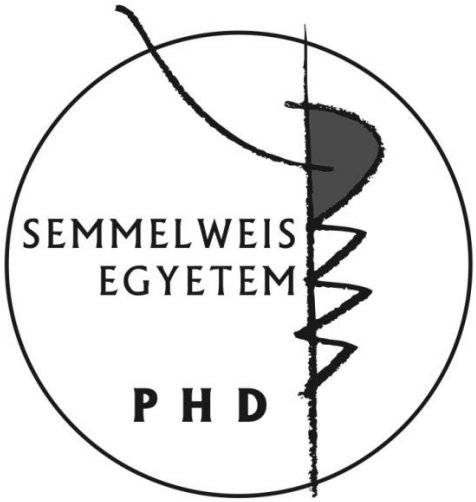


PHD SCIENTIFIC DAYS
2015

9-10 April 2015
Semmelweis University
NET Building

INTRODUCTION

It is a great pleasure for me to welcome participants of the PhD Scientific Days 2015 Conference. This event provides an opportunity for PhD students from each of the seven Doctoral Schools of Semmelweis University to network and present their latest research and clinical findings during the 7 oral presentation and 2 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 2015 Conference, professors András Matolcsy and Zoltán Papp, holders of "Excellent PhD Supervisor Award", and a guest speaker, Dr Gábor Zacher 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 2015 Conference and promise you a pleasant and professionally rewarding time.

Dr. Károly Rácz
Head of the Doctoral Council

SCIENTIFIC PROGRAM

9. APRIL 2015 (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. Zoltán Papp, professor* ***Research ethical challenges during my scientific curriculum"***
09.50 – 10.10	**"Excellent PhD Supervisor" Award recipient:** *Dr. András Matolcsy, professor* ***Milestones in the career of a scientist***
10.10 – 10.40	***Coffee break***
10.40 – 13.00	**Oral presentations:** E-I/1 – E-I/13 (Mental Health Sciences)
13.00 – 14.00	***Lunch***
14.00 – 14.20	**Invited lecture:** *Dr. Gábor Zacher* *Rabszolgától az alphahímig: szakmánk kor-és kórtörténete*
14.20 – 16.00	**Oral presentations:** E-II/1 – E-II/10 (Molecular Medicine)
14.20 – 16.40	**Poster presentation:** P-I/1 – P-I/13 (Mental Health Sciences)
16.00 – 16.30	***Coffee break***
16.30 – 17:40	**Oral presentations:** E-III/1 – E-III/7 (Dentistry)

10. APRIL 2015 (FRIDAY)

08.30 – 10.40	**Oral presentations:** E-IV/1 – E-IV/13 (Clinical medicine)
10.40 – 11.10	***Coffee break***
11.10 – 13.00	**Oral presentations:** E-V/1 – E-V/11 (Oncology)
13.00 – 14.00	***Lunch***
14.00 – 16.00	**Oral presentations:** E-VI/1 – E-VI/12 (Clinical medicine: Cardiology, Gastroenterology)
15.00 – 17.30	**Poster presentations:** P-II/1 – P-II/16 (Varied)
16.00 – 17.00	***Coffee break***
16.20 – 18.30	**Oral presentations:** E-VII/1 – E-VII/13 (Pharmaceutical sciences)
18.30 – 18.45	**Closing of the conference** **Awards ceremony**

TABLE OF CONTENTS

E/II - MOLECULAR MEDICINE *oral presentations*

Chairpersons: Dr. László Tretter, Dr. Barna Vásárhelyi

E/III - DENTISTRY *oral presentations*

Chairpersons: Dr. Péter Hermann, Dr. Gábor Varga

E/IV - CLINICAL MEDICINE I. *oral presentations*

Chairpersons: Dr. Anikó Somogyi, Dr. László Kopper

E/V - ONCOLOGY *oral presentations*

Chairpersons: Dr. Ilona Kovalszky, Dr. András Kiss

E/VI - CLINICAL MEDICINE II. - CARDIOLOGY, GASTROENTEROLOGY

oral presentations

Chairpersons: Dr. Dávid Becker, Dr. László Herszényi

E/VII - PHARMACEUTICAL SCIENCES *oral presentations*

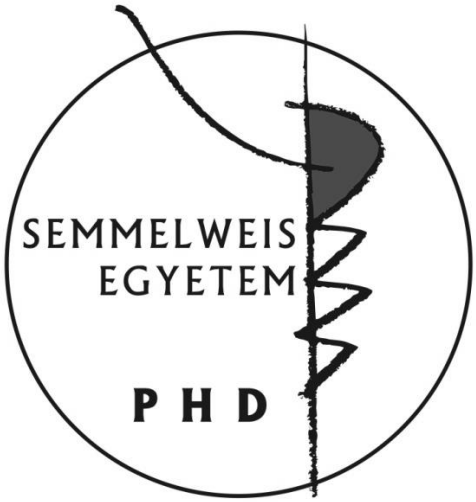
Chairpersons: Dr. György Stampf, Dr. Norbert Szoboszlai, Dr. Tamás Tábi

P/I - MENTAL HEALTH SCIENCES *poster presentations*

Chairpersons: Dr. György Bagdy, Dr, Katalin Hegedüs, Dr. Zsuzsa Széman

P/II - VARIED POSTERS *poster presentations*

Chairpersons: Dr. Zoltán Benyó, Dr. Attila Szabó



E/I
MENTAL HEALTH SCIENCES
ORAL PRESENTATIONS

Chairpersons:

Dr. István Bitter
Dr. Róbert Bódizs
Dr. Beáta Dávid (Pethesné)

E/I-1
MENTAL HEALTH OUTCOMES OF PARENTS AND CHILDREN LIVING IN LARGE FAMILIES

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[2] *Corvinus University of Budapest, Budapest*

The important effect of family background and social support on well-being and other mental health outcomes has long been known. The majority of studies exploring the issue, assume the differences between each family, but ignore the pattern of well-being outcomes within families. Our research aims not only to reveal, how some characteristics of families effect the well-being of its members, but also the importance of roles fulfilled by the individual members of a family.
Data were collected from 600 randomly selected member families of the National Association of Large Families (NOE), in a manner that both parents and children at the age of 15 or above and still living in the household were asked. The total number of the respondents was 1717. We applied the five items of WHO well-being index (WBI-5), the self-assessment of happiness, satisfaction with life, and several explanatory variables like family size or birth order. To test the hypothesis that families are not homogeneous in the terms of the dependent variables studied, multilevel analysis was applied. Our results confirmed the presumption that significant differences can be detected among members of the family. These differences are largely explained by the role fulfilled by the individual in the family.

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E/I-2
CHILDREN OF THE 1989 TRANSITION: CHILDBEARING INTENTIONS

Veronika Bóné[1], Beáta Dávid[1,2]

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[2] *Hungarian Academy of Science, Budapest*

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 out the questionnaires plus 50 in-depth mother interviews were made. Since 2011 the Hungarian Scientific Research Fund has been funding a research to continue this special family panel data, to follow up the life history of the families taking part in the research 20 years before. 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, it seems particularly important to reveal those significant factors that might influence the childbearing intentions of the youth.
63% of the grown-up children (N=84) are planning to have a family with 2 children, 16% of them envisage 3 or more, 18% would be content with 1 child, and 3% would remain childless. The aim of our presentation is to explain the influencing factors behind their childbearing decisions by analysing their childhood data and using the scales of Parental Bonding Instrument, Purpose in Life Test, and Relationship Questionnaire.

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E/I-3
POSTTRAUMATIC STRESS DISORDER SYMPTOM STRUCTURE IN A SAMPLE OF RWANDANS WITH GENOCIDAL TRAUMA

Kinga E. Fodor[1], Richard Neugebauer[2,3]

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[2] *Department of Psychiatry, Columbia University Medical Center, New York, USA*
[3] *New York State Psychiatric Institute, New York, USA*

The latent structure of posttraumatic stress disorder has been predominantly studied in Euro-American populations. Only a few confirmatory factor analytic (CFA) studies investigated PTSD symptom structure in sub-Saharan Africa. We compared alternative models of DSM-IV PTSD factor structure with CFA in a sample of Rwandan adults. DSM-IV PTSD symptoms were assessed with the Posttraumatic Stress Disorder Checklist – Civilian version. A cluster random survey was conducted and interviews were held in Rwandan households. The sample comprised 465 Rwandan adults who experienced some sort of genocidal trauma during the 1994 genocide. The five competing models were the DSM-IV, the emotional numbing, the dysphoria, the aroused intrusion, and the dysphoric arousal models. Models were further tested for convergent validity and gender differences. The emotional numbing, dysphoria, and dysphoric arousal models all had good fit indices and fit the data significantly better than the DSM-IV and the aroused intrusion model. There were gender differences in PTSD factors. Results suggest that the latent structure of DSM-IV PTSD symptoms in Rwanda are comparable to that found in Euro-American samples.

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E/I-4
THE „COST OF CARING" FOR SERIOUSLY ILL PATIENTS – COMPASSION FATIGUE OR SATISFACTION

Adrienne Kegye[1], Edit Révay[2], Ágnes Zana[1], Katalin Hegedűs[1]

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[2] *Department of Sociology, Sapientia College of Theology, Budapest*

Background: The aim of the research launched in 2013 is to assess the mental and physical conditions of hospice workers, examine working factors, monitor burnout and coping mechanisms and develop the current educational and workplace supporting systems by using the relevant data. As the related literary sources show– according to research findings – it is a fairly new element to study the relation between burnout, compassion satisfaction and compassion fatigue originating from working with severely ill patients.
Methods: The base of the online questionnaire was the Hungarostudy 2013 Questionnaire (Kopp M, Székely A, Susánszky É), completed with particular questions about hospice care.
Results: The questionnaire was sent to 87 hospice services. Altogether 187 were completed and sent back. Respondents' ages varied between 23 and 76; 163 women and 24 men. 41.7 % work in home care and 55.1 % are nurses. 57.2 % work ten or more hours daily, 45.5 % work at more than one workplaces. Many are overweight, only 42.7 % do sports regularly. 75.1 % claimed that their work requires more and more efforts. They mainly reported fatigue and acute pain rather than chronic illnesses. Despite all that, most of them were satisfied with their hospice work (96%), their supervisory support (90.7%), and their personal relationships (93.8%), however, 40.2% were unsatisfied with their financial situation.
Summary: We met several personal and professional surviving strategies for compassion fatigue, which enable work not only to endanger, but also to strengthen job-satisfaction and the workers' well-being. However, our early research findings show that people working in Hungarian hospice services with professional calling, with increased mental and physical burden, and struggling with subsistence problems are in particular danger of burnout. At the same time, people caring for severely ill patients rarely apply or are unaware of methods to prevent burnout.

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E/I-5
ASSOCIATIONS BETWEEN PATTERNS OF ADULT ATTACHMENT, RELIGIOUSNESS AND RELATIONSHIP SATISFACTION

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Institute of Mental Health, Semmelweis University, Budapest

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 the past decades research evidence also showed that mother-and-child attachment experiences are connected to the personal relationship to God and thus it forms the basis ofreligious faith.
Finally, a series of studies evidenced connection between religiousness and the functioning of marriage relationship. Religious couples usually show higher stability and relationship satisfaction level, whereas lower occurrence of physical abuse and divorce.
***Aims*:** Classification of the relationship pattern types of couples from the sample group through cluster analysis. Presentation of the correlation between types of attachment displayed within the relationship, religious characteristics and the relationship satisfaction
Methods: In the study we implemented cross-sectional data assessment in 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-H (Martos et al, 2014) and Relationship Scales Questionnaire – RSQ (Bartholomew, Horowitz, 1991) Attachment to God Inventory – AGI (Beck&MacDonald, 2004) Satisfaction With Life Scale – SWLS-H (Martos et al, 2014).
Results: Using cluster analysis on attachment dimensions, five types of relationships could be identified in the couples: secure woman – secure man, anxious-avoidant woman – secure man, anxious woman – secure man, anxious woman – avoidant man, secure woman – anxious- avoidant man. Furthermore, couples with different types of relationships showed significant differences in relationship satisfaction, satisfaction with life and religious characteristics.
Conclusion: The presented evidence corroborates that the adult attachment framework possesses strong explanatory power for a better understanding of the functioning of romantic relationships.

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E/I-6
VITAL EXHAUSTION, COPING STRATEGIES AND THE QUALITY OF MARITAL RELATIONSHIP RELATED TO INFERTILITY STRESS

Enikő Lakatos[1,2], Réka Cserepes[3], Gábor Szabó[4], Piroska Balog[1]

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[2] *Mental Health Sciences Doctoral School, Semmelweis University, Budapest*
[3] *Institut für Medizinische Psychologie, Karls-Ruprecht Universität, Heidelberg, Germany*
[4] *Budapest College of Communication and Business, Budapest*

Introduction: Infertility is a life-changing experience that often carries unexpected stressors and potential stigmatization. Vital exhaustion has been defined as a clinical syndrome characterized by loss of energy, increased irritability and general demoralization and has been linked mainly with heart diseases. Even though infertility is a chronic stressor, based on our knowledge, vital exhaustion - as an indicator of chronic stress - has not been studied yet among infertile patients. The aim of this study was to analyze within the same regression model the independent effects of vital exhaustion, the quality of marital relationship and that of different coping strategies in predicting infertility stress.

Methods: A cross-sectional study was conducted involving 195 Hungarian infertile women, who were recruited both online and from clinical settings. Among socio-demographic and health characteristics, infertility related stress (Fertility Problem Inventory), vital exhaustion (shortened Maastricht Questionnaire), the quality of marital relationship (Shortened Marital Stress Scale), and coping strategies (Shortened Ways of Coping) have been measured. Pearson's correlation coefficients and standardized betas from stepwise linear regression model were added.

Results: Vital exhaustion ($r= 0{,}510$ $p<0{,}001$) has the strongest positive correlation with infertility-related stress. Marital stress ($r= 0{,}337$ $p<0{,}001$) and coping strategies were slightly related to the infertility stress (Cognitive reappraisal $r= -0{,}188$, $p=0{,}008$ Stress reduction $r= 0{,}361$, $p<0{,}001$ and Problem analysis r= ns., Passive avoidance $r= 0{,}145$ $p=0{,}042$). In the stepwise multiple regression analyses we found that vital exhaustion (ß= 0,381 $p<0{,}001$), marital stress (ß= 0,195 $p=0{,}002$) and stress reduction (ß= 0,186 $p=0{,}004$) had predictive effect for infertility stress.

Conclusion: Vital exhaustion, marital stress and coping strategies correlated with increased infertility stress should be identified and targeted in interventions designed for women undergoing infertility treatments.

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E/I-7
'BONDING' OR 'BRIDGING'? – SOCIAL CAPITAL OF ROMA UNIVERSITY STUDENTS

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Since 2011 the research-team of the Institute of Mental Health (Semmelweis University) is conducting a longitudinal research to follow up the students of Christian Roma Colleges. Besides the changes on Roma identity, norms and mental health status, the research focuses on the personal network composition and structure of these Roma university students.
The main purpose of the social network analysis is to measure how embedded Roma university students are in their social environment, which relations are related to mobility and integration.
To map the students' personal network composition we use contact diary, whereby we observe size, consistency and homogeneity of the networks, plus we measure tie strength. For the network structure analysis we use Egocentric Network Study Software (McCarty 2007).
Analyzing the results of the first two waves (76 egocentric networks) we see that students often find themselves in a social vacuum: struggling between being part of the minority or majority, in other words it is a struggle of the past and present. The socio-demographical background of Roma university students is a mostly low-educated and ethnically homogeneous environment; whereas the host (present) milieu is predominantly composed by non-Roma intelligentsia.
Roma university students have to reconsider their formal "binding" and "bonding" ties which provided them protection formerly, meanwhile they acquire several new "bridging" ties at the university.
For successful coping Roma College students possess and choose different supportive techniques and resources; they activate their personal network relying on "bonding" or "bridging" kind of relations. Our expectation is that the equilibrium between these different kind of ties and groups has an impact on coping strategies and identity-formation, too.

Keywords: *Roma integration, mobility, personal network, social capital*

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E/I-8
SOCRATES' DEMON 'IN THE MIRROR OF DEATH'

Ferenc Mújdricza

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My research is on the possible relationship between fear of death and social trust on social theory background. The first stage aims to trace the most important ideas of Western thanatology from the Ancient Greeks till present times. In this paper I present the results of my investigations concerning the Socratic-Platonic philosophy of death and its relationship with the concept of Socrates' irony elaborated by Hegel and Kierkegaard. The Platonic theory on death is based on the Orphism and the philosophies of Pythagoras and of Empedocles, however it is not only much more elaborated but it is in the axis of his entire philosophy not just a marginal topic. Socrates' irony is related to his divine 'daimonion' that gave him, according to Kierkegaard, only negative, destructive suggestions. Socrates became an 'incomplete oracle' lacking the positive intuition of the real oracles, but he became the first individual freed from the burden of the polis society by following this demon. By contrast, I found that Socrates' irony could be viewed as a strategy to veil his positive demon. I call it 'The Feint of Socrates' because if he really wanted to have the most freedom possible (as Hegel and Kierkegaard state it), he had to avoid to become an oracle. Oracles had the greatest internal subjective freedom but they had no external freedom because their society made a fortune-telling tool of them. If we look at his dialogues on death, we find that Socrates seems to have had the positive demon as well, but he never let it speak until he had to face death itself. We can watch the fusion of the ironic philosopher with the repressed intuitive oracle in the face of death through the collectivist law-worshipping sentences of the *Crito* and the vision-like passages on death of the *Phaedo.*

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E/I-9
INVESTIGATION OF THE PSYCHOLOGICAL ASPECTS OF DRY EYE DISEASE

Ildikó Szakáts[1], Margit Sebestyén[1], Emma Birkás[2], György Purebl[2]

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[2] *Institute of Behavioral Sciences Semmelweis University, Budapest*

Purpose: To investigate the psychological characteristics of patients with dry eye symptoms and/or dry eye disease and to analyse the correlations between these psychological aspects, the severity of ocular surface symptoms and the objective parameters of dry eye.
Methods: Participants completed the following questionnaires: Ocular Surface Disease Index (OSDI), Shortened Health Anxiety Inventory, Shortened Beck Depression Inventory, Beck Anxiety Inventory. Participants underwent ophthalmic examination and the following objective tests for dry eye disease were carried out: tear osmolarity, tear film break-up time (TBUT), ocular surface staining, Schirmer 1 test and meibomian gland dysfunction assessment.
Results: Of the 84 participants enrolled, 56 were symptomatic and 28 asymptomatic, based on the OSDI score. By the objective parameters, 48/56 (85.7%) in the symptomatic group and 23/28 (82.1%) in the asymptomatic group were diagnosed with dry eye disease. In terms of the objective parameters, except for TBUT, there were no statistically significant differences between the symptomatic and asymptomatic groups ($p>0.108$), or between the subgroups with objectively proven dry eye ($p>0.233$). The results of the psychological questionnaires were significantly worse in the symptomatic group ($p<0.01$) and the symptomatic subgroup with objective dry eye ($p<0.05$), than in the asymptomatic groups. In the overall study population the scores of the psychological questionnaires demonstrated significant positive correlations with the OSDI scores ($r>0.306$, $p<0.01$).
Conclusions: These results support the role of underlying psychological disturbances in dry eye disease, and may serve as an explanation for the lack of correlation between subjective symptoms and objective signs of the disease.

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E/I-10
THE ROLE OF INTERPARENTAL CONFLICTS IN CHILDREN'S ANXIETY AND DEPRESSIVE SYMPTOMS

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Background: It is well-known that interparental conflicts are related with children's anxiety and depressive symptoms but the mechanisms of these phenomena are less understood. Our aim was to assess the main aspects of these mechanisms.
Methods: 336 parent-child pairs participated in this cross-sectional questionnaire study. Children (ages 9-12 years) completed Children's Perception of Interparental Conflict Scale, anxiety (STAI-C) and depression (CDI) scales. Demographical data were elicited from parents. In logistic regression analysis, adjusted for demographic variables (age, gender, family income), the effects of interparental conflicts on prognosis of anxiety and depression were examined, odds ratios (OR) and 95% confidence intervals were added.
Findings: We found that independently of age, gender, family income and how frequently and intensely their parents dispute, those children have anxiety disorders whose parents solve their conflicts poorly (OR=1,27 (1,07-1,51)) and those children who feel threatened (OR=1,23 (1,10-1,38)) and blame themselves (OR=1,26 (1,01-1,57)) for their parents' conflicts. In regard to depression, independently of age, family income and the interparental conflict properties, boys are less prone to depression (OR=0,29 (0,11- 0,80)) and those children who are not able cope with their parents' conflicts (OR= 1,24 (1,04-1,48)) are more prone to depression.
Discussion: Our analysis shows that independently of demographic variables, those children are at higher risk of having anxiety symptoms who experience poor conflict solution, feel threatened, and have greater self-blame. In the case of depression the low coping efficacy means greater risk.

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E/I-11
READING DISABILITY SPECTRUM EARLY AND LATE RECOGNITION SUBTRESHOLD AND FULL COMORBIDITY

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Background/Aims: Several studies have reported high comorbidity for reading disability (RD) and psychiatric disorders. The aim of this study was to investigate the comorbidity of subthreshold and full psychiatric disorders with RD and comparing sub-groups based on age of recognition of RD (early RD; late RD).
Methods: We analyzed data from 130 children with RD and 82 typically developing children aged 7-18 years. RD was assessed with the Dyslexia Differential Diagnosis, Maastricht, Hungarian standard Test. Psychiatric diagnoses were based on the Mini International Neuropsychiatric Interview Kid. Chi-squared tests were used for group comparisons of the prevalence of sub-threshold and full disorders.
Results: A higher proportion of children in the RD group were assessed as having internalizing or externalizing disorders than in the control group ($\chi^2(2)=10.894$ $p=.004$ Cramer's $V=.227$). When subthreshold and full diagnoses were considered together the prevalence of internalizing but not externalizing pathology was higher in the RD group than the control group ($\chi^2(2)=25.053$ $p<.001$ Cramer's $V=.334$ and $\chi^2(2)=.247$ $p=.620$, respectively). The prevalence of internalizing pathology was similar in the early and late RD sub-groups ($\chi^2(2)=1.256$ $p=.262$), but externalizing pathology was more common in the late RD sub-group ($\chi^2(2)=11.007$ $p<.001$ Cramer's $V=.313$). When subthreshold and full diagnoses were considered together mood disorder and externalizing pathology were more prevalent in the late RD sub-group than the early RD sub-group ($\chi^2(2)=12.676$ $p<.001$ Cramer's $V=.336$ and $\chi^2(2)=18.788$ $p<.001$ Cramer's $V=.409$, respectively).
Conclusions: This study demonstrated that early recognition of RD may play a role in determining comorbid psychopathology and should therefore be an educational and clinical priority. Clinicians should routinely screen children with RD for comorbid disorders including subthreshold pathology.

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E/I-12
CHALLENGES FOR CARERS OF ELDERLY FAMILY MEMBERS

Anett Mária Tróbert

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Ageing raises many health and social challenges as the increase in the average life span is not bringing a comparable increase in healthy life expectancy. Due to financing difficulties, more and more informal carers are appearing in eldercare in a growing number of countries and the role of family members is also increasing. Family helpers bear a heavy burden that has a significant impact on all dimensions of their lives. The research aims on the one hand to investigate the life quality of these helpers and the burden they bear. The worldwide problem of ageing is one of the main driving forces behind current innovative solutions in social care. Analysis of the results of the research can also help to develop infocommunication tools for prevention. The paper will discuss the first phase of the research: the experience gained from depth interviews in preparation for the survey by questionnaire.

