2 and JNK1/2, and elevated level of PDGF-β and TGF-β were observed in HT-29 cells following IL-24 treatment. After administration of ERK1/2 and JNK1/2 inhibitors number of PDGF-β and TGF-β positive cells decreased.

Conclusion: Elevated level of IL-24 suggests its involvement in the pathomechanism of IBD. Its effect on PDGF-β and TGF-β may refer to its potential role during fibrotic processes in IBD mediated by ERK1/2 and JNK1/2 signaling pathways. However further studies are needed we suggest that IL-24 may be a potential therapeutic target in the future.

Doctoral School: *Clinical Medicine*
Program: *Pediatrics*
Supervisor: *Ádám Vannay*
E-mail: *pap.doma@gmail.com*

E/VII-8
PORTAL VEIN LIGATION INDUCED LIVER REGENERATION FOLLOW UP BY MULTIMODAL PET/MRI MEASUREMENTS

András Fülöp[1], Olivér Rosero[1], Dávid Garbaisz[1], Zsolt Túróczi[1], László Harsányi[1], Krisztián Szigeti[2], Attila Szijártó[1]

[1] I. Department of Surgery, Semmelweis University, Budapest, Hungary
[2] Department of Biophysics and Radiation Biology; Semmelweis University, Budapest, Hungary

Objectives: Portal vein ligation (PVL) is often used to induced liver regeneration before extended hepatectomy. It is unknown how PVL affects the metabolic patterns of healthy liver tissues. The aim of this study is to evaluate the effect of PVL on glucose metabolism, using PET/MRI imaging in healthy rat liver.

Materials and Methods: Male Wistar rats (n=30) underwent PVL. 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG) PET/MRI imaging and morphological/histological examination were performed before; 1-, 2-, 3-, 7-days after PVL. Dynamic PET data were collected and the standardized uptake values (SUV) were calculated in relation to cardiac left ventricle (SUV_{VOI}/SUV_{CLV}) and mean liver SUV (SUV_{VOI}/SUV_{Liver}).

Results: PVL induced atrophy of ligated lobes, while non-ligated liver tissue showed compensatory hypertrophy characterized by intensive mitotic activity of hepatocytes. Dynamic PET scan revealed altered FDG kinetics in liver lobes. SUV_{VOI}/SUV_{CLV} significantly increased in lobes, with a maximal value at the 2nd postoperative day and returned near to the baseline 7 days after the ligation. The ligated liver lobes, however, showed significantly higher tracer uptake compared to the non-ligated lobes (significantly higher SUV_{VOI}/SUV_{Liver} values were observed at postoperative day 1, 2 and 3). The homogenous tracer biodistribution observed before PVL reappeared by 7th postoperative day.

Conclusion: After PVL the healthy liver tissues show an altered FDG uptake dynamics, which should be taken into account during the assessment of PET data until the PVL induced atrophic and regenerative processes are completed.

Doctoral School: *Clinical Medicine*
Program: *Gastroenterology*
Supervisor: *László Harsányi*
E-mail: *fulop.andras2@gmail.com*

E/VII-9
LEVOSIMENDAN AND ISCHAEMIC POSTCONDITIONING IN A MODEL OF LOWER LIMB ISCHAEMIA

Péter Arányi[1], Zsolt Túróczi[1], Dávid Garbaisz[1], János Geleji[2], Gábor Lotz[3], László Harsányi[1], Attila Szijártó[1]

[1] *I. Department of Surgery, Semmelweis University, Budapest, Hungary*
[2] *Faculty of Science, Institute of Mathematics, Eötvös Loránd University, Budapest, Hungary*
[3] *II. Department of Pathology, Semmelweis University, Budapest, Hungary*

Aims and objectives: A most severe complication of infrarenal aortic and lower extremity major arterial reconstructions in vascular surgery is an acute renal failure. The underlying mechanism is the vascular occlusion, an ischaemia-reperfusion injury of a vast mass of muscle tissues, and a consequential metabolic upset and haemodynamic redistribution.

The aim of the study was to apply (ischaemic) postconditioning and also the inodilator and mitochondrial K^+_{ATP}-channel agonist levosimendan, as a "pharmacological postconditioning", and investigate their effects on the muscle ischaemia-reperfusion injuries and the corollary renal dysfunction.

Methods: Male Wistar rats underwent bilateral lower limb ischaemia for 180 min followed by reperfusion. Postconditioning consisted of 6 cycles of 10 sec aortic reocclusion and 10 sec declamping. Levosimendan (Simdax®, OrionPharma Ltd., Hungary, dissolved in 5% glucose solution) was administered continuously (0,02 μg/bwkg/h) throughout the whole course of ischaemia and the first 3 hours of reperfusion (6 hours in total) through the left jugular vein. Results of the treatment groups were compared with sham-operated and ischaemia-reperfusion control groups, respectively. Hemodynamic monitoring was performed by invasive arterial blood pressure registering and a kidney surface laser Doppler flowmetry. After 4 and 24 hours of reperfusion serum, urine and histological samples were collected.

Results: Muscle viability studies showed no significant improvement with the use of postconditioning in terms of ischemic rhabdomyolysis, on the other hand levosimendan administration resulted in significantly preserved viability at both measured time points. At the same time renal functional laboratory tests and kidney histology demonstrated significantly less expressed kidney injury in postconditioned and levosimendan-treated animals. Systemic hemodynamics improved only in the postconditioned group after reperfusion, but kidney microcirculation was significantly less impaired in both treatment groups.

Conclusion: The results claim a protective role for postconditioning and also levosimendan "pharmacological postconditioning" in major vascular surgeries to prevent renal complications.

Doctoral School: *Clinical Medicine*
Program: *Clinical and experimental research in Angiology*
Supervisor: *Attila Szijarto*
E-mail: *aranyi.p@gmail.com*

E/VII-10
SURGICAL SITE INFECTION AFTER PRIMARY DEGENERATIVE LUMBAR SPINE SURGERIES AND ITS EFFECT ON LONG-TERM OUTCOME

István Klemencsics, Áron Lazáry, Péter Pál Varga

National Center for Spinal Disorders, Budapest, Hungary

Introduction: Surgical site infection (SSI) is one of the most serious complications after spinal surgery. Predisposing factors as well as the long-term consequence of the SSI treated according to the current guidelines are less reported.

Aim: Aims of the study were to analyze the risk for SSI in a prospective lumbar surgical cohort and to determine the impact of SSI on long-term outcome.

Patients and Methods: Seven hundred twenty four consecutive patients underwent one- or two-level lumbar microdiscectomy, decompression (DE) or fusion (TLIF) surgery were included into the study. Patients completed self-reported health status measurement questionnaires - Oswestry Disability Index (ODI), Core Outcome Measurement Index (COMI), Zung Depression Scale (ZDS) and Modified Somatic Perception Questionnaire (MSPQ) – and Visual Analogue Scale for pain at baseline and two years after the surgery. SSI was defined according to the latest CDC (Centers for Disease Control and Prevention) guideline and treated according to the current recommendation of the National Orthopaedic and Infectious Diseases Societies. Effect of baseline characteristics, comorbidities, pain history and surgical data on the occurrence of SSI was determined in uni- and multivariate regression models. Five-point Likert scale on self-reported outcome was classified into two categories ("good" and "poor" result) and influence of SSI on outcome was analyzed. SPSS 20.0 statistical program package was used for the analyses where $p<0.05$ was considered significant.

Results: The final cohort consisted of 387 DE and 337 TLIF surgeries. The incidence of SSI in our cohort was 3.5% (2.6% superficial and 0.8% deep wound infection). In the multivariate backward regression model age, BMI and anxiety proved to be the significant predictors for SSI ($p_{model}=0.011$). There were no significant difference in changes of mean scores of pain and outcome questionnaires comparing patients without and with SSI (Pain: $p=0.42$, ODI: $p=0.79$, COMI: $p=0.79$) and subjective judgment about the success of the index surgery was not influenced by the occurrence of SSI (Chi-square=3.35, df=1, $p=0.067$)

Conclusion: No significant difference was found in the incidence of SSI in one- and two-level non-instrumented and instrumented lumbar degenerative surgeries. Predisposing factors for SSI were age, BMI and anxiety. Analyzing the long-term outcome of surgical treatment, no significant difference was found if the SSI was treated according to the recent guidelines.

Doctoral School: *Clinical Medicine*
Program: *Physiology and Pathology of the musculoskeletal system*
Supervisor: *Áron Lazáry*
E-mail: *ester.kovari@gmail.com*

E/VII-11
VITAMIN D RECEPTOR POLYMORPHISMS ARE ASSOCIATED WITH MUSCLE PERFORMANCE

Árpád Bozsódi, Áron Lazáry, Annamária Somhegyi, Péter Pál Varga

National Center for Spinal Disorders, Budapest, Hungary

Introduction: The associations between the muscle function and spinal disorders have been studied from different aspects. In recent years growing evidence have been published on the genetic background of muscle performance in case-control study designs. The role of vitamin D in muscle function has been previously described, thus the gene of its receptor is one of the most important candidates in genetic association studies.

Purpose: The aim of the study was to investigate the association between vitamin D receptor (VDR) gene variants and hand-grip strength (as muscle function and general health status phenotype) in a healthy general population.

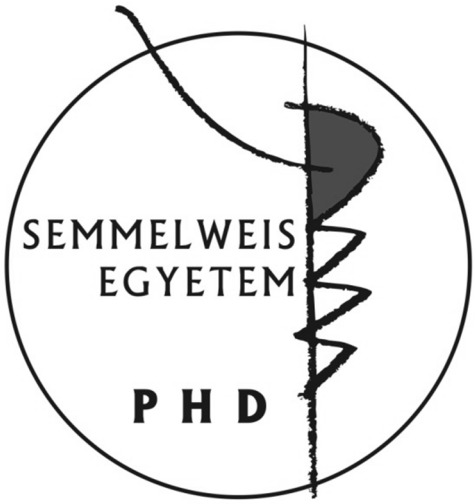
Materials and methods: Genetic association study on quantitative traits of muscle function in a general population. Seven hundred eighty-eight schoolchildren (7-12y) were included into the study from seven Hungarian primary schools. Genomic DNA was extracted from saliva samples and seven single nucleotide polymorphisms (SNPs) across the VDR gene were genotyped with Sequenom MassARRAY technique. Hand grip strength was measured with a digital dynamometer in both (dominant and non-dominant) hands. Single marker and haplotype associations were tested using the SNPassoc and Thesias software packages. All analyses were adjusted for age, sex, weight and height and $p<0.05$ was considered signficant.

Results: Three SNPs (rs4516035, rs1544410, rs731236) and a haploblock constructed by 3 SNPs (rs1544410-rs731236-rs10783215) were significantly associated with hand grip strength of the dominant hand and the haploblock above had also significant effect ($p<0.01$). The „ACT" haplotype was associated with the highest grip strength in both hands ($p<0.005$).

Conclusions: Our results proved that genetic variants in VDR gene are significantly associated with hand grip strength. The new results related to the genetic background of hand grip strength can be important in the sport and general health researches.

The research leading to these results received funding from the European Community's Seventh Framework Programme (FP7, 2007-2013).

Doctoral school: *Clinical Medicine*
Program: *Physiology and Pathology of the musculoskeletal system*
Supervisor: *Áron Lazáry*
E-mail: *arpad.bozsodi@gmai.com*



P/I
POSTER PRESENTATIONS

Chairman:
Dr. Gábor Békési

P/I-1
MICRORNA MIR-34A IS A REGULATOR OF ARYL HYDROCARBON RECEPTOR INTERACTING PROTEIN (AIP) EXPRESSION

Judit Dénes[1,2], Leandro Kasuki[3], Giampaolo Trivellin[1], Leandro M. Colli[4], Christina M. Takiya[5], Craig E. Stiles[1], Sayka Barry[1], Margaret de Castro[4], Mônica R. Gadelha[3], Márta Korbonits[1]

[1] Department of Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK
[2] Division of Endocrinology, II. Department of Medicine, Health Center, Hungarian Defense Forces, Budapest, Hungary
[3] Endocrinology Unit, Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[4] Department of Internal Medicine, Endocrinology Laboratory, Ribeirão Preto Medical School, São Paulo University, São Paulo, Brazil
[5] Biofísica Carlos Chagas Filho Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Patients with germline *AIP* mutations typically have large, invasive somatotroph adenomas and poor response to somatostatin analogues (SSA). Sporadic pituitary adenomas showing low AIP protein expression show similar phenotype.

Aims*:* To study the mechanism of low AIP protein expression 31 sporadic somatotropinomas with no *AIP* mutations with low (n=13) or high (n=18) AIP protein expression were analyzed for expression of *AIP* mRNA and 12 microRNAs (miRNAs) predicted to bind the 3'UTR of *AIP*. Luciferase reporter assays of wild-type and deletion constructs of *AIP*-3'UTR were used to study the effect of the selected miRNAs in GH3 cells. Endogenous AIP protein and mRNA levels were measured after miRNA over- and underexpression in HEK293 and GH3 cells.

Results*:* No significant difference was observed in *AIP* mRNA expression between tumors with low or high AIP protein expression suggesting that AIP protein levels may be regulated post-transcriptionally by miRNAs. miR-22 and miR-34a were highly expressed in low AIP protein samples compared to adenomas with high levels of AIP protein. miR-34a levels were inversely correlated with response to SSA therapy. miR-34a inhibited the luciferase-*AIP*-3'UTR construct, suggesting that miR-34a binds to *AIP*-3'UTR, while miR-22 showed no inhibition. Deletion mutants of the 3 different predicted binding sites in *AIP*-3'UTR identified the c.*6-30 site to be involved in miR-34a's activity. miR-34a overexpression in HEK293 and GH3 cells resulted in inhibition of endogenous AIP protein expression.

Conclusion*:* Low AIP protein expression is associated with high miR-34a expression. miR-34a can down-regulate AIP-protein but not RNA expression *in vitro*. miR-34a is a negative regulator of AIP-protein expression and could be responsible for the low AIP expression observed in half of somatotropinomas with an invasive phenotype and resistance to SSA.

Doctoral School: *Clinical Medicine*
Program: *Molecular Genetics, pathomechanism and clinical aspects of metabolic disorders*
Supervisor: *Miklós Góth*
E-mail: *denes.judit82@gmail.com*

P/I-2
BODY COMPOSITION MEASUREMENT AMONG IBD PATIENTS

Ágnes Anna Csontos[1], Andrea Molnár[2], Katalin Lőrinczy[1], Dorottya Kocsis[1], Márk Juhász[1], Pál Miheller[1]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] Semmelweis University School of PhD studies, Budapest, Hungary

Background: Many patients with inflammatory bowel disease (IBD) are affected by low body mass and moreover altered fat and fat free mass distribution. These factors cannot be detected by routine clinical assessment. Abnormal body composition may affect illness outcome, quality of life and may lead to even more complications. The bioelectrical impedance analysis (BIA) is a widely used method to examine body composition.

Methods: We included 121 patients with Crohn's disease (CD) and 52 with ulcerative colitis (UC). High quality body analyzer (InBody 720, using 6 different frequencies 5 body segments) was used to assess the body weight, body mass index (BMI), body fat percent, skeletal muscle mass (SMM), fat free mass (FFM), visceral fat area (VFA), body water content (TBW). 100 age and gender matched healthy individuals (HC) were included as a control.

Results: 16.2% (n=28) of the patients was had low BMI (<18.5), 3.5% of them (n= 6) had BMI< 16. 55.5% (n=45) of patients with normal BMI had low muscle mass, 33.3% (n=27) had decreased and 58.0% (n=47) increased body fat. Patients with IBD had lower FFM (53.16±11.76 vs. 56.92±14.06, $p<0.01$), SMM (29.38±7.28 vs. 31.95±8.49, $p<0.01$) VFA (98.61±53.89 vs. 79.23±47.06, $p<0.01$) and TBW (39.09±8.65 vs. 41.71±10.3, $p<0.01$) compared to HC. These results were not differed in CD vs. UC patients. Patients with inflammatory type had significantly less FFM (51.58±12.11 vs. 55.46±10.66; $p<0.05$) and TBW (40.75±7.83 vs. 37.92±8.89, $p<0.05$) compared to patients with penetrating type CD. They also had significantly lower FFM, SMM and TBW content than healthy controls (51.58±12.11 vs. 56.92±0.40, $p<0.01$; 28.25±7.63 vs. 31.95±8.49, $p<0.005$; 37.92±8.89 vs. 41.74±10.30, $p<0.05$; respectively). We found no significant difference between body compositions of CD patients depending on disease location. These parameters did not varied in UC with different location. Patients were divided into 3 groups based on their efficacious maintenance medications (mesalazine, azathioprine, biological). FFM, SMM, TBW in patients using immunosuppressive therapy was significant better than patient using ASA in UC (58.55±12.71 vs. 49.78±12.21<0.05; 32.82±7.43 vs. 27.47±7.52, $p<0.05$; and 43.22±9.90 vs. 36.62±8.94, $p<0.05$; respectively). Significant correlation was detected between disease duration and BMI ($r=0.036$), SMM ($r=0.046$) and body fat percent in CD patients ($r=0.045$).

Conclusion: According to our findings, IBD patients' body composition differed from HC. The results suggest that BMI is not a sufficient parameter to estimate body composition. BIA seems to be more informative regarding nutritional status than routine clinical methods, and it may play a role in IBD patient care in the future.

Doctoral School: *Clinical Medicine*
Program: *Gastoenterology*
Supervisor: *Pál Miheller*
E-mail: *denes.judit82@gmail.com*

P/I-3
DIAGNOSTIC PERFORMANCE OF CARDIAC CT IN DETECTING LEFT ATRIAL THROMBUS

Gyöngyi P. Major[1], Bálint Szilveszter[2], Tamás Horváth[1], Attila Kovács[2], Szabina Pataki[2], László Szidonya[2], Béla Merkely[1], Pál Maurovich-Horvat[1]

[1] Semmelweis University Heart Center, HAS-SU "Lendület" Cardiovascular Imaging Research Group, Budapest, Hungary
[2] Semmelweis University Heart Center, Budapest, Hungary

Purpose: The exclusion of left atrial thrombus is essential before the electrical- or pharmacological cardioversion in patients with atrial fibrillation. In clinical practice transoesophagial echocardiography (TEE) is the reference standard method to diagnose left atrial thrombus. We aimed to evaluate the diagnostic performance of cardiac computed tomography angiography (CTA) regarding the detection of left atrial thrombus compared to the gold standard TEE.

Methods: In total 444 patients were referred to left atrial angiography before atrial fibrillation ablation procedure (149 women, 295 men, mean age 56y) between February 2011 and January 2014. We have investigated the patients who subsequently underwent TEE (n=201).

Results: CTA excluded left atrial thrombi in 178 cases. In all negative CTA cases were confirmed by TEE (true negatives). In 23 cases CTA showed incomplete contrast filling in the left appendage: 19 false positives and 4 true positives. According to our results sensitivity of cardiac CT is 100% [95% CI: 40.2%-100%], specificity was 90.4% [95% CI: 85.4%-94.1%], negative predictive value was 100% [95% CI: 97.9%-100%] and positive predictive value was 17.4%[95% CI: 5.1%-38.8%].

Conclusion: Cardiac CT is a very sensitive modality diagnosing left atrial thrombus, the negative predictive value proved to be 100%. In patients where cardiac CTA excludes left appendage thrombus subsequent TEE examination may be unnecessary.

Doctoral School: *Clinical Medicine*
Program: *Cardiovascular diseases*
Supervisor: *Pal Maurovich-Horvat*
E-mail: *gyongyipmajor@gmail.com*

P/I-4
VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND INTERLEUKIN-1 RECEPTOR ANTAGONIST (IL1RA) CORD SERUM CONCENTRATIONS IN GESTATIONAL DIABETES MELLITUS (GDM)

Orsolya Hadarits[1], Zahra Al-Aissa[2], Michael Feichtinger[3], Ágnes List[3], András Zóka[2], Dagmar Bancher-Todesca[3], István Sziller[4], János Rigó[1], Anikó Somogyi[2], Gábor Firneisz[2], Klára Rosta[1]

[1] I. Department of Obstetrics and Gynaecology, Semmelweis University, Budapest, Hungary
[2] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[3] Department of Obstetrics and Fetomaternal Medicine, Medical University of Vienna, Vienna, Austria
[4] Department of Obstetrics and Gynecology, Szent Imre Teaching Hospital, Budapest, Hungary

Background: The aim of this study was to measure the concentrations of angiogenic factor VEGF and anti-inflammatory cytokine IL1RA in cord blood serum samples of neonates born to mothers with gestational diabetes mellitus (GDM) and non-diabetic controls. GDM is frequently associated with altered fetoplacental angiogenesis and endothelial dysfunction. VEGF is a key angiogenic factor, while IL1RA is predicted the progression of metabolic syndrome to clinically incident type 2 diabetes.

Methods: 158 pregnant women were enrolled to the study in Hungary and Austria after OGTT at 24-28th gestational week. Cord blood samples were obtained at delivery from all pregnant women. Cord plasma VEGF levels and IL1RA concentrations were determined with Quantikine solid phase Elisa Kit (R&D Systems).

Results: Cord serum VEGF and IL1RA concentrations did not differ between the GDM and control groups. VEGF concentration in smokers tended to be higher, however due to the limited sample size in the smoking group our results are preliminary. IL1RA concentration tended to be lower in cord serum of preterm deliveries and higher by postterm deliveries (post hoc test, $p=0.0627$) .

Conclusion: Despite that a previous report indicated that the cord plasma VEGF levels were decreased in the presence of villous immaturity in cord samples of neonates born to mothers with GDM we could not detect any alteration in the circulating VEGF levels. IL1RA cord serum concentrations tended to be higher in paralel with the increasing gestational age at delivery and might also reflect a physiological alteration. The complex process of altered placental angiogenesis and homeostasis might be influenced by additional maternal and fetal angiogenic factors in GDM and urges further studies.

Doctoral School: *Clinical Medicine*
Program: *Hormonal regulations*
Supervisor: *Klara Rosta*
E-mail: *hadaritso@yahoo.com*

P/I-5
METAGENOME ANALYSIS OF PLASMA DERIVED CELL FREE DNA IN COLON DISEASES

Barbara Kinga Barták[1], Sándor Spisák[2], Norbert Solymosi[3], Péter Ittzés[3], András Bodor[3], Dániel Kondor[3], Gábor Vattay[3], Zsófia Brigitta Nagy[1], Alexandra Kalmár[1], Zsolt Tulassay[2], István Csabai[3], Béla Molnár[2]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Humgary
[2] Molecular Medicine Research Group, Hungarian Academy of Sciences, Budapest, Hungary
[3] Department of Physics of Complex Systems, Eötvös Loránd University, Budapest, Hungary

Introduction: Cell-free DNA (cfDNA) can be derived from both normal and tumor cells, however the exact nucleotide composition is unknown. We are constantly exposed to foreign DNA from various sources like benign or malicious microbes in and on our body or as the largest amount with the daily food supply. Here we show the presence of foreign DNA molecules in the circulating system, using high throughput next-generation (NGS) sequencing technique.

Aims: Our main objectives were to define the DNA content of cfDNA in healthy, IBD, colorectal adenoma (AD) and –cancer (CRC) plasma samples and identify differences among these clinical groups. Our further aim was to analyse the unmapped read from NGS sequencing data.

Methods: CfDNA was isolated from plasma samples which were collected from 50-50 normal, IBD, AD and CRC patients. Extracted DNA were separated into three fractions via electrophoresis and DNA fragments were recovered from the gel slices. After fragmentation and barcoding, DNA fragment library sequencing was performed on SOLiD IV system. To validate our results 900 independent sequences downloaded from database were aligned to bacteria genomes.

Results: On average above 70% of the reads were mapped to the human reference genome, therefore the non-aligning reads were aligned to genomes of other organisms. Significant portion of the sequence tags (0.5-50 ppm) can be mapped back with high confidence to the genome of Enterobacteriaceae (Escherichia coli, Shigella sonnei). Since these bacteria are normally present in the human gut, our results suggest that the isolation between the gut and the circulatory system is not perfect.

Conclusion: Using high throughput next-generation sequencing data we have identified traces of foreign DNA molecule in the human cfDNA samples. The foreign DNA fragments are large enough to carry complete genes and they align to various bacteria genomes.

Doctoral School: *Clinical Medicine*
Program: *Gastroenterology*
Supervisor: *Béla Molnár*
E-mail: *bartak.barbara@gmail.com*

P/I-6
GENE EXPRESSION-BASED HIGH-THROUGHPUT SCREENING REVEALS COL1A2, PTGDR, SFRP2 AND SOCS3 AS POTENTIAL NOVEL METHYLATION MARKERS OF LEFT-SIDED COLORECTAL CANCER

Alexandra Kalmár[1], Bálint Péterfia[3], Péter Hollósi[2], Sándor Spisák[3], Barnabás Wichmann[3], Vivien Kubák[2], Katalin Kiss[2], Zsolt Horváth[2], Gábor Valcz[3], Béla Molnár[3], Zsolt Tulassay[3]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] I. Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
[3] Molecular Medicine Research Unit, Semmelweis University, Budapest, Hungary

Background and aims: Aberrant DNA methylation can lead to dysregulated expression of certain genes that is proven to contribute to colorectal cancer (CRC) formation. Our aims were to identify DNA methylation markers in left-sided CRC samples on the basis of gene expression and to analyze their methylation levels.

Materials and methods: Whole genome expression profiling was performed by using HGU133 Plus 2.0 microarrays (Affymetrix) on healthy colonic (n=49), colorectal adenoma (n=49) and CRC (n=49) biopsy samples and also on laser microdissected (LCM) epithelial and stromal cells from healthy (n=6) and CRC (n=6) samples. Transcripts with gradually altering expression along the adenoma-carcinoma sequence were selected on the basis of Kendall analysis. Methylation status of identified genes were analyzed on macrodissected (n=10) and LCM (n=5) healthy colonic, adenomatous biopsy (n=10) and LCM (n=5), macrodissected (n=10) and LCM (n=5) CRC samples using bisulfite-sequencing PCR (BS-PCR) and pyrosequencing. Immunohistochemistry for PTGDR and SFRP1 was also performed.

Results: A set of transcripts (including MAL, SFRP1, PRIMA1, PTGDR) showed decreasing expression ($p \leq 0,01$) in biopsy samples along adenoma-carcinoma sequence. Expression of PTGDR and SULT1A1 genes were found to be significantly downregulated ($p \leq 0,01$) in tumor epithelial cells, whereas MAL and PRIMA1 showed significantly decreased expression ($p \leq 0,0,5$) in tumor stromal cells compared to healthy samples. Hypermethylation of SFRP2 (10/10 cases), COL1A2 (9/10 cases), SOCS3 (9/10 cases) and PTGDR (5/10 cases) could be detected in CRC samples compared to healthy specimens. Increased methylation levels were found predominantly in tumor epithelial cells. Decreasing protein levels of PTGDR and SFRP1 could be observed along adenoma-carcinoma sequence.

Conclusion: Genome-wide gene expression-based screening was found to be a suitable approach for idetification of genes, that can be potentially regulated by DNA methylation. Hypermethylation of selected markers (COL1A2, PTGDR, SFRP2, SOCS3) might result in reduced expression and could contribute to the formation of colorectal cancer.

Doctoral School: *Clinical Medicine*
Program: *Gastroenterology*
Supervisor: *Béla Molnár*
E-mail: *alexandra.kalmar@gmail.com*

P/I-7
NORMAL AND TUMOROUS DNA ACTS DIFFERENTLY VIA TLR9 SIGNALLING ON COLON CARCINOMA CELLS INDUCING CANCER CELL MOBILITY

István Fűri[1], Ferenc Sipos[1], Györgyi Műzes[1], Barnabás Wichmann[2], Sándor Spisák[2], Barbara Barták[1], Alexandra Kalmár[1], Béla Molnár[2], Zsolt Tulassay[2]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] Molecular Medicine Research Unit, Hungarian Academy of Sciences, Budapest, Hungary

Background: In case of tumorous and inflammatory conditions, self-DNA is released to the extracellular compartment. The Toll-like receptor 9(TLR9)-mediated immunobiologic effect of self-DNA of normal and tumorous origin may be different.

Aims: We aimed to compare the TLR9- and pro-inflammatory cytokine-associated effects of self-DNA originated from normal and tumorous colorectal cancer epithelium on HT-29 colorectal cells

Matherial and Methods: We isolated DNA from normal and tumorous part of a fresh frozen colonic epithelium. We performed RNAse digestion and made a 6 hour treatment on HT-29 colon carcinoma cells. We isolated total RNA and performed Affymetrix u133 2.0 microarray system and q RT-PCR for the elements of TLR9 signalling pathway.

Results: At HT-29 cells treatment with both types of DNA showed significant overexpression of IL-1β gene (dct in control vs. tumorous vs. normal DNA treated samples were: 25.87 ± 0.1627 vs. 23.54 ± 0.2613 vs. 24.28 ± 0.2253, $p<0.05$)

Immunocytochemistry of CK 20, E-cadherin showed that tumorous DNA promotes cellular invasion of cancer cells. A DNA methylation specific enzyme DNMT3a showed overexpression at the tumorous DNA treated HT29-cells.

Whole genome expression analysis at HT-29 cells: 3 metalloproteinase genes MT1X, MT1F, MT1H, TACSTD2, CEACAM, MACC, MALAT1 showed significant overexpression at tumorous DNA treated HT29 cells.

Conlusions: Our results confirmed that tumorous DNA as a ligand of TLR9 signalling promotes cancer cell invasion through increasing matrix metalloproteinase activity and the quantity of pro-metastatic proteins.

It has seen that tumorous DNA from tumorous colon epithelium is a potent proinflammatory factor in tumorous condition via TLR9 MYD88 dependent activation and the high number of overexpressed pro-metastatic genes showed that tumorous DNA is a potent metastatic factor.

Doctoral School: *Clinical Medicine*
Program: *Gastroenterology*
Supervisor: *Béla Molnár*
E-mail: *furiistvan88@gmail.com*

P/I-8
SKELETAL MUSCLE AND RENAL COMPLICATIONS FOLLOWING LOWER LIMB VASCULAR SURGERY: A NEW DRUG THERAPY

Dávid Garbaisz[1], Zsolt Turóczi[1], Péter Arányi[1], András Fülöp[1], Olivér Rosero[1], Péter Ónody[1], Edit Hermesz[3], Gábor Lotz[2], László Harsányi[1], Attila Szijártó[1]

[1] I. Department of Surgery, Semmelweis University, Budapest, Hungary
[2] II.Department of Pathology, Semmelweis University, Budapest, Hungary
[3] Department of Biochemistry and Molecular Biology, University of Szeged, Szeged, Hungary

Objectives: Operation on the infrarenal aorta and large arteries of lower extremities could cause ischemic-reperfusion (IR) injury and consequently rhabdomyolysis of skeletal muscle, which could induce remote kidney injury. NIM-811 (N-metyl-4-isoleucine-cyclosporine) has mitochondria specific effects. Our aim was to reduce damages in skeletal muscle and in the kidney after IR of the lower limb with NIM-811.

Methods: Wistar rats underwent 180 minutes bilateral lower limb ischemia and 240 minutes reperfusion. Animals were divided into four groups called Sham (vehicle; n= 10pcs), NIM-sham (NIM-811+vehicle; n=10pcs), IR (vehicle+IR; n=10pcs), and NIM-IR (NIM-811+vehicle+IR; n=10pcs). Serum, urine and histological samples were taken in the end of reperfusion. NADH-tetrazolium staining, muscle Wet/Dry (W/D) ratio calculations, laser Doppler-flowmetry (LDF) and mean arterial pressure (MAP) monitoring were performed. Renal peroxynitrite concentration, serum TNF-α and IL-6 levels were measured.

Results: Lesser extent of histopathological alterations was present in the NIM-IR group compared to the IR group. The serum necroenzyme levels were significantly lower in the NIM-IR group than in the IR group (LDH:$p=0.01$; CK:$p=0.04$). Muscle mitochondrial viability proved significantly higher ($p<0.001$) and renal function parameters were significantly better (creatinin:$p=0.002$; FENa:$p=0.01$) in the NIM-IR group compared to the IR group. Level of serum TNF-α was significantly lower ($p=0.04$) and level of IL-6 was moderate, as well as W/D ratio and peroxynitrite concentration were significantly lower (W/D:$p=0.04$; peroxynitrite concentration:$p=0.003$) in the NIM-IR group compared to the IR group.

Conclusion: NIM-811 could have the potential of reducing rhabdomyolysis and the impairment of the kidney after lower limb IR injury.