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E/I-13
INDIVIDUAL AND SOCIAL-LEVEL PSYCHOLOGICAL FACTORS IN THE BACKGROUND OF HUNGARIAN HIGH SCHOOL STUDENTS' HEALTH RISK BEHAVIORS

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[2] *Department of Behavioural Sciences, University of Szeged, Szeged*

Background: Health risk behaviors of adults usually originate in adolescence. Thus, it is highly important to study and understand these behaviors in this age group.
Aims: To examine the correlation between social- and individual-level psychological factors and health risk behaviors (cigarette and alcohol use) among Hungarian adolescents.
Methods: Our sample contains adolescents from 22 classes of three high schools, which were selected randomly. Altogether, 501 (33,9% boys, 65,9% girls; mean age = 16,37) high school students were surveyed. The participation was anonymous and voluntary. Among individual-level psychological variables, frequency of psychosomatic symptoms, shyness, loneliness, self-esteem, need to belong, and competitiveness were included. Individual, best friend's and peer group's smoking and alcohol use were also measured.
Results: According to our results, primary determinants of Hungarian students' risk behaviors are the social-level factors. Among individual-level variables, self-esteem, competitiveness and psychosomatic symptoms correlated with higher level of smoking and alcohol use. On the other hand, shyness and loneliness were inversely related to these risk behaviors.
Conclusions: In a peer group, which supports risk behaviors, several dimensions of psychological well-being can correlate with higher level of alcohol use and smoking. Therefore, it is important that prevention should focus on the norms of the high school class as well. We think that health promotion cannot work effectively without the involvement of the whole high school class and society.

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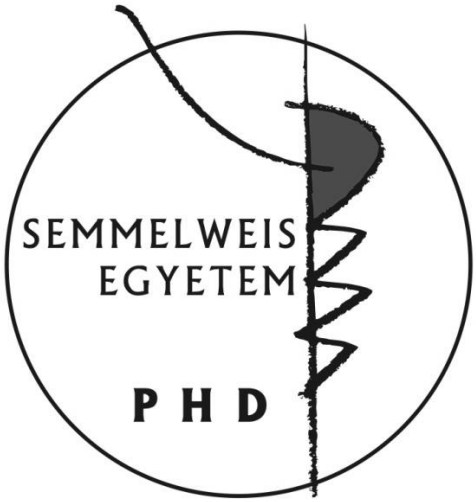

E/II
MOLECULAR MEDICINE
ORAL PRESENTATIONS

Chairpersons:

Dr. László Tretter

Dr. Barna Vásárhelyi

E/II-1
SYNDECAN-1 IN LIVER FIBROSIS AND REGENERATION

Eszter Regős

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Aims: Syndecan-1 is a transmembrane proteoglycan, participating in various pathological conditions including inflammation, carcinogenesis and regeneration. Physiologically syndecan-1 appears on the basolateral surface of hepatocytes. As syndecan-1 expression increases during fibrosis, we aimed to understand its role by inducing liver fibrosis and regeneration in wild type (WT) and trangenic mice, overexpressing human syndecan-1 (SynTG) in their liver.

Materials and Methods: We examined the overexpression and localization of human syndecan-1 by immunohistochemistry. Plasma level of shedded syndecan-1 was measured by ELISA. Liver fibrosis was induced by thioacetamid (TA). The percentage of accumulated connective tissue was determined by morphometrical analysis. Activated myofibroblasts were detected using αSMA immunostaining. Connective tissue degradation was measured by gelatinase and caseinase assays. We detected TIMP-1 gene expression using qRT-PCR. Signaling pathways were examined by Western-blot. Binding of syndecan-1 to TGFβ, the main mediator of fibrosis was tested by dot-blot. Expression of TIEG, the early response gene of TGFβ, was analyzed by qRT-PCR.

Results: Production of the recombinant protein was stable in SynTG animals. Without experimental challenge, overexpression of syndecan-1 did not cause any pathological condition. When exposed to TA, development of liver fibrosis was slower in SynTG mice compared to WT. However, after TA withdrawal, transgenic animals exhibited slower regeneration than that of wild type. Gelatinase assay proved attenuated activation of MMP-2 and 9 in SynTG animals interfering with connective tissue degradation. Various signaling pathways were found activated in fibrosis, most of them with lower activity in transgenic animals. By dot-blot analysis we proved that the shedded syndecan-1 directly binds TGFβ1.

Conclusion: Syndecan-1 overexpression modifies the accumulation and degradation of connective tissue in liver fibrosis and regeneration in part by binding and inactivating TGFβ and downstream signaling pathways.

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E/II-2
THE EFFECT OF GENETICALLY ABLATING THE ATP-FORMING SUBUNIT OF SUCCINYL-COA LIGASE ON MITOCHONDRIAL BIOENGERETIC PARAMETERS

Dóra Ravasz, Gergely Kacsó

Department of Medical Biochemistry, Semmelweis University, Budapest

The citric acid cycle enzyme succinyl-CoA ligase catalyzes the reversible conversion of succinyl-CoA, phosphate and ADP or GDP to succinate, CoASH, and ATP or GTP in the mitochondrial matrix. This reaction - termed mitochondrial substrate-level phosphorylation - can produce high-energy phosphate intermediates in the absence of oxygen. Succinyl-CoA ligase is a heterodimeric enzyme, composed of an invariant alpha-subunit and a substrate-specific beta-subunit. The alpha-subunit is encoded by SUCLG1, the beta-subunit is encoded by either SUCLA2 or SUCLG2, resulting in either an ATP- or a GTP-forming enzyme.
As shown by our previous work, substrate-level phosphorylation plays an important role in preventing extramitochondrial ATP consumption of mitochondria during respiratory inhibition.
Here we investigated whether a reduction in succinyl-CoA ligase activity affects mitochondrial substrate-level phosphorylation. SUCLA2 +/- herterozygote mice were generated; liver, heart and brain mitochondria were isolated from wild type and SUCLA2 +/- heterozygote littermates of 3, 6 and 12 month- old mice. Western blot analysis showed an approximately 50% decrease in the ATP-forming beta-subunit expression in the mitochondria of SUCLA2 +/- heterozygote mice. Oxygen consumption and mitochondrial membrane potential were measured, in an experimental protocol that is suitable for identifying mitochondria as extramitochondrial ATP consumers during respiratory inhibition.
Our results show that genetic ablation of the ATP-forming subunit of succinyl-CoA ligase does not turn mitochondria into extramitochondrial ATP consumers during impaired respiration. This was likely due to a compensatory upregulation of the genetically unmodified GTP-forming subunit in the examined tissues, as it was revealed by western blot analysis. Furrhermore, the rate limiting factor of substrate-level phosphorylation is succinyl-CoA provision by the alpha-ketoglutarate dehydrogenase complex. Thus it could be possible that a decrease in the expression of succinyl-CoA ligase ATP-forming subunit may not lead to significant changes in the ATP-producing capacity of substrate-level phosphorylation, if sufficient succinyl-CoA is available.

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E/II-3
YAP1 IN THE HIPPO PATHWAY INFLUENCES THE RISK OF ASTHMA

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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, fourteen, 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=0.033), 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 bronchial epithelial cell percentages (r=-0,515, P=0,012), which confirms the role of *YAP1* gene in asthmatic progress. Additionally, other studied genes have shown significant result with sputum eosinophils, or neutrophils. During the genotyping studies of asthma susceptibility and several asthma endophenotypes SNP rs2846836 showed a significant association with exercise-induced asthma (OR=2,076 [1,256-3,431], P=0,004, power=0,83). Furthermore, SNP rs11225138 showed a significant difference between GINA 1-2 and GINA 3 statuses in a dominant model (OR=2,8 [1,40-5,57], P=0,003, power=0,827).
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.

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E/II-4
ACTIVATION OF ATMPK9 THROUGH AUTOPHOSPHORYLATION INDEPENDENTLY OF THE CANONICAL MAPK CASCADES

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Mitogen activated protein kinases (MAPKs) are part of a three-tiered signal transduction modules in eukaryotes, wherein MAPKs are activated by bisphosphorylation in their TXY motif of the T loop by the pertinent dual-specificity MAPK kinases (MAPKKs). In contrast to this canonical activation mechanism, atypical MAPKs are elicited in a MAPKK independent manner. AtMPK9, a representative of unique, plant MAPK family, possesses a TDY phosphoacceptor site, a long C-terminal extension, lack the common MAPKK binding docking motif, and its activation mechanism awaits for depiction.

Aim: Our aim was to characterize the regulation of AtMPK9 activity by using *in vitro* translation and protoplast protein overexpressing systems.

Result: We present *in vitro* and *in vivo* data that AtMPK9 is activated independently of any upstream MAPKKs, but it is activated through autophosphorylation. We mapped the autophosphorylation sites by mass spectrometry to the TDY motif and to the C-terminal regulatory extension. We mutated the phosphoacceptor sites on the TDY, which confirmed the requirement for bisphorylation at this site for full kinase activity. Next, we demonstrated that the kinase inactive mutant form of AtMPK9 is not transphosphorylated on the TDY site when mixed with an active AtMPK9 implying intramolecular autocatalytic phosphorylation. Furthermore, we show that *in vivo* AtMPK9 is activated by salt and is regulated by okadaic acid-sensitive phosphatases. We conclude that the plant AtMPK9 shows similarities in terms of activation mechanism to mammalian atypical MAPKs, ERK7/8.

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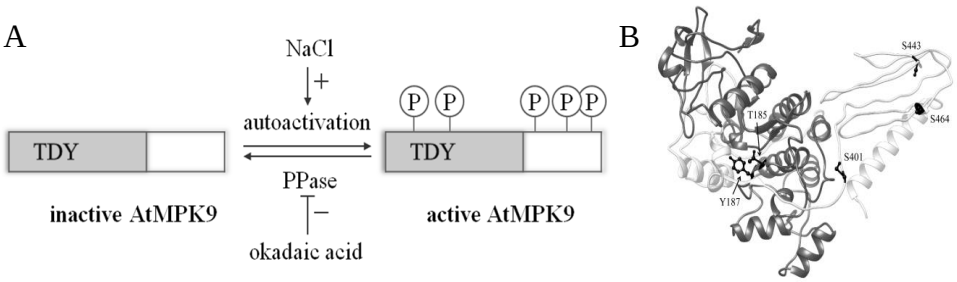

Figure 1. *– Regulation mechanism of AtMPK9 (A) and identified phospohorylation sites (B)*

E/II-5
NUCLEASE RESISTANT OLIGONUCLEOTIDE RECEPTOR FOR TROPONIN DIAGNOSTICS

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Cardiac specific troponins are standard markers of myocardial infarction; thus, various systems have been developed for their fast and sensitive detection. In the recent years, antibodies, the most generally applied receptor molecules in protein detecting devices, have been rivalled by appearance of short single stranded oligonucleotides with highly discriminative molecular recognition and binding capacity. These molecules are superior to antibodies in many ways; they are in vitro selected, chemically synthesized, possesses a relatively small size and insensitive to chemical and physical conditions, however their application is hampered due to their susceptibility to enzymatic degradations. Spiegelmers can be seen as biostable version of oligomers because they consist of L-sugar instead of naturally occurring D enantiomer. Considering their advantages, we aimed at producing cardiac troponin I (cTnI) specific Spiegelmers to provide alternative receptors for biosensor development. Our results suggest that protein selective Spiegelmers can be effectively selected by rational identification of protein epitopes and high-throughput screening of isolated candidates. Furthermore, the results of surface plasmon resonance measurements demonstrated that the characterized oligonucleotide bind to cTnI with low nanomolar affinity and discriminate their target even in a complex protein matrix such as blood serum. In order to test applicability of the selected Spiegelmer in sandwich ELISA based assays, we developed an Amplified Luminescent Proximity Homogenous Assay (ALPHA) using our receptor and a commercial cTnI selective antibody. The obtained data corroborated our assumption; the developed assay could differentiate the cTnI positive and negative clinical samples. These results indicate that Spiegelmers could be reasonable alternatives of antibodies in diagnostics.

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E/II-6
LIVER METABOLIC ALTERATIONS INFLUENCE PXE-LIKE PHENOTYPE

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ABCC6-related diseases, such as *Pseudoxanthoma elasticum* (PXE) and *Generalized Arterial Calcification in Infancy* (GACI) can be attributed to the loss-of-function of the *ABCC6* gene. Although *ABCC6* is mainly expressed in the liver the disease has dermatologic, ocular and cardiovascular symptoms. The severity of the symptoms is highly variable between patients. We have investigated the transcriptional regulation of the gene. We have mapped the binding of CCAAT/Enhancer binding protein ß (C/EBPß) and the conserved hepatocyte nuclear factor 4α (HNF4α). Short-term activation of the ERK1/2 cascade leads to decreased HNF4α binding on *ABCC6*. We also observed similar decrease of HNF4α binding genome-wide in ChIP-Seq experiments. Furthermore, in accordance with transcription factor binding alterations, we have observed changes in the pattern of histone modifications. We have proved that HNF4α is directly phosphorylated by ERK1/2 *in vitro* at several sites. The effect of phosphomimetic HNF4α mutants was also investigated by luciferase reporter gene assays. Our results suggest that ERK1/2 activity contributes to HNF4α metabolic balance in hepatocytes. We consider that metabolic status of the patients contributes to the PXE-associated phenotypes.

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E/II-7
EVIDENCE FOR THE CYTOSOLIC LOCATION OF NAD(P)H CYTOCHROME B5 OXIDOREDUCTASE

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The recently discovered NADH cytochrome b_5 oxidoreductase (Ncb5or) is a soluble natural fusion protein of unrevealed function. The two redox domains of this soluble enzyme are homologous to Cytochrome b5 (Cyb5) and Cyb5 reductase (Cyb5R) integral membrane proteins of the endoplasmic reticulum (ER). Their concerted action in fatty acid desaturation is well characterized. This structural homology along with the marked alterations in lipid metabolism observed in Ncb5or (-/-) mice strongly suggest the involvement of Ncb5or in fatty acid desaturation. The enzyme likely transfers electrons from NADPH to the desaturase enzyme in the ER membrane. However, controversial data have been published regarding the cytosolic or ER localization of the protein.
In order to clarify whether Ncb5or uses the common cytosolic NADPH or utilizes the separate pyridine nucleotide pool of the ER lumen, we aimed to elucidate the intracellular location of this soluble protein.
Green fluorescent EGFP-Ncb5or fusion protein was expressed in transiently transfected human HEK293T cells and detected by fluorescent microscopy. The location of endogenously expressed Ncb5or was assessed in HEK293T cells by two methods. Cells were harvested and homogenized to separate the subcellular fractions by differential centrifugation. Ncb5or and specific marker proteins of various cellular organelles were detected by Western blot. In addition, the endogenous protein was also visualized by using in vitro immunocytochemistry. Subcellular fractions of rat livers were also isolated and analyzed for the presence of Ncb5or protein.
Purity of the generated nuclear, microsomal, mitochondrial and cytosolic cell fractions were confirmed by immunoblot with characteristic marker proteins of the organelles. Ncb5or could only be detected in the cytosolic fractions of HEK293T cells and rat livers by using Westren blot. EGFP-Ncb5or fusion protein was detected in the cytoplasm of the cells, and it was not co-localized with fluorescent markers labeling either the nucleus or the ER. Similar location of endogenous Ncb5or protein was observed by immunocytochemistry.
Our results clearly prove that Ncb5or is located in the cytoplasm in cultured cells and in liver *in vivo*. Therefore, the utilization of ER luminal reducing equivalents by this enzyme can be ruled out. Further research is needed to confirm the putative role of Ncb5or in the fatty acid desaturation, which in turn will help to understand the contribution of this novel protein to the protection of pancreatic β-cells against lipotoxicity.

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E/II-8
THE ROLE OF B-ARRESTINS IN THE HETEROLOG REGULATION OF TYPE 1 ANGIOTENSIN RECEPTOR

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β-arrestins regulate AT1 angiotensin receptor's function through a number of mechanisms. They uncouple receptors from G proteins, initiate their internalization and initialize new signaling events. It has been accepted that β-arrestin binding is dependent on receptor's activation and its phosphorylation by G protein-coupled receptor kinases. In our experiments, we checked if phosphorylation by other kinases, like protein kinase C, could lead to regulation of receptor's sensitivity by initiating its β-arrestin binding and internalization in the absence of agonist.
β-arrestin binding and internalization of AT_1R were followed by a bioluminescence resonance energy transfer (BRET)-based approach in HEK293T cells. After transient transfection, the BRET signal was measured between luciferase-tagged AT_1R and yellow fluorescent protein tagged β-arrestin2 or the early endosome marker Rab5. To examine the heterologous regulation of AT_1R, we coexpressed and stimulated the G_q protein coupled α_{1A}-adrenergic receptor ($\alpha_{1A}R$). The $\alpha_{1A}R$ agonist A61603 induced a BRET signal elevation with both β-arrestin2 and Rab5, reflecting the β-arrestin binding and internalization of the AT_1R. These results were confirmed by confocal microscopy. The increase of the BRET signal after A61603 treatment was hindered by specific PKC inhibitor (bisindolylmaleimide I) in both assays. Additionally, substituting the known PKC phosphorylation sites of AT_1R (S331, S338, S348) to alanins diminished the effects of the $\alpha_{1A}R$ agonist, demonstrating the crucial role of PKC in this mechanism. On the other hand, the AT_1R antagonist candesartan did not alter the effects of the $\alpha_{1A}R$ agonist, showing that the active conformation of AT_1R is not necessary for its β-arrestin binding and internalization.
Our results represent a new regulatory mechanism of AT_1R, which may have significant physiological and pharmacological consequences.

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E/II-9
INCREASED ACTIVATION OF POLY(ADP-RIBOSE)POLYMERASE IN PAEDIATRIC PATIENTS WITH CROHN'S DISEASE

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Objectives and Aims: The pathomechanism of Crohn's disease (CD) is not fully understood, however several data suggest that inflammation, oxidative-nitrative stress and consequential poly(ADP-ribose)polymerase (PARP) activation are involved. As PARP activation in CD has not been examined in a human setting yet, therefore our aim was to examine the colonic PARP activation in paediatric patients suffering from CD. Previously, it has been suggested that TNF-α, which is a key molecule of CD, can influence the expression of PARP in other inflammatory disorders. However, the connection of TNF-α and PARP activation is not examined in CD. Therefore, we investigated the connection between TNF-α and PARP activation in HT-29 colon epithelial cell line.
Methods: Colonic biopsies of CD patients with macroscopically intact (CDintact) and inflamed (CDinflamed) mucosa, and control biopsies (C) were analyzed. PARP-1 mRNA expression was measured by real-time PCR from fresh-frozen biopsy samples (CDintact: n=10, CDinflamed: n=10, Control: n=10). Paraffin embedded sections of biopsies were immunostained with anti-PAR (end product of PARP) antibody to estimate the localization of active PARP (CDintact: n=7, CDinflamed: n=10, Control: n=12). The degree of PAR positivity was determined by a blinded experimenter (scoring: 1-10).
Results: PARP-1 expression was significantly elevated in the inflamed mucosa of CD compared to the control and CDintact biopsies (CDinflamed vs. C or CDintact, $p \leq 0.05$). The amount of PAR was significantly higher in the colon mucosa of CD patients compared to the controls (CDintact vs. C, $p \leq 0.01$; CDinflamed vs. C, $p \leq 0.001$). The observed increment correlated with the elevated Paediatric Crohn's Disease Activity Index, the neutrophil, lymphocyte counts and serum C-reactive protein levels.
Conclusion: Activation of PARP can be observed in the colon mucosa of children with CD. PARP activity associated with the intestinal inflammation and clinical activity of the disease. These data suggest that PARP plays an important role in the pathomechanism of CD. Further studies are required to explore the exact regulatory pathways of the PARP activation and its consequences.
Acknowledgment: This work was supported by grants OTKA-PD113022,-K105530, -PD83431, -PD105361, "Lendület" Research Grant LP008/2014 and KMR_12-1-2012-0074. Horváth E. M. is holder of the János Bolyai Research Scholarship.

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E/II-10
LOCAL MUCOSA INSTRUCTS MURINE CD8+ RESIDENT MEMORY T CELLS TO DEVELOPUNIQUE PHENOTYPES MEETING LOCAL NEEDS

Nikolett Lupsa[1,2], Barbara Érsek[1,2], Péter Pócza[3], Eszter Sarzsinszky[1,2], Anett Tóth[1,2], Bence Bagita[1,2], András Bencsik[1,2], Hargita Hegyesi[4], András Matolcsy[3], Edit Buzás[2], Zoltán Pós[1,2]

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Here we sought a better understanding of environmental adaptation procedures implemented by murine CD8+ CD103+ resident memory T (Trm) cells establishing residence in various mucosal tissues. We combined transcriptome and proteome profiling to compare different mucosal CD8+ Trm subsets with each other, and circulating nonresident CD8+ T effector memory (Tem) or CD8+ T effector (Teff) cells infiltrating the same tissues, serving as reference.

We found that Trmsof the small intestinal lamina propriaare frequently re-activated, have a stable subset expressing granzymes A and B, various CTL chemokines, and are enriched ribosomal proteins and histones typical for re-activated, rapidly expanding memory T cell clones performing intense protein synthesis and DNA replication. On the other hand, these cells characteristically down-regulate expression of lymphotoxinsalpha and beta (LTA, LTB).

In contrast, lung Trms, are enriched in several cyclins and cyclin-dependent kinases selectively supporting G1/S phase transition (CCND3, CCND2, CCNE, CDK4), and thus seem to be prone to rapid clonal expansion. Also, they show preferential transcription of LTA, LTB, and, like human lung Trms, over-express CD94/KLRD1, but not granzymes. Finally, Trm cells identified in the liver, a rather tolerogenic environment, are largely dormant, but frequently display CXCR4, the ligand of which, SDF-1, is released by liver umbilical epithelial cells capable of docking Trms via E-cadherin-CD103.

Next we sought to clarify whether these differences were exclusive to CD8+ Trm cells, or could bealso evoked in other, nonresident CD8+ T cells homing to the same organs. Indeed, in experimental acute GVHD, some CD8+ Trm features could be evoked from OT-I CD8+ Teff cells infiltrating the same mucosal tissues and engaging act-mOVA targets.

These data suggest that the Trm phenotype is actively shaped by the local microenvironment of mucosal tissues, and is affected by both unique, Trm-specific, and non-Trm-restricted mechanisms of environmental adaptation.

Doctoral School: *Molecular Medicine*
Program: *Basis of Human Molecular Genetics and Gene Diagnostics*
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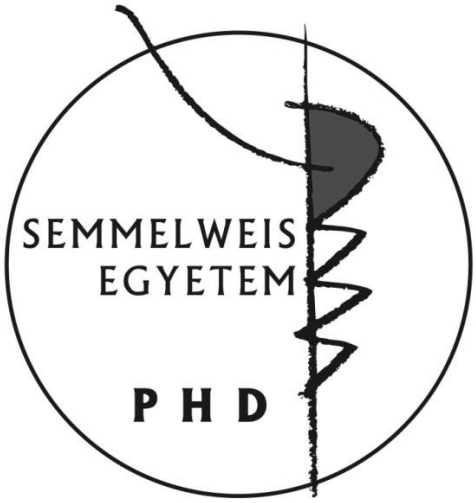

E/III
DENTISTRY
ORAL PRESENTATIONS

Chairpersons:

Dr. Péter Hermann

Dr. Gábor Varga

E/III-1
EFFECTS OF (-)-DEPRENYL ON HUMAN DENTAL PULP STEM CELLS

Krisztián Benedek Csomó

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(-)-Deprenyl is a widely used drug to treat neurodegenerative diseases. It has also been shown that the drug has antidepressant and neuroprotective properties. (-)-Deprenyl has a psychostimulant effect, which is separate from the catecholamine release caused by amphetamine and methamphetamine, and at the same time it is a strong MAO inhibitor.