Doctoral School: *Clinical Medicine*
Program: *Clinical and experimental research in Angiology*
Supervisor: *Attila Szijártó*
E-mail: *garbaiszdavid@t-online.hu*

P/I-9
INTESTINAL POSTCONDITIONING: PATCHING THE LEAKING PIPES

Olivér Rosero[1], Péter Ónody[1], Tibor Kovács[1], Dávid Molnár[2], Gábor Lotz[3], Szilárd Tóth[4], Zsolt Turóczi[1], András Fülöp[1], Dávid Garbaisz[1], László Harsányi[1], Attila Szijártó[1]

[1] I. Department of Surgery, Semmelweis University, Budapest, Hungary
[2] Department of Human Morphology and Developmental Biology, Semmelweis University, Budapest, Hungary
[3] II. Department of Pathology, Semmelweis University, Budapest, Hungary
[4] National Center of Epidemiology, Budapest, Hungary

Background: Mesenteric ischemia-reperfusion (IR) is associated with impairment of the gut barrier function and the initiation of a proinflammatory cascade with life-threatening results. Therefore methods directed to ameliorate IR-injury are of great importance. We aimed at describing the effects of postconditioning (PC) on the alterations of the intestinal mucosal function and the inflammatory response upon mesenteric IR. **Material and Methods:** Male Wistar rats were gavaged with green fluorescent protein-expressing E.coli suspensions. Animals were randomized into three groups (n=15), Sham-operated, IR- and PC-groups, and underwent 60 minutes of superior mesenteric artery occlusion, followed by 6 hours of reperfusion. Postconditioning was performed at the onset of reperfusion. Blood and tissue samples were taken at the end of reperfusion, for histological, bacteriological and plasma examinations. **Results:** The PC-group presented a more favorable claudin-2, claudin-3, claudin-4 and zonula occludens-1 expression profile, and significantly lower rates of bacterial translocation to distant organs and plasma D-lactate levels compared to the IR-group. Histopathological lesions, plasma-I-FABP, -IL-6, and -TNF-α levels were significantly lower in the PC-group compared to the IR-group. **Conclusion:** The use of postconditioning improved the integrity of the intestinal mucosal barrier upon mesenteric IR, and thus reduced the incidence of bacterial translocation and development of a systemic inflammatory response.

Doctoral School: *Clinical Medicine*
Program: *Gastroenterology*
Supervisor: *Attila Szijártó*
E-mail: *oliveross@gmail.com*

P/I-10
DIFFERENTIAL MICRORNA EXPRESSION IN TWO TYPES OF SAMPLES (FFPET AND FRESH FROZEN) FROM VARIOUS COLON PRECANCEROUS AND CANCEROUS LESIONS

Zsófia Brigitta Nagy[1], Barnabás Wichmann[2], Alexandra Kalmár[1], Barbara Kinga Barták[1], Nha Le[1], Bálint Péterfia[2], István Fűri[1], Zsolt Tulassay[2], Béla Molnár[2]

[1] II. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2] Molecular Medicine Research Group, Hungarian Academy of Sciences, Budapest, Hungary

Background: MicroRNAs are readily detected and stable in formalin-fixed, paraffin-embedded (FFPE) tissue samples. Thus, different gene expression methods have described the changes of the microRNA expression in various stages of the precancerous and cancerous lesions of the colorectal cancer.

Aims: Our primary aim was to identify the microRNA expression alterations between normal colonic tissue (N), adenoma (AD) and colorectal cancer (CRC) samples. Another purpose was to determine the microRNAs which would be reproducible in both of the different types of sample (fresh frozen and FFPET) and methods (microarray and RT-qPCR).

Methods: Sixty fresh frozen biopsy samples (n=20 normal, n=11 tubular adenoma, n=9 tubulovillous adenoma, n=20 colorectal cancer) were collected; and, total RNA were isolated by High Pure miRNA Isolation Kit. Affymetrix miRNA 3.0 array platform was processed separately for screening of the altered microRNA profile. Then, a series of pools of RNA from the same groups of samples was made; and, the PCR was done to validate the data of the microarray. The PCR was conducted by Exiqon microRNA Ready-to-Use PCR. Then, RT-qPCR data of FFPET tissues (n=3 normal, n=3 CRC) were compared to the microarray and PCR results from fresh-frozen samples.

Results: microRNAs, which showed differential expression between tumor and normal tissue, were detected. Out of the 1733 analyzed microRNAs, 88 microRNAs were found to be altered between N and CRC. Expression of 44 microRNAs was confirmed by real-time PCR; and, 21 microRNAs were consistent with the microarray real-time PCR validation. Interestingly, we also found 6 microRNAs whose expression was decreased in CRC throughout the three proposed methods.

Conclusion: The findings from this study indicate that the results from microarray analysis are consistent with data from other gene expression methods. Six decreased microRNAs can be potential in future molecular-based screening trials.

Doctoral School: *Clinical Medicine*
Program: *Gastroenterology*
Supervisor: *Béla Molnár*
E-mail: *nagyzsofiab@gmail.com*

P/I-11
CHARACTERISTICS OF SPECIFIC MICRORNA EXPRESSION IN COLONIC MUCOSA IN PEDIATRIC PATIENTS WITH CROHN'S DISEASE

Nóra Béres[1], Dolóresz Szabó[1], András Arató[1], András Kiss[2], Gábor Lendvai[2], Gábor Veres[1]

[1] I. Department of Pediatrics, Semmelweis University, Budapest, Hungary
[2] II. Department of Pathology, Semmelweis University, Budapest, Hungary

Background: Crohn's disease (CD) is a chronic inflammatory disease that may involve any part of the gastrointestinal tract. The pathomechanism of CD is unknown. In recent years, there is an increased interest in epigenetic factors, such as a specific group of small, non-coding RNAs, called microRNAs (approximately 21-24 nucleotides), which participate in the regulation of the gene expression at the posttranscriptional level, by connecting to the 3' untranslated region of the mRNA and controlling their stability and translation. The altered microRNA expression has been linked to several cell function, such as differentiation, proliferation, apoptosis, furthermore, it is estimated that microRNAs play an important role in many diseases, but only a small number of studies have been done in children with CD.

Aim*:* To analyze the miR-146a, miR-155, miR-122 expressions in the colonic mucosa of pediatric patients with CD. We studied these microRNAs because of their known role in inflammation.

Methods*:* We analyzed three types of intestinal paraffin fixated biopsies: intestinal biopsy with CD (CD: n=22), with macroscopically intact (uninflamed) (CDintact: n=11) and inflamed (CDinflamed.: n=11) colonic mucosa, and healthy controls (C: n=16). MicroRNAs expressions were measured by Real-time PCR after RNA isolation.

Results*:* The expressions of miR-146a and miR-155 were significantly higher in the intestinal mucosa of children with CD compared to the control group. This increment was observed in macroscopically inflamed intestinal biopsies in comparison to controls (C vs. CD, $p \leq 0.05$; C vs. CDinflamed, $p \leq 0.001$; CDintact vs. CDinflamed $p \leq 0.05$). MiR-122 expression was significantly higher in macroscopically intact mucosal biopsies (CO vs. CDintact, $p \leq 0.05$).

Conclusions*:* These results suggest, microRNAs play an important role in pathogenesis of CD. Further studies are required to explore the function of these microRNAs regarding their role in illnesses and possible usage as therapeutic targets and in differential diagnosis.

Doctoral School: *Clinical Medicine*
Program: *Prevention of chronic diseases in childhood*
Supervisor: *Gábor Veres*
E-mail: *bnora1988@gmail.com*

P/I-12
THE EFFECT OF RAAS INHIBITION ON THE ARTERIAL STIFFNESS IN DIABETIC RATS

Arianna Dégi[1], Éva Kis[1], Orsolya Cseprekál[2], Sándor Kőszegi[1], Ádám Hosszú[1], Lilla Lénárt[1], Renáta Gellai[1], Judit Hodrea[1], Andrea Fekete[1], György L. Nádasy[3], György Reusz[1]

[1] I. Department of Pediatrics, Semmelweis University, Budapest, Hungary
[2] I. Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[3] Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary

Several studies indicate the major role of the renin-angiotensin-aldosterone system (RAAS) in development of cardiovascular and renal diseases. In diabetic nephropathy, excessive activation of the RAAS results in progressive renal damage, and RAAS blockade is the cornerstone of treatment of diabetic renal disease. Pulse wave velocity (PWV) is considered the gold standard for measurements of central arterial stiffness. A new device (PulsePenLab) was developed for determining non-invasive PWV measurements in rats.

Our aim was to determine PWV in healthy and type 1 diabetic rats and to examine the effect of RAAS inhibition on arterial stiffness.

We induced diabetes in male Wistar rats with streptozotocin. Five week after diabetes onset the animals were randomized to different treatment and control groups (healthy and untreated diabetic rats and animals treated per os with enalapril, losartan, eplerenone, spironolactone (n = 6-8 per group). After two weeks of treatment PWV and blood pressure measurements were taken under isoflurane anesthesia. The animals were sacrificed, laboratory tests and histological analysis were performed.

We found no difference in blood pressures and blood glucose levels between the groups of animals treated with RAAS inhibitors. The lower GFR associated with higher blood sugar levels and with increased heart weight ($r<-0.3$, $p<0.03$). PWV depends on the animal's body weight, systolic and diastolic blood pressure ($r>0.29$, $p<0.03$). PWV was lower in rats treated with enalapril ($p<0.003$). The heart weight, the intima media thickness and the media cross-section area did not differ between groups.

Non-invasive measurement of PWV could be achieved in rats and allows longitudinal studies. Enalapril has positive effect on the vascular stiffness still at a dose that not influence blood pressure. ACE inhibitors exert a beneficial effect in diabetes already before the onset of hypertension.

Grant: OTKA 100909.

Doctoral School: *Clinical Medicine*
Program: *Prevention of chronic diseases in childhood*
Supervisor: *György Reusz*
E-mail: *degiarianna@gmail.com*

P/I-13
NEW ROUTINE ECHOCARDIOGRAPHIC PARAMETER FOR THE DETECTION OF SUBTLE LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION AND ITS PRECURSOR CONDITIONS

Zsuzsanna Szelényi[1], Gábor Szénási[2], András Vereckei[3]

[1] Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[2] Institute of Pathophysiology, Semmelweis University, Budapest, Hungary
[3] III. Department of Medicine, Semmelweis University, Budapest, Hungary

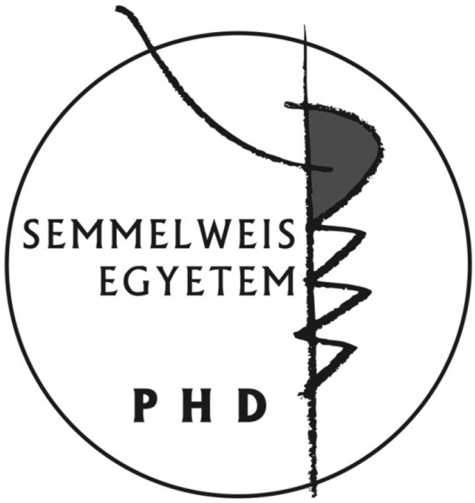
Aim*:* To find a routine echocardiographic left ventricular (LV) systolic function parameter suitable for the detection of subtle LV systolic dysfunction revealed by imaging studies measuring myocardial deformation in patients with heart failure with preserved ejection fraction (HFPEF) and its precursor conditions.

Methods*:* To this end, ≥60-year-old 18 control and 94 hypertensive patients with normal ejection fraction (EF) were studied with echocardiography. Detailed assessment of systolic and diastolic LV function, LV myocardial mass (LVM) and online mitral annular velocity, offline LV myocardial strain (S) and strain rate (SR) measurements by tissue doppler imaging were done.

Results: LV diastolic dysfunction was not found in 38/94(40%) hypertensive patients (HTDD- group) and mild LV diastolic dysfunction was verified in 56/94(60%) hypertensive patients (HTDD+ group). No between-groups difference was found in EF and mitral annular velocities. The body mass index (BMI) increased ($p<0.05$ for HTDD- and $p<0.01$ for HTDD+ groups) and the absolute values of mean peak longitudinal LV systolic S ($p<0.05$) and SR ($p<0.001$) decreased in both patient groups vs. controls. The LVM and LVM/BMI increased ($p<0.001$ and $p<0.01$ respectively) in the HTDD+ group, the EF/LVM/BMI decreased in both patient groups ($p<0.05$ for HTDD- and $p<0.001$ for HTDD+ groups) vs. controls. LVM increased ($p<0.05$) and EF/LVM/BMI decreased ($p<0.05$) in the HTDD+ group vs. HTDD- group, and in the HTDD- group ($p<0.05$ for both parameters) vs. controls. Using ROC analysis EF/LVM/BMI proved to be the best parameter of LV systolic function, its cutoff value <15.73 m^2/kg^2 indicated LV systolic dysfunction as accurately as myocardial deformation parameters.

Conclusions: In contrast to EF, the routine echocardiographic parameter EF/LVM/BMI detects subtle LV systolic dysfunction as accurately as myocardial deformation parameters in patients with HFPEF and its precursor state hypertension regardless whether LV diastolic dysfunction, representing transition of hypertensive heart disease to HFPEF, is present or not.

Doctoral School: *Basic Medicine*
Program: *Cardiovascular Disorders: Physiology and medicine of ischaemic circulatory diseases*
Supervisor: *András Vereckei*
E-mail: *zsuzsanna_sz@yahoo.com*



P/II
POSTER PRESENTATIONS

Chairman:
Prof. Dr. József Tímár

P/II-1
PREDICTION OF ROTARY SPUN FIBER FORMING PROPERTIES OF HYDROXYPROPYL CELLULOSE GELS AND PREPARATION OF DRUG LOADED CELLULOSE BASED FIBERS

Péter Szabó[1], Romána Zelkó[2]

[1] Gedeon Richter Plc., Formulation R&D, Budapest, Hungary
[2] University Pharmacy Department of Pharmacy Administration, Semmelweis University, Budapest, Hungary

Aims: The aim of this study was to investigate how the textural properties of hydroxypropyl cellulose gels of different concentrations and molecular weights influence the fiber formation ability. The optimal polymer concentration was applied for the preparation of drug loaded fibers. The primary purpose of the fiber formation was to increase the water solubility of different active pharmaceutical ingredients.

Results*:* An unequivocal correlation was determined between the adhesiveness of gels determined by texture analysis and their fiber forming ability. The adhesiveness has a local minimum where the productivity of the fiber formation process and the micromorphology of the emitted fibers were optimal.

Production of drug loaded fibers were successfully carried out from hydroxypropyl cellulose gels made using solutions of different pharmaceutics. These fibers were applied in the formulation of orally administered dosage forms with the aim to increase the rate of drug release and its consequent absorption.

Doctoral School: Pharmaceutical Sciences
Program: Modern trends in pharmaceutical scientific research
Supervisor: Romána Zelkó
E-mail address: szabo.peter@pharma.semmelweis-univ.hu

P/II-2
PREDICTION OF CIRCULAR DICHROISM SPECTRA OF MODIFIED NATURAL PRODUCTS WITH M06-2X FUNCTIONAL

Ákos Urai[1], Balázs Komjáti[2], József Nagy[2], Levente Szőcs[1], Sándor Hosztafi[1], Péter Horváth[1]

[1] Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary
[2] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary

Electronic circular dichroism (ECD) spectroscopy in combination with quantum chemical computations is a powerful tool in the determination of absolute configuration of organic molecules. TD-DFT is the most widely used computation method for UV-VIS and ECD spectroscopies, different functionals may gave different result, PBE0 and B3LYP are the most frequently used, however for some molecules with complicated electronic structure they fail to produce applicable spectra. M06-2X is a heavily parameterized hybrid meta-GGA functional, it is expected to overcome the shortcomings of older methods. Accuracy of B3LYP, PBE0 and M06-2X functionals were tested on a set of modified natural products, including derivatives of codeine, chloramphenicol and camphor. Computations were carried out on the Superman cluster of BUTE with Gaussian 09. Results show that M06-2X is more accurate than B3LPY and PBE0 especially for aromatic nitro compounds, thus making predictions more reliable.

Doctoral School: *Pharmaceutical Sciences*
Program: *Modern trends in pharmaceutical scientific research*
Supervisor: *Sándor Hosztafi*
E-mail: *urai.akos@pharma.semmelweis-univ.hu*

P/II-3
DEVELOPMENT AND PERMEABILITY STUDY ON A PAMPA MODEL WITH SUPPORTED LIPID BILAYER AS MEMBRANE

Gábor Vizserálek[1], Bálint Sinkó[1,2], Tamás Bozó[3], Krisztina Takács-Novák[1]

[1] Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary
[2] SinkoLAB Scientific, Budapest, Hungary
[3] Department of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary

Measuring the exact permeability value of the potentially active compounds in early stage of drug development is essential. For this purpose, parallel artificial membrane permeability assay (PAMPA) was introduced to serve as a rapid, high throughput *in vitro* method for the estimation of passive transcellular permeability. The artificial membrane in PAMPA method contains phospholipid(s) dissolved in organic solvents, forming unorganized structures inside the filter channels. The direct contact between the membrane and the filter may cause the decrease of mobility of the lipids and fluidity of the membrane, which may results in difference from the permeation through biological membranes.

The aim of our work was to develop a new PAMPA model with non-fragile single lipid bilayer system that fits to HT approach. For this reason, a supported membrane was prepared in every single well. The conventional Stirwell™ PAMPA plates (pION Inc.) and two hydrophilic filter plates with pore size 0.22 and 0.45 μm (Millipore) were used for this study. In case of hydrophilic plates a polymer supported membrane was prepared, where the lipid bilayer was supported by a hydrated polymeric cushion. In the other hand, the Stirwell™ PAMPA plates required to develop a complex supporting system on the surface of the filter. Permeability measurement was performed using model compounds (verapamil, atenolol, diclofenac, salicylic acid) with diverse acid-base properties and structures. The donor pH varied from 5.5 to 9.4 in case of bases and from 3.5 to 7.4 in case of acids. Correlation analysis was carried out between permeability data obtained by other non-bilayer PAMPA systems and the permeability values measured in this model.

The presented data serve as a solid starting point for further evaluation of lipid bilayers as artificial membranes, therefore more experiment will be performed to complete the study and to have a better understanding on these systems.

Doctoral School: *Pharmaceutical Sciences*
Program: *Experimental and clinical Pharmacology*
Supervisor: *Krisztina Takács-Novák, Bálint Sinkó*
E-mail: *vizseralekgabor@gmail.com*

P/II-4
DETERMINATION OF NMDA MODULATOR AMINO ACIDS WITH CE-LIF IN VARIOUS BIOLOGICAL SAMPLES

Tamás Jakó[1], Eszter Szabó[1], Tamás Tábi[1], Gergely Zachar[2], András Csillag[2], Éva Szökő[1]

[1] Department of Pharmacodynamics, Semmelweis University, Budapest, Hungary
[2] Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, Hungary

Contrary to long time belief recent results suggest that beside L-amino acids, the D-enantiomers of several amino acids are also present in mammalian including human tissues. D-serine and D-aspartate have been detected in the central nervous system where their neuromodulator function on NMDA glutamate receptors has been suggested. While the effect of D-serine is rather established, the function of D-aspartate is less well understood. It is probably involved in modulation of neurogenesis, neuronal plasticity and memory formation. Analyzing D-amino acids is challenging, because of their small amount in the samples compared to the L-enantiomers. Moreover the typical sample volume available is only a few μL e.g. in case of microdialysates. To overcome these difficulties an appropriate analytical technique, capillary electrophoresis has been applied. This method has the known advantages of low sample volume requirement and high separation efficiency. Since amino acids lack of easily detectable moiety, fluorescent labeling was chosen for their detection. A fluorogenic agent (7-fluoro-4-nitro-2,1,3-benzoxadiazole, N-BDF) was used for the derivatization. NBD-F offers some advantages compared to other fluorescent tags, such as fewer reaction sideproducts and relatively fast derivatization reaction. Distinguishing between the enantiomers is rather difficult, as they share common physical and chemical properties. An amino-modified ß-cyclodextrin (6-monodeoxy-6-mono (3-hydroxy) propylamino-ß-CD) was tested for the chiral separation of the amino acids. The method was optimized and validated. At 6 mM concentration of appropriate chiral and chemical selectivity could be achieved with baseline separation of D-aspartate, L-aspartate, L-glutamate, D-serine and L-serine in 50 mM HEPES buffer, pH 7. All the determinations were accomplished in a polyacrylamide coated capillary and reverse polarity was used for the analysis of the negatively charged analytes. The method was used for the determination of D-aspartate and D-serine, in microdialysates and brain tissue samples of experimental animals.

Doctoral School: *Pharmaceutical Sciences*
Program: *Experimental and clinical pharmacology*
Supervisor: *Éva Szökő*
E-mail: *jako.tamas88@gmail.com*

P/II-5
EVALUATION OF CARDIAC ALLOGRAFT VASCULOPATHY WITH COMPUTED TOMOGRAPHY IN HEART TRANSPLANT PATIENTS

Andrea Bartykowszki, Zsófia D. Drobni, Alexisz Panajotu, Csilla Celeng, Ferenc Suhai, Ádám L. Jermendy, Csaba Csobay-Novak, Pál Maurovich-Horvat, Béla Merkely

Semmelweis University, Heart and Vascular Center, HAS-SU "Lendület" Cardiovascular Imaging Research Group, Budapest, Hungary

Purpose: According to the recommendation of International Society for Heart and Lung Transplantation (ISHLT) the annual assessment of coronary status in heart transplant recipients with invasive coronary angiography (ICA) and with intravascular ultrasound (IVUS) is necessary due to the risk of allograft vasculopathy. The serial invasive examination is a great burden to the patients. The coronary CT angiography (CCTA) has a very high negative predictive value, thus the method could be a choice in the replacement of ICA. Our aim was to evaluate the feasibility of 256-slice CCTA in heart transplant recipients.

Methods: 256-slice CCTA was performed in 21 heart transplant recipients as a part of the regular one or two year follow-up visits. All of the examinations were performed with prospective ECG triggering (step-and-shoot protocol). To heart rate control procorolan (75%), esmolol (12%) and metoprolol (6%) were used.

Results: Mean heart rate was 69±8 bpm, estimated mean radiation dose was 5±2 mSv. All of the evaluated coronary segments were diagnostic. No coronary atherosclerosis were described in 7 cases (33.3%) and mild stenosis was identified in 11 cases (52.3%). In 3 cases (14.3%) significant coronary stenosis were described and ICA was indicated. According to the ICA in 2 cases stent implantation was necessary.

Conclusions: According to our initial experience CCTA can be a useful method in the identification of non-obstructive coronary disease and in the follow-up of coronary status in heart transplant recipients. With the use of CCTA the burden on the patients can be reduced without a significant increase in the radiation dose.

Doctoral School: *Basic Medicine;*
Program: *Cardiovascular Disorders: Physiology and medicine of ischaemic circulatory diseases*
Supervisor: *Pál Maurovich-Horvat*
E-mail: *bartyandi@gmail.com*

P/II-6
ABCC6 GENE EXPRESSION IS REGULATED BY HNF4A VIA DIRECT PHOSPHORYLATION BY ERK1/2 IN HEPG2 CELLS

Borbála Vető[1], Caroline Bacquet[1] Attila Horváth[2], Szabolcs Sipeki[3], Endre Barta[2], Dávid Jónás[2], László Buday[1], Bálint L. Bálint[2], László Nagy[2], András Váradi[1], Tamás Arányi[1]

[1] Institute of Enzymology, Research Center for Natural Sciences, Hungarian Academy of Sciences Budapest, Hungary
[2] Department of Biochemistry and Molecular Biology, Medical and Health Science Center, University of Debrecen Debrecen, Hungary
[3] Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University Budapest, Hungary

Mutations in the *ABCC6* gene are responsible for the development of *Pseudoxanthoma elasticum*. The expression of the human *ABCC6* gene is tissue specific; it is primarily present in the liver. The transcriptional regulation of the gene has been described (de Boussac et al, 2010; Ratajewski et al, 2012; Arányi et al, 2013). Our previous results have shown that activation of the ERK1/2 signalling pathway downregulates *ABCC6* expression, through the inhibition of HNF4a (hepatocyte nuclear factor 4 alpha), a major regulator of metabolic genes in hepatocytes. HNF4a expression is inhibited by ERK1/2, but based on our recent results we hypothesized that HNF4a is also regulated at the post-transcriptional level by ERK1/2. Here we show that ERK1/2 is capable of directly phosphorylating HNF4a *in vitro*. Furthermore, we demonstrate the rapid and 24 hours' effects of ERK1/2 on HNF4a-binding on regulatory regions of *ABCC6* (promoter, exon 31) and other hepatic genes by ChIP-qPCR and ChIP-seq analyses in human HepG2 cells. We have observed a decreasing but not disappearing signal of binding affinity of HNF4a to the target genes. Our data suggest that this pathway plays an important role in the regulation of *ABCC6* and other hepatic genes' expression. *ABCC6* gene regulation has physiological relevance. While in normal conditions, there is *ABCC6*-dependent ATP transport in hepatocytes, upon ERK activation resulting in stress, *ABCC6* expression is decreased because of ATP depletion.

Doctoral School: *Molecular Medicine*
Program: *Pathobiochemistry*
Supervisor: *András Váradi*
E-mail: *vetoborbala@gmail.com*

P/II-7
THE ROLE OF GADD34 AND CHOP IN ENDOPLASMIC RETICULUM STRESS: SURVIVAL OR DEATH?

Anita Andrea Kurucz

Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University Budapest, Hungary

Accumulation of incorrectly folded proteins in the endoplasmic reticulum (ER) lumen leads to harmful ER stress. The cell tries to cure itself by autophagy-controlled self-cannibalism; however excessive level of ER stress enhances apoptotic cell death. Complex signal transduction cascades, known collectively as the unfolded protein response (UPR), serve to avoid cell damage in respond to ER stress. One of the ER stress-transducing kinases is PERK, which has two essential roles. PERK blocks protein translation and it also activates a transcription factor, called ATF4. Two downstream targets of ATF4 are Gadd34 and CHOP. CHOP is a transcription factor that controls expression of genes involved in apoptosis, while Gadd34 promotes autophagy.

Aims: Our study focuses on the PERK-induced autophagy inductor Gadd34 and apoptosis activator CHOP. The main question of my PhD study is how the two qualitatively different stress responses can be regulated similarly by the same molecule with respect to ER stress. Namely, the autophagy-dependent survival mechanism is always followed by apoptosis, but how these processes can be controlled by ATF4 and their targets is still unknown. We claim that the proper order of activation of surviving and self-killing mechanisms is controlled by negative and positive feedback loops of PERK pathway.

Results: We confirmed that autophagy was activated for cell survival after ER stress even if it was followed by apoptotic cell death. We claim that the sigmoid activation profile of Gadd34 is connected to autophagy, while apoptotic cell death is induced by the switch-like characteristic of CHOP induction under severe ER stress.

Doctoral School: *Molecular Medicine*
Program: *Pathobiochemistry*
Supervisors: *Gábor Bánhegyi, Orsolya Kapuy*
E-mail: *kurucz.anita88@gmail.com*

P/II-8
A STUDY ON GLYCOSIDASES AND SULFATASES IN RHEUMATIC DISEASES

Barbara Sódar[1], Mária Szente-Pásztói[1,2], Krisztina Pálóczi[1], Ágnes Kittel[3], András Falus[1,2], Edit I. Buzás[1]

[1] Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary
[2] Inflammation Biology and Immunogenomics Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary
[3] Department of Pharmacology, Institute of Experimental Medicine, Budapest, Hungary

Rheumatic diseases are characterised by the progressive destruction of synovial cartilage. According to our former results, not only proteinases but also glycosidases are capable of degrading hyaline cartilage. Furthermore, their gene expression is under negative regulation by locally expressed cytokines. Except for these data, in the literature only very small attention has been paid to the role of carbohydrate-degrading enzymes in joint diseases.

Aims: In this study, we focused on the expression of the previously uninvestigated glycosidases (fucosidases (FUCA1-2); heparanases (HPSE1-2); neuraminidases (NEU1-4); hexosaminidase D (HEXDC)) and the two extracellular sulfatases (SULF1-2) in synovial fibroblasts and synovial membrane samples of patients with rheumatoid arthritis (RA) and osteoarthritis (OA). Our goal was to clarify if synovial fibroblasts contribute to the synovial release of above enzymes.

Results: First, we isolated primary synovial fibroblast cell strains from synovial membrane samples of patients with RA and OA. Then we treated them with recombinant IL-1β, IL-17, TNF-α and TGF-β1. The expression of the genes encoding for the above mentioned glycosidases was measured by realtime PCR. Enzyme activities were determined by chromogenic substrates.

Most glycosidases and sulfatases showed outstandingly high gene expressions unaltered by most of the tested cytokines. However, TGF-β1 and IL-1β slightly decreased the expression of HEXDC, FUCA1, HPSE, NEU1, and SULF2 genes. More interestingly, TGF-β1 selectively increased the expression of SULF1 gene in RA synovial fibroblasts. We were the first to provide data about the human expression and disease relevance of the recently described hexosaminidase D enzyme. We have found that its enzyme activity is associated with synovial fibroblast-derived extracellular vesicles.

The robust expression and strict regulation of the investigated enzymes support the significance of the enzyme family in regulating the homeostasis of the extracellular matrix, and drives attention to the possible role of these enzymes in the pathogenesis of RA.

Doctoral School: *Molecular Medicine*
Program: *Basis of human molecular genetics and gene diagnostics*
Supervisor: *Edit I. Buzas, Mária Pásztói*
E-mail: *sobarbi@gmail.com*

P/II-9
GENETIC VARIANTS OF AKR1C3 IN ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Nóra Kútszegi[1], Máté Sipos[1], Ágnes F. Semsei[1], Orsolya Lautner-Csorba[1], Dániel J. Erdélyi[2], Gábor T. Kovács[2], Csaba Szalai[1,3]

[1] Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary
[2] II. Department of Paediatrics, Semmelweis University, Budapest, Hungary
[3] Heim Pál Children's Hospital, Budapest, Hungary

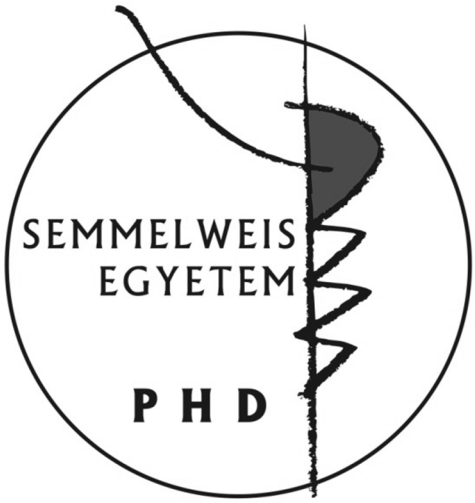
Aims: The main dose limiting side-effect of anthracyclines is late cardiotoxicity. Survivors of anticancer therapy have increased risk for cardiovascular problems and have higher such mortality. Our previous results suggested that the *ABCC1* rs246221 and the *AKR1A1* rs2088102 variations were associated with altered left ventricular function in late survivors of childhood acute lymphoblastic leukaemia. In addition, we tried to identify novel genetic markers focusing on the *AKR1C3* gene in the metabolic pathway of anthracyclines.

Methods: We studied 112 paediatric acute lymphoblastic leukaemia (ALL) patients who had been treated with ALL BFM protocols. They had cardiac ultrasound scans at the time of the diagnosis and at the end of the treatment. Left ventricular function was assessed as fractional shortening (LVSF). Germline genotypes of 5 single nucleotide polymorphisms (SNPs) in the *AKR1C3* gene were measured by using KASP™ (Kompetitive Alelle Specific PCR) technology. Multifactorial general linear model was used to test for associations.

Results: The SNPs in *AKR1C3* gene showed no association with left ventricular function.

Conclusion: On the basis of these results we could not identify novel genetic risk factors of anthracycline cardiotoxicity.

Doctoral School: *Molecular Medicine*
Program: *Basis of human molecular genetics and gene diagnostics*
Supervisor: *Csaba Szalai*
E-mail: *norakutszegi@hotmail.com*



P/III
POSTER PRESENTATIONS

Chairpersons:
Prof. Dr. Ferenc Túry
Prof. Dr. Endre Nagy
Dr. Gábor Csukly

P/III-1
THE ROLE OF BULLYING IN DEVELOPMENT OF CHRONIC SHAME

Gabriella Vizin[1], Julianna Bircher[2], Zsolt Unoka[1]

[1] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary
[2] Faculty of Education and Psychology, Eötvös Loránd University, Budapest, Hungary

Objective: Number of studies are indicating a strong relationship between mental disorders and traumatization. A widespread form of social traumatization in childhood and adolescence is teasing and bullying at school, that may induce chronic shame. To our knowledge relatively few studies have investigated the association between bullying shame and mental disorder. In our study we examined the associations between bullying and teasing and shame proneness in a clinical and a matched healthy control sample.

Design: 148 inpatients (mood and anxiety disorders, personality disorders) from a psychiatric clinic in Hungary and matched (age, sex, education) 148 healthy control subjects participated in this cross-sectional questionnaire study (Age M: 37.32; SD: 13.00).

Methods: Shame was measured with The Experience of Shame Scale (ESS), teasing and bullying were measured with Teasing Questionnaire (TQ). In addition SCL-90-R was used to assess psychological symptoms. In this study we performed two-sample t-test, Chi2 test, and correlation analysis.

Results: Between bullying and shame there was a significant and positive correlation ($r=0,41$, $p<0,0001$). The level of bullying was significantly higher in the clinical sample in comparison with the healthy control group ($Chi2=46,69$, $p<0,0001$).

Conclusion: Our results suggest that there is a strong association between bullying and teasing and shame proneness. In the life-history of patients there is a higher frequency of bullying in comparison with healthy controls.