Main objective: The aim of our study is to analyze the dose-dependent effect of the compound (-)-deprenyl on the viability of stem cell cultures derived from dental pulp (DPSC), and the effect on the neuronal differentiation potential of the cultures, which is shown by the expression of neurotrophins.

***Materials and methods*:** Following the isolation and culture of human dental pulp stem cells (DPSCs) (originating from impacted wisdom teeth using our previously published protocols), we examined the dose-dependent effect of (-)-deprenyl on the DPSC cultures, specifically the effect on cell proliferation and neuronal differentiation. WST-1 reagent was used to examine cell proliferation in spectrophotometric measurements, while quantitative real-time PCR (qPCR) was used to detect the neuronal differentiation markers.

Results: Application of (-)-deprenyl on the stem cell cultures increased cell proliferation of the dental pulp stem cells (DPSC) in a dose-dependent manner. The presence of neuronal markers was shown as well with the qPCR examination in controls and also their differential expressional changes following (-)-deprenyl treatment.

Conclusions: These results are important in respect of the therapeutic potential of DPSCs, specifically considering a possible positive effect of the compound on neuronal differentiation of dental pulp derived mesenchymal stem cells.

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E/III-2
A NEW PRECLINICAL MODEL OF BONE REMODELING AROUND TITANIUM IMPLANTS

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Introduction and aim: Functional tooth replacement and bone regeneration are in the daily practice of modern dentistry. The constant flow of innovations in bone grafting biomaterials, titanium surface functionalization justified numerous animal studies. We aim to develop a new animal model to evaluate bone regeneration and osseointegration of titanium implants.

Materials and methods: Female Wistar rats (Crl(Wi)Br, Charles River; 250–370 g) were used for our experiments (ethical permission No: 1799/003/2004). Customized implants were used. For implant placement we used a special guided approach at the level of the C4-C5 vertebrae. Validation of the bone remodeling around the titanium implants was performed at 4, 8 and 16 weeks after surgery. Implant stability was measured using a non-invasive system utilising RFA. Stability was displayed in Implant Stability Quotient (ISQ). This test was followed by micro-CT evaluation. Biomechanical properties were further characterized by histomorphometric analyses and with measuring the maximum extraction force.

Results: A positive correlation was found in our in vivo measurements (r=0.8498) applying various techniques. We observed statistically significant differences between different (4, 8, 12, 16 weeks) evaluation periods, due to the gradually increasing strength of osseointegration. Histomorphometry and micro-CT results showed the new bone formation on implant surfaces suggesting the development of direct connection between bone and titanium.

Conclusion: Our results provide evidence that the caudal vertebrae implant is a useful standard model for preclinical evaluation of osseointegration of titanium implants. Based on the outstanding similarities in bone architecture and embryological development of rat caudal vertebrae and mandibular bone, this model may serve for preclinical modelling of surgical validations steps in medical and dental implantology.

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E/III-3
TOOTH-DERIVED STEM CELL CULTURING ON AMINO-ACID BASED HYDROGELS

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Introduction: In the past few years stem cells were successfully isolated from tooth-associated tissues, which have multi-differention potential and immunomodulatory effects. Conditions supporting the in vitro 3D proliferation and differentiation of these cells may increase their applicability in clinical processes. Amino acid-based hydrogels could mimic the properties of the native ECM and provide optimal conditions for the cells.
Objective: Our aim is to analyse dental pulp (DPSC), and periodontal ligament (PDLSC) derived stem cell culture viability, morphology and differentiation potential on various poly(amino acid) based hydrogels which have different physico-chemical properties. Our long-term goal is to tailor these properties to find the exquisite composition, which may subsequently be used in regenerative therapy.
Materials and methods: Cells originated from impacted human wisdom teeth according to our previously published protocols. The cells were seeded on the PASP (polyaspartic acid) -based hydrogels having different mechanical properties and containing thiol groups. The morphology of the cells was examined by phase-contrast microscope. To visualize the cells growing into the gels, they were labeled with the fluorescent vital dye Vybrant DiD. The examination was carried out with two-photon microscopy. For analyzing cell viability, we use WST-1 reagent.
Results: Our cells are able to attach and grow on PASP-based hydrogels. The highest population of viable cells can be observed when cultivating PASP gels containing thiol groups. We found that the increase of the hardness of the gel increases the adhesion and the proliferation of the cells. Phase-contrast and two-photon microscopic analysis also confirmed this result and showed that these cells can grow inside the gel matrix.
Conclusions: The thiol-containing PASP gels proved to be suitable for culturing PDL and DP stem cells, since they ensure the conditions for adhering, reproduction and migration. These gels would be a good candidate as a scaffold in stem cell-based tissue engineering.

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E/III-4
EFFECTS OF CHLORHEXIDINE CONTAINING VARNISH ON ORAL AND DENTAL HEALTH IN HIGH RISK PATIENTS

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The purpose of this study was to determine the effects of chlorhexidine containing varnish on level of oral acidic bacteria [Streptococcus mutans (SM)] and Lactobacilli (LB)] and on development of White Spot Lesions (WSL) in patients with fixed orthodontic appliances. Altogether 29 patients were examined (mean age 16.5±2.75 ys). At baseline levels of acidic bacteria were determined in saliva and plaque using chairside tests (CRT Bacteria, Ivoclar-Vivadent, Schaan, Liechtenstein) and number of WSL was registered. After placing the fixed orthodontic appliance Cervitec Plus and Placebo varnishes (Ivoclar-Vivadent, Schaan, Liechtenstein) were applied around brackets and tubes randomly in the right and the left quadrants of the same dental arch (*Test* and *Control* sides). Varnishes were used according to the instructions of manufacturer's guide, applied monthly during a six months period. Every occasion before application of varnishes the level of SM and LB were determined in saliva and level of SM in plaque on 1st, 3rd, 5th, 6th teeth in the same way. At the sixth month the number of new WSL was determined. Wilcoxon test, descriptive statistics were used. The ratio of saliva samples belonging to low-risk category was significantly more frequent ($p \leq 0.05$) compared to baseline both in SM (76 vs. 52%) and LB (69 vs. 52%) groups from 2nd month. During the six month period level of SM in plaque decreased continuously in both sides. By the end of the period reduction was significantly greater in *Test*, than in *Control* sides (6.69±1.71, 4.45±1.60, respectively) ($p \leq 0.05$). Mean number of new WSL was significantly lower in *Test* (0.06±1.60), than in *Control* quadrants (1.13±1.50) ($p \leq 0.05$). Conclusion: chlorhexidine varnish can reduce level of acidic bacteria in saliva and plaque, and development of caries lesions.

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E/III-5
INVESTIGATION OF RELATIONSHIPS BETWEEN ORAL MICROBIAL AND DENTAL CONDITIONS AND ORAL CANCER

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***Introduction*:** Hungary is the leader both of incidence and mortality of oral cancer in Europe. The etiology of oral cancer is multicausal, smoking, alcohol abuse, mechanical irritation, HPV virus are well-known risk factors. The poor oral hygiene is commonly described as a risk factor, in spite of different oral bacterial flore of caries and periodontal diseases. These two groups of patients are not distingushed in the literature. Only a few trials investigated the role of bacteria in oral carcinogenesis. Bacteria isolated from patients with oral sqamous cell carcinoma were mainly periodontopathogenic. Candida has been described as a risk factor of oral cancer also, but the exact pathogenesis is unclear, further exploration is needed.
Aims: The aim of our study is to identify relationships between bacterial and fungal strains and oral cancer. The virulence factors of Candida isolates will be further analyzed to explore their role in carcinogenesis.
Patients and Method: 50 patients having oral malignant/premalignant lesion compared with 50 tumor-free patiens with serious periodontitis (CPI 3-4) and 50 healthy person without periodontitis (CPI 0-2). The clinicaly examination includes the registration of patients' complete general and dental health history, the registration of the periodontal and cariology status, the conventional oral mucosal examination, the autofluorescence oral screening, and collecting non-stimulated saliva sample using Eswab kit. The microbiological examination includes quantitative aerob and anaerob bacterial and fungal culturing, furthermore the analysis of virulence factors of isolated candida specimens.
Prospective results: Isolating an indicator bacterial and candida species from oral tumor affected patients would be a first step to develop an unexpensive, quick, point of care diagnostic method in the future. Detecting of importance of some candidal virulence factors in carcinogenesis could help us to further explore its uncleare pathomechanism as well.

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E/III-6
VASCULAR TOPOGRAPHIC AND DEPTH OF FIELD INVESTIGATIONS BY TRANSPARENT, TRUE 3D MICROSCOPY OF GINGIVA AND SUBMANDIBULAR SALIVARY GLAND

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Objective: Our methodical innovation, the stereomedical system consists of 1.) The development of triethanolamine based optical clearing solutions to increase tissue transparency, 2.) The microscopic true three-dimensional investigating system, and 3.) The development of a 3D measuring and modeling computer software based on stereophotogrammetric methods for the analysis of spatial structures and functions.
Aims: To examine the normal and inflamed vascular morphology of gingiva and submandibular salivary gland and to determine the depth of field (DOF) that can be examined.
Methods: In anesthetized rats we perfused the vessels of oral structures with black ink through both carotid arteries or stained them with hemalaun *in vivo*. After excision we cleared and examined them with our system. In another group of animals periodontal inflammation was induced by 2-0 silk ligature tied around the mandibular left first molar and gingival tissues from both lower sides were processed as above. To measure the DOF we applied tilted Rochi plate which creates known reference lines located in space.
Results: With the aid of our clearing materials we were able to make the structures of deeper tissue layers examinable. Due to the increase of magnification and the relative enlargement of DOF, quite thick tissue blocks were imaged. We found that in case of the currently used infinity-corrected lenses, the DOF measured by our tilted Ronchi plate method was lower than the values calculated by the Berek's formula based on the data of the microscope. By the application of our true 3D measuring and modeling computer system, the microscopic structures were covered by a spatial point cloud and spline surfaces, furthermore, their spatial description was performed. In angiography of healthy and inflamed tissues a lot of fine topographical characteristics (widenings, "Knopfloch") were observed. In case of gingival inflammation the architecture of the vascular network has completely changed (tortuosity).

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E/III-7
FUNCTIONAL MEASUREMENTS OF ION-TRANSPORTERS INVOLVED IN PH REGULATION OF AMELOBLAST CELLS

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Although, ameloblasts are known to express a number of transporters and channels involved in pH-regulation and bicarbonate transport, there is no functional evidence for their activity in these cells. Therefore, we developed a novel cellular ameloblast model to investigate these mechanisms, using the HAT-7 rat ameloblast cell line. Earlier we reported the expression of sodium/proton exchangers (NHE1), anion exchangers (AE2) and the sodium/potassium/chloride cotransporter (NKCC1, previously not investigated in ameloblasts) in these cells.
Our aim was to provide functional evidence for the role of these transporters in this model. We planned to testify the localized activity of these transporters.
Methods: To obtain monolayers, HAT-7 cells were seeded on Transwell membranes and cultured in differentiation medium for 4 days. We monitored transepithelial resistance as an indicator of tight junction formation and polarization. We evaluated intracellular pH changes by microfluorometry using BCECF fluorochrome. The activity of anion exchangers were tested by withdrawal of chloride-ions, and using anion exchange inhibitor H_2DIDS. With ammonium-pulse technique, we inspected the compensation after a rapid intracellular alkalization/acidification by withdrawal and subsequent restoration of sodium ions. The activity of NHE was investigated by its inhibitor amiloride in a bicarbonate/CO_2-free solution. NKCC activity was also tested in this setting by its inhibitor bumetanide.
Results: We detected NHE activity, a sodium-dependent amiloride-sensitive compensation after acidosis, exclusively at the basolateral side of HAT-7 cells. We found basolateral, DIDS-sensitive anion exchanger activity, most probably AE2, and basolateral NKCC activity, very likely due to NKCC1.
Conclusions: Our HAT-7 model can be useful to conduct functional studies on the molecular mechanisms of amelogenesis. We could verify the activity of several transporters affecting the pH regulation of ameloblast originated cells. NKCC should have a role in the intracellular chloride accumulation mechanism in the cells.

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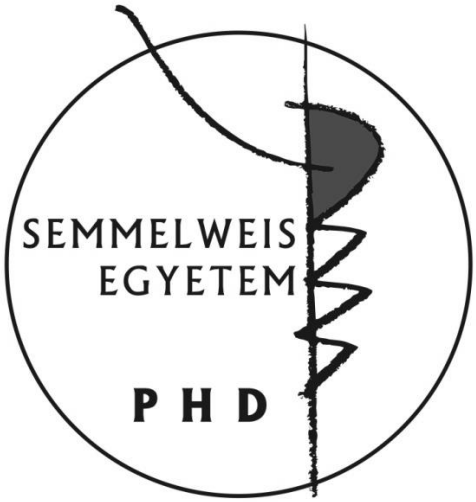

E/IV
CLINICAL MEDICINE I.
ORAL PRESENTATIONS

Chairpersons:

Dr. Anikó Somogyi

Dr. Kopper László

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E/IV-1
EVALUATION OF THICKNESS AND OPTICAL PROPERTY CHANGES OF THE MACULA LUTEA IN PATIENTS WITH MULTIPLE SCLEROSIS

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***Aims*:** To assess the changes in the structure and optical properties of the macula lutea in patients with multiple sclerosis (MS) and to evaluate their utility in the detection of neurodegenerative processes using optical coherence tomography (OCT) image segmentation.
***Methods*:** Thirty-nine patients with MS were examined using Stratus OCT. The raw macular OCT data were exported and processed by a custom-built software. Seven intraretinal layers were labeled and thickness, contrast, fractal dimension, layer index and total reflectance parameters were measured. The enrolled eyes were divided into two groups, based on MS associated optical neuritis (ON) in the history (MSON+ group, n=39 and MSON-group, n=34). Data of 32 eyes of healthy subjects were used as controls (H). Mixed-model analysis was used for the comparisons. The level of significance was set at $p<0.001$.
***Results*:** Significant thinning of the retinal nerve fiber layer (RNFL), ganglion cell/inner plexiform layer complex (GCL+IPL) and outer plexifom layer (OPL) was observed between study groups in all comparisions except MSON- vs MSON+ in OPL. Significant difference was found in contrast in the RNFL, GCL+IPL, inner nuclear layer (INL) and OPL. A significant increase was observed between H vs. MSON- and H vs. MSON+ groups in fractal dimension in GCL+IPL, INL and OPL layers. A significant decrease was measured in layer index in the RNFL and GCL+IPL layers in all comparisions except H vs. MSON-. A significant difference was found in total reflectance in the RNFL layer in all comparisions and in the GCL+IPL layer between H and MSON+ groups.
***Conclusion*:** According to our results the inner retinal layers show significant texture and optical property changes in MS which is more relevant in eyes following optic neuritis. These findings may help to improve the diagnostic efficacy of OCT in MS.

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E/IV-2
EFFECTS OF INTERVAL TRAINING AND PROBIOTIC SUPPLEMENTATION ON COGNITIVE FUNCTION IN A TRANSGENIC MICE MODEL OF ALZHEIMER'S DISEASE

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Approximately 23 million people worldwide suffer from Alzheimer's disease (AD). The illness is associated with the loss of acquired knowledge and the ability to learn. Inflammation and neuron loss indicated by Amyloid-beta peptide accumulation underly this disease. So far there is no effective treatment, but it is proven that physical exercise protects against neurodegenerative diseases, while numerous studies support the positive effects of healthy gut flora on these processes.

Aims: We suggest that the use of interval treadmill running and the probiotic supplementation attenuates the ongoing loss of cognitive function, delays the AD progress and reduces the local inflammation caused by the illness.

Results: Our result are based so far on cognitive tests and morphological measurements. The brain/body mass (BM) ratio in the combined group were significantly higher than that of the control group, suggesting minor neuron loss. Heart/BM ratio in exercise group were significantly increased, musculus quadriceps/BM ratio in combined and training group were higher compared to control group indicating the myogenic effects of exercise. During cognitive test we have observed continous development in the performance of the animals on combined treatment. During the Moris maze test, on the second day the animals showed significantly better performance, and on the 3rd and 4th day a tendency was shown for improved learning skills. Also in the spontaneous alternation test, a remarkable increase in performance was shown, demonstrating better exploratory activity, meaning a better preservation of cognitive function.

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E/IV-3
RESPONSE TO SOCIAL CHALLENGES: THE ROLE OF 2-ARACHIDONOYLGLYCEROL SIGNALING

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In the previous years the impact of endocannabinoid signaling on emotional behavior was widely studied as this signaling pathway presents a promising target in the pharmacological treatment of emotional disorders. Recent studies suggest that endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG) affect behavior differentially. Anandamide has been investigated extensively but studies on the specific behavioral roles of 2-AG only recently became possible and its involvement in social behaviors has not yet been investigated. In the present work we conducted a comprehensive investigation on the social impact of 2-AG. With the employment of JZL184 a monoacylglycerol lipase (MAGL) inhibitor 2-AG signaling was enhanced in mice who were later submitted to the resident-intruder, sociability and social interaction paradigms, respectively. In the resident-intruder paradigm JZL184 near completely abolished aggressiveness and increased victimization in the residents while the level of defensiveness remained unaltered despite the large increase in bites received. In the case of intruders, JZL184 exerted similar negative effects on bites and offensive behavior, while interestingly agitation and defensiveness during, and the corticosterone response to aggressive encounters were also increased. Our results regarding sociability and social interactions suggest that JZL184 treatment has broader effects on social behavior and deeply affects the way in which the animal responds social challenges. Taken together our findings show that 2-AG has an unusually strong negative influence on aggressive behavior and plays an important role in the modulation of social behavior.

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E/IV-4
COMPARISONS OF INTRINSIC AND ASSOCIATIVE CONNECTIONS OF THE PRIMATE SOMATOSENSORY CORTEX

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Somatosensory cortical areas 3b and 1 have strong connectional relationship and both include a topographically organized body representation, which provide the opportunity to study structure-function relationships in these areas. While the functional distinction of areas 3b and 1 is an open question, there are characteristic differences such that the different magnification factors in the two regions. Different size of horizontal and perhaps laminar spatial distribution of connections within and between areas 3b and 1 can be in part responsible for the observed difference in the magnification factor. To investigate this possibility we used bidirectional tract tracing via injections into distal finger pad representations of area 3b and area 1 of the squirrel monkey. The sizes of injections were matching the size of submodality specific tactile modules in both areas. Irrespective of the origin, retrograde and anterograde labeling exhibited supragranular dominance, making these layers the main site of interactions. Thick axonal processes, which could be a structural correlate of fast information exchange, connected predominantly the homotopic distal finger pad representations of the two areas. Kernel density analysis of retrograde labeling suggests that similar size of neuronal populations provide input to column-size cortical regions within and between the two areas. In area 3b intrinsic connections formed significantly higher densities of bouton-like structures than afferents originating from area 1. However, in area 1 densities of bouton-like elements originating from intrinsic and interareal afferents showed similar densities. In summary, the size of the horizontal spread of connectivity does not differ significantly between area 3b and 1. Therefore the difference in magnification is apparently not due to the smaller horizontal spread of cortical connectivity within area 1. However, because of the smaller magnification factor the similar spatial spread of cortical connectivity of area 1 could subserve higher level integration than that of area 3b.

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E/IV-5
SCREENING OF MONOGENIC AUTISM FORMS IN HUNGARIAN COHORT USING THE NEXT GENERATION SEQUENCING (NGS)

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Autism spectrum disorder is a neurodevelopmental disorder with multiple genetic and non-genetic causes. The genetic background of ASD is highly heterogeneous. The first step is to distinct the monogenic forms from complex, multifactorial forms.
Our aim was to explore the monogenic forms in our cohort, and estimate the frequency of mutationt in genes related to ASD.
Our cohort consisted of 47 patients, who met the DSM-5 criteria for ASD. After Fragile-X syndrome screening we performed next generation sequencing on MiSeq platform targeted on 103 known and candidate genes related to ASD (Illumina Trusight Autism). Before the NGS analysis the FMR1 gene full and premutations were screened out by Asuragen AmplideX FMR1 PCR Kit.
The genetic analysis detected in 45 patients rare variants in 39 genes. Phenotypically 29 patients were considered as idiopathic ASD patient, and 18 had an additional feature beside autism, noted as syndromic ASD patients. In a 48-years-old man and 8-years-old girl we detected FMR1 full mutation. In 1 case the ASD associated to muscular dystrophy, the NGS detected point mutations in the dystrophin genes. In a boy presenting the symptoms of CHARGE syndrome, we found a CHD7 frameshift mutation and confirmed the diagnosis. In case of a 17-years-old boy profoundly affected with sever developmental delay, cachexia, microcephaly, multifocal epilepsy, no visual or social responses, the CDKL5 missense mutation is supposed to be pathogenic on bases of a similar case. In the most cases pathogenic SNPs were found in CDH8, MET, NLGN-s, SHANK2, VPS13A genes supporting their strong predisposing effect on the neurodevelopmental spectrum disease. Segregation analysis is going on.
Conclusion: The identification of the monogenic forms of the ASD is extremely important because only in this case we can determine the reoccurrence risk and can offer prenatal testing to the families having children diagnosed with ASD.

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E/IV-6
ELEVATED LEVELS OF POTENTIALLY *MEN1*-TARGETING MICRORNAS IN SPORADIC COMPARED TO MEN-1 SYNDROME ASSOCIATED PRIMARY HYPERPARATHYROIDISM

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Background and aim: Primary hyperparathyroidism (PHPT) is a frequent endocrine disorder leading to hypercalcaemia, osteoporosis and nephrolithiasis. Vast majority of the cases are sporadic, but PHPT may be a consequence of multiple endocrine neoplasia syndrome type 1 (MEN-1), a familial disorder caused by germline mutations of menin-encoding gene *MEN1*. Beside mutations of *MEN1*, other mechanisms including microRNA-mediated silencing of the *MEN1* gene have been proposed as an important factor in the pathogenesis of PHPT. Our aim was to examine the expression of potentially *MEN1*-targeting microRNAs in MEN-1 associated and sporadic PHPT tissues.

Materials and methods: MicroRNAs potentially targeting *MEN1* were chosen upon *in silico* analysis. Immunohistochemical analysis of menin as well as RNA isolation from formalin-fixed, paraffin embedded specimens was performed in 16 MEN-1 associated and 41 sporadic PHPT tissues. MicroRNA expression analysis was performed using predesigned TaqMan microRNA assays on a real-time qPCR instrument. Additionally, *MEN1* status was examined by Sanger sequencing. Statistical analysis using IBM SPSS Statistics software was used to determine significant differences in expression.

Results: Immunohistochemical analysis confirmed the deficient nuclear menin expression in all MEN-1 associated as well as in 29,3% of sporadic PHPT tissues. MicroRNA expression analysis revealed the elevated expression of potentially *MEN1*-targeting microRNAs: hsa-miR-24 and hsa-miR-28 in sporadic compared to MEN-1-associated PHPT tissues ($p=0.011$ and $p=0.019$, respectively).

Conclusions: *MEN1*-targeting microRNAs might contribute to the tissue-specific silencing of tumour suppressor menin, leading to sporadic parathyroid tumourigenesis.

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E/IV-7
PROSPECTIVE INVESTIGATION OF GENETIC ALTERATIONS IN SAMPLES COLLECTED BY FINE NEEDLE BIOPSY FROM THYROID NODULES IN HUNGARY

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Only a fraction of the nodular diseases of thyroid gland is malignant. The most reliable tool for the differential diagnostic examination of thyroid nodules is the fine needle biopsy, but in 10-40% of the samples the presence of malignancy cannot be unequivocally confirmed. In medical daily routine there are a few genetic markers (BRAF, RAS, RET/PTC and PAX8/PPAR-gamma), which can be used only experimentally in case of differentiated tumours of thyroid gland.

Aims: The purpose of our prospective study was to document that the diagnostic and prognostic value of genetic mutations found in thyroid nodules. These can be instrumental in the recognition and adequate treatment of thyroid tumours. 799 aspirated cytological samples collected from thyroid nodules were examined in our observational study. The RAS gene family and somatic one-point nucleotide polymorphisms of BRAF genes were tested by the method of LigthCycler melting-point analysis, while the re-arrangements of genes were examined by real-time polymerase chain reaction. During a 3 year period the follow-up of events related to medical condition of patients participating in our study was performed by regularly repeated phone interviews.

Results: In samples collected from thyroid nodules 39 BRAF mutations, 33 RAS mutations and 1 RET/PTC gen re-arrangement were found. No PAX8/PPAR-gamma re-arrangement was confirmed. There were 52 malignant thyroid tumour diagnosed. During 3 years follow-up we determined, that the specificity of genetic testing is high (93,3%-96,4%-96,2%), although the sensitivity is low (46,2%-30%-38,5%) while the negative predictive value is significant (96%-95,6%-96,6%). The latest result means, that in case of uncertain cytological findings the number of diagnostic thyroidectomies might be reduced. Our results show, that the high specificity and major negative predictive value of genetic assays can help the exclusion of malignant tumours.

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E/IV-8
GLUCOCORTICOID RECEPTOR AND HSD11B1 GENE POLYMORPHISMS MAY INFLUENCE THE THERAPEUTICAL DOSAGE AND THERAPY-ASSOCIATED MORBIDITIES IN PATIENTS WITH ADDISON'S DISEASE

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Objective: Prereceptorial glucocorticoid signaling includes enzymes involved in the local synthesis and metabolism of glucocorticoids performed mainly by 11-ß-hydroxysteroid dehydrogenase enzymes (HSD11B) and from receptor itself (GR). Polymorphysms (SNPs) of HSD11B1 and GR have been associated with altered sensitivity against glucocorticoids.
Aim: Our aim was to asses whether SNPs of GR and HSD11B1 genes (N363S-rs6195, BclI-rs41423247, A3669G-rs6198 of GR; and rs12086634, rs4844880 of HSD11B1) may influence the glucocorticoid replacement dosage, and clinical/laboratory parameters in patients with Addison's disease.
Patients and methods: 67 patients with primary adrenal insufficiency diagnosed and treated at the 2nd Department of Medicine Semmelweis University were studied. Clinical, laboratory data and dosage of hormone replacement therapy were collected. Peripheral blood DNA was isolated. GR gene SNPs were examined using allele-specific PCR (for BclI and N363S) or Taqman assay on Real Time PCR (for A3669G, rs12086634, rs4844880). Genotype distribution was compared to those observed in the general Hungarian population using Chi square or Fischer exact t-test. ANOVA followed by power analysis was used for association studies.
Results: The allele frequency of N363S polymorphism was higher in patients compared to the control group. The disease appeared significantly earlier in patients harboring A3669G SNP. The BMI of homozygous carriers of BclI SNP was significantly higher than those of the heterozygous carriers ($p=0.007$), and the need of total hydrocortisone equivalent supplementation dose was significantly lower ($p=0.006$). The rs4844880 SNP associated with higher BMI and higher bodyweight-adjusted glucocorticoid substitution dose, the disease developed in significantly later age in carriers. Annual decrease of bone mineral density, represented by T-score and Z-score at lumbal spine was significantly lower in carriers.
Conclusion: SNPs of GR and HSD11B1 genes may be important genetic factors in the pathogenesis and therapy-related morbidities in patients with primary adrenal insufficiency, and may influence the individual need of glucocorticoid supplementation.

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E/IV-9
GENE AND PROTEIN EXPRESSION PATTERN OF CYTOKINES IN DISC HERNIATION DEPEND ON TIME OF SYMPTOMS

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Background: Sciatica caused by lumbar disc herniation is a frequent clinical condition. The development of the radicular pain is explained by mechanical and biological (inflammatory) factors. Spontaneus pain relief in the first weeks is not uncommon, but a significant part of the patients have got persistent (and/or recurrent) disabling pain requiring surgical intervention. The biological background of the alteration in clinical symptoms is still unknown.
Objective: The aim of this study was to investigate the protein and mRNA expression of different cytokines in human herniated disc tissues.
Methods: Twenty-four patients underwent lumbar microdiscectomy were included into the study. Sequestred disc tissue was collected during the surgery and analyzed using a Human Cytokine Array Panel (R&D Systems) and TaqMan Gene Expression Assays to determine the protein (N=12) and mRNA expression (N=12) of different cytokines. Cytokine expression levels were analyzed in relation to the duration of the symptoms ('acute': less than 6 weeks, 'chronic': more than 3 months). Non-parametric statistical tests were used to determine significant differences in protein/mRNA expression. A minimum of 1.5-fold difference and $p<0.05$ was considered significant.
Results: IL-6, -8 and GRO-a were expressed significantly higher in acute disc herniations either in protein and mRNA levels. RANTES, IFN-g and G-CSF proteins were found to be increased in chronic herniations and higher expression of RANTES and IFN-g were confirmed at mRNA level.
Conclusions: Cytokine profile in herniated disc tissue changes with time. It can be associated with an altered inflammation process and the consequent change of the clinical picture. New biological approach selectively modulating the inflammatory response can be one of the future developments in the non-surgical management of intervertebral disc herniation.

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E/IV-10
COMPARISON OF AIRWAY AND SYSTEMIC MALONDIALDEHYDE LEVELS FOR ASSESSMENT OF OXIDATIVE STRESS IN CYSTIC FIBROSIS

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Introduction: Oxidative stress plays an important role in the pathogenesis of cystic fibrosis (CF). In this study airway and systemic oxidative stress was investigated in CF using malondialdehyde (MDA), an established by-product of polyunsaturated fatty acid peroxidation.
Methods: The study included 40 stable CF patients and 25 healthy controls. Exhaled breath condensate (EBC), sputum and plasma were collected from during routine clinical visits. The concentration of MDA was measured by high performance liquid chromatography (HPLC). The receiver operating characteristic (ROC) curve analysis was used to determine the discriminatory power of the MDA measurement. The relationships between the levels of MDA and clinicopathological factors were also assessed..
Results: MDA levels in sputum (279.8±14.7 vs. 92.7±9.2 nmol/L, $p<0.0001$), EBC (139.9±6.7 vs. 71.5±4.3 nmol/L, $p<0.0001$) and plasma (176.1±15.9 vs. 129.6±12.9.nmol/L, $p<0.05$) were increased in patients with CF compared to healthy controls. MDA measurement in sputum (area under ROC curve [AUC]: 0.977, $p<0.0001$) or EBC (AUC: 0.94, $p<0.0001$) distinguished between patients and controls with greater accuracy than in plasma (AUC: 0.677, $p<0.05$). There were significant associations between sputum MDA levels and the serum concentration of C-reactive protein (CRP) ($r=0.42$, $p<0.05$) and the erythrocyte sedimentation rate (ESR) ($r=0.47$, $p<0.05$). Sputum and EBC MDA levels were elevated in patients with severe pulmonary dysfunction (forced expiratory volume in 1 sec [FEV1]<50% predicted) compared to those with mild-to-moderate functional impairment (FEV1>50% predicted) ($p<0.05$). MDA concentrations in CF patients colonized either with Pseudomonas aeruginosa or with other bacteria were similar (p=NS). Inhaled corticosteroid (ICS) treatment did not affect MDA levels (p=NS). The intra- and inter-assay repeatability of MDA measurements was similar in all three types of samples, while the between-visit variability was higher in plasma.
Conclusions: MDA is a potential new airway marker of oxidative stress in patients with CF. Sputum MDA differentiates best between patients and healthy subjects.

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E/IV-11
NEW DIAGNOSTIC METHOD FOR PRADER - WILLI SYNDROME (PWS)

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Introduction: PWS is a complex disease with a prevalence of 1:20-30 000. Main characteristics vary with age. Hypotonia of muscles and feeding problems during infancy are dominant while later in childhood excessive eating, obesity, behavioral problems, developmental delay, mental retardation are determinative. Diagnosis is based on clinical features and genetic analysis. The "gold standard" for molecular diagnosis is MS-MLPA (Methylation-Specific Multiplex Ligation-dependent Probe Amplification) with a sensitivity of 99%. In Hungary only more expensive alternative methods with lower sensitivity like FISH (Fluorescence In Situ Hybridization) and MSA (Microsatellite Analysis) were available until now.

Aims: The aim of our study was to develop a fast, sensitive and cheap methylation based molecular diagnostic method for suspected PWS.

***Materials and methods*:** We studied blood samples of 17 patients and 6 parents. We used two unaffected individuals' DNA samples as negative controls. All patients fulfilled the clinical criteria of PWS. After isolating DNA, we performed bisulfite treatment, BS-PCR (Bisulfite Sensitive Polymerase Chain Reaction) and HRM (High Resolution Melting Analysis). To control our method we analysed all samples with MS-MLPA, as well.

Results: Out of 17 patients with suspected Prader - Willi Syndrome in 6 cases were the diagnosis confirmed by HRM methylation based genetic testing. Comparing our HRM results with "gold standard" MS-MLPA no false negative cases were found.

***Conclusion*:** We suggest that HRM might be a good method for the diagnosis of PWS suspected cases in the first row.

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E/IV-12
SURGICAL SITE INFECTION AFTER PRIMARY DEGENERATIVE LUMBAR SPINE SURGERIES AND ITS EFFECT ON LONG-TERM OUTCOME

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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 factors for SSI in patients requiring routine lumbar surgery because of disc degeneration cohort and to determine the impact of SSI on long-term outcome. Reliability of the results of was tested using a prospectively recruited validation cohort.
Patients and methods: One thousand thirty (N=1030) patients were included into the study. All subjects underwent one or two-level decompression or instrumented lumbar fusion. 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 Orthopedic 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 logistic regression models. The performance of the final multivariate regression model was assessed by measuring its discriminative ability (c-index) in ROC analysis. Five-point Likert scale on self-reported outcome was classified into two categories ("good" and "poor" result) and influence of SSI on outcome was also analyzed. SPSS 20.0 statistical program package was used for the analyses where $p<0.05$ was considered significant.
Results: The incidence of SSI in the test cohort was found 3.5% and 3.9% in the validation cohort. The significant ($p<0.001$) multivariate regression model predictive for the occurrence of SSI contained the patient's age, body mass index (BMI) and the presence of some comorbidities such as diabetes, ischaemic heart disease, arrhythmia, liver disease and autoimmune disease. The c-index of the model was 0.71 showing good discriminative ability and it was confirmed by the data of the independent validation cohort (c =0.72). There was no significant difference in changes of mean scores of pain and outcome questionnaires comparing patients with and without SSI (pain: $p=0.42$, ODI: $p=0.79$, COMI: $p=0.79$). The self-reported overall outcome of the index procedure 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 older age, higher BMI and the presence of certain comorbidities. Analyzing the long-term outcome of surgical treatment, no significant difference was found if the SSI was treated according to the recent guidelines. Our predictive model for SSI was validated on an independent prospective cohort.

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E/IV-13
COMPARISON OF INTRACYTOPLASMIC SPERM INJECTION (ICSI) AND CONVENTIONAL IN VITRO FERTILIZATION (IVF) OUTCOMES IN VIEW TO SEMEN QUALITY

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Introduction: Intracytoplasmic sperm injection (ICSI) was developed to treat severe male factor infertility. Since its introduction the indications extended, even though the use of ICSI has higher risk of congenital anomalies. Increase in de novo sex and autosomal chromosome aberrations, in the risk of imprinting disorders in ICSI children has been reported.

Materials and methods: Data of 1132 IVF cycles from 2009 to 2014 were retrospectively analyzed. Only the first or the second IVF cycle of a patient was included. Three groups were created according to sperm quality (SP(I): <15 million, SP(II): 15-30 million, SP(III:) ≥30 million progressive motile sperm in the native sample), and were also classified according to female age (Age1:≤31, Age2:32-36, Age3:37-40, Age4:≥41) and number of retrieved oocytes (O1:1-3, O2:4-6, O3:7-9, O4:≥10).

Results: There was no significant difference between fertilization rates in SPII in any of the age or oocyte groups. In SPIII fertilization rates were significantly higher after IVF in every oocyte groups (O2: 69.6±23.1%vs.60.2±26.9%, p=0.018; O3: 67.7±21.4%vs.56.8±20.7%, p<0.01; O4: 65.7±20.2%vs.58.7±19.1%, p=0.013) except O1 where no IVF were performed, and in Age2 (67.9±21.4%vs.59.0±31.6%, p=0.046) and Age4 group (69.6±20.6%vs.52.2±29.6%, p=0.016). Clinical pregnancy rate was higher after IVF (49.4%vs.37.2%, p<0.01) in all groups and also in SPIII (49.8%vs.25.9%, p<0.01). There was no difference in any of the oocyte groups between blastomere number, morphology score and fragmentation of transferred embryos in SPII. Blastomere number in O2 (6.3±2.2vs.5.7±2.8, p=0.038) and O4 (8.0±1.7vs.7.3±2.1, p<0.01) was higher, morphology score (2.5±0.6vs.3.7±0.6, p=0.012) and fragmentation (10.5±7.0%vs.15.3±11.2%, p<0.01) in O3 were lower in SPIII after IVF.

Conclusions: Conventional IVF could be efficiently used in more cases. In case of good quality semen sample, fertilization rate is higher, quality of transferred embryos is better, and also in case of moderate sperm quality fertilization rate and embryo quality is not worse after IVF.

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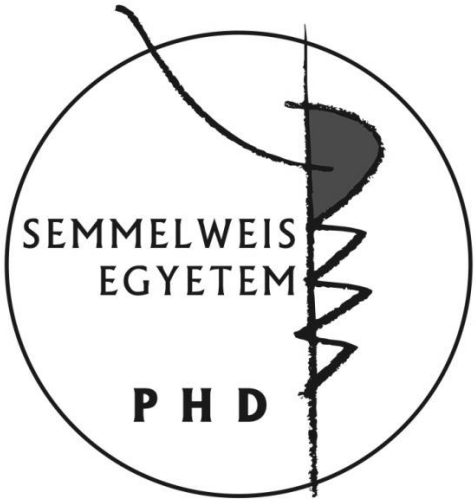

E/V
ONCOLOGY
ORAL PRESENTATIONS

Chairpersons:

Dr. Ilona Kovalszky

Dr. András Kiss

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E/V-1
DIGITAL IMAGE-ANALYSIS PROCESSES TO DETERMINE KI-67 PROLIFERATION INDEX IN BREAST CANCER

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Introduction: Regarding breast cancer, in addition to hormone receptor and Her2 status, proliferation markers (mitotic index, Ki-67 proliferation index = KIPI) also have therapeutic implications. In daily pathological routine utilized semiquantitative "eye-balling" method to determine Ki-67 proliferation index might be associated with remarkable intra-/interobsever variability.
Methods: In our study, 177 breast cancer patients' samples and follow-up data were included. Tissue microarrays (TMA) were prepared from the representative paraffin-embedded tumor blocks. After performing Ki-67 immunoreaction, conventional evaluation of, KIPI and digital image-analysis (PatternQuant for fully automatic tumor tissue recognition and KIPI detection, and CellQuant for investigator-based annotation of tumor cells and automatic KIPI detection = semi-automatic) were applied to digitial slides (Pannoramic Viewer v15.3 and QuantCenter 2.0 by 3DHistech Ltd.). Upon statistical analysis, digital pathological methods were compared to the - currently gold standard - semiquantitative determination of KIPI using SPSS 22 program.
Results: Dichotomizing Ki-67 index value in accordance with the 2013 St. Gallen guideline, significant difference has occurred between the automatic and semi-automatic and eye-balling methods ($p<0.001$), although all three methods represented strong correlation with each other ($\rho=0.700$-0.765). The results of digital image-analysis processes (PatternQuant vs. CellQuant) also represented significant difference regarding KIPI ($p=0.012$). For prognosis prediction, CellQuant and the conventional method was able to perform statistically significant splitting the cohort at 14% ($p<0.001$), although digital pathology method classified twice as many patients into the high risk group of recurrence compared to the semiquantitative evaluation.
Conclusion: The digital image-analysis processes are rapid and objective methods of determination of Ki-67 proliferation index, and in our opinion it is also able to reduce intra-/interobsever variability, however the semiquantitative evaluation is still faster. Further refinement and validation are needed to verify applicability of tumor pattern recognition software in pathological routine.

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E/V-2
THE PROGNOSTIC IMPACT OF TERT PROMOTER MUTATION AND POLYMORPHISM IN MALIGNANT PLEURAL MESOTHELIOMA

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Introduction: Activity of the telomerase enzyme complex is detected in a variety of malignant tumors. It is involved in the maintenance of telomere length, thus in the immortalization of tumor cells. Part of this complex is the telomerase reverse transcriptase enzyme encoded by the gene TERT. Mutations of the TERT promoter at positions −57, −124 and −146 bp from ATG start site have been described to lead to TERT-overexpression by creating a new binding site for Ets/TCF transcription factors. The promoter mutation has first been identified in malignant melanoma and later on in several other tumor types, such as glioblastoma, hepatocellular carcinoma, lung cancer and mesothelioma. It was first described in bladder cancer that the polymorphism rs2853669 of the TERT gene influences positively the prognosis of those patients harboring a promoter mutation by disrupting an Ets/TCF binding site of the protein.
Aims: Accordingly, we evaluated the prognostic role of the TERT promoter mutation and the modifying effect of the polymorphism rs2853669 on the prognosis in malignant tumors of the pleura.
Results: We isolated DNA from formalin fixed paraffin embedded samples of 63 malignant pleural mesotheliomas, as well as from 21 cell lines established from malignant pleural mesothelioma. Mutation and polymorphism status was determined by next generation sequencing. We found 6 mutant cases (9.5%) in our patient cohort. The presence of the mutation was very strongly associated with non-epithelioid subtype. The median survival of the patients harboring the somatic mutation was 268 days compared to 528 days in the non-mutant cases. In the 21 established cell lines we found 8 mutations (38%). The higher percentage of TERT promoter mutation in the cell lines suggests that it may support the in vitro growth potential. The polymorphism rs2853669 was present in 54% of the patients and in 47.6% of the cell lines. So far no prognostic significance could be determined for the polymorphism in MPM.

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E/V-3
ALTERATION OF BIOENERGETIC PATHWAYS DETECTED BY MASS SPECTROMETRIC METHODS AND MTOR ACTIVITY RELATED PROTEINS IN TUMOR CELLS

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The malignant phenotype correlates significantly to the metabolic alterations in tumor cells e.g. impaired oxidative phosphorylation, high glucose uptake, intensive production of lactic acid. Genetic mutations, the shifts in extracellular microenvironment and the metabolic profile of tumors are different. There is high demand to develop and introduce appropriate assays, especially methods for bioenergetic mapping in experimental and clinical cancer research.

For the present study two human tumor cell lines, HT-1080 fibrosarcoma and ZR-75.1 mammary adenocarcinoma were selected according to the following consideration: radioactive glucose and acetate showed significant difference in the contribution of CO_2 production.

Herein, we report our results and experiences with mass spectrometry (LC-MS/MS and GC-MS) methods development for the analysis of the ratio of different citrate cycle, glycolysis and pentose phosphate pathway metabolites. The incorporation of labeled carbon atoms (^{13}C) from glucose and acetate into glycolytic and TCA metabolites were analysed in ZR-75.1 and HT-1080 cells. Furthermore, mTOR complexes and their targets related to bioenergetic mechanisms were investigated by Western blot.

The two tumor cell lines were characterized by different ratio of ^{13}C lactate/^{13}C malate and ^{13}C ribose-5-phosphate/^{13}C malate. The different ratios refer that in HT-1080 cells glucose utilization, the glycolysis is dominant, whereas TCA cycle is dominant in ZR-75.1 cells. This result reveals the dominant function of citrate cycle in ZR-75.1 cells and impaired citrate cycle in HT-1080 cells. The LC-MS technique allows the determination of number of ^{13}C atoms which incorporate to citrate molecules. The glycolytic phenotype of HT-1080 tumor cells is associated with high mTORC1 activity related protein expression and with negligible protein level of mTORC2.

We confirmed that the presented methods are suitable for characterization of metabolic profile of different tumor cells and provide help for therapeutic/prognostic prediction and development of metabolism related targets in personalized drug therapy.

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E/V-4
CONVERGENCE OF SOMATIC MUTATIONS WITHIN THE JAK-STAT SIGNALLING PATHWAY IN A NOVEL *RUNX1*-MUTATED PEDIGREE

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Germline mutations in the transcription factor *RUNX1* confer an autosomal dominant predisposition to familial platelet disorder (FPD) and myelodysplasia/acute myeloid leukaemia (MDS/AML). We describe a novel *RUNX1*-mutated family, where 3 young siblings presented with secondary AML, providing a rare opportunity to compare the molecular events initiating disease (*Figure 1A*).

We performed whole exome sequencing (WES) on bone marrow (BM) DNA from 4 siblings with MDS/AML. Peripheral blood (PB) DNA samples from both healthy parents were also sequenced to enable exclusion of inherited variants in the 4 children.

Direct Sanger sequencing of the 4 siblings (II.1-II.4) and their mother (I.1) revealed the germline *RUNX1* mutation, p.R201X. *Figure 1B* summarises the clinical timeline, with the key molecular and cytogenetic lesions detected in each sibling with their mother (45y) remaining an asymptomatic carrier with no evidence of peripheral cytopenias and normal trilineage haematopoiesis.

WES revealed molecular addiction to JAK2 signalling in 3 siblings (II.1, II.2 and II.4). II.2 and II.4 both acquired *JAK2* V617F mutations, with homozygosity of the mutant allele observed in II.2 due to 9p acquired uniparental disomy (aUPD). In II.1, we detected a somatic mutation in *SH2B3* (p.R392Q), with apparent homozygosity caused by aUPD of 12q. The p.R392Q mutation was localised to the SH2 domain, which normally binds both mutant and WT isoforms of JAK2, inhibiting their phosphorylation. Further somatic mutations occurred in *CDC27* (II.2 and II.4), *RBBP8* (II.2) and *U2AF2* (II.4). Notably, all 3 siblings with somatic JAK2-signalling lesions had aggressive disease.

In summary, we describe a novel FPD-AML pedigree with molecular convergence upon JAK-STAT signalling in 3 siblings with MDS/AML. Since *JAK2* mutations are reported in <5% of sporadic *RUNX1*-mutated AML, our findings suggest somatic mutations in FPD/AML may be enriched within distinct signalling pathways, often associated with aUPD to increase the mutant allele burden within tumours.