Doctoral School: *Mental Health Sciences*
Program: *Clinical Psychology and Psychiatry*
Supervisor: *Zsolt Unoka*
E-mail: *vizin.gabriella@med.semmelweis-univ.hu*

P/III-2
READING DIFFICULTY SPECTRUM AND COMORBID ANXIETY DISORDERS: SYSTEMATIC REVIEW AND CURRENT STATUS OF OUR RESEARCH

Krisztina Törő[1], Judit Balázs[2,3]

[1]*Vecsés City Local Government, Department of Children and Family Services, Vecsés, Hungary*
[2] *Institute of Psychology, Eötvös Loránd University, Budapest, Hungary*
[3] *Vadaskert Child and Adolescent Psychiatry Hospital, Budapest, Hungary*

Background/Objective. Reading difficulty spectrum disorders frequently co-occur with other mental disorders. The aims of this poster are to present: 1) a *systematic review* of the literature on reading disorder (RD) and comorbid anxiety disorders, 2) the current status of *our research* on RD and comorbid subthreshold disorder among children.

Methods. *Systematic review:* Published literature of the past 20 years was systematically searched by the following keywords from 5 databases (Science Direct, Medline, Scopus, Proqest, Psychinfo): anxiety, dyslexia, reading disorder, reading disability, internalizing symptomps, internalizing disorders. *Our research*: At the Vecsés City Local Government, Department of Children and Family Services two groups (age under 18 years) were enrolled: children with RD and healthy controls. Measurements: 3-DMH dyslexic test**,** Mini International Neuropsychiatric Interview Kid, Strengths and Difficulties Questionaire, Invertar zur Erfassung der Lebensqualität bei Kindern und Jugendlichen and a demografic questionnaire.

Results. *Systematic review:* The variety of terminology used in the studies for RD does not reflect to the position of the actual reading problem on the RD spectrum. Anxiety disorder co-occures with RD spectrum disorders in 9.00-25.00%. RD seems to be a predictive factor for developing anxiety disorder. When anxiety disorder co-occurs with RD, the prevalence of other comorbid disorders – e.g. attention deficit hyperactivity disorder, depression – is higher than in cases without RD. *Our research*: We enrolled 133 children with dyslexia, 78 boys (mean age: 9.79 years, SD=1.94) and 55 girls (mean age: 10.95 years, SD= 2.29) and 50 children without RD, 19 boys (mean age: 10.42 years, SD= 2.54) and 31 girls (mean age: 9.87 years, SD= 2.28). The data entry is ready.

Conclusion. Based on our *sytematic review*, we emphasize the importance of early recognision and treatment of both RD and comorbid anxiety. In *our research* we just start the data analyses, which we plan to present next year.

Doctoral School: *Menthal Health Sciences*
Program: *Clinical Psychology and Psychiatry*
Supervisor: *Judit Balázs*
E-mail: *torokrist@]hotmail.com*

P/III-3
PERSONAL NETWORK COMPOSITION OF ROMA UNIVERSITY STUDENTS

Ágnes Lukács[1], Beáta Dávid[1], Éva Huszti[2], Tünde Szabó[1], Péter Török[1]

[1] Institute of Mental Health, Semmelweis University, Budapest, Hungary
[2] Faculty of Health, University of Debrecen, Nyíregyháza, Hungary

In 2011, four of the Hungarian churches founded five Christian Roma Colleges for Roma university students. The research-team of Institute of Mental Health (Semmelweis University) designed a longitudinal research to follow up Roma college students. The research focuses on the changes on their identity, personal network structure, norms and mental health status.

Aims*:* The main purpose of personal network analysis is to measure how embedded Roma university students are in their milieu, which relations are related to mobility and coping. We consider personal network not just as a social capital, but also a deterministic factor, which has a considerable effect on identity-construction and integration, as well.

Methods*:* To map the students' social network composition we use contact diary, whereby we can observe size, consistency and homogeneity of the networks, and we can measure the strengths of the ties, too. From the second wave of the research we've integrated Egocentric Network Study Software into the data-collection to capture the structure of each egocentric network too.

Results: Based on the results of the first wave, we identified three dominant groups in the personal network of Roma college students, like family members, Roma college students or other Roma intelligentsia, and Non-Roma peers and intelligentsia. In our analysis we tried to map and cluster the networks with similar patterns.

Doctoral School: *Mental Health Sciences*
Program: *Sociological and mental health approaches to resources for individuals and communities*
Supervisor: *Beáta Dávid*
E-mail: *agnes.rozi.lukacs@gmail.com*

P/III-4
MENTAL IMAGE GENERATION ABILITYOF NEUTRAL STIMULI ACROSS AFFECTIVE DISORDERS

Kinga E. Fodor, Dóra Perczel Forintos

Department of Clinical Psychology, Faculty of Medicine, Semmelweis University, Budapest, Hungary

Introduction: Recent research has pointed out that distressing, intrusive mental imagery (mental representation not by direct perception but by memory or imagination) is a pervasive phenomenon that is not only the hallmark symptom of PTSD but may occur in various psychopathologies across the affective spectrum. While former investigations relied heavily on self-report measures and explored negative, self-relevant mental imagery, only a few focused on a more objective index of the underlying process itself.

Objectives*:* The present study aims to assess mental image generation ability of neutral stimuli in clinical and control groups.

Methods*:* The clinical sample consists of patients with PTSD, social anxiety and major depression. All four groups are planned to comprise of 25 participants. Clinical symptoms are assessed by SCID I. interviews and common self-report symptom measures (BDI, STAI, IES-R, LSAS-SR). Image generation ability is tested by a paradigm (Podgorny & Sheppard; 1978; Kosslyn et al., 1988; Morrison et al., 2011) verified to be a valid task for this purpose.

Procedure: The subjects are presented with a set of uppercase block letters in 4 x 5 grids to study. Then they complete a computerized task where lowercase letters are followed by empty grids. An X mark in one of the cells of the grid prompts participants to decide whether the X would have been covered by the corresponding block letter if the block version of the letter were superimposed on the grid. Image generation ability is assumed by response latencies for differences in locations of early to late segments of letters.

Hypotheses*:* Whilst patient groups are known to experience intrusive, negative imagery activity, based on earlier findings we hypothesize that clinical samples have greater impairment in image generation of neutral stimuli compared to controls and show longer response latencies in the task.

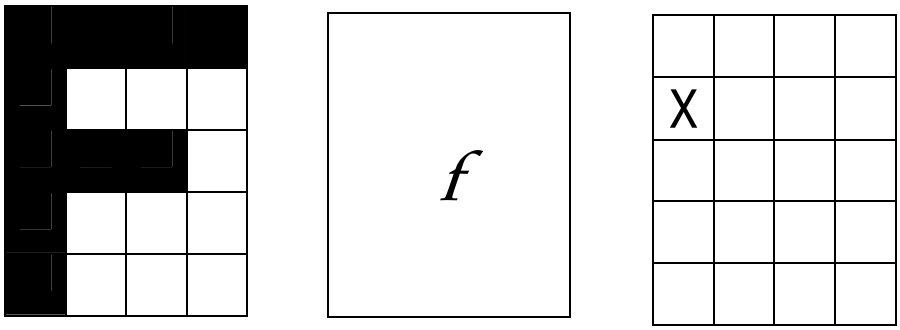


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Figure 1. Image generation task: study phase, script cue and image generation task

Doctoral School: *Mental Health Sciences*
Program: *Psychiatry*
Supervisor: *Dóra Perczel Forintos*
E-mail: *fodor.kinga@med.semmelweis-univ.hu*

P/III-5
THEORETICAL MODELS AND PARADIGMS REGARDING INFERTILITY

Enikő Lakatos, Nikolett Pápay, Szilvia Ádám, Piroska Balog

Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary

Background: The profound advancement of research on reproductive problems in the 20th century brought about the refinement of the method of scientific theory related to infertility. In the conceptualization of infertility the different models use various methodological instruments; therefore the interpretation of infertility shows a varied picture on an individual and community level. .

Methods: An overview of the national and international literature of theoretical models and paradigms regarding infertility.

Results: Biomedical condition addressed infertility as reproduction problems to be connected to the consequences of biological linear (cause-effect) factors. The demographic and sociographic approaches do not investigate the cause of fecundity but focus on the general analysis of lower fertility and try to reveal the economical and socio-cultural factors which could explain this phenomenon. Evolutionary approaches view infertility as an individual adaptation to environmental condition. Psychogenic model supposes that reproduction difficulties have psychological problems (inter or intra) in their background. The psychological consequence model in contrast with the psychogenic' hypothesis assumed that negative psychological response, such as stress, anxiety and depression are supposedly caused by infertility. The cyclical hypothesis postulated that infertility can cause higher level of psychosocial distress which may induce physiological disturbance (primarily through neuroendocrine mechanisms). These changes have a negative impact on the outcome of the assisted reproduction treatment as playing an important role by infertility. The coping model emphasizes the role of pathogenic individual coping style in infertility as a stress situation. The psycho-sociological model presents the most comprehensively the negative psychological responses caused by the reproduction problems, considering the bio-psycho-social and cultural aspects of reproduction at the couple's and personal level.

Conclusion*:* The different approaches in the research methodology of certain paradigms widen the framework of scientific thinking about infertility and improve the treatment options.

Doctoral School: *Menthal Health Science*
Program: *Menthal health sciences*
Supervisor: *Balog Piroska*
Email: *lakatoseniko_@hotmail.com*

P/III-6
MEASURING INTERPARENTAL CONFLICTS: THE HUNGARIAN VERSION OF THE INTERPARENTAL CONFLICT SCALE

Mária Szepes[1], Edit Czeglédi[1], Róbert Urbán[2], Klára Horváth[1], Piroska Balog[1]

[1] *Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary*
[2] *Institute of Psychology, Eötvös Loránd University, Budapest, Hungary*

Background*:* The Children's Perception of Interparental Conflict Scale is a widely used measure for assessing perceived interparental conflicts and children's subsequent adjustments.

Aims*:* Our aims were to prepare the Hungarian adaptation and evaluate the psychometric properties of the Hungarian version of Children's Perception of Interparental Conflict Scale.

Methods*:* 143 child-parent pairs participated in this cross-sectional questionnaire study. Children between the ages of 9–12 years (mean of age 10.8 years, SD = 1.05 years, range: 9–12 years) completed the CPIC, anxiety (STAI-C) and depression (CDI) scales, whereas the parent's battery of tests contained the short version of the Marital Stress Scale (MSS).

Results*:* The results of the confirmatory factor analysis did not support the theoretical eight-factor structure of the CPIC (χ^2 = 1355.0, DF = 1052, p<.001, CFI = .892, TLI = .884, RMSEA = .048, RMSEA CI_{90}: .040–.055, p = .698). The model fit indices became acceptable after the deletion of three items of the Triangulation subscale: ($\chi^2_{(917)}$ = 1113.4, p<.001; CFI = .929; TLI = .924; RMSEA = .041, RMSEA CI_{90}: .032–.049, p = .960). The four-factor alternative theoretical model showed significantly worse fit than the eight-factor model ($\Delta\chi^2$ = 66.5, Δdf = 22, p<.001). The internal consistency of the CPIC was acceptable (Cronbach-alpha: .63–.81) except the Triangulation subscale (Cronbach-alpha: .40). Construct validity was supported by the expected association in the case of six subscales with depression, anxiety and the self-reported marital stress.

Conclusion: Although the number of participants in the present study was suboptimal, the Hungarian version of the Children's Perception of Interparental Conflict Scale seemed to have adequate psychometric properties. We recommend the introduction of this scale to the Hungarian research and its further investigation.

Doctoral School: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Piroska Balog*
E-mail: *szepes.maria@gmail.com*

P/III-7
RELIABILITY AND VALIDITY OF THE HUNGARIAN VERSION OF THE OCULAR SURFACE DISEASE INDEX QUESTIONNAIRE

Ildikó Szakáts[1], Emma Birkás[2], Margit Sebestyén[1], György Purebl[2]

[1] Department of Ophthalmology, St. Pantaleon Hospital, Dunaújváros, Hungary
[2] Institute of Behavioral Sciences, Semmelweis University, Budapest, Hungary

Objective: To investigate the reliability and validity of the Hungarian version of the Ocular Surface Disease Index (OSDI) questionnaire.

Methods: 78 patients (58 women, 20 men, mean age 63±10.8 (37-85) years) were included in the study. After completing the OSDI questionnaire patients underwent ophthalmic examination including the most commonly used objective tests for dry eye (TBUT, ocular surface staining – using the Oxford scheme, Schirmer I test). On the basis of objective parameters patients were divided into three groups: healthy controls, mild/moderate dry eye and severe dry eye groups. Statistical analysis of the survey's internal reliability, discriminative validity and test-retest reliability were performed, as well as the correlations between the OSDI total score and dry eye tests were examined.

Results: The internal reliability of the questionnaire proved to be excellent (Cronbach's alpha=0.888). The survey's discriminant validity was demonstrated by the significant differences in OSDI total scores between the control and the dry eye group ($p=0.003$). The test-retest reliability of the questionnaire was satisfactory ($r=0.777$, $p<0.001$). The OSDI score demonstrated significant negative correlations with tear film break up time ($r=-0.309$, $p=0.006$), and positive correlations with ocular surface staining ($r=0.396$, $p<0.001$), but no correlation were found between the OSDI score and the results of the Schirmer I test ($r=-0.200$,$p=0.079$).

Conclusion: The analysis regarding the reliability and validity of the Hungarian version of the Ocular Surface Disease Index questionnaire are supportive for its applicability on Hungarian population.

Doctoral school: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *György Purebl*
E-mail: *szakatsildiko@gmail.com*

P/III-8
THE BORN AND UNBORN CHILDREN OF THE 1989 TRANSITION: EFFECTS OF THE SOCIO-CULTURAL CIRCUMSTANCES OF CHILDBEARING

Veronika Bóné

Institute of Mental Health, Semmelweis University, Budapest, Hungary

In 1989 the Sociological Institute initiated a longitudinal panel study among parents expecting their first child in the southern region of the Budapest agglomeration in Hungary. In the first phase of the study 300 pregnant women were asked to fill out standardized questionnaires. In the second phase, the families were revisited 3-13 months after giving birth. Then altogether 193 families (both mothers and fathers) filled the questionnaires plus 50 in-depth mother interviews were made. From 2011 the Hungarian Scientific Research Fund has funded a research to (re)continue this special family panel data, to follow up the life history of the families taking part in the research 20 years ago. In the current research we have interviewed members from 117 families (mothers, fathers and the grown-up children) and through their different perspectives we tried to reveal and explain the socio-demographic and personal factors behind the life course decisions. Since in the last few decades Hungary has been facing a permanent decline in its fertility figures , The aim of our presentation is to reveal those personal turning points that might influence the propensity of childbearing. Like the majority of the Hungarian women, mothers participating in the first wave of our research began their adult life with the intention of having a family with 2 children. Analyzing the data of the birth-panel study it is evident that the decision on the birth of the second and further children depends on several factors such as social support, quality of personal relationships, financial situation, crises and coping strategies. In the focus of our interest is not only to describe the characteristics of those families who initially had the same intentions but eventually either had only one or more than two children but to explain the influencing factors behind the different childbearing behaviours.

Doctoral School: *Mental Health Sciences*
Program: *Sociological and mental health approaches to resources for individuals and communities*
Supervisors: *Beáta Dávid, Szabolcs Török*
E-mail: *semsey_veronika@hotmail.com*

P/III-9
PSYCHIATRIC ASPECTS OF THE ANTIVIRAL TREATMENT OF HEPATITIS C INFECTED PATIENTS

Gergely Horváth[1], Gábor Gazdag[2]

[1] Reitox National Focal Point, National Center for Epidemiology, Budapest, Hungary
[2] Center for Psychiatry and Addiction Medicine, Szent István and Szent László Hospital, Budapest, Hungary

Several studies have examined psychiatric side effects of the 'two-combination' antiviral treatment with interferon-alpha and ribavirin in hepatitis C infected patients. Most common psychiatric side effects are depressive and anxiety symptoms affecting 30-70% of patients depending on the methods employed. Besides fatigue, psychiatric side-effects are the most common causes of cessation of antiviral treatment. Little is known, however, about the psychiatric aspects of the newest 'three-combination' antiviral treatment, in which the above mentioned medicines are supplemented by a protease inhibitor (eg. boceprevir or telaprevir); though similar mental issues are anticipated. Psychiatric side effects can be prevented or effectively treated with adequate psycho-pharmacotherapy thereby maximizing the effects of antiviral treatment. Further complication of the 'three-combination' is the potential interaction of the protease inhibitors with most of the psychopharmacons. Early detection of psychiatric symptoms, therefore, is of crucial importance.

Aims*:* The aim of the study is to follow and monitor quality of life and psychiatric aspects of the 'three-combination' antiviral treatment of hepatitis C infected patients. The study is designed in longitudinal way, patients' statuses are recorded at the beginning of the antiviral treatment and monitored in every three months thereafter, applying the same instruments. For the quality of life, the SF-36 questionnaire was used. Depression is screened for by the 21-item Beck Depression Inventory. For the detection of minor neurocognitive impairments, the computer-assisted Vienna Test System (Schuhfried Inc.) was applied on different domains, such as visual memory, visumotor coordination, non-verbal learning ability, executive functions and reaction time. Test results were supplemented by data from the medical documentation on treatment history and status.