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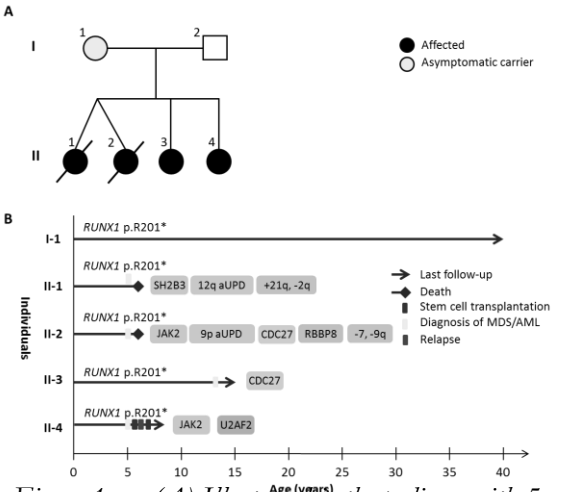

Figure 1. – (A) Illustrated is the pedigree with 5 individuals carrying the germline RUNX1 p.R201* *mutation. (B) The timeline summarizes the clinical course with key molecular and cytogenetic alterations detected in each sibling.*

E/V-5
THE ROLE OF CD49D EXPRESSION IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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Chronic lymphocytic leukemia (CLL) is the most common B-cell leukemia of adults in Western countries. The disease is characterized by variable clinical courses, which can be predicted by various prognostic factors. Among them is the recently discovered CD49d, which predicts poor outcome. The CD49d, also known as the α4 integrin subunit, is associated with the CD29 (β1) molecule. The ligands of the CD49d/CD29 complex are VCAM-1 and fibronectin. It is well known that CLL cells resist apoptosis and show increased proliferation as a result of their interaction with the microenvironment.

Aims: We investigated whether the VCAM-1 or fibronectin stimulation alone or the bone marrow stromal cells (BMSCs) by themselves can induce the survival and proliferation of CLL cells. We examined the change in the expression of adhesion antigens, cytokine receptors of CLL cells under different culturing conditions. We determined the conformation of CD29 on the surface of CLL cells.

Results: Peripheral blood mononuclear cells from 30 CLL patients with different CD49d expression were cultured on VCAM-1 or fibronectin coated plates as well as in a co-culture with BMSCs. BMSCs reduced the spontaneous apoptosis of CLL cells after 7 days, while VCAM-1 and fibronectin did not. The apoptosis rate was independent of the CD49d expression of CLL cells. The proliferation rate of CLL cells was not altered in the different culture conditions. The CLL cells co-cultured with BMSCs have increased expression of CD5, CD19, and decreased CXCR4; the VCAM-1 and fibronectin did not change the surface antigen levels. We detected only the low affinity conformation of CD29 on the CLL cell surface.

Our results suggest that the interaction of CD49d and its ligands do not, but BMSCs are able to prevent apoptosis of CLL cells.

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E/V-6
MTOR INHIBITOR TREATMENT REDUCES THE PROLIFERATION IN HL CELL LINES WITH CONSTITUTIVELY ACTIVE NOTCH1

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Growing evidence identified deregulation of signalling elements of Notch and PI3K–AKT–mTOR pathways in correlation to each other related to cellular functions and malignancies for example in T-ALL. However, these are poorly characterized in Hodgkin lymphomas (HL).
We studied the mTOR and Notch signalling elements in human HL cell lines and biopsies by using p-S6, Rictor, Raptor, Notch1, cleaved-Notch1 immunohistochemistry and Western-blotting. Cells were treated with mTORC1 inhibitor, different γ-secretase inhibitors (GSI) and Notch1-ligand and with their combinations in vitro. The proliferation and apoptosis were studied by AlamarBlue® and flow cytometry. The tumour growth was also observed in xenografts' treatments. Mutations in genes of PI3KCa, Notch-1 and FBXW7 and expression of hes-1, c-myc target genes related to signals were also studied (qPCR, DNA sequence analysis).
Increased signalling activation was detected in all HL cell lines and in patients' biopsies. The mTOR activity related expression showed differences but Notch receptors and ligands were confirmed in the studied HL cells. In vitro GSI and Notch-ligand could not influence the proliferation, apoptosis and target genes, only SAHM1 (Notch-1 transcriptional inhibitor) inhibited the proliferation and hes-1, c-myc expression. The base of GSI resistance could be the detected constitutive Notch-1 activation in HL cell lines (cleaved-Notch1 expression after GSI treatment as well). However, rapamycin and its GSI combination reduced the growth of HL cells both in vitro and in vivo. The molecular background of this is unclear; the NOTCH1, PI3KCA, FBXW7 are not mutated in cells.
Constitutive activation of Notch1 and GSI resistance draw attention to the importance of mTOR activity in the context of Notch-1 signals. The detected constitutively activated Notch1 could be targeted in HL therapy at the targets of this signal or at the other consequently activated protein's level like mTOR as was showed in our models.

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E/V-7
THE INFLUENCE OF GLIVEC ON LIVER REGENERATION IN MOUSE

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Background: Ductular reaction is a collective name for small, bile duct like structures appearing in the liver parenchyma in connection with chronic liver injuries. The origin and role of ductular reactions are still highly debated. Some of them certainly derive from progenitor cells and participate in liver regeneration, but they may promote fibrogenesis and tumor formation as well. There is a close, mutual interaction between ductules and myofibroblasts. Glivec (imatinib), the clinically widely used tirosine kinase inhibitor has been described to slow down the progression of hepatic fibrosis via the inhibition of myofibroblasts. In our present experiment we investigated the influence of Glivec on experimental ductular reactions induced in mouse liver.
Methods: Ductular reaction was induced in C57Bl male mice with choline deficient, ethionine supplemented diet (CDE) or 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) treatment. Animals in the study groups were treated with Glivec, 25 mg/kg/day per os. Picro Sirius Red staining and immunohistochemical reactions (cytokeratin 19 for ductular reaction; desmin for myofibroblasts; β-catenin and Hepatocyte Nuclear Factor-4 combination for characterization of hepatocytes) were performed. The slides were digitalized for quantitative, morphometric evaluation.
Results: Glivec treatment in the CDE model significantly decreased the area occupied by fibrosis, ductular reaction and myofibroblasts. However, the ratio of peculiar „small hepatocytes" increased in the Glivec treated mice. Neither of these changes were observed in the DDC+Glivec model.
Conclusions: Our results in the CDE model support the antifibrotic effect of Glivec. The boosting of small hepatocyte formation indicates more efficient regeneration. Therefore, Glivec treatment decreased the adverse (fibrosis), but increased the favourable (regeneration) concomitant phenomenon of the CDE induced ductular reaction. Furthermore, the different outcomes on two differently induced ductular reactions underline a strong suspicion. Namely, there are major differences between ductular reactions and their rational classification is absolutely necessary if we want to understand their biological functions.

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E/V-8
FDG-PET/CT AND DIFFERENT RESPONSE CRITERIA AFTER PRIMARY SYSTEMIC THERAPY IN BREAST CANCER

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Aims: To assess the value of a metabolism based (mPET) and a combined, metabolism and morphology based (cPET) PET/CT evaluation system in early prediction of chemotherapeutic response to primary systemic therapy (PST) of breast cancer. We also evaluate the prognostic value of these response criteria for progression free (PFS) and overall survival (OS).

***Methods*:** Seventy-one patients were enrolled in the study who underwent FDG-PET/CT imaging before and after the PST. PET/CTs were evaluated semiquantitatively by changes in maximum Standardized Uptake Value (SUVmax) and tumor size. mPET and cPET criteria were also applied to predict pathological complete remission (pCR). Because tumor metabolic behavior and remission rate could vary between biological subtypes, the effect of the subtypes on tumor response – measured by changes in SUVmax, tumor morphology or by the applied response criteria – was also analyzed.

***Results*:** 23/71 patients showed pCR (32.4%). Comparing pCR and non-pCR patient groups significant differences were detected by percentage changes in SUVmax ($p=0.000012$) and tumor size ($p=0.00016$) regarding the primary breast lesions. For detecting pCR, cPET criteria had higher sensitivity (75% vs. 43.75%) and negative predictive value (60% vs 43.75%) with lower false negativity rate (12 vs. 27) than mPET. Despite the detected significant differences between the five biological subtypes in changes in SUVmax and size of the primary tumors ($p=0.0044$; $p=0.035$), subtypes did not show any significant impact on response evaluation with mPET and cPET criteria ($p=0.7405$; $p=0.0529$). In this study nor clinical CR (defined by mPET or cPET) or pCR was predictor of longer PFS/OS.

***Conclusions*:** Our results suggest that cPET criteria are more predictive of pCR than mPET. The effect of biological subtypes should still be taken into consideration during the response evaluation; however the subtypes did not show an impact on response evaluation with mPET and cPET criteria.

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E/V-9
EFFECTIVENESS OF 9-CIS RETINOIC ACID AND MITOTANE COMBINATION IN AN ADRENOCORTICAL CANCER XENOGRAFT MODEL

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Background: There are few effective treatment options for adrenocortical carcinoma (ACC) and intensive efforts are going on to find novel agents. In our former study using functional genomics tools, retinoid signaling via the retinoid X receptor (RXR) was identified as a major pathogenic pathway in ACC. Furthermore, we have shown the in vitro activity of 9-cis retinoic acid (9-cisRA) acting via the RXR on adrenocortical NCI-H295R cells and also found that 9-cisRA has antitumoral effects in a small pilot xenograft study.
Objective: To investigate the antitumoral effect of 9-cisRA and its combination with mitotane in an extended xenograft study.
Methods: 43 male severe combined immunodeficiency (SCID) mice were xenografted with NCI-H295R cells, and then treated in four groups (i. control – corn oil vehicle, ii. 5 mg/kg 9-cisRA, iii. 200 mg/kg mitotane, iv. 5 mg/kg 9-cisRA + 200 mg/kg mitotane) for 28 days. Tumor size follow-up, histological and immunohistochemical (Ki-67) analysis and gene expression microarray (4x44K Agilent Whole Genome Microarray) were carried out. For the validation of the microarray results and to detect circulating microRNAs, quantitative real-time-PCR (TaqMan) was applied.
Results: Tumor growth was decreased relative to control both 9-cisRA- and mitotane-treated groups, but significant tumor size reduction was only achieved with the combination of the two agents. The Ki-67 index was significantly reduced in both 9-cisRA and 9-cisRA+mitotane groups. 483 genes with significant differences in expression were revealed by gene expression analysis, however, only without Benjamini-Hochberg correction. For validation by qRT-PCR, seven genes have been selected, but only one (*APOA4*) was found significantly up-regulated in the combined group compared to the control. The expression of circulating *hsa-miR-483-5p* was significantly decreased in the combined treatment group relative to control.
Conclusions: These data support that 9-cisRA might be used in the treatment of ACC primarily in combination with mitotane, but its mechanism of action awaits further investigations.

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E/V-10
IMPACT OF *GRIA1* POLYMORPHISMS ON ASPARAGINASE HYPERSENSITIVITY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Survival rates for patients have remarkably improved over the last decades with higher than 80% of children are cured. The intensive use of L-asparaginase (ASP) has a key role in this great achievement. However, hypersensitivity reactions to ASP are major challenges in pediatric patients, because these can lead to suboptimal treatment response. In addition, in serious cases these reactions can be potentially life-threatening requiring urgent interventions. Therefore, our aim was to identify genetic variants that predispose to ASP hypersensitivity.

Samples and clinical data collection was carried out from 576 pediatric ALL patients who were treated between 1990 and 2012 in 9 Hungarian pediatric hematology centers according to four consecutive trials using protocols from the Berlin-Frankfurt-Münster Study Group (ALL-BFM 90, 95, ALL IC-BFM 2002 and 2009). A total of 20 single nucleotide polymorphisms (SNPs) in *GRIA1* and *GALNT10* genes were genotyped by using KASPar on Demand prevalidated assays (LGC Genomics, Berlin, Germany) on 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Multi-adjusted logistic regression was performed by using IBM SPSS Statistic software, version 20.0 to test for associations.

We found statistically significant associations between two polymorphisms (rs4958351 and rs2055083) in *GRIA1* genes and the development of hypersensitivity to *Escherichia coli*-derived ASP. Patients with rs4958351AA/AG genotype had lower risk to ASP hypersensitivity compared to patients with GG genotype in T-ALL subgroup (p=0.00047, OR=0.05, 95% CI [0.01-0.26]). Regarding the medium risk group patients with rs2055083AA/AG genotype had lower risk to develop hypersensitivity reactions compared to patients with GG genotype (p=0,00085, OR=0,21 95% CI [0,09-0,53]). SNPs in *GALNT10* showed no association with ASP hypersensitivity.

Our results suggest that polymorphisms in *GRIA1* gene can influence the risk to ASP hypersensitivity. Further replication is required before these markers can be considered as predictive.

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E/V-11
TESTING OF ELECTRO-HYPERTHERMIA INDUCED PROGRAMMED CELL DEATH MECHANISM IN A COLORECTAL ALLOGRAFT MODELL

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The electric field and the concomitant heat of <42°C, generated by modulated electro-hyperthermia (mEHT) through capacitive impedance-coupled radiofrequency, can selectively target malignant tumors due to their elevated glycolysis, ion concentration and conductivity compared to normal tissues. mEHT has been used as a complementary to either radio- and chemotherapy of human malignancies.
Our earlier xenograft studies in immunocompromised mice showed that mEHT can provoke programmed cell death response and damage associated molecular pattern (DAMP) signal sequence in cancer cells compatible with immunogenic cell death (ICD).
Aims: In this works we tested the molecular background of mEHT related tumor damage and immune response in C26 colorectal cancer allografts in immunocompetent (Balb/C) mice.
Results: mEHT resulted in significant and progressive cell damage in treated tumors planted into the right legs of the animals compared to their untreated left legs. The programmed cell death response proved to caspase-dependent resulting in the significant increase of cleaved/activated caspase-3 levels in the treated tumors, without significant translocation from the mitochondria into cell nuclei of apoptosis-inducing factor (AIF), or displacement from cytosol to mitochondria of Bcl-2-associated X protein (BAX). Furthermore, the number of Ki67 positive tumor cells in the intact tumor areas was significantly increased in the mEHT treated compared to the untreated tumors.
Elevated release of stress associated Hsp70 and HMGB1 proteins was also observed in mEHT treated tumors, which are known participants of DAMP signalling and promoters of ICD. In line with this, the number of CD3 positive T cells was significantly elevated in the treated tumors. In addition, mEHT supplemented with the i.p. administration of a CD8+ T-cell promoting agent seemed to initiate a systemic tumor destructive effect.
In conclusion, mEHT can induce caspase-dependent programmed cell death and the release of stress associated Hsp70 and HMGB1, which may support T cell mediated tumor immunity.

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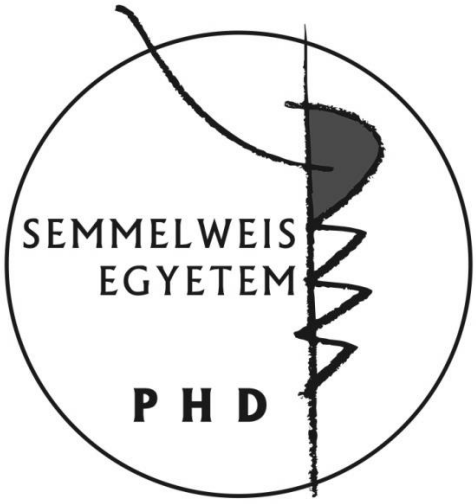

E/VI
CLINICAL MEDICINE II. - CARDIOLOGY, GASTROENTEROLOGY
ORAL PRESENTATIONS

Chairpersons:

Dr. Dávid Becker

Dr. László Herszényi

E/VI-1
GENE POLYMORPHISMS AS RISK FACTORS FOR PREDICTING THE CARDIOVASCULAR MANIFESTATIONS IN MARFAN SYNDROME

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Background: Folic acid metabolism enzymes polymorphisms are believed to be responsible for the elevation of homocysteine (Hcy) concentration in the blood plasma, which correlates to the formation of certain cardiovascular diseases such as aortic aneurysms and dissection.
Purpose: Our aim was to investigate the four gene polymorphisms of Methylenetetrahydrofolate reductase (MTHFR), Methionine synthase (MTR) and Methionine synthase reductase (MTRR) in patients with Marfan syndrome.
Methods: We studied 78 Marfan patients divided into groups based on the severity of cardiovascular manifestations: no involvement n=34 (Group A); mild involvement required intervention n=17 (Group B); severe cardiovascular involvement n=27 (Group C) subdivided into aortic dilatation n=14 and aortic dissection n=13 (Group C1 and C2), and 117 control subjects. We evaluated Hcy, folate, vitamin B12 and the polymorphisms of MTHFR C677T and A1298C, MTR A2576G and MTRR A66G.
Results: Multiple comparisons showed significantly higher levels of Hcy in Group C2 compared to Group A, B, C1 and control group ($P<0.0001$, $P<0.0001$, $P=0.001$ and $P=0.003$, respectively). Similarly, folate differed significantly, being lower in Group C2 than in Group A, B, C1 and control subjects ($P<0.0001$, $P=0.02$, $P<0.0001$ and $P<0.0001$). Multivariate logistic regression analysis revealed, that homocysteine plasma level was an independent risk factor for the severe cardiovascular involvement (Group C; OR 1.85, 95% CI 1.28-2.66, $P=0.001$) as well as for aortic dissection (Group C2; OR 2.49, 95% CI 1.29-4.78, $P=0.006$).
Conclusions: Our findings indicate that patients with more severe cardiovascular involvements in Marfan syndrome, and in particular with aortic dissection are associated with higher Hcy plasma levels and prevalence of homozygous genotypes of folic acid metabolism enzymes' than in patients with mild or no cardiovascular manifestations. These results suggest an important role for the proper homeostasis of folic acid metabolism in the development and remodelling of the extracellular matrix of the aorta, and could indicate a preventional supplementation of folic acid and vitamin B12 for Marfan patients.

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E/VI-2
THE ROLE OF THE WHITE BLOOD CELLS IN THE RESYNCHRONIZATION THERAPY OF CHRONIC HEART FAILURE

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Aims: The low lymphocyte counts and high neutrophil leukocyte fractions have been associated with poor prognosis in chronic heart failure. We hypothesized that the baseline ratio of the neutrophils to the lymphocytes (NL ratio) would predict the outcome of chronic heart failure patients undergoing cardiac resynchronization therapy (CRT).

Methods: The qualitative blood count and the serum levels of NT-proBNP (N-terminal of the prohormone brain natriuretic peptide) of 122 chronic heart failure patients and 122 healthy controls were analysed. We considered the 2-year mortality as primary endpoint and the 6-month reverse remodelling (≥15% decrease in the end-systolic volume) as secondary endpoint. Multivariable adjusted logistic and Cox regression analyses were applied and validated by reclassification methods: net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results: The NL ratio was elevated in chronic heart failure patients as compared to the healthy controls (2.93 [2.12-4.05] vs. 2.21 [1.64-2.81], p<0.0001). The baseline NL ratio exceeding 2.95 predicted the lack of the 6-month reverse remodelling (n=63, odds ratio=0.38 [0.17-0.85], p=0.01; NRI=0.49 [0.14-0.83], p=0.005; IDI=0.04 [0.00-0.07], p=0.02) and the 2-year mortality (n=29, hazard ratio=2.44 [1.04-5.71], p=0.03; NRI=0.63 [0.24-1.01], p=0.001; IDI=0.04 [0.00-0.08], p=0.02) of the patients independently of NT-proBNP levels or other factors.

Conclusions: The NL ratio is elevated in chronic heart failure and predicts outcome after CRT. According to the reclassification analysis, 4% of the patients would have been better categorized in the prediction models by combining the NT-proBNP with the NL ratio. Thus, a single blood count measurement could facilitate the optimal patient selection for the CRT.

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E/VI-3
ENVIRONMENTAL OR GENETIC EFFECTS INFLUENCE THE MORPHOLOGY OF THE AORTIC ROOT? A CLASSICAL TWIN STUDY

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Background: Configuration of the aortic root can be related to healthy ageing and/or to variety of disorders. Previous investigations using 2D echocardiography revealed that common environmental effects have a strong influence on the aortic root dimensions. 3D imaging modalities can provide more accurate measurements of the aortic dimensions.
Aims: In this study therefore we aimed to determine the CTA based heritability of the aortic root geometry within a sample of Hungarian twins.
Methods: In total, 102 twin pairs [61 monozygotic (MZ), 41 dizygotic (DZ); mean age for MZ and DZ were 55.5±9.6 and 58.5±8.4 years] were evaluated by a 256-slice CT-scanner. We used a semi-automated software tool developed for transcatheter aortic valve implantation CTA planning. The following anatomical structures were assessed: diameter of left ventricular outflow tract (dLVOT), of the annulus (dAn), of the sinus Valsalva (dSV), of the sinotubular junction (dSTJ) and ascending aorta (dAA). Age and gender adjusted ACE models were constructed to assess heritability. In the ACE model, "A" refers to additive genetic effects, "C" to common and "E" to unique environmental influences. Beside the full-fledged ACE model, partial models (AE, CE and E) were defined. The most parsimonious model for all phenotypic variables was the AE sub-model.
Results: CTA-derived measurements were identical between mono- and dizygotic twins (dLVOT: p=0,73; dAn: p=0,45, dSV: p=0,89; dSTJ: p=0,44; dAA: p=0,25). Additive genetic effects were dominant for all phenotypes: 81% for aAn, 78% for dAn, 77% for dLVOT, 84% for dSV, 82% for dSTJ and 80% for dAA.
Conclusion: In this classical twin study we demonstrated that based on the CTA measurements the metrics of the aortic root are strongly inherited. Our results contradict previous findings derived by 2D echocardiography, which indicated a dominant role of the common environmental effects.

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E/VI-4
THE ROLE OF FRAILITY IN THE RISK STRATIFICATION FOR CARDIOVASCULAR SURGERY

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Introduction: The use of risk stratification systems for operative risk assessment was an important step in the reduction of mortality and complications. The clinical experience, that patients of the same age and conventional risk, undergoing the same operation shoved significantly different outcomes suggested that there should be other, still unrecovered risk factors. Frailty, as a new score of psychosocial factors refines the former risk stratification, based on clinically measured and anamnestic data, enabling a more precise assessment of the length and difficulty of healing and recovery after surgery.
Aims: The aim of our present study was to identify preoperative physiological, psychosocial factors predicting the outcome after cardiac and vascular surgical procedures.
Materials and Methods: We used the data of 64 patients admitted to elective cardiac or vascular operations to The Heart and Vascular Center of Semmelweis University between September and December 2014 in the present preliminary analysis of our prospective study. We used questioners to evaluate the psychosocial and neuropsychological background of our patients including Beck Depression Inventory (BDI), Mini, Mental State (MMS), Geriatric Depression Scale (GDS), State-Trait Anxiety Inventory (STAI), Type D and Hungarostudy 2013 queries. We also recorded quantifiable anamnestic data, as well as preoperative and intraoperative clinical data. We used postoperative complications, length of ICU and hospital stay and in-hospital mortality as primary endpoints.
Results: The presence of postoperative arrhythmia was associated with higher BDI scores ($p=0.013$), longer mechanical ventilation was needed in patients with postoperative infection ($p=0.001$). Comparing our material with a representative control group, we found that our patients were more happy and satisfied with their lives and avowed themselves to be more religious ($p=0.01$, $p=0.04$, $p< 0.001$, respectively).
Conclusion: The use of frailty, assessed by queries mentioned above, as a predictor of postoperative outcome seems to be a promising additional factor in the improvement of patient safety and hospital utilization.

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E/VI-5
BLOOD LOSS REDUCING EFFICACY OF A NEW, SYNTHETIC APROTININ-ANALOGUE IN A CANINE MODEL OF CARDIOPULMONARY BYPASS

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Introduction: Pharmacological agents are used in cardiac surgery to reduce postoperative blood loss. The serine-protease inhibitor aprotinin was a widely used antifibrinolytic drug for decades in cardiac surgery. It was withdrawn from marketing in 2008 based on the results of the BART trial, which showed that aprotinin increases postoperative mortality. Today tranexamic acid (TA) is available to clinicians to reduce postoperative blood loss, the efficacy of which is questioned in many clinical trials.
Aims: Our primary aim was to evaluate the efficacy of a new, low molecular weight, synthetic aprotinin-analogue (BAY794709) in terms of blood loss reduction and anti-inflammatory properties in a clinically relevant canine model of cardiopulmonary bypass (CPB).
Methods: Foxhound dogs were randomized into 3 groups (n=8 each): control, BAY794709 and TA. The heparinized animals underwent 60 minutes of CPB, which was followed by 120 minutes of observation. Hemodynamic parameters were continuously monitored, blood loss and standard parameters of coagulation were regularly assessed. Thromboelastography (ROTEM) was used to investigate hemostasis in its complexity. CPB induces systemic inflammatory reactions, thus plasma levels of inflammatory markers (IL-6, IL-8, IL-10 and TNF-α) were measured using enzyme-linked immunosorbent assay.
Results: Postoperative blood loss was significantly reduced by TA (216$\pm$23ml vs. 295$\pm$20ml Control, $p<0.05$), but BAY794709 was significantly more effective even than TA (146$\pm$8ml, $p<0.05$ vs. TA). Hemodynamic indices, standard parameters of coagulation and ROTEM parameters were not significantly different among the groups. BAY794709 significantly reduced the plasma level of all investigated inflammatory citokines, therefore it might have more potent antiinflammatory effects than TA.
Conclusions: The new aprotinin-analogue reduces blood loss and inflammatory reaction more significantly than the currently used TA. Furthermore, it does not have either hemodynamic, or prothrombotic effects. According to our results, synthetic aprotinin-analogues might be used in cardiac surgery safely and effectively.

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E/VI-6
THE EFFECTS OF THE CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH MITRAL REGURGITATION OF VARIOUS SEVERITY

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Purpose: The resynchronization therapy (CRT) is effective in patients with heart failure (HF). According to literature, the two-third of the patients respond to the treatment (responders), but in one-third the disease is worsening despite device treatment (non-responders). The objective of our study was to assess the role of mitral regurgitation of different pathomechanisms.

Methods: We enrolled 117 patients, who underwent CRT. Our measurements were taken by standard 2D echocardiography immediately before the device implantation and 6 months and 2 years later. The data were analysed offline (Xcelera). We measured the volume of MR (RegVol) by the quantitative proximal iso velocity surface area method. We determined the ejection fraction and the volumes of the left ventricle by biplan Simpson method. We measured the electromechanical activation delay of midventricular segments adjacent to papillary muscles, and we compared the groups of synchronous and dyssynchronus papillary muscles. Our primary endpoints were the cardiovascular mortality. Secondary endpoints were the hospitalization because of the acute heart failure and the improvement in NYHA grade.

Results: The mean age of patients were 70.21±10.36 years, 78% were male. Initially 50.8% of patients had mild, 38.4% moderate and 10.8 % severe MR. The risk factors and the severity of HF did not differ significantly between the groups. After 6 months 91.5%, after 2 years 82.9% of patients responded favourably concerning the primary endpoints. The secondary endpoints mended significantly at mid- and long-term too, but comparing to the midterm data, the longterm results did not differ significantly. There was not significant difference between the three groups concerning results at the primary and secondary endpoints. The MR significantly reduced in each groups. According to the MR severity at 6 months the 2 years mortality differed significantly (mild vs. moderate vs. severe: 14.3% vs 22.2% vs 100%; $p<0.01$).

Regurgitation volume (RegVol) did not differ significantly between the groups of synchronous and dyssynchronus papillary muscles before the implantation (S vs DS. 32±20 ml vs 30±24ml). MR was reduced significantly after 6 months (RegVol before the implantation vs 6 months: 33±22 vs 22±15 ml, $p<0,001$) in both groups (dRegVol S vs DS: -9,8±15,1 ml vs. -11,1±25,3 ml, $p=0,732$).

Conclusion: The initial MR does not affect the favourable response to the CRT. Changes occure mainly in the first six months, after that there were not significant changes. The severity of the midterm MR corellates to the long-term mortality. CRT is effective in reducing functional MR regardless of etiology.

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E/VI-7
LEFT ATRIAL THROMBUS DETECTION BEFORE CARDIOVERSION: CT VERSUS TEE

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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. Our aim was 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 and Materials: In total 661 patients were referred to left atrial angiography before atrial fibrillation ablation procedure between February 2011 and October 2014. We have investigated 277 patients who subsequently underwent TEE within 2 weeks after CTA (mean age=60.4±10.3; 77 female, 200 male; CHA2DS2-VASc score 1.7±1.3). We calculated diagnostic performance characteristics.

Results: CTA excluded left atrial thrombi in 254 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 cases were false positives and 4 were true positives. According to our results sensitivity of cardiac CT is 100% [95% CI: 40.2%-100%], specificity was 93.0% [95% CI: 89.3%-95.8%], negative predictive value was 100% [95% CI: 98.5%-100%] and positive predictive value was 17.4% [95% CI: 5.1%-38.8%].

Conclusion: Cardiac CT is a very sensitive modality to detect 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.

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E/VI-8
ACCELERATED TREATMENT STRATEGY IN INFLAMMATORY BOWEL DISEASES; IS IT ASSOCIATED WITH A CHANGE IN THE DISEASE COURSE?

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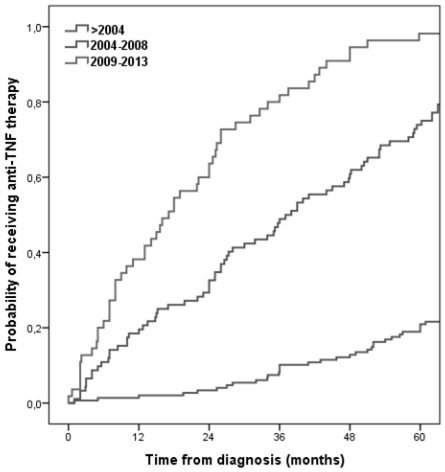
Background and aims: Evidence from new clinical trials in inflammatory bowel diseases (IBD) suggests that tight disease control and early aggressive therapy is associated with superior outcomes in patients with poor prognostic factors. The aim of the present study was to investigate the evolution of the treatment strategy and probability of resective surgery/colectomy in three IBD-centers according to the era of diagnosis.
Methods: Data of 352 consecutive anti-TNF treated IBD patients (CD/UC: 296/56, males: 48.3%/42.9%, 1st anti TNF infliximab/adalimumab: 300/52, median age at diagnosis: 22/25.5 years, follow-up from diagnosis: 8.5/5.5 years, complicated disease behavior and ileocolonic location in CD: 48% and 57.1%, extensive location in UC: 39.3% at diagnosis) were analysed. Both in- and outpatient records were collected and comprehensively reviewed.
Results: The time to anti-TNF, immunosuppressives and steroids was significantly and progressively shortened in both CD ($p_{LogRank}$<0.001 for all, Figure 1) and UC ($p_{LogRank}$<0.003 for all) according to the era of diagnosis (A: <2004, B: 2004-2008, C: 2009-2013). Mean time to anti TNFs and immunosuppressives was 123.8/76.6, 40.8/16.8 and 20.5/8.8 months in CD in Groups A, B and C (p_{ANOVA}<0.001, $pScheffe_{A.vs.B/C}$<0.001). Despite similar disease phenotype, the era of diagnosis was not associated with the time to resective surgery or colectomy ($p_{LogRank}$CD=0.08, $p_{LogRank}$UC=NS) in the total cohort. However, need for resective surgery decreased over time in CD patients treated with infliximab as 1st anti-TNF ($p_{LogRank}$=0.034) and in patients with perianal disease ($p_{LogRank}$=0.04).
Conclusions: An accelerated treatment strategy was observed in this referral IBD cohort. Further data are required to determine whether accelerated treatment strategy is associated with superior long-term outcomes in IBD.



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E/VI-9
HETEROGENEOUS EFFECTS OF OVER-EXPRESSION OF GRß IN COLONIC MUCOSAL CELL LINE PARTLY REFLECTS ALTERATIONS FOUND IN IBD

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The glucocorticoid receptor (GR) is widely expressed in human tissues and plays a crucial role in inflammatory responses. As a consequence of alternative splicing it has several isoforms. Of these isoforms the GRß was frequently found overexpressed in various autoimmune diseases, including inflammatory bowel diseases (IBD). Our research group previously created an intestinal cell line that stably over-expresses the GRß isoform (Caco-2GRβ).

Aims: In our current study we wished to compare the gene expression profile found in GRß over-expressed cell line to archetypal gene expression alterations found in colonic samples obtained from patients with IBD (both Crohn's disease, CD and colitis ulcerosa, UC).

Methods: Whole genome microarray analysis was performed in both normal and GRß over-expressing Caco-2 cell lines. IBD related genes were identified from reanalysis of gene expression profiles of microarray performed on samples obtained from patients with IBD and healthy individuals and deposited in the Gene Expression Omnibus and ArrayExpress databases. Overlapping genes were subjected to pathway analysis.

Results: Increased GRß expression altered the transcription of 852 genes (196 repressed and 656 induced). We identified 737 differently (281 decreased and 456 increased) regulated genes in CD. Of these two lists 64 genes were common and regulated in the same manner (55 up-regulated and 19 down-regulated). Pathway analysis indicated that these genes are involved in adhesion of tumor cell lines, cell proliferation, adhesion of immune cells, necrosis of epithelial tissue and chronic inflammatory disorders. The comparison of GRß related genes with the transcriptome observed in UC showed no major differences compared to CD.

Conclusion: Transcriptome alterations caused by increased expression of GRß in Caco-2 intestinal cell line partly mimic those found in IBD. Our findings warrant further studies to clarify the impact of GRß in IBD.

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E/VI-10
LOW INCIDENCE OF VENOUS THROMBOEMBOLISM IN INFLAMMATORY BOWEL DISEASES: PREVALENCE AND PREDICTORS FROM A POPULATION-BASED INCEPTION COHORT

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Objective: Patients with inflammatory bowel disease (IBD) are considered to have an increased risk for venous thromboembolism (VTE). The aim of the present study was to analyse the incidence and risk factors of VTE in a population based inception cohort in the Veszprem province database between 1977 and 2012.
Material and methods: A total of 1708 incepted IBD patients were included (male/female: 879/829; CD (Crohn's disease): 648, age at onset: 29, IQR: 22-39; UC (ulcerative colitis): 1060, age at onset: 36, IQR: 26-50 years). Both in- and outpatient records were collected and comprehensively reviewed and followed-up for a total of 21369 patient-years.
Results: Twenty-two VTE events were identified in 19 patients (6 events in 5 CD and 16 in 14 UC patients). The incidence rate of VTE in IBD was 1.03 per 1000 patient-years. The risk of VTE in UC was associated with extensive location (OR: 3.25, 95%CI: 1.13-9.35), presence of fulminant episode during the disease course (OR: 4.15, 95%CI: 1.28-13.5), smoking (OR: 3.46, 95%CI: 1.14-10.5) and need for steroids (OR: 2.97, 95%CI: 0.99-8.92).
Conclusions: The incidence of VTE was lower than previously reported. The incidence was higher in males and in UC it was associated with extensive disease, fulminant episodes, corticosteroids-requiring disease and smoking, but not with age at onset.

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E/VI-11
INVESTIGATING THE UNDERLYING MECHANISM OF REMOTE ISCHEMIC PERCONDITIONING: THE NEURAL HYPOTHESIS

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Introduction: Despite the efforts of the last decade, there is no general agreement within the scientific community concerning the mechanism of remote ischemic perconditioning (RIPER). In the present study we aimed to investigate the potential role of neural elements in the transfer of protective signals evoked by perconditioning.
Methods: Male Wistar rats were randomly allocated into 6 groups: sham, IR, RIPER±denervation (n=7/group). Half of the animals underwent left femoral and static nerve resection. In the IR and RIPER groups we induced partial exclusion on 2/3 of the liver. In the perconditioned group RIPER protocol (4x5min IR, left femoral artery) was applied during hepatic ischemia. Hepatic microcirculation (laser Doppler monitor) and systemic blood pressure were parallel measured during the first post-ischaemic hour. Liver samples were taken after 24 hours of reperfusion. Necrosis quantification was performed with automated image analysis software (Fraunhofer Mevis). Liver samples were harvested to analyse the changes of redox-status, serum was used to evaluate the transaminases and total bilirubin (tBi) levels.
Results: Microcirculation and blood pressure showed significant improvement in the RIPER-group. This phenomenon was abolished by nerve resection and values in RIPER+denervation group were comparable to the results of the IR-groups ($p<0.05$; RIPER vs. IR, IR+denervation, RIPER+denervation). Results of necrosis quantification showed similar pattern ($p<0.01$; 6.6 ± 2.5 vs. 37.9 ± 3.1, 29.8 ± 6.4, 34.7 ± 4.7). Beside the noncharacteristic changes of AST levels, ALT values were significantly lower in the RIPER-group compared to the further three groups underwent IR injury. Mild but significant elevation of tBi levels was observed in the IR, IR+denervation and RIPER+denervation groups ($p<0.05$ vs. sham). Results obtained from the analysis of redox-homeostasis were consistent with the findings detailed above.
Conclusions: Perconditioning was able to reduce the IR injury of the liver in our model. The presence of a certain inter-organ neural pathway can be assumed behind this protective response.

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E/VI-12
ALTERATIONS IN SEGMENTAL LIVER FUNCTION AFTER PORTAL VEIN LIGATION - AN EXPERIMENTAL STUDY

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Introduction: Portal vein ligation (PVL) is a technique used before extended hepatic resections, resulting in atrophy of portal deprived lobes, and hypertrophy of the non-ligated liver segments. Although, these volumetric alterations are well-documented, the parallel alterations in segmental liver function are still the subject of controversy. Therefore, the aim of the present study was to evaluate the functional alterations caused portal vein ligation in a well-established rat model.
Methods: Male Wistar rats (n=36) underwent 80% PVL. Before PVL, as well as 1-, 2-, 3-, 5-, 7 days after that, liver morphology (liver weight; histology), liver hemodynamics (laser Doppler flowmetry), and liver function (hepatic bile flow; plasma disappearance rate of indocyanine-green (PDR); the percentage of biliary ICG excretion rate (ICG%)) were examined.
Results: PVL induced atrophy of ligated lobes and compensatory hypertrophy of non-ligated lobes, while the total liver weight remained unchanged. Total hepatic bile flow did not change significantly after the operation. Nevertheless, PDR and biliary indocyanine-green excretion indicated a temporary impairment in total liver function with the lowest value on the 2nd day which normalized by the 5th day. The bile production and biliary indocyanine-green excretion of ligated lobes rapidly decreased after the operation and remained persistently suppressed, while the secretory function of non-ligated lobes - after a temporary decline - increased in a greater extent than the weight of the lobes.
Conclusions: PVL induced a temporary impairment in total liver function, followed by a rapid recovery mainly caused by the increase in the function of non-ligated liver lobes. In the non-ligated lobes, the functional increase was more pronounced than suggested by the degree of hypertrophy. Consequently, the functional capacity of the liver was shifted towards the regenerating lobes in a greater extent than would be expected according to the volumetric alterations.

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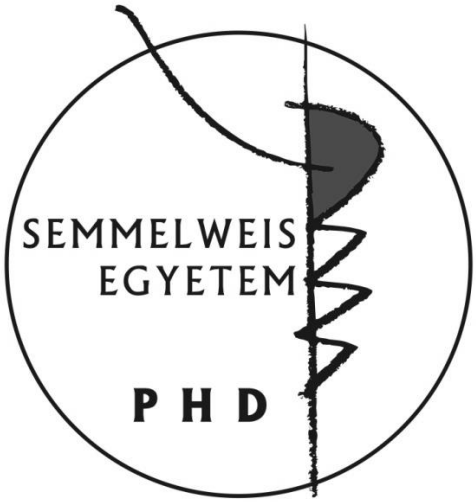

E/VII
PHARMACEUTICAL SCIENCES
ORAL PRESENTATIONS

Chairpersons:

Dr. György Stampf
Dr. Tamás Tábi
Dr. Norbert Szoboszlai

E/VII-1
DETERMINATION AND QUANTIFICATION OF 2'-*O*-FUCOSYLLACTOSE AND 3-*O*-FUCOSYLLACTOSE IN HUMAN MILK BY GC-MS

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2'-*O*-fucosyllactose (2'-FL) is the most abundant oligosaccharide in human milk. Its linkage isomer 3-*O*-fucosyllactose (3-FL) is found to be less abundant, however it has still a major contribution to the total oligosaccharide content of human milk. In the artificial nutrition business, manufacturers put a huge effort in producing infant formulas which contain oligosaccharides to mimic the complexity of the human milk. As 2'-FL and 3-FL are found in significant amounts in human milk and colostrum, it is likely that they are among the first candidates for the infant formulas to be enriched with.

The aim of our study was to develop a GC-MS method suitable for the determination and quantification of 2'-FL and 3-FL in human milk and possibly in infant formulas for the first time. After a derivatization step with hexamethyldisilazane the TMS-oxime derivatives of the standards were analyzed by GC-MS. The developed method was able to identify the trisaccharides not only by their retention times but also by their selective fragment ions (538 *m/z* for 2'-FL and 361 *m/z* for 3-FL, respectively). The fragmentation pattern was interpreted in detail, the developed GC-MS method was fully validated in the terms of specificity, selectivity, precision, linearity, LOD, LLOQ, accuracy and stability.

Finally, human milk samples from two nursing mothers were analyzed to present the applicability of the method in complex biological matrices as well. In the first week of lactation the concentration of the two compounds in both mothers were constant. The 2'-FL/3-FL ratio in *donor A* milk was found to be 15, while in the case of *donor B* this ratio was 20. These results are in accordance with the expected ratios based on the mothers' secretor status.

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E/VII-2
SYNTHESIS OF NOVEL FUNCTIONALIZED NEOFLAVANS AND THEIR ANALOGS VIA ELECTROPHILIC RING CLOSURE FROM MESYLATES

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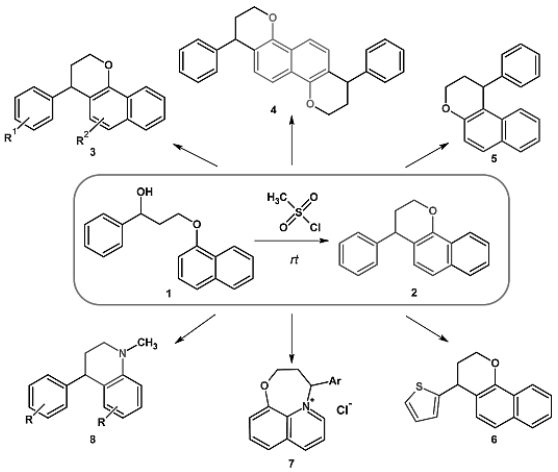
Toward the synthesis of dapoxetine[1] we discovered a novel ring closure strategy which enables the formation of condensed oxygen heterocycles. The obtained neoflavans (4-aryl-3,4-dihydro-2*H*-chromenes (**2**) in red part) or substituted chromanes are ubiquitous substructures present in biologically active natural compounds[2].
We found that the mesylation of alcohol **1** enables a subsequent carbon-carbon bond formation resulting a tricyclic compound (**2**, 4-phenyl-2*H*,3*H*,4*H*-naphtho[1,2-b]pyran) via cationic intermediate. The effect of substituents on the ring closure was studied with several substituted naphthol derivatives (**3**). The reaction was successfully extended to a thiophene derivative (**6**). Further naphthols such as naphthalanediol and *β*-naphthol also provided the desired tetracyclic (**4**) and positional isomeric compound (**5**). In case of quinolin-8-ol, a polar seven-membered ring containing quaternary nitrogen (**7**) was isolated. Finally, the reaction was accomplished with tertiary aniline derivatives providing piperidine derivatives **8**.



We have developed a simple and practically applicable strategy for the synthesis of functionalized neoflavans and other *N*-containing heterocyclic compounds. Regarding the mechanism of the reaction we suppose that the cyclization takes place via electrophilic aromatic substitution. The key carbocationic intermediate formes "*in situ*" by the elimination of the mesylate under the mild reaction conditions.

Supported by OTKA PD109373 and the János Bolyai Research Scholarship (Sz. B.).

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[2] Shen, H. C.; Tetrahedron 2009, 65, 3931.

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E/VII-3
ANALYSIS OF NMDA MODULATORS WITH CE-LIF IN DIFFERENT BIOLOGICAL SAMPLES

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L-amino acids are the building blocks of proteins and only their formation and presence in biological systems were believed till a few decades ago. However, recent results suggest that several D-amino acids like D-aspartate and D-serine occur in many living organisms, including the human body. These amino acids possess neuromodulator function in the Central Nervous System (CNS) as their main target is the N-methyl-D-aspartate receptor, which plays important role in neuroplasticity, memory formation, learning processes and some pathological conditions. Our aim was to develop a chiral capillary electrophoresis method to quantitate D-aspartate and D-serine in biological samples. Capillary electrophoresis method for enantioseparation of aspartate and serine has been developed and applied for their determination in various brain areas of newborn and adult mice after the animals were sacrificed. For the sensitive laser-induced fluorescence (LIF) detection of amino acids their derivatization with NBD-F was used. An amino-modified ß-cyclodextrin, HPA-β-CD was found suitable for chiral analysis of various amino acids. Using 50 mM pH 7 HEPES buffer containing 6 mM concentration of this chiral selector provided baseline separation of aspartate and serine enantiomers. All determinations were accomplished in a polyacrylamide coated capillary using reverse polarity for the analysis of the negatively charged analytes. The developed method has been validated. The applicability of the method was tested by determination of D-amino acid neuromodulators in brain samples from newborn and adult mice. The brains from newborn mice contain D-aspartate in higher concentration compared to the adult brain samples, while the opposite was found in case of D-serine. Among analysed adult brain samples, amygdala, hippocampus and prefrontal cortex were rich in both D-amino acids. The higher level of D-aspartate found in brain samples of newborn mice is in line with previous results suggesting its role in neurogenesis. Higher level of NMDA receptor modulators could be detected in brain regions playing important role of memory formation. The developed capillary electrophoresis method is suitable for quantitation of D-aspartate and D-serine in brain samples from laboratory animals of various disease models.

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E/VII-4
AMORPHOUS FAMOTIDINE STABILIZED IN ELECTROSPUN POLYMER FIBERS AS A MODEL OF ODW FORMULATION FOR ACTIVE AGENTS WITH POOR INTRAORAL SOLUBILITY

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Electrostatic spinning is a fast and gentle, solvent-based, continuous technology originating from the textile/filtration industry, which is capable of producing very thin polymer fibers via extremely fast evaporation of the solvent. Recently, many medicine-related fields, including pharmaceutical technology, show notable attention towards this technique, due to the large surface-area of the prepared fibers and the possibility of incorporating and stabilizing various active pharmaceutical ingredients (APIs) in the fibers in amorphous form. These advantages result in enhanced dissolution properties. Famotidine is an important H2 histamine antagonist drug of poor solubility, especially in the small amount of saliva. Moreover the literature information is very limited on its amorphous forms or preparation.

Objectives: This work aimed at the preparation and thorough characterization of electrospun famotidine 'orally dissolving web' system (ODW), and studying its stabilizing effect on amorphous famotidine.

Methods: Morphology of the samples was characterized by polarization microscopy and scanning electron microscopy. Effectiveness of amorphization and physical stability were studied by differential scanning calorimetry, powder X-ray diffraction, micro-Raman and solid state NMR spectroscopy, while chemical stability was tested by solution NMR and LC-MS. Dissolution properties were studied at pH 6.8 with both the conventional and a new, small-volume method for an improved modeling of intraoral conditions.