Results: Patient inclusion is ongoing. Poster presentation demonstrates only the cross-sectional analysis of patients' baseline data at the onset of treatment. Preliminary results confirm however, that among hepatitis C positive patients and particularly among HCV patients in antiviral treatment mood disorders are prevalent, that often pose a threat on the continuation of antiviral treatment. Neurocognitive disorders are also prevalent and clinically important complications in the treatment of hepatitis C positive patients. These indicators show correlation with the treatment outcome and are good predictors of a possible drop-out. Although these symptoms can be compensated, because of the progressing nature of the disease the patients do need continuous monitoring.

Doctoral School: *Mental Health Sciences*
Program: *Clinical Psychology and Psychiatry*
Supervisor: *Gábor Gazdag*
E-mail: *horvath.gergely@oek.antsz.hu*

P/III-10
MENTAL AND PHYSICAL CONDITION OF HEALTH CARE WORKERS DEALING WITH SERIOUSLY ILL PATIENTS

Adrienne Kegye[1], Edit Révay[2], Ágnes Zana[1], Katalin Hegedűs[1]

[1] Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary
[2] Department of Sociology, Sapientia College of Theology, Budapest, Hungary

Background: Several studies have been carried out lately on the mental and physical condition of health care workers dealing with seriously ill patients by the Institute of Behavioural Sciences at Semmelweis University (e.g. Hegedűs et al., 2004, 2006, 2008, 2010) The results showed that their mental and physical sate as well as their family life is worse than that of those who do not work in health care.

Aims and hypothesis: Our current study is focusing on Hospice workers in Hungary (over 1500 people according to the annual Hospice Report in 2012). Our hypothesis is that people working with seriously ill patients have worse mental and physical condition; their partnerships and relatiosnships are more endangered than that of those who work in other areas of health care or outside health care. They have less success and satisfaction while there is a higher risk of burnout. Fear of death has a stronger presence in their lives, although it is less conscious among palliative hospice care workers.

Applied methods: The basis for the self-completed, anonymous online questionnaire is a group of tests chosen from the Hungarostudy 2013 Questionnaire. It is supplemented with tests on health care workers' attitude to death (Neimeyer and Moore, 1994; Zana et al, 2006), burnout (Maslach and Jackson, 1993) and coping methods (Folkman, Lazarus 1980, Rózsa et al, 2003). Questions are aimed specifically at hospice work, the scope of activities, the length of the hospice career and the methods to pervent burnout.

Summary: This questionnaire enables the regular assessment of the mental and physical condition of workers dealing with seriously ill patients. It also makes possible to examine and compare working and training factors, burnout and coping parameters.

Results can subserve the development of current educational and workplace supporting systems as well as working out adequate modules meeting current demands and needs.

Doctoral School: *Mental Health Sciences*
Program: *Mental health sciences*
Supervisor: *Katalin Hegedűs*
E-mail: *kegyepalfi@t-online.hu*

P/III-11
BURNOUT AMONG LAYPERSONS NURSING CHRONICALLY ILL ELDERLY RELATIVES AT HOME

Anett Mária Tróbert

Institute of Mental Health, Semmelweis University, Budapest, Hungary

Burnout research has focused mainly on professionals and especially the helping professions, but it has not studied the phenomenon among laypersons nursing chronically ill, elderly relatives at home.

The planned research will be two-pronged: one aim is to explore the particular risk factors of burnout among carer relatives. This element of the research will be based on the WebNurse internet portal launched in 2014 that uses infocommunication tools in a complex approach to help lay carers. An important element of mental health prevention on the portal is the psychological support module that will be developed and expanded in response to the concrete needs as they are identified. As part of the research the statistical data of the page will be processed – number of visitors, returning visitors, frequency of visits to the different pages – as well as visitors' feedback. We will first conduct a survey by questionnaire among users, applying the following tools: Orientation to Life Questionnaire (Antonovsky), Satisfaction With Life Scale (Diener, Emmons et al.), Beck Depression Inventory, Maslach Burnout Inventory. This will be followed by depth interviews with a group of respondents.

The other direction of the research will be an investigation of meaning in life among elderly recipients of care. The results will be comparable with the findings of the investigation among carers and can be used to improve the quality of life of the elderly chronically ill. Tools to be used for the quantitative measurement: Orientation to Life Questionnaire (Antonovsky), Satisfaction With Life Scale (Diener, Emmons et al.), Geriatric Depression Scale (Yesavage), Meaning in Life Questionnaire (Steger, Frazier et al.). The questionnaire-based research in this group too will be supplemented with qualitative tools and interviews.

Doctoral School: *Mental Health Sciences*
Program: *Sociological and mental health approaches to resources for individuals and communities*
Supervisor: *Zsuzsa Széman*
E-mail: *trobert.maria@gmail.com*

P/III-12
ASSOCIATIONS BETWEEN ADULT ATTACHMENT STYLE AND RELATIONSHIP SATISFACTION IN MARRIED AND COHABITING COUPLES

Csilla Lakatos, Katalin Horváth-Szabó, Tamás Martos

Institute of Mental Health, Semmelweis University, Budapest, Hungary

Introduction*:* The majority of recent authors agree that adult attachment is one of the crucial concepts for explaining adult romantic relationships, couples' satisfaction, relationship trust, degree of intimacy and well-being of partners. In general, secure attachment was related to higher and insecure attachment to lower marital satisfaction. In specific dyadic configurations, however, the positive effects of secure and the negative effects of insecure attachment styles were either amplified or attenuated depending on the attachment of the partner.

Aims: Our study has been designed to examine associations between adult attachment style and relationship satisfaction, and to investigate the differences in adult attachment style of married and cohabiting couples.

Methods*:* In the study we implemented a single-occasion, cross-sectional design using a sample of 270 heterosexual couples (aged 18-65) from Budapest and surrounding areas.

Couples were asked to complete the Hungarian version of the Relationship Assessment Scale - RAS (Hendrick, 1988) and Relationship Scales Questionnaire - RSQ (Bartholomew, Horowitz, 1991). Statistical analysis: SPSS v. 19. (Chi-Square test, Hierarchical multiple regression analyses)

Results*:* The results of the hierarchical multiple regression analyses showed that individual attachment style and partner attachment style are able to predict couple satisfaction but there is a difference between genders. In males relationship satisfaction was presaged negatively by strength of their own avoidant attachment style and the partner's dependent attachment style (beta= -0.187 and -0.204 in mentioned order, in both cases $p<0.05$). In females relationship satisfaction was presaged only by strength of their own dependent attachment style (beta= -0.226, $p<0.05$).

Conclusion*:* The results of the present study show that individuals' own attachment to romantic partners, the partners's attachment style, and their combination account for relationship satisfaction. The presented evidence further corroborates that the adult attachment framework possesses strong explanatory power for a better understanding of the functioning of romantic relationships.

Doctoral School: *Mental Health Sciences*
Program: *Sociological and mental health approaches to resources for individuals and communities*
Supervisor: *Katalin Horváth-Szabó*
E-mail: *lakatos.csilla@chello.hu*

P/III-13
PSYCHOTHERAPISTS' EXPERIENCES AND ATTITUDES ABOUT COLLABORATION CONCERNING SPIRITUALITY – A QUALITATIVE ANALYSIS

Zsuzsanna Jáki, Teodóra Tomcsányi, Edit Kiri, Viola Sallay, Tünde Szabó, András Ittzés

Institute of Mental Health, Semmelweis University, Budapest, Hungary

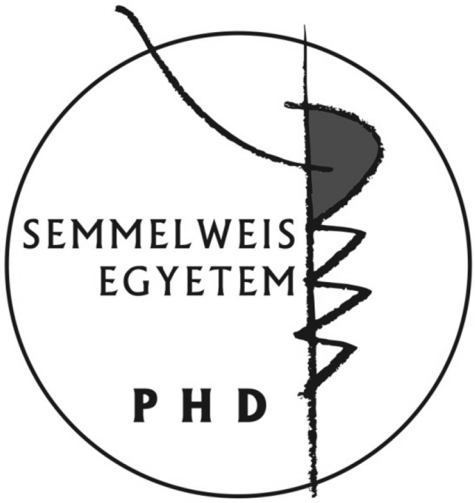
Introduction: A research started in 2009 in the Institute of Mental Health, Semmelweis University, which focused on the question, what happens to the spiritual contents -brought in by the patient- in psychotherapy. My research is connected to the mentioned work, but studies the professional collaboration in the theme of spirituality.

Aims*:* The goal of this investigation is to chart what the present situation is among Hungarian psychotherapists in the field of collaboration concerning spirituality: to what extent does the topic of spirituality emerge in the training of psychotherapist, in their professional contacts, in supervision? What are their experiences and attitudes about the collaboration with spiritual helping professionals, such as the spiritual guide?

Method*:* Thirty semi-structured in depth interviews are analyzed using the grounded theory method. Grounded theory is a text-analyzing process, which does not use initial hypothesis. With the use of the body text, a coding team formulates the codes (short statements, meaningful units, derived from the content of the interviews), and unfold the three-level category system, which they fit into. The final outcome is the wording of the grounded theory itself.

Results*:* 110 codes emerged, which are not yet definitive, the categories are beginning to take shape, but they are not yet final. So far the results suggest, that the attitudes and practice of psychotherapists differ in the question of collaboration. Only in some schools does spirituality emerge as a topic during training. Often this subject is missing from professional contacts also, and when it's present, it's often surrounded by misunderstandings, uncertainty and conflicts. At the same time the interest is growing towards the theme, the number of publications is increasing. Apart from the positive experiences various questions emerge to be reflected on: the competencies, the dynamics called forth by the collaboration, and these influence on the psychotherapeutic work.

Doctoral School: *Mental Health Sciences*
Program: *Sociological and mental health approaches to resources for individuals and communities*
Supervisor: *Teodóra Tomcsányi, András Ittzés*
E-mail: *zsuzsannajaki@gmail.com*



P/IV
POSTER PRESENTATIONS

Chairman:
Prof. Dr. Péter Lakatos

P/IV-1
ALTERED GENE EXPRESSION RELATED TO DNA REPAIR CAPACITY PREDICTS IRINOTECAN RESISTANCE IN BREAST CANCER CELL LINES

Zsófia Sztupinszki

I. Department of Pediatrics, Semmelweis University, Budapest, Hungary

Introduction: To overcome acquired drug resistance is a major challenge in the treatment of metastatic breast cancer. In recent years, the topoisomerase I inhibitor irinotecan emerged as a therapeutic option in the treatment of advanced colorectal cancera and several studies investigate its efficiency in breast cancer treatment. The active metabolite of irinotecan, SN-38 inhibits DNA replication, DNA repair, and induces DNA strand breaks. In case of several tumor types (eg: breast cancer) the damage of DNA repair mechanism was observed. This damage leads to the accumulation of genetic alterations (eg: gene copy number variation, double-strand DNA breakage). Our hypothesis is that the number of these genetic changes is proportional to the irinotecan sensitivity. Our aim was to quantify the damage in DNA repair based on altered geneexpression, and to identify new predictice biomarkers for irinotecan resistance.

Methods: Our team previously established 29 doxorubicin and paclitaxel resistant cell line derivatives from two breast cancer cell lines (MCF-7, MDA-MB-231). The geneexpression patterns of these cell lines were measured on custom Agilent microarray chips. SN-38 sensitivity of the cell lines was measured by MTT cell proliferation assay. After classifying cell lines into sensitive and resistant groups, I compared the gene expression of the two groups with SAM (Significance Analysis of Microarrays) in R statistic enviroment to identify significantly differently expressed genes.

Results: Although the resistant cell lines were established from 1-1 parental cell line, they differ significantly in the aquired resistance mechanism. We found common genes associated with drug sensitivity in MCF-7 and MDA-MB231, and also a few genes with altered expression in a small group of cell line. In summary, we were able to identifiy biomarkers of irinotecan resistance in breast cancer cell lines.

Doctoral School: *Pathological Sciences*
Program: *Oncology*
Supervisor: *Balázs Győrffy*
E-mail: *sztup@hotmai.com*

P/IV-2
ESTABLISHING MTOR ACTIVITY RELATED MIRNA EXPRESSION STUDIES IN FORMAL FIXED PARAFFIN EMBEDDED (FFPE) COLON CARCINOMA TISSUES

Noémi Nagy, Anna Molnár, Ágnes Márk, Titanilla Dankó, Mónika Tóth, László Kopper, Anna Sebestyén

I. Department of Pathology and Experimental Cancer Research, Budapest, Hungary

MicroRNA (miRNA) is a small non-coding RNA which regulates gene expression. Aberrant expression of miRNAs modifies the signalling pathways and it could associate with different types of cancer. Novel miRNA-profile screenings have been developed as a biomarker of colorectal cancer but the high capacity screening of miRNA-profile makes several conflicting data and information. The mammalian target of rapamycin (mTOR) is an important element of signalling network, which regulates the cellular proliferation and survival. In our work we started to study the expression of different miRNAs context of mTOR signalling activity. This work needs relevant normalisation of real time PCR and using appropriate control tissues, so we established and tested several internal standards, some oncomiRs and mTOR related miRNAs on few colon carcinoma cases.

We isolated miRNA from 10 colon carcinoma and 5 normal FFPE tissues for laser microdissection (LMD), separated the tumor cells from stroma and normal epithelial cells from microenvironment. We set the best method for using samples, compared the sample preparation with and without applying Preamplification (Applied Biosystems). We used RNU6b, RNU44, RNU49, miR-16, miR-103 as potential endogenous controls, miR-21, miR-155 oncomiRs and miRs which usually could alter in colon carcinomas and some other miRs which could regulate mTOR signalling. We analysed miRNA expression by Taqman assay (Applied Biosystems) in different whole and LMD tissues.

The results were similar after Preamplification or without it. Preamplification allows using fewer samples, which is important in the case of LMD materials. The most stabile endogenous control was miR-16, RNU44, however showed high variability between normal and tumor samples. The others appeared to be better, they were expressed nearly equivalent, in this case oncomiRs and colon carcinoma specific miRs showed approximately the expected published data.

Accordingly to our investigations, we will use the theses controls and Preamplification protocol in our miRNA examinations context of mTOR activity and we also suggest using these in other similar experiments.

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Doctoral School: *Pathological Sciences*
Program: *Experimental Oncology*
Supervisor: *Anna Sebestyén*
E-mail: *n.noncsi@freemail.hu*

P/IV-3
AREAL AND LAMINAR DISTRIBUTION OF INTERNEURONS TARGETED BY SOMATOSENSORY CORTICAL AFFERENTS IN THE NON-HUMAN PRIMATE *SAMIRI SCIUREUS*

Emese Pálfi[1,2], Orsolya Kántor[2], Mária Ashaber[1,2], Anna W. Roe[3], Robert M. Friedman[3], Csaba Dávid[5,6], Roland Nitschke[4], László Négyessy[1]

[1] Department of Theory, Institute for Particle and Nuclear Physics, Wigner Research Centre for Physics, Hungarian Academy of Sciences, Budapest, Hungary
[2] Department of Anatomy, Histology and Embryology, Semmelweis University Medical School, Budapest, Hungary
[3] Department of Psychology, Vanderbilt University, Nashville, USA
[4] Life Imaging Center, Center for Biological Systems Analysis (ZBSA), Albert-Ludwigs-University, Freiburg, Germany
[5] Laboratory of Thalamus Research, Institute of Experimental Medicine Hungarian Academy of Sciences, Budapest, Hungary
[6] Department of Human Morphology and Developmental Biology, Semmelweis University Medical School, Budapest, Hungary

In areas 3b and 1 the precise somatotopic representation of the fingers is a major factor of the neural mechanisms of tactile functions. Neighboring distal finger pad representations form strong neuronal connectivity within areas 3b and 1. However, connections between areas 3b and 1 are largely confined to the homotopic fingertip representations. It is also known that inhibition is essential for optimal cortical functioning. However, the role of cortical inhibition in shaping tactile perception is not known.

Aims*:* We used laser scanning confocal microscopy and neuronal tract tracing combined with multiple immunfluorescent labeling to examine the prevalence of close appositions between labeled afferents and different types of GABAergic interneurons.

Results*:* Of all labeled boutons identified 3.9% targeted immunolabeled interneurons. Parvalbumin (PV) positive interneurons were the most prevalent target of the labeled afferents. Somatostatin (SOM) and calretinin (CR) positive neurons were targeted less frequently. For horizontal connections within and between areas, SOM targeted afferents appeared more often in the supragranular layers. Only a slight supragranular dominance was found for intrinsic PV targeting afferents; however, inter-areal fibers were observed more frequently in the infragranular layers. These findings point to the intricate, regional and laminar specific role of GABAergic interneurons in the cortical processing of tactile information. Supported by: FIRCA NS059061 (to A.W.R. and L.N.), NS044375 (to A.W.R.) and the Hungarian Scientific Research Fund OTKA NN79366 (to L.N.).