Results and conclusion: Electrostatic spinning was suitable for preparing and stabilizing famotidine in amorphous form. The API incorporated in polymer fibers was fully amorphous and physically stable after more than 17 months compared to purely amorphous samples showing deliquescence and/or crystallization in a couple of days. Dissolution of the incorporated API was almost immediate. Furthermore, small-volume dissolution revealed significant solubility-increase when compared to the two polymorphic forms as well as to physical mixtures with the polymer, thus showing properties of an ODW formulation.

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E/VII-5
QUANTITATIVE SILYLATION SPECIATIONS OF PRIMARY PHENYLALKYL AMINES, INCLUDING MESCALINE, AMPHETAMINE AND 3,4-METHYLENEDIOXY-AMPHETAMINE, PRIOR TO THEIR ANALYSIS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY

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A novel, comparative derivatization study of thirteen primary phenylalkyl amines - including illicit compounds, such as mescaline, amphetamine and 3,4-methylenedioxy-amphetamine - was noted: contrasting analytical performance characteristics in acylation with hexamethyldisilazane (HMDS) & perfluorocarboxylic acids (PFCAs) and in trimethyl-silylation (TMS) with *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (MSTFA) reagents.
Selectivity and efficiency of acylation and silylation processes were characterized with retention properties, selective fragmentation patterns and response values of derivatization products under comparable gas chromatographic-mass spectrometric conditions. Processes' stoichiometry was obtained on the basis of reagents' source and composition.
The practical utility and consequences of methods' comparison were shown by analyses of amphetamine in urine and mescaline in *Lophophora williamsii* cactus samples.
Acylation and silylation protocols are fully validated: proving proportionality and analytical performance characteristics in details.

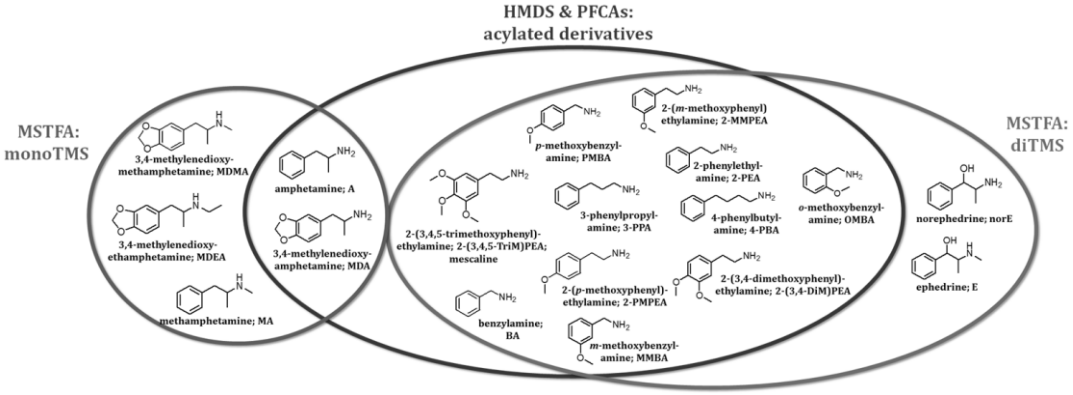

Figure 1. *– Comparative derivatization study of phenylalkyl amines*

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E/VII-6
SYNTHESIS AND CHARACTERIZATION OF NOVEL C_3 SYMMETRIC TRIPODAL TRIAZOLES

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Small molecules with receptor-like ion-binding properties, especially symmetric polydentate complexing agents are of great interest in medicinal and coordination chemistry, as shown by the large number of C_3 symmetric structures that have recently been synthesized.
One of the highly capable moieties for metal ion complexation is 1,2,3-triazole, and with the still-evolving methods of click reaction, 1,2,3-triazole became a resilient building block with a wide variety of substituents.
Aims: Synthesis and profiling of triazole containing C3 symmetric ion-binding compounds with a cyclohexane core. Studies on their proton- and Cu(I)-binding properties.
Results: Utilizing click and Sonogashira reactions ion-binding triazole and pyridazin-3(2H)-one units were built in with cyclohexane 1,3,5-tricarboxylic acid forming C_3 symmetric polydentate ligands. The structures of the derivatives were characterized by ^{1}H, ^{13}C 1D and 2D NMR techniques along with HRMS and IR. Their protonation processes were monitored by ^{1}H NMR-pH titrations, the macroscopic and site-specific constants were determined by custom-tailored evaluation method. The copper(I)-binding abilities were investigated by mass spectrometry, UV and NMR spectroscopy, and by using them as additives in model copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reactions (Figure 1).

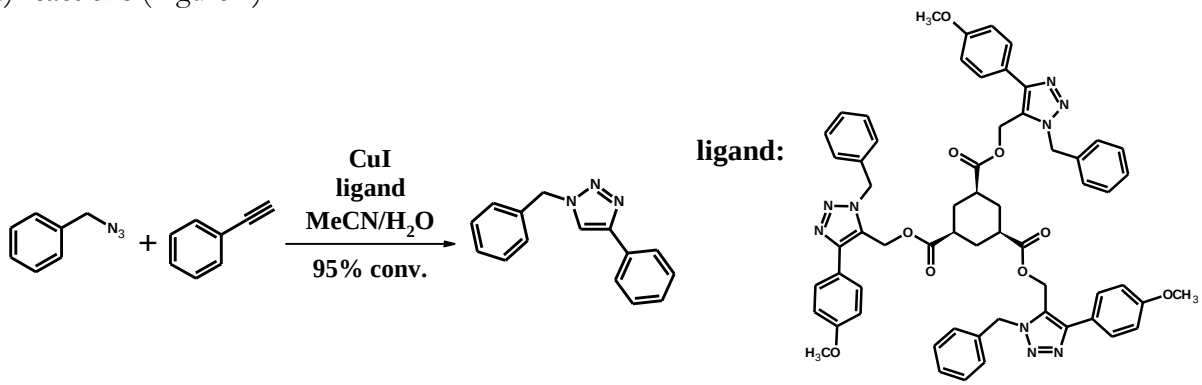

Figure 1. *– Model CuAAC reaction, the structure of one of the symmetric products.*

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E/VII-7
PREPARATION AND STABILITY STUDY OF CARVEDILOL LOADED HYDROXYPROPYL CELLULOSE MICROFIBERS AND THEIR FORMULATION TO ORODISPERSIBLE TABLETS FOR IN VITRO DISSOLUTION ENHANCEMENT

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Aims: The aim of this study was to demonstrate the importance of novel formulation approaches, such as fiber formation methods in the overcoming poor aqueous solubility, one of the most urgent issues arising during drug development. Our intention was to formulate a solid oral dosage form employing rotary-spun microfibers containing carvedilol, a nonselective beta blocker/alpha-1 blocker in order to improve in vitro dissolution properties of the incorporated drug. Carvedilol belongs to the Biopharmaceutical Classification System Class II, where the oral bioavailability of the drug is confined by the limited water solubility. The prepared carvedilol loaded microfibers were subjected to accelerated tests.

Results: Microfiber based orodispersible tablets containing 10 mg of carvedilol were successfully prepared by direct compression applying common tableting excipients. All of the investigated tablet parameters (hardness, firability, in vitro disintegration time) complied with the pharmacopoeial requierements. The performed dissolution study indicated that the drug dissolution from the microfiber based formula was rapid, complete and independent from the pH of the applied media, while the dissolution from the control tablets, containing crystalline carvedilol was incomplete and was strongly influenced by the pH of the applied media. Complex physicochemical characterization of microfibers including powder X-ray diffraction, differential scanning calorimetry, attenuated total reflectance Fourier transform infrared spectroscopy, and positron annihilation spectroscopy indicated amorphous transition of carvedilol and supramolecular ordering of chains of polymer matrix, which is the suggested reason of the observed dissolution enhancement. The accelerated stability study (40 ± 2 °C/75 ± 5% RH) indicated a large stress tolerance capacity of fibers, since only a partial crystallization of the active compound was observable at the last sampling point.

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E/VII-8
MOUSE MODELS FOR TESTING DRUGS IN DIFFERENT SENSORINEURAL HEARING LOSS FORMS

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Despite the fact that hearing loss (HL) is the most common human sensory deficit, there is no specific effective drug therapy against its sensorineural forms - i.e., ototoxic drug-, noise-induced hearing loss (NIHL) and age-related hearing loss (AHL). Although there are many similarities in the pathogenesis of SNHLs, potency of protective drug candidates needs to be tested individually in the different forms of the disease.
In our laboratory, the aminoglycoside antibiotic-induced hearing loss mouse model has been set up and successfully applied to the detection of otoprotective drug candidates in vivo.
To test the effect of drugs against NIHL, we developed a ventilated noise box and exposed CD1 and BALB/c mice to 90, 98 and 110 dB, 8 – 16 kHz white noise for 15 and 30 min. Temporary (TTS) and permanent (PTS) threshold shifts were determined by ABR. Based on the measured threshold shifts, the 30 min, 98 dB noise exposure was chosen for further experiments. N-Acetylcysteine, a compound shown to be protective against NIHL, were used to validate the model. Our candidate compound exerted a slight, but significant protection against both TTS and PTS.
Protective effect of the candidate compound against AHL was started to test in two inbred strains of mice (DBA/2J and BALB/c), which carry the ahl8/ahl genes and show early/later onset AHL, respectively. Hearing threshold changes are planned to follow for a year by measuring ABR in every month. Early results demonstrated the progressive impairment of hearing and a moderate protection by the test compound.
The complex, multifactorial pathomechanism of SNHLs most likely requires drugs acting on multiple targets for effective therapy. On the other side, drugs with multi-target action might be useful in different SNHL forms, what needs to be tested in vivo.

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E/VII-9
SITE- AND SPECIES-SPECIFIC HYDROLYSIS RATES OF COCAINE

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Ester group is an abundant unit in bio- and drug molecules, and also, in illicit drugs of abuse. Some of the prime examples are: acetyl-choline, membrane-forming phosphatidylcholines, acetyl-salicylic acid, procaine, heroin, cocaine. The most common biotransformation pathway of the ester group is hydrolysis. Hydrolysis of drugs results in most cases in loss of biological activity, whereas the contrary happens to prodrugs. The quantitation of ester hydrolysis is therefore an important element to reveal details of drug metabolism and prodrug design. The hydrolysis rate is well-known to depend on extramolecular factors such as temperature, solvent, pH. Much fewer, and largely qualitative data are available only on how the state of protonation and conformation of the intramolecular vicinity influences the parameters of ester hydrolysis.

The two best-known, infamous "hard drug" agents, heroin and cocaine are molecules that uniformly bear two ester and one basic amine moieties. Their partial hydrolysis yields intermediate products of one ester and two acid-base functions, the states of which heavily influence their effects. The exact kinetic and thermodynamic description of these systems needs new methods.

In order to determine the site- and species-specific ester-hydrolysis rates of cocaine and its hydrolysis products (benzoyl ecgonie and ecgonine methyl ester) we carried out time- and pH-dependent ^{1}H NMR spectroscopic measurements on all of these compounds and used a new custom–tailored evaluation method.

As important constituents of the above evaluation process, we also determined the site- and species-specific protonation constants of cocaine, benzoyl ecgonine, ecgonine methyl ester, benzoyl ecgonine amide and ecgonine. The resulting kinetic and thermodynamic constants are interpreted in terms of the intramolecular effects of the adjacent moieties. These data make the hydroxide-catalyzed ester hydrolysis rates understandable and allow the design of subtle effects on hydrolysis rates for prodrugs.

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E/VII-10
PROTECTIVE EFFECT OF RESVERATROL ON SERUM DEPRIVATION INDUCED CASPASE ACTIVATION IN NON-TRANSFORMED CELLS

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Introduction: Resveratrol is a widely investigated phytoalexin compound, which can be found in numerous plants, mainly in red grapes. It was reported to possess multiple pharmacological properties; however, its effect on the apoptosis is contradictory in the literature, as both pro- and antiapoptotic effect have been described. The cell type used can be one of the major differences between the various models and the compound might differentially affect tumorigenic and non-transformed cells.
Aims: The aim of our present study was to investigate the effect of resveratrol on caspase 3 activation and protection of non-transformed cells following serum deprivation. The specific background mechanisms involved were also to be determined.
Methods: In this study primary mouse embryonic fibroblasts were used as a non-transformed cell culture model. Apoptosis was induced by serum deprivation. Caspase activation and cell viability were assayed by fluorescent methods. The involvement of various signaling pathways was examined by using selective inhibitors.
Results: Serum deprivation of primary fibroblasts induced significant caspase 3 activation within 3 hours and reduced cell viability after 24 hours. Resveratrol dose dependently prevented caspase activation and improved cell viability with IC50 value of 50-100 microM, and it was also able to reduce the already upregulated caspase 3 activity suggesting its rescue effect. Among the major signaling pathways p38 kinase was found to be critical in the cytoprotective effect of resveratrol suggesting the role of mild stress in its effect.
Conclusions: We demonstrated the p38 MAPK signaling pathway dependent cytoprotective effect of resveratrol against serum deprivation induced caspase 3 activation in primary fibroblasts. Furthermore, our results show that resveratrol also exhibits a rescue effect and reduces the already upregulated caspase 3 activity, suggesting that it may be capable of not only preventing, but treating of aging-related degenerative diseases.

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E/VII-11
APPLICATION OF MITSUNOBU REACTION FOR THE SYNTHSES OF 6β-ACYLAMINOMORPHINAN COMPOUNDS

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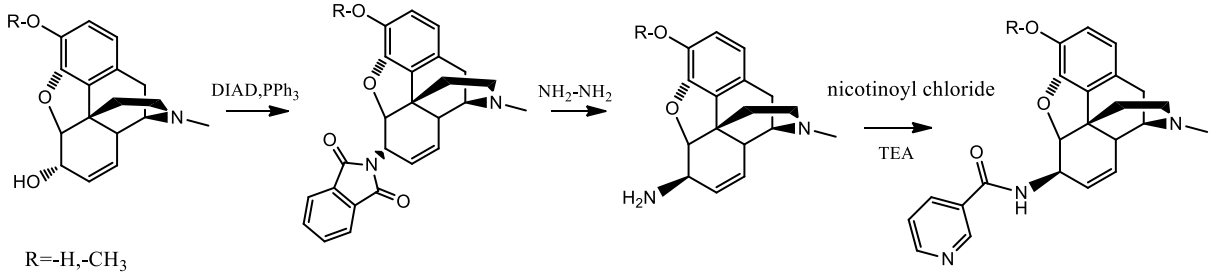
Treatment of chronic pain is still an important area of pharmaceutical research. Researchers are trying to develop more potent analgesics with less side effects. In our research project 6β-amino derivatives of morphine were synthesized with Mitsunobu reaction then acylated with nicotinoyl chloride or isonicotinoyl chloride. We synthesized more than 10 new substances, in vitro and in vivo testes were carried out in the Memorial Sloan-Kettering Cancer Center.

For structure determination mass spectroscopy, nuclear magnetic resonance spectroscopy and combination of circular dichroism spectroscopy and quantum chemical computations were utilized.



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E/VII-12
COMPARABLE EVALUATION OF RP-HPLC, SFC, UPC^2 TECHNIQUES IN THE PARTHENOLIDE ANALYSIS OF *TANACETUM PARTHENIUM* L. SUPERCRITICAL EXTRACTS

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Feverfew (*Tanacetum parthenium* L.) is a perennial medicinal plant which has been used to relieve the symptoms of migraine, rheumatoid arthritis and has many pharmacological properties. The herb contains various potentially active constituents such as sesquiterpene-γ-lactones, flavonoids and volatile oil. The main sesquiterpene-lactone in feverfew is parthenolide which is considered to be responsible for the therapeutical effects.
The aim of our work was to develop and compare selective, accurate and reproducible coupled chromatographic methods to measure the parthenolide content of feverfew. Supercritical CO_2 extraction was carried out at different pressures (10-30MPa), temperatures (40-80°C) and co-solvent contents (0-10% ethanol) in order to study the extraction yield and the parthenolide recovery of the extracts. Leaves collected before and during flowering and flower heads were investigated. A factorial experiment using a full 3^3 design was followed during the experiments and response surface methodology was implemented to analyze the influence of the variables and optimize the extraction. The critical values of parthenolide content were found to be 7% EtOH, 22MPa and 64°C in case of all three samples. It was determined, that the optimal conditions of the extraction, where the maximum parthenolide content and extract yield can be reached, do not coincide. To measure the parthenolide content of the extracts three chromatographic method was developed and validated. High Performance Liquid Chromatography (RP-HPLC), Supercritical Fluid Chromatography (SFC) and Convergence Chromatography (UPC^2) determinations were carried out using external standard calibration and were validated for accuracy, linearity, limit of detection, limit of quantification, repeatability and intermediate precision. The results of all three methods were consistent with the ICH guidelines for biological samples. The convergence chromatographic method has shown outstanding validation data with advantages of high resolution, sensitivity, very good reproducibility and short analysis time. The RP-HPLC and the SFC measurements showed lower values, than the previous UPC^2.

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E/VII-13
NEW *IN VITRO* PERMEABILITY TEST FOR TRANSDERMAL AND LOCAL THERAPEUTIC PATCHES

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

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Using the skin as absorption site presents unique advantages that have facilitated the progression of transdermal drug delivery in the past decades. Efforts in drug research have been devoted to find a quick and reproducible model for predicting the skin permeation of molecules. The Parallel Artificial Membrane Permeability Assay (PAMPA) has provided a suitable platform to develop a fast, cost-efficient and high throughput technology called Skin PAMPA™. This is an in-vitro, 96-well plate based method containing a completely artificial membrane which can mimic the barrier properties of stratum corneum. Its high prediction capability has been demonstrated; therefore it appears to be a useful tool for preliminary absorption prediction, for API or formulation ranking and for understanding the permeation modifying effect of each formulation component.
The present study aims to extend the Skin PAMPA™ method for testing transdermal and local therapeutic patches. The original method was modified and seven commercially available transdermal and local therapeutic patches with four different active pharmaceutical ingredients (nicotine, fentanyl, rivastigmine and ketoprofen) were studied. Data were compared to the declared delivery rates that are indicated by the manufacturers. *Ex vivo* permeation study was also performed in order to compare the permeated amount of the released drugs obtained by the two methods. The flux across the artificial membrane as well as the human skin (*ex vivo*) has been calculated and compared to the *in vivo* flux deduced from the labelled delivery rate and the active area of the patches.
The results discussed in our presentation suggest that Skin PAMPA™ system can serve as a useful tool for evaluation and classification of the transdermal patches.

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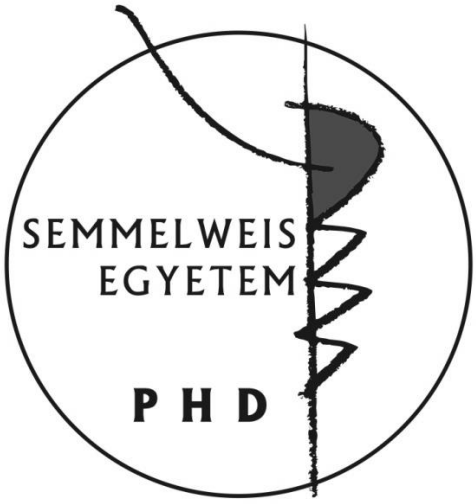

P/I
MENTAL HEALTH SCIENCES
POSTER PRESENTATIONS

Chairpersons:

Dr. György Bagdy
Dr. Katalin Hegedüs
Dr. Zsuzsa Széman

P/I-1
VISUALLY IMPAIRED CHILD IN THE FAMILY: CHARACTERISTICS OF FAMILY FUNCTIONING IN FAMILIES RAISING VISUALLY IMPAIRED CHILDREN

Erika Kiss
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In my research I seek to answer how parents raising visually impaired children adapt to their specific situation. I also endeavour to identify factors that increase the parents' positive adaptation (protective factors) and factors that enhance their difficulties (risk factors).

The Hungarian and international scholarly publications discussing the topic (Pálhegyi, 1991, Komlósi, 1992, Radványi 2006, 2013., Rutter, 2007, Kálmán, 2004.) mainly focus on the functioning of families with mentally and physically disabled children. To date I have not yet found data concerning the adaptive functioning of families raising visually impaired children.

Based on the cited research findings (Eddy-Engel, 2008, Danis-Kalmár, 2011, Garai-Kovács, 2013.) I presume that visual impairment is an aggravating circumstance that brings about changes in the family functioning. My hypothesis is that the efficiency of the adaptation in families raising visually impaired children is a multifactoral process in which, besides the socioeconomic status, (SES), social (external support, resources within the family) and personal characteristics (the intellect of the child, the nature and severity of the impairment, additional impairments or illnesses) play an important role.

In my research I use *quantitative and qualitative analytical methods*: based on an investigation of demographic features retrieved from the anamnestic data of 1707 visually impaired (blind and low vision) children aged 0-16, I attempt to describe the changes that the presence of such children might bring about in the family (e.g. discontinuing relationship, moving to different locations, not having more children etc.). Furthermore, emphasis will be laid on how the personal characteristics of the child (the severity of the visual impairment, additional disabilities) influence the family functioning. I also plan to request more than a hundred concerned couples and single parents alike (in groups matched by main demographic data) to fill in a questionnaire in which I aim to identify the protective and risk factors that affect the acceptance of the visually impaired children.

From the quantitative analytical section of the research undertaken so far it is clearly seen that the discontinuation of parental relationships has a far greater likelihood in families with low vision children than in those with blind children, and furthermore, that beyond the severity of the visual impairment the additional disabilities (e.g. mental and physical disabilities) also exert a strong influence on the quality of the family relations. The data obtained clearly indicate that, besides the above factors, the place of residence and the age and education of the parents also play a significant role in the adaptive functioning of the families.

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P/I-2
ELEMENTARY SENSORY DEFICITS IN SCHIZOPHRENIA INDEXED BY IMPAIRED VISUAL MISMATCH NEGATIVITY

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***Introduction*:** Mismatch negativity (MMN) is an automatic brain response to unexpected events. It represents a prediction error (PE) response, reflecting the difference between the sensory input and predictions. While deficits in auditory MMN are well known in schizophrenia, only few studies investigated impairments in predictive visual processing in schizophrenia. These studies used complex stimuli such as motion direction and emotional facial expressions. Here we studied whether automatic predictive processing of elementary features such as orientation is also impaired in schizophrenia.

***Methods*:** Altogether 28 patients with schizophrenia and 27 healthy controls matched in age, gender, and education participated in the study. EEG was recorded using 128 channels in the two experimental blocks. Using an oddball paradigm, horizontal stripes of Gabor patches were presented as frequent standards and vertical stripes as rare deviants in one block. Stimulus probabilities were swapped in the other block. Mismatch responses were obtained by subtracting responses to standard from those to deviant stimuli.

***Results*:** We found significant mismatch responses in healthy controls but not in patients in the prefrontal and occipital-parietal regions in the 90-200ms interval. Furthermore patients showed significantly decreased deviant minus standard difference waveforms relative to controls in the same regions with moderate to large effect sizes.

***Conclusions*:** Our findings demonstrate that predictive processing of unattended low-level visual features such as orientation is impaired in schizophrenia. Our results complement reports of sensory deficits found in tasks requiring attentive processing and suggest that deficits are present in automatic visual sensory processes putatively mediated by glutamatergic functioning.

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P/I-3
THE EFFECTS OF FOLATE PATHWAY GENES *MTHFR* AND *MTHFD1L* ON DEPRESSIVE RUMINATION IN TWO EUROPEAN WHITE POPULATIONS

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Rumination is an endophenotype and risk factor for major depression, since it denotes a cognitive persevaration on distress. Folate pathway includes common risk factors for perseverative cognition and depression, but it has never been investigated in the genetic background of depressive rumination.