Doctoral School: *János Szentágothai „Neurosciences”*
Program: *Neuromorphology and cell Biology*
Supervisor: *László Négyessy*
Email: *palfi.emese@gmail.com*

P/IV-4
INDUCTION OF TRANSFORMING GROWTH FACTOR BETA PROTEINS FOLLOWING MCAO IN THE RAT BRAIN

Gabriella Pál, Árpád Dobolyi

Laboratory of Neuromorphology, Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, Hungary

Transforming growth factor-βs (TGF-β1-3) regulate cellular proliferation, differentiation, and survival. TGF-β binds to type I (TGF-βRI) and type II (TGF-βRII) transmembrane kinase receptors, and an accessory type III receptor (TGF-βRIII). TGF-β may also utilize a second type I receptor, ALK1. TGF-β is neuroprotective as injection of TGF-β decreased, while its antagonist increased the infarct size following middle cerebral artery occlusion (MCAO). Recently, we reported the expression pattern of TGF-β1-3 after MCAO.

The present study describes the induction of TGF-βRI, RII, RIII and ALK1 at 24h, 72h and 1 month after transient and 24h following permanent occlusion using in situ hybridization. To identify the cell types expressing TGF receptors, we used a combination of in situ hybridization histochemistry and immunolabeling with markers of neurons, astrocytes, microglia, endothels, and smooth muscle cells.

In the intact animals, the expression of TGF-βRI was significant in neurons of the cerebral cortex. At 24h after the occlusion, TGF-β receptors were not induced. At 72h following MCAO, TGF-βRI and RII appeared in the penumbra and also in the ischemic core, and co-localized with Iba-1, a microglial marker. TGF-βRIII and ALK1 were induced around the vessels within the infarct area at 72h, and co-localized with vWF, an endothelial marker. All four TGF-β receptors were induced within the lesion 1 month after the occlusion.

These data suggest that TGF-β receptors are induced after MCAO in a timely and spatially regulated fashion, which is also coordinated with the induction of TGF-βs.

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Doctoral School: *János Szentágothai „Neurosciences”*
Program: *Neuromorphology and cell Biology*
Supervisor: *Arpád Dobolyi*
E-mail: *gabriellapal4@gmail.com*

P/IV-5
CAN PROPARGYLAMINES REDUCE SENSORINEURAL HEARING LOSSES?

Viktória Humli[1],Gábor Polony[2,3], Réka Andó[2], Máté Aller[3], Tamás Horváth[4,1], Andrea Harnos[5], László Tamás[2], E. Sylvester Vizi[3,1], Tibor Zelles[1,3]

[1] Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary
[2] Department of Otorhinolaryngology, Head and Neck Surgery, Semmelweis University, Budapest, Hungary
[3] Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary
[4] Department of Otorhinolaryngology, Bajcsy-Zsilinszky Hospital, Budapest, Hungary
[5] Department of Biomathematics and Informatics, Szent István University, Budapest, Hungary

Sensorineural hearing losses (SNHLs; e.g., ototoxicant- and noise-induced hearing loss or presbycusis) are among the most frequent sensory deficits, but they lack effective drug therapies. The majority of recent therapeutic approaches focused on the trials of antioxidants and reactive oxygen species (ROS) scavengers in SNHLs. The rationale for these studies was the prominent role of disturbed redox homeostasis and the consequent ROS elevation. Although the antioxidant therapies in several animal studies seemed to be promising, clinical trials have failed to fulfil expectations.

We investigated the potential of rasagiline, an FDA-approved MAO-B inhibitor type antiparkinsonian drug, as an otoprotectant. We showed a dose-dependent alleviation of the kanamycin-induced threshold shifts measured by auditory brainstem response (ABR) in an ototoxicant aminoglycoside antibiotic-based hearing loss model in mice. This effect proved to be statistically significant at a 6 mg/kg (s.c.) dose. The most prominent effect appeared at 16 kHz, which is the hearing sensitivity optimum for mice. The neuroprotective, antiapoptotic and antioxidant effects of rasagiline in animal models, all targeting a specific mechanism of aminoglycoside injury, may explain this otoprotection.

The dopaminergic neurotransmission enhancer effect of rasagiline might also contribute to the protection. Dopamine (DA), released from lateral olivocochlear (LOC) fibres, was shown to exert a protective action against excitotoxicity, a pathological factor in the aminoglycoside-induced SNHL. We have shown that rasagiline enhanced the electric stimulation-evoked release of DA from an acute mouse cochlea preparation in a dose-dependent manner. Using inhibitors of voltage-gated Na^+-, Ca^{2+} channels and DA transporters, we revealed that rasagiline potentiated the action potential evoked-release of DA by inhibiting the reuptake.

The complex, multifactorial pathomechanism of SNHLs most likely requires drugs acting on multiple targets for effective therapy. Rasagiline, with its multi-target action and favourable adverse effects profile, might be a good candidate for a clinical trial testing the otoprotective indication.

Doctoral School: *János Szentágothai „Neurosciences”*
Program: *Functional neurosciences*
Supervisor: *Tibor Zelles*
E-mail: *humli.viktoria@med.semmelweis-univ.hu*

P/IV-6
EMOTION RECOGNITION PATTERN IN ADOLESCENT BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Nikoletta Áspán[1,2], Csilla Bozsik[3], Judit Inántsy-Pap[3], Péter Nagy[2], Péter Vida[2], Júlia Gádoros[2], József Halász[2]

[1] Szentágothai János Doctoral School of Semmelweis University, Budapest, Hungary
[2] Vadaskert Child Psychiatry Hospital, Budapest, Hungary
[3] Institute of Psychology, University of Debrecen, Debrecen, Hungary

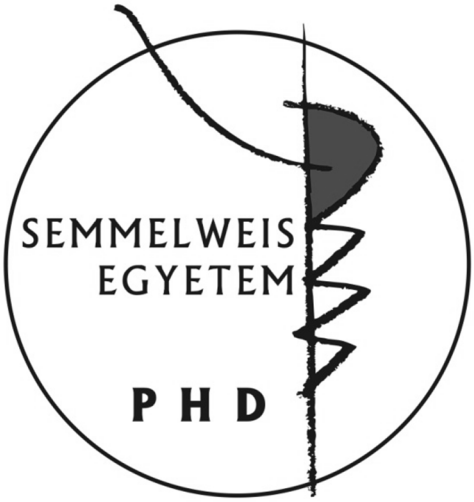
Background. Social and emotional deficits were recently considered as inherent features of attention-deficit/hyperactivity disorder (ADHD), but only sporadic literature data exist on emotion recognition in adolescents with ADHD. The aim of the present study was to establish emotion recognition profile in adolescent boys with ADHD in comparison with control adolescents.

Methods. Adolescent boys (N=44, 13-16 years) were involved in the study after informed consent; 22 boys had a clinical diagnosis of ADHD, while data were also assessed from 22 adolescent control boys matched for age and Raven IQ. Parent and self-reported hyperactivity/inattention measures were also assessed by the means of the Strengths and Difficulties Questionnaire. The recognition of six basic emotions was established by the "Facial expressions of emotion- stimuli and tests".

Results. Compared to controls, adolescents with ADHD were more sensitive in the recognition of disgust ($p<0.05$), worse in the recognition of fear ($p<0.05$) and showed a tendency for impaired recognition of sadness. In the overall sample, both parent and self-reported hyperactivity measures were inversely correlated with the recognition of fear (parent: Spearman $R=-0.315$, $p<0.037$; self-report: Spearman $R=-0.502$, $p<0.0005$).

Conclusion. Our data suggest that adolescent boys with ADHD have alterations in the recognition of specific emotions.

Doctoral School: *János Szentágothai „Neurosciences"*
Program: *Neuroendocrinology*
Supervisor: *József Halász*
Email: *nikoletta.aspan@yahoo.com*



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Program: Cardiovascular Disorders, Physiology and medicine of ischemic circulatory diseases

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Program: Cardiovascular Disorders, Physiology and medicine of ischemic circulatory diseases

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Program: Cardiovascular Disorders, Physiology and medicine of ischaemic circulatory diseases

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Program: Cardiovascular Disorders: Physiology and medicine of ischaemic circulatory diseases

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Program: Molecular Genetics, pathomechanism and clinical aspects of metabolic disorders

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Program: Physiology and Pathology of the musculoskeletal system

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Program: Physiology and Pathology of the musculoskeletal system

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Program: Clinical and experimental research in Angiology

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Program: *Physiology and Pathology of the musculoskeletal system*

E/VII-11 VITAMIN D RECEPTOR POLYMORPHISMS ARE ASSOCIATED WITH MUSCLE PERFORMANCE

Árpád Bozsódi, Áron Lazáry, Annamária Somhegyi, Peter Paul Varga

Program: *Physiology and Pathology of the musculoskeletal system*

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Gyöngyi P. Major, Bálint Szilveszter, Tamás Horváth, Attila Kovács, Szabina Pataki, László Szidonya, Béla Merkely, Pál Maurovich-Horvat

Program: *Cardiovascular diseases*

P/I-4 VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND INTERLEUKIN-1 RECEPTOR ANTAGONIST (IL1RA) CORD SERUM CONCENTRATIONS IN GESTATIONAL DIABETES MELLITUS (GDM)

Orsolya Hadarits, Zahra Al-Aissa Michael Feichtinger, Ágnes List, András Zóka, Dagmar Bancher-Todesca, István Sziller, János Rigó, Anikó Somogyi, Gábor Firneisz, Klára Rosta

Program: *Hormonal regulations*

P/I-5 METAGENOME ANALYSIS OF PLASMA DERIVED CELL FREE DNA IN COLON DISEASES

Barbara Kinga Barták, Sándor Spisák, Norbert Solymosi, Péter Ittzés, András Bodor, Dániel Kondor, Gábor Vattay, Zsófia Brigitta Nagy, Alexandra Kalmár, Zsolt Tulassay, István Csabai, Béla Molnár

Program: *Gastroenterology*

P/I-6GENE EXPRESSION-BASED HIGH-THROUGHPUT SCREENING REVEALS COL1A2, PTGDR, SFRP2 AND SOCS3 AS POTENTIAL NOVEL METHYLATION MARKERS OF LEFT-SIDED COLORECTAL CANCER

Alexandra Kalmár, Bálint Péterfia, Péter Hollósi, Sándor Spisák, Barnabás Wichmann, Vivien Kubák Katalin Kiss, Zsolt Horváth; Gábor Valcz; Béla Molnár, Zsolt Tulassay

Program: *Gastroenterology*

P/I-7 NORMAL AND TUMOROUS DNA ACTS DIFFERENTLY VIA TLR9 SIGNALLING ON COLON CARCINOMA CELLS INDUCING CANCER CELL MOBILITY

István Fűri, Ferenc Sipos, Györgyi Műzes, Barnabás Wichmann, Sándor Spisák, Barbara Barták, Alexandra Kalmár, Béla Molnár, Zsolt Tulassay

Program: *Gastroenterology*

P/I-8 SKELETAL MUSCLE AND RENAL COMPLICATIONS FOLLOWING LOWER LIMB VASCULAR SURGERY: A NEW DRUG THERAPY

Dávid Garbaisz, Zsolt Turóczi, Péter Arányi, András Fülöp, Olivér Rosero, Péter Ónody, Edit Hermesz, Gábor Lotz, László Harsányi, Attila Szijártó

Program: *Clinical and experimental research in Angiology*

P/I-9 INTESTINAL POSTCONDITIONING: PATCHING THE LEAKING PIPES

Olivér Rosero, Péter Ónody, Tibor Kovács, Dávid Molnár, Gábor Lotz, Szilárd Tóth, Zsolt Turóczi, András Fülöp, Dávid Garbaisz, László Harsányi, Attila Szijártó

Program: *Gastroenterology*

P/I-10 DIFFERENTIAL MICRORNA EXPRESSION IN TWO TYPES OF SAMPLES (FFPET AND FRESH FROZEN) FROM VARIOUS COLON PRECANCEROUS AND CANCEROUS LESIONS

Zsófia Brigitta Nagy, Barnabás Wichmann, Alexandra Kalmár, Barbara Kinga Barták, Nha Le, Bálint Péterfia, István Fűri, Zsolt Tulassay, Béla Molnár

Program: *Gastroenterology*

P/I-11 CHARACTERISTICS OF SPECIFIC MICRORNA EXPRESSION IN COLONIC MUCOSA IN PEDIATRIC PATIENTS WITH CROHN'S DISEASE

Nóra Béres, Dolóresz Szabó, András Arató, András Kiss, Gábor Lendvai, Gábor Veres
Program: *Prevention of chronic diseases in childhood*

P/I-12 THE EFFECT OF RAAS INHIBITION ON THE ARTERIAL STIFFNESS IN DIABETIC RATS

Arianna Dégi, Éva Kis, Orsolya Cseprekál, Sándor Kőszegi, Ádám Hosszú, Lilla Lénárt, Renáta Gellai, Judit Hodrea, Andrea Fekete, György L. Nádasy, György Reusz
Program: *Prevention of chronic diseases in childhood*

PHARMACEUTICAL SCIENCES DOCTORAL SCHOOL

E/I-1 CYCLODEXTRIN-BASED CAPILLARY ELECTROPHORETIC ENANTIOSEPARATION OF TAPENTADOL STEREOISOMERS

Ida Fejős, Szabolcs Béni
Program: *Modern trends in pharmaceutical scientific research*

E/I-2 SYNTESIS OF 6A- AND B-ACYLAMINO MORPHINAN DERIVATIVES AND PHARMACOLOGICAL CHARACTERIZATION

Ákos Urai, Péter Horváth, Sándor Hosztafi, Béla Noszál
Program: *Modern trends in pharmaceutical scientific research*

E/I-3 EXPLORATION OF AN UNEXPECTED SIDE REACTION IN DAPOXETINE SYNTHESIS

András Darcsi, Szabolcs Béni
Program: *Modern trends in pharmaceutical scientific research*

E/I-4 CHARACTERIZATION AND QUANTITATION OF ISOMERIC DISACCHARIDES: N-ACETYLLACTOSAMINE AND LACTO-N-BIOSE IN HUMAN MILK

Réka Balogh, Péter Jankovics, Szabolcs Béni
Program: *Experimental and clinical Pharmacology*

E/I-5 CHARACTERIZATION OF A NOVEL INFLAMMATORY PATHWAY INHIBITOR USING DIFFERENT INFLAMMATORY CELL MODELS

Attila Varga, Pál Gyulavári, Zoltán Greff, Tamás Németh, Krisztina Kerekes, Diána Brauswetter, Márton Kokas, Anna Erdei, Attila Mócsai, György Kéri, Tibor Vántus
Program: *Modern trends in pharmaceutical scientific research*

P/II-1 PREDICTION OF ROTARY SPUN FIBER FORMING PROPERTIES OF HYDROXYPROPYL CELLULOSE GELS AND PREPARATION OF DRUG LOADED CELLULOSE BASED FIBERS

Péter Szabó, Romána Zelkó
Program: *Modern trends in pharmaceutical scientific research*

P/II-2 PREDICTION OF CIRCULAR DICHROISM SPECTRA OF MODIFIED NATURAL PRODUCTS WITH M06-2X FUNCTIONAL

Ákos Urai, Balázs Komjáti, József Nagy, Levente Szőcs, Sándor Hosztafi, Péter Horváth
Program: *Modern trends in pharmaceutical scientific research*

P/II-3 DEVELOPMENT AND PERMEABILITY STUDY ON A PAMPA MODEL WITH SUPPORTED LIPID BILAYER AS MEMBRANE

Gábor Vizserálek, Bálint Sinkó, Tamás Bozó, Krisztina Takács-Novák
Program: *Experimental and clinical Pharmacology*

P/II-4 DETERMINATION OF NMDA MODULATOR AMINO ACIDS WITH CE-LIF IN VARIOUS BIOLOGICAL SAMPLES

Tamás Jakó, Eszter Szabó, Tamás Tábi, Gergely Zachar, András Csillag, Éva Szökő
Program: *Experimental and clinical pharmacology*

MENTAL HEALTH SCIENCES DOCTORAL SCHOOL

E/VI-1 THE BODY MASS INDEX AND ITS CONNECTIONS WITH RELATIONSHIP QUALITY AND SEXUALITY AMONG HUNGARIAN YOUTH

Tamás Dömötör Szalai
Program name: *Mental health sciences*

E/VI-2 MENTAL WELL-BEING, HEALTH RISK BEHAVIORS AND SOCIOECONOMIC STATUS AMONG HIGH SCHOOL STUDENTS

Szabolcs Varga, Bettina F. Piko
Program: *Mental health sciences*

E/VI-3 SEX DIFFERENCES IN SLEEP EEG CORRELATES OF INTELLIGEN

Péter P. Ujma, Boris Konrad, Péter Simor, Adrián Pótári, János Körmendi, Ferenc Gombos, Martin Dresler, Axel Steiger, Róbert Bódizs
Program: *Mental health sciences*

E/VI-4 THE ROLE OF SOCIAL SUPPORT DURING LOW-DOSE INTERFERON TREATMENT IN MELANOMA PATIENTS

Péter Kovács, Gitta Pánczél, Gabriella Liszkay, György Bagdy, Gabriella Juhász
Program: *Clinical Psychology and Psychiatry*

E/VI-5 POTENTIAL INTERACTIONS BETWEEN MEDIA USE (MAGAZINE, TELEVISION, INTERNET) AND EATING DISORDER SYMPTOMATOLOGY

Kornélia Szabó, Irena Szumska, Edit Czeglédi, Ferenc Túry
Program: *Mental health sciences*

E/VI-6 PSYCHOSOCIAL WORK CONDITINONS AMONG HEALTHCARE WORKERS: A COMPARATIVE STUDY

Katalin Nistor, Anikó Nistor, Szilvia Ádám, Adrienne Stauder
Program: *Mental health sciences*

E/VI-7 THE DIFFERENCES AMONG PILS IN DESCRIPTIONS OF CURATIVE EFFECTS CAN INFLUENCE PEOPLE'S CHOICES AMONG OTC-MEDICINES WITH THE SAME EFFECT

Ildikó Komsa
Program: *Mental health sciences*

E/VI-8 BEHAVIOURAL-EPIDEMIOLOGICAL ANALYSIS OF ADOLESCENTS' PROBLEM BEHAVIOURS IN A POPULATION OF A SMALL TOWN AND ITS AREA BETWEEN 2008 AND 2013

Mate A. Balazs, Bettina F. Piko
Program: *Mental health sciences*

E/VI-9 HIGH FREQUENCY EEG ACTIVITY DURING SLEEP IS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN KIDNEY TRANSPLANT RECIPIENTS

Katalin Z. Rónai, András Szentkirályi, Alpár S. Lázár, Ákos Ujszászi, Anett Lindner, Katalin Fornadi, Mária E. Czira, Rezső Zoller, Csilla Z. Turányi, Zsolt I. Lázár, István Papp, István Mucsi, Róbert Bódizs, Miklós Z. Molnár, Márta Novák
Program: *Mental health sciences*

E/VI-10 THE ONTOGENY OF DREAMING IN THE MIRROR OF COGNITIVE AND AFFECTIVE DEVELOPMENT

Piroska Sándor, Sára Szakadát, Katinka Kertész, Róbert Bódizs
Program: *Mental health sciences*

E/VI-11 EXAMINING DYSKINESIA IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH AND WITHOUT ONGOING METHYLPHENIDATE TREATMENT

Ágnes Keresztény, Judit Balázs
Program: *Clinical Psychology and Psychiatry*

E/VI-12 OUTCOME OF MAJOR DEPRESSIVE EPISODE AND PERSONALITY TRAITS. A FOLLOW UP STUDY

Nóra Garamvölgyi, Erika Szádóczky, Edina Gauland, Sándor Rózsa, Zoltán Rihmer
Program: *Psychiatry*

E/VI-13 CHANGING IDENTITY OF CHRISTIAN ROMANIES

Gellert László Gyetvai
Program: *Sociological and mental health approaches to resources for individuals and communities*

E/VI-14 NATIONWIDE SURVEY ON UNSUCCESSFUL ADOPTIONS

Júlia Andrási
Program: *Sociological and mental health approaches to resources for individuals and communities*

E/VI-15 DIFFICULTIES IN MIDWIVES HELPING PREGNANT WOMEN TO QUIT SMOKING

Ágnes Szélvári, László Kalabay , Adrienne Stauder, Róbert Urbán
Program: *Mental health sciences*

E/VI-16 FUNCTIONAL GENE CLUSTERS IN SCHIZOPHRENIA: RESULTS FROM THE SCHIZOBANK WHOLE EXOME SEQUENCING STUDY

Attila J. Pulay, Júlia Koller, Attila Horváth, Péter Balicza, Judit Benkovits, Gábor Zahuczky, Endre Barta, István Likó, György Németh, Zoltán Urbányi Judit Mária Molnár, László Nagy, János M. Réthelyi
Program: *Clinical psychology and psychiatry*

P/III-1 THE ROLE OF BULLYING IN DEVELOPMENT OF CHRONIC SHAME

Gabriella Vizin, Julianna Bircher, Zsolt Unoka
Program: *Clinical Psychology and Psychiatry*

P/III-2 READING DIFFICULTY SPECTRUM AND COMORBID ANXIETY DISORDERS: SYSTEMATIC REVIEW AND CURRENT STATUS OF OUR RESEARCH

Krisztina Törő, Judit Balázs
Program: *Clinical Psychology and Psychiatry*

P/III-3 PERSONAL NETWORK COMPOSITION OF ROMA UNIVERSITY STUDENTS

Ágnes Lukács, Beáta Dávid, Éva Huszti, Tünde Szabó, Péter Török
Program: Sociological and mental health approaches to resources for individuals and communities

P/III-4 MENTAL IMAGE GENERATION ABILITYOF NEUTRAL STIMULI ACROSS AFFECTIVE DISORDERS

Kinga E. Fodor, Dóra Perczel Forintos
Program: Psychiatry

P/III-5 THEORETICAL MODELS AND PARADIGMS REGARDING INFERTILITY

Enikő Lakatos, Nikolett Pápay, Szilvia Ádám, Piroska Balog
Program: Menthal health sciences

P/III-6 MEASURING INTERPARENTAL CONFLICTS: THE HUNGARIAN VERSION OF THE INTERPARENTAL CONFLICT SCALE

Mária Szepes, Edit Czeglédi, Róbert Urbán, Klára Horváth, Piroska Balog
Program: Mental health sciences

P/III-7 RELIABILITY AND VALIDITY OF THE HUNGARIAN VERSION OF THE OCULAR SURFACE DISEASE INDEX QUESTIONNAIRE

Ildikó Szakáts, Emma Birkás, Margit Sebestyén, György Purebl
Program: Mental health sciences

P/III-8 THE BORN AND UNBORN CHILDREN OF THE 1989 TRANSITION: EFFECTS OF THE SOCIO-CULTURAL CIRCUMSTANCES OF CHILDBEARING

Veronika Bóné
Program: Sociological and mental health approaches to resources for individuals and communities

P/III-9 PSYCHIATRIC ASPECTS OF THE ANTIVIRAL TREATMENT OF HEPATITIS C INFECTED PATIENTS

Gergely Horváth, Gábor Gazdag
Program: Clinical Psychology and Psychiatry

P/III-10 MENTAL AND PHYSICAL CONDITION OF HEALTH CARE WORKERS DEALING WITH SERIOUSLY ILL PATIENTS

Adrienne Kegye, Edit Révay, Ágnes Zana, Katalin Hegedűs

Program: Mental health sciences

P/III-11 BURNOUT AMONG LAYPERSONS NURSING CHRONICALLY ILL ELDERLY RELATIVES AT HOME

Anett Mária Tróbert

Program: Sociological and mental health approaches to resources for individuals and communities

P/III-12 ASSOCIATIONS BETWEEN ADULT ATTACHMENT STYLE AND RELATIONSHIP SATISFACTION IN MARRIED AND COHABITING COUPLES

Csilla Lakatos, Katalin Horváth-Szabó, Tamás Martos

Program: Sociological and mental health approaches to resources for individuals and communities

P/III-13 PSYCHOTHERAPISTS' EXPERIENCES AND ATTITUDES ABOUT COLLABORATION CONCERNING SPIRITUALITY – A QUALITATIVE ANALYSIS

Zsuzsanna Jáki, Teodóra Tomcsányi, Edit Kiri, Viola Sallay, Tünde Szabó, András Ittzés

Program: Sociological and mental health approaches to resources for individuals and communities

SPORT SCIENCES DOCTORAL SCHOOL

E/IV-7 TRAINING-INDUCED DIFFERENCES IN MITOCHONDRIAL BIOGENESIS IN RAT TESTICULAR TISSUE

Melitta Pajk, Orsolya Marton, Enikő Nagy, Lauren Gerard Koch, Steven Britton, Zsolt Radák

Program: Physical training, regulation, metabolism

E/IV-8 CHANGES IN THE FUNCTIONAL CHARACTERISTICS OF THE ATHLETE'S HEART WITH THE TRAINING SEASON IN ELITE YOUNG ENDURANCE ATHLETES

Eszter Csajági, Péter Horváth, Zsuzsanna Major, Gábor Pavlik

Program: Training and adaptation

„JÁNOS SZENTÁGOTHAI" NEUROSCIENCES DOCTORAL SCHOOL

P/IV-3 AREAL AND LAMINAR DISTRIBUTION OF INTERNEURONS TARGETED BY SOMATOSENSORY CORTICAL AFFERENTS IN THE NON-HUMAN PRIMATE *SAMIRI SCIUREUS*

Emese Pálfi, Orsolya Kántor, Mária Ashaber, Anna W. Roe, Robert M. Friedman, Csaba Dávid, Roland Nitschke, László Négyessy

Program: *Neuromorphology and cell Biology*

P/IV-4 INDUCTION OF TRANSFORMING GROWTH FACTOR BETA PROTEINS FOLLOWING MCAO IN THE RAT BRAIN

Gabriella Pál, Árpád Dobolyi

Program: *Neuromorphology and cell Biology*

P/IV-5 CAN PROPARGYLAMINES REDUCE SENSORINEURAL HEARING LOSSES?

Viktória Humli, Gábor Polony, Réka Andó, Máté Aller, Tamás Horváth, Andrea Harnos, László Tamás, E. Sylvester Vizi, Tibor Zelles

Program: *Functional neurosciences*

P/IV-6 EMOTION RECOGNITION PATTERN IN ADOLESCENT BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Nikoletta Áspán, Csilla Bozsik, Judit Inántsy-Pap, Péter Nagy, Péter Vida, Júlia Gádoros, József Halász

Program: *Neuroendocrinology*

MOLECULAR MEDICINE DOCTORAL SCHOOL

E/IV-1 YAP1 IN THE HIPPO PATHWAY INFLUENCES THE RISK OF ASTHMA

Lili E. Fodor, Ildikó Ungvári, Ágnes F. Semsei, Orsolya Lautner-Csorba, András Bikov Csaba Szalai

Program: *Basis of human molecular genetics and gene diagnostics*

E/IV-2 THE DIFFERENT REGULATION OF IL-17 AND IL-22 PRODUCTION DURING THE HUMAN IN VITRO TH17 CELL DIFFERENTIATION

Eszter Baricza, Barbara Érsek-Molnár, Edit I. Buzás, György Nagy

Program: *Basis of human molecular genetics and gene diagnostics*

E/IV-3 ONTOGENESIS OF HEMOPOIETIC CELLS OF YOLK SAC ORIGIN

Dávid Dóra

Program: Embryology, theoretical, experimental and clinical developmental Biology

E/IV-4 IMPACTS OF O-GLCNAC ON ENDOTHELIAL NITRIC OXIDE SYNTHASE IN DIABETIC NEPHROPATHY

Renáta Gellai, Judit Hodrea, Lilla Lénárt, Sándor Kőszegi, Ágota Vér, Nóra Fanni Bánki, László Wagner, Norbert Fülöp, Ágnes Molnár, Ádám Vannay, Attila J. Szabó, Andrea Fekete

Program: Pathobiochemistry

E/IV-5 GAIN OF COPY NUMBER OF PIK3CA IN HEAD AND NECK CANCERS (HNSCCS)

Diána Brauswetter, Kornél Dános

Program: Pathobiochemistry

E/IV-6 IMPROVED CHARACTERIZATION OF EXTRACELLULAR VESICLE PREPARATIONS BASED ON PROTEIN/LIPID RATIO AND LIPID PROPERTIES

Xabier Osteikoetxea, Andrea Balogh, János Matkó, Krisztina Pálóczi, Dániel Vértessy, Andrea Németh, Bence György, Ágnes Kittel, Tamás G. Szabó, Katalin Szabó-Taylor, Barbara Sódar, Maria Pásztói, Edit I. Buzás

Program: Basis of human molecular genetics and gene diagnostics

P/II-6 ABCC6 GENE EXPRESSION IS REGULATED BY HNF4A VIA DIRECT PHOSPHORYLATION BY ERK1/2 IN HEPG2 CELLS

Borbála Vető, Caroline Bacquet, Attila Horváth, Szabolcs Sipeki, Endre Barta, Dávid Jónás, László Buday, Bálint L. Bálint, László Nagy, András Váradi, Tamás Arányi

Program: Pathobiochemistry

P/II-7 THE ROLE OF GADD34 AND CHOP IN ENDOPLASMIC RETICULUM STRESS: SURVIVAL OR DEATH?

Anita Andrea Kurucz

Program: Pathobiochemistry

P/II-8 A STUDY ON GLYCOSIDASES AND SULFATASES IN RHEUMATIC DISEASES

Barbara Sódar, Mária Szente-Pásztói, Krisztina Pálóczi, Ágnes Kittel, András Falus, Edit I. Buzás

Program: Basis of human molecular genetics and gene diagnostics

P/II-9 GENETIC VARIANTS OF AKR1C3 IN ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Nóra Kútszegi, Máté Sipos, Ágnes F. Semsei, Orsolya Lautner-Csorba, Dániel J. Erdélyi, Gábor T. Kovács, Csaba Szalai

Program: Basis of human molecular genetics and gene diagnostics

PATHOLOGICAL SCIENCES DOCTORAL SCHOOL

E/III-1 NEW ONSET DIABETES MELLITUS AND THE ANALYSIS OF DIPEPTYDIL-PEPTIDASE-4 AFTER LIVER TRANSPLANTATION

György Gámán

Program: Clinical and experimental transplantation

E/III-2 DIFFERENTIAL RESPONSE TO BRAF INHIBITION IN TUMOR CELLS WITH ONCOGENIC BRAF MUTATION

Eszter Molnár, Tamás Garay, Walter Berger, Balázs Döme, József Tímár, Balázs Hegedűs

Program: Oncology

E/III-3 POLYMYXIN-RESISTANCE IN KLEBSIELLA PNEUMONIAE AND ENTEROBACTER ASBURIAE

Béla Kádár, Béla Kocsis, Károly Nagy, Dóra Szabó

Program: Study of the immunbiological effects of microorganisms and of their components at molecular and cellular level and in the microorganisms

E/III-4 UNUSUAL HOST RANGE OF THE FELINE ADENOVIRUS

Balázs Stercz

Program: Alterations of cells, fibres and extracellular matrix and diagnostic pathomorphological studies in the course of heart and vascular diseases and in certain tumours. Experimental and diagnostic pathomorphological studies

E/III-5 CELL CYCLE ANALYSIS CAN DIFFERENTIATE THIN MELANOMAS FROM DYSPLASTIC NEVI AND REVEALS ACCELERATED REPLICATION IN THICK MELANOMAS

Gergő Kiszner

Program: Experimental Oncology

E/III-6 EFFECT OF IONIZING RADIATION ON BBB ENDOTHELIAL DISRUPTION AND RECOVERY. AN IN VIVO STUDY

Boglárka Schilling-Tóth, Nikolett Sándor, Violetta Léner

Program: Experimental Oncology

E/III-7 CONNEXIN 43 EXPRESSION AND CELL COUPLING IN GIANT CELL TUMOR OF BONE (GCTB)

Péter Balla, Máté Előd Maros, Nóra Meggyesházi, Gergő Kiszner, Tibor Krenács
Program: *Experimental Oncology*

E/III-8 PROGRAMMED CELL DEATH AND IMMUNOGENIC CELL DEATH SIGNALS INDUCED BY MODULATED ELECTROHYPERTHERMIA IN COLORECTAL ADENOCARCINOMA MODEL

Nóra Meggyesházi, Gábor Andócs
Program: *Experimental Oncology*

E/III-9 DECORIN DEFICIENCY PROMOTES HEPATIC CARCINOGENESIS

Zsolt Horváth, Ilona Kovalszky, Alexandra Fullár, Katalin Kiss, Kornélia Baghy
Program: *Oncology*

P/IV-1 ALTERED GENE EXPRESSION RELATED TO DNA REPAIR CAPACITY PREDICTS IRINOTECAN RESISTANCE IN BREAST CANCER CELL LINES

Zsófia Sztupinszki
Program: *Oncology*

P/IV-2 ESTABLISHING MTOR ACTIVITY RELATED MIRNA EXPRESSION STUDIES IN FORMAL FIXED PARAFFIN EMBEDDED (FFPE) COLON CARCINOMA TISSUES

Noémi Nagy, Anna Molnár, Ágnes Márk, Titanilla Dankó, Mónika Tóth, László Kopper, Anna Sebestyén
Program: *Experimental Oncology*

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