Aims: We explored the association of depressive rumination with two genes from the folate pathway: 5,10-methylenetetrahydrofolate reductase *MTHFR* and mitochondrial monofunctional 10-formyl-tetrahydrofolate synthetase *MTHFD1L*. We chose one single nucleotide polymorphism from each gene to test the association, in a European white population recruited from Budapest (N=895) and Manchester (N=1309). If an association existed, we were also interested in that if it could be replicated separately in Budapest and Manchester, and if depression phenotypes mediated the effect.

Results: *MTHFR* C677T (rs1801133) did not show any association with depressive rumination in our study, and had showed inconclusive associations with depression in other studies, albeit it has a strong functional effect on enzymatic activity. However, *MTHFD1L* rs11754661, which had proven to be a genome-wide significant risk factor for Alzheimer's disease, was associated with depressive rumination in our population. This association could be replicated in Budapest and Manchester, separately. The effect of rs11754661 on rumination was partially mediated by Brief Symptom Inventory depression score and lifetime depression in both Budapest and Manchester, and also in the combined population.

Conclusion: *MTHFD1L* is a more important part of the folate pathway in the genesis of depressive rumination and thus depression than *MTHFR* is, at least among white Europeans. The importance of folate pathway in depressive rumination highlights the potential of a preventive depression treatment with folate.

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P/I-4
THE EXPERIENCES OF BREAST CANCER PATIENS AND THE ROLE OF PURPOSE IN COPING – A QUALITATIVE ANALYSIS

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Theoretical background: Diagnosing a breast tumor can bring significant pressure to the lives of both the patient and her partner. (Balog, Dégi, 2005). Because of the severe nature of the disease and the threat of losing femininity – e.g. mastectomy or chemotherapy that induces hair loss – in order to minimize anxiety and stress for the patient the way she precieves support and satisfaction in the relationship (Holland, 2010). Another possible way to support Another way we can help patients cope with cancer is by setting up personal goals, creating a representation of their future. (Martos et al, 2006).

Goals: Our goal was to introduce the interrelation between goals and the relationships of women suffering from this disease with respect to the personal experience of the disease.

Methods: With the eight breast cancer patients appointed for this study (age: 38,6 ± 8,4) we used a semi-structured interview. During these interviews we revealed their personal goals and plans, and additionally the way these two are present in their relationships. The correlation between these factors and coping with the disease was also explored.

Analysis and expected results: we used a qualitative method, the Interpretative Phenomenological Analysis (IPA) which is rapidly gaining popularity between qualitative health psychologists. During the analysis the following topics have emerged: Drawing boundaries and contrasts, Resources and obstacles, Relationships and the need for change. By applying IPA we can close up on how breast cancer patients experience their relationships and their personals plans and innermost motivations, expectations.

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P/I-5
STUDY OF SOCIAL CAPITAL AND SELECTION OF UNIVERSITY PROFESSIONAL RELATIONSHIP AT SEMMELWEIS UNIVERSITY FOUR FACULTIES

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The concept of social capital is a social / human relations. Concept design of researchers - Bourdieu, Coleman, Putnam - varies.

Coleman, the social context of education examination led to the concept of social capital. According to the definition of the term includes "social relations" on pages that promote a particular individual or group achieve its goals, to implement interests" (Coleman, 1990).

The research on social capital helps students interpret the happenings, decisions it helps to understand the micro-environment in which they spend time studying. The assumed relationship between decisions made by the students of social capital and empirical verification of social capital should be measurable.

Aim: The research aims to examine whether each type of students originating from the social capital of the influence of the vocational choice of their decision. It is assumed that students with stronger social capital prefer the more prestigious faculty, as a general practitioner or dentist faculty.

Method: The test methods: quantitative online survey data collection among the students of the Semmelweis University. The database is recorded at the Semmelweis University in 2014, doctor, dentist, pharmacist or health administration (BSc) students of our own, who filled out the online questionnaire constructed for this purpose (N = 353).

The statistical analysis tools: descriptive statistics, contingency tables, logistic regression.

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P/I-6
RELATIONSHIP BETWEEN BURNOUT AND ORGANIZATIONAL FACTORS AMONG HUNGARIAN UNIVERSITY HOSPITAL PHYSICIANS, THE HOUPE STUDY

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Background: Burnout -a chronic work stress-related condition- affecting physicians became a serious public health issue as it may adversely impact the quality of patient care. In Hungary, the prevalence of burnout among physicians is particularly high, while the health status of the population is generally poor. While data on task-level determinants of burnout is abundant, little is known about the relationship between burnout and organizational-level factors.

Aims: The study aims at determining the level of burnout among the physicians working at Semmelweis University. Our goal is to analyze the relationship between organizational factors and exhaustion, respectively disengagement.

Methods**:** Cross-sectional study conducted among 162 Hungarian physicians (50.6% male, 49.4% female). The average age of the sample was of 44.21 years (SD=10.47). For the assessment of the two dimensions of burnout (exhaustion and disengagement) the MOLBI questionnaire was used. Scales of the QPS-Nordic were used for the assessment of organizational factors such as human resource primacy, empowering leadership, innovative climate, role conflict respectively control of work pacing. The scales of the applied questionnaires showed good reliability, with α values between 0.63-0.88.

Results: Around half of the physicians reported higher than average levels of exhaustion (54.9%) and disengagement (45.7%). Controlling for age and gender, stepwise multiple regression analysis showed that exhaustion was predicted by human resource primacy (β=-.34, p<.001), role conflict (β=.19, p=.016), innovative leadership (β=-.23, p=.009) as well as control over work pace (β=-.19, p=.012). They explained 20.4% of the variance (R^2=22.4, F(4,155)=11.16, p<.001). Disengagement was predicted by human resource primacy (β=-.23, p=.004), role conflict (β=.2, p=.015), and the age group of 30-34 years (β=.23, p=.002), accounting for 18.8% of the variance (R^2=20.4, F(3,156)=13.3, p<.001).

Conclusion: Our results call for urgent policy changes concerning work structure and improved leadership skills in order to reduce the prevalence of burnout among university hospital physicians.

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P/I-7
IMPROVEMENT OF THE CONSENSUS RORSCHACH TEST'S PROCESSOMETRIC EVALUATION SYSTEM

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Introduction: At our poster we present data on the improvement of the Consensus Rorschach Test's (CRT) processometric evaluation system (Bagdy et al, 2006). This methodology is suitable for deeper understanding of interpersonal functioning types of the couples.

Aims: To show how a couple's communication process can be analyzed in detail across the dimensions of dominance, constructiveness and emotional distance by our improved evaluation system. We also aim to present data on the concurrent results of CRT and other psychological tests.

***Methods*:** Heterosexual couples in committed long term relationships from a larger database (N = 18 couples) were tested through CRT. The results were compared with other psychological tests, among others the Hungarian version of the Relationship Assessment Scale (RAS-H, Martos et al, 2014) and the Personal Project Assessment Schedule for Couples (PPA-C, Martos and Sallay, 2014).

Analysis and results: The CRT data are analyzed both qualitatively and quantitatively. The connections are analysed between the partners' communication (dominance, constructiveness and emotional distance), the relationship satisfaction and the relationship experiences gained through the realization of the future plans of couples.

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P/I-8
FACIAL EMOTION EXPRESSION DURING A FACIAL EMOTION RECOGNITION TASK IN A CLINICAL SAMPLE OF ADOLESCENTS WITH PEER PROBLEMS

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Introduction: The connection between specific difficulties of facial emotion recognition and certain psychopathologies related to social behavior (e. g. conduct disorder) is well established in the literature. However, patterns of facial emotion expression in these conditions have not yet researched systematically. The aim of this study was to analyze the descriptive parameters of facial emotion expression during Ekman 60 Faces Test and their possible connections to overall emotion recognition performance, with the help of the Noldus FaceReader program.

Method: Twenty-three adolescents aged between 13 and 18 years (girls: n=11; mean age=14.2; Standard Error of Means; SEM=3.0) with peer problems participated in the study. All participants were recruited from the inpatient care system of the Vadaskert Child Psychiatric Hospital. The sample is a part of the study "Dimensional Approach in Externalization Disorders" research. Ekman 60 Faces test was used to assess emotion recognition performance. Facial emotion expressions were analyzed by Noldus FaceReader program. Statistical analyses were performed by Pearson's correlations and General Linear Modell (GLM).

Results: Mean overall emotion recognition performance was 70.0% (SEM=14.6%). During the test, most expressed emotion was sadness (mean=22.8%; SEM=4.8%), followed by happiness (m=10.2%; SEM=2.1%). Least expressed emotion was fear (m=0.4%; SEM=0.08%). Overall emotion recognition performance showed a tendency of positive correlation with happiness expression during the test (r=0.395; p=0.065). To further analyze this connection, two groups were formed from participants with high or low happiness expression frequencies. According to GLM, the group with high happiness expression frequency performed significantly better in the emotion recognition task than the low happiness group (F=8.69; p=0.010). Between these two groups, there were no significant differences in happiness recognition.

Discussion: Data from this study shows that there is a connection between the frequency of happiness expression and overall emotion recognition performance. Our results suggest that additional to the misinterpretation of signals from social environment an additional expression bias might be described, and this effect should be further analyzed in specific psychopathologies related to social disturbances.

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P/I-9
SCREENING OF AMNESTIC MILD COGNITIVE IMPAIRMENT

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Introduction: In our aging society prevalence of dementia is increasing, treatment of these patients is a heavy burden on the society.

According to neuropathological researches, dementia is preceded by a long presymptomatic phase, when histological deviations are present, but the symptoms of dementia cannot be observed.

Such a presymptomatic phase is amnestic mild cognitive impairment (aMCI), which is characterized by memory disturbances that often precedes Alzheimer diseases. Approximately 10-15% of patients with aMCI convert to dementia within a year.

That was the reason we started to look for imaging diagnostic methods, which could provide precise screening and early diagnoses.

Aim: The aim of this study was to identify those central nervous system structures which could help diagnosing aMCI.

Methods: Of the 50 participants 18 had the symptoms of aMCI, while 32 were healthy elderly people. The cognitive status of the participants was tested by the Rey Auditory Verbal Learning Test (RAVLT) and the Addenbrook Cognitive Examination (ACE). The diagnoses of aMCI was set based on the results of Rey test and the Petersen criteria. In order to exclude pseudodementia depression and anxiety were also examined by using the Geriatric Depression Scale (GDS) and the State and Trait Anxiety Inventory (STAI).

Based on previous studies we calculated the volumes of several temporal lobe structures.

In the statistical analysis a logistic regression model was applied with the hippocampal gyrus, parahippocampal gyrus and precuneus volumes as predictive variables. Age, gender and the whole intracranial volume were served as covariates.

Results: Patients with aMCI could be differentiated from healthy controls with 80% sensitivity and 91 % specificity.

Conclusion: The study suggests that structural magnetic resonance imaging examination of temporal lobe structures can predict early mental decline, which could support early and more efficient treatment.

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P/I-10
GENDER DIFFERENCES - ADOLESCENTS KNOWLEDGE ABOUT MEDICINE AND MEDICINE USE

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Studies about adolescents' medicine use are quite rare in comparison with adolescents' alcohol or tobacco use. However, more and more teenagers use different kinds of over-the-counter (OTC) drugs or other prescribed drugs every day. Females are especially vulnerable population regarding medicine use and psychosomatic symptomatology.

The current study was conducted to provide baseline data about Hungarian teenagers' knowledge, attitude and practice about OTC drugs, prescribed medications and other substances use.

Our sample consisted of 387 pupils from elementary schools (Grade 7-8). The study was performed in Bekes county in Hungary involved seven small towns and villages. Self-administered questionnaires were applied that measured sociodemographics variables, psychosomatic symptoms, beliefs and attitudes related to substance use and knowledge about medicine use. Descriptive statistics, cross tabulations and chi square test were used to test these relationships with SPSS MS 19.0 statistical program.

We could identify several fields where pupils' knowledge is insufficient. For instance, the use of antibiotics and eyedrops. We gained information about the pattern of medicine use among teenagers and the characteristics of psychosomatic symptoms and medical problems in this age group. In case of adolescents' knowledge about medicine and psychosomatic symptomatology we found significant differences between male and female pupils.

During health promotion and prevention programs we should pay attention to adolescents' legal and illegal drug use, especially in terms of knowledge about of these substances, furthermore, we could identify subpopulations at high risk. It suggests the need for government-sponsored education efforts regarding correct use of medicines.

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Keywords: *medicine use, adolescents, gender differences, psychosomatic symptoms*

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P/I-11
THE TOPOGRAPHICAL DISTRIBUTION OF DELTA POWER: CAN THE CAUDO-ROSTRAL SHIFT OF BRAIN MATURATION BE SPOTTED IN THE AGE RANGE OF 4 TO 8 YEARS?

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Deep (slow wave) sleep is characterized by extensive maturational changes across the developmental trajectory of humans in parallel to a massive synaptic remodeling in the brain and cortical maturation both structurally and behaviorally. NREM slow wave activity (SWA, EEG spectral power between 1-4.5 Hz) decreases during childhood in parallel with a recently reported back-to-front shift in its topographical distribution. Moreover, this shift was hypothesized to reflect the development of specific functions and skills over the age range of 2-26 years, cohering with the concept of caudo-rostral pattern of cortical maturation - meaning roughly that electrophysiological, structural and behavioral maturation processes work early at the posterior cortical areas of vision and with time move gradually towards the frontal areas responsible for executive functioning.

Aims: We aimed to test the associations of the maturational level of SWA with cognitive performance and the indices of dreaming in a narrower age range by investigating the relationships between the topographical distribution of SWA, executive functions.

Results: Regarding the caudo-rostral cortical maturation the few significant correlations we found could not confirm the robust positive associations of delta power topography with age and cognitive functions. The posterior-anterior maturational pattern could only be caught by the SWA Maturational Index of (Kurth et al, 2012), but associations with behavioural data were non-significant in this case as well. In sum we could say that the caudo-rostral shift of delta power distribution may be a global cortical developmental pattern, but the examination of a narrower age range at higher resolution suggests that a more subtle approach and/or higher subject number is needed to map the relationships between the topography of sleep-related cortical functioning and maturational level of cognitive skills in children.

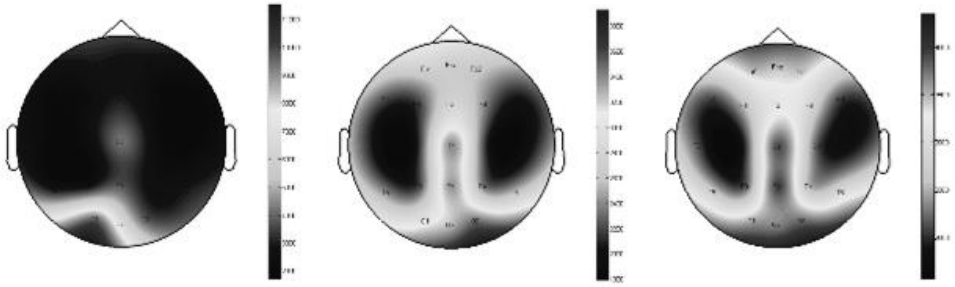

Figure 1. – Delta (1-4.5 Hz) power maps of the 3 age groups (from left to right: 1. age group (4.64±0.45 years), 2. age group (5.94± 0.29 years), 3. age group (8.14±043 years)) based on the spectrum analysis of the first 60 min of NREM sleep referenced to AVG.

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P/I-12
FACTORS OF THERAPY CHOICE
A MEDICAL ANTHROPOLOGICAL ANALYSIS OF INTERACTING BIOMEDICAL AND ALTERNATIVE EXPLANATORY MODELS OF ILLNESS

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Introduction: Biomedicine interacts with other medical systems, whether it retains the status of a culture's conventional medicine or serves as an alternative to indigenous remedies. Medical pluralism signifies a cultural milieu, a junction of distinct worldviews from which various, oftentimes conflicting, concepts of body and illness derive. The aim of this research is to investigate how illness-interpretations are altered vis-à-vis concepts of alternative medicine among patients and practitioners primarily socialized in a biomedical setting. Correspondingly, the research aims to unveil factors of therapy choice among those utilizing complementary or alternative medicine.

Research and method: Medical anthropological methods offer a hands-on perspective in mapping explanatory models of illness, the foundation of therapy choice and evaluation. The results are based on anthropological fieldwork commencing in September 2014, at 3 Traditional Chinese Medicine clinics in Hungary, functioning as "social hubs" for alternative medicine. During the on-going research, thus far 15 in-depth interviews have been conducted with patients and practitioners.

Results: Therapy choice is largely contingent on illness-interpretation, but moreover constitutes a response to both biomedical culture and greater societal phenomena. Major issues concerning the allopathic healthcare system include loss of trust and experiences with particular shortcomings (such as failing to obtain diagnosis, effective treatment, or a personally meaningful biomedical explanation of illness), which issues may also occur due to a discrepancy in the patient's expectations and their evaluation of what they received. Other factors in therapy choice involve the need for more personal control throughout the therapeutic process and in the doctor-patient relationship. Additionally, societal and global changes play a vital role in therapy choice, as, for example globalization, is altering concepts of self, man, world and conjointly, illness.

Comments: The foundation for therapy choice lies in the patient's subjective response to biomedicine and large-scale societal changes, which form a reciprocal relationship with their explanatory model of illness. This medical anthropological inquiry aids our understanding of culture's determining role in patient behavior.

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P/I-13
THE EFFECT OF MATERNAL BONDING AND THE CHRNB2 GENE ON SMOKING-RELATED DEPRESSIVE SYMPTOMS

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Background: The beta 2 subunit of the neuronal acetylcholinergic receptors (nAChRs) plays a crucial role in mediation of psychoactive effects of nicotine in smokers. However, data on gene encoding for nAChRβ2 (CHRNB2) in association with nicotine dependence (ND) and smoking-related depression (SRD) are poorly available. Although the association between depressive symptoms and maternal rearing style has been well-documented in the general population, less is known about this relationship among smokers.

The aim of this study was to investigate the association of maternal bonding and the CHRNB2 gene on SRD.

Methods: A sample of 232 treatment-seeker smokers was investigated in this study. DNAs were extracted from buccal mucosa cells and were genotyped for an SNP in 3'UTR of CHRNB2 (rs2072660). All participants completed the Fagerström Test for Nicotine Dependence (FTND), the Zung Self-Rating Depression Scale (ZSDS) and the Parental Bonding Instrument (PBI). Besides the total score of ZSDS (ZSDS-TS), suicidal ideation (ZSDS-S) and impulsivity subscale (ZSDS-S) of ZSDS were also investigated. ZSDS scores in the different maternal bonding groups were investigated by GLM and ANOVA tests adjusted for age and gender.

Results: We found that individuals with high maternal care scored lower on ZSDS-TS (p=0.005), ZSDS-I (p=0.002), and ZSDS-S (p<0.001) also. Conversely, high protection elevated the risk for depression (p=0.020), suicidal ideation (p=0.004), and impulsivity (p=0.017). Significant association of rs2072660 and FTND was observed (p=0.010). In interaction with rs2072660, Affectionless control (the combination of high care and low protection subgroups on PBI) was significantly associated with higher ZSDS-S score (p=0.005).

Conclusions: These data indicate an association between maternal bonding and severity of SRD. Our results suggest that CHRNB2 can be a shared molecular component between ND and SRD implying pharmacogenomic significance since nAChRβ2 is an important target for cessation medications, and SRD is one of the most important side-effect of them.

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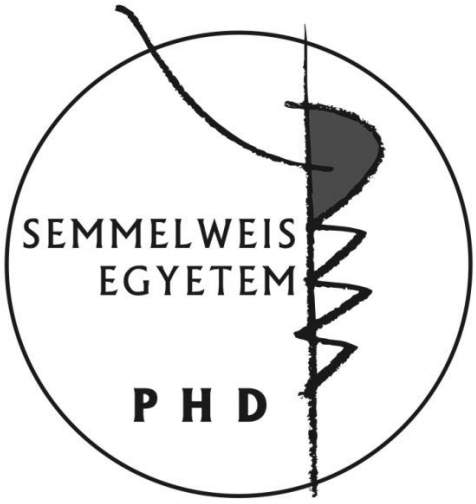

P/II
VARIED POSTERS
POSTER PRESENTATIONS

Chairpersons:
Dr. Zoltán Benyó
Dr. Attila Szabó

P/II-1
DISCRIMINATING COLON CANCER SUBTYPES BASED ON MICROARRAY GENE EXPRESSION

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Introduction: Colon cancer is a genetically heterogeneous disease, thus pathological staging fails to accurately predict recurrence and identify patients with high risk of reduced survival. In clinical practice there is no gene expression signature that has proven reliable to predict prognosis. And moreover it is also undecided how many molecular subtype would most accurately describe the tumours characteristics.

Aim: Our goal was to compare 4 widely used colon cancer gene-expression based classifier.

Methods: Using the publicly available GEO database repository we established a database containing clinical and microarray data for 1593 colon cancer patients. The gene expression measured on Affymetrix HG-U133A and HG-U133 Plus2.0 arrays were normalized with MAS5 algorithm in R using the simpleaffy package.

Marisa et al. classified the patients into 6 groups, Sadanandam et al. used 5 clusters, de Sousa and Clark-Langone's colon assay both enrolled the patients into 3 groups.

We reprogrammed, reproduced these classificators and compared the recurrence free survival of the patients.

Results: Comparing the incidence of the subtypes of these methods whit chi-square test we found significant dependence between the classes in all possible combinations ($p<0.01$). However, when comparing certain groups there was a minimal overlapping between the classes of classficators. In the survival analysis, from the clinicopathological properties stage ($p<0.01$) proved to be significant and grade and gender had no effect on survival. Clark-Langone's colon assay achieved the most significant results with the Kapla-Meier analysis.

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P/II-2
EFFECTS OF TARGETED THERAPY ON INTRATUMOR HETEROGENEITY IN RENAL CELL CARCINOMA PATIENTS

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Introduction: Next-generation sequencing technologies have provided us the possibility to sequence entire human genomes, which may help diagnostics, research and drug discovery. Tumor sample sequencing is a challenging task, since tumors are usually genetically heterogeneous. This heterogeneity may foster the survival of tumor cells, which may be interpreted as an evolutionary process. Heterogeneous tumors have a higher probability to acquire drug resistance, which may become a selection marker after a treatment.

Methods and results: The analyzed data contained whole exome sequencing (WXS) datasets of 10 renal cell carcinoma (RCC) patients downloaded from the EGA (European Genome/Phenome Archive) repository. Six of these patients were treated with everolimus prior to the study. Each patient had a sequenced normal sample, paired with multiple intra-tumor samples. Somatic mutations where identified with the MuTect algorithm, using default settings. A post-analysis filtering was applied to remove low coverage and low quality mutations.

During our analysis we were able to split the patients into two groups based on overall mutation counts: 1) homogeneous subgroup, which contained few low frequency/coverage mutations, and 2) heterogeneous subgroup, which contained an order of magnitude more low frequency/coverage mutations in the sequencing datasets. Phylogenetic reconstruction using high coverage mutations showed higher intra-tumor phylogenetic distances in the homogeneous group. Clinical data revealed that patients treated with everolimus from the homogeneous group had larger tumor sizes compared to their pre-treatment size, while the tumor sizes in the heterogeneous group decreased during treatment.

Discussion: Our findings showed that everolimus treatment had great impact on intra-tumor heterogeneity. Therapy resistant patients had high phylogenetic distances between their intra-tumor samples (comparable to the untreated patients), suggesting the presence of multiple drug-resistant sub-clones before treatment. Drug sensitive patients had lower intra-tumor phylogenetic distances, which may be caused by drug resistant sub-clone selection.

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P/II-3
ENDODERM DERIVED SONIC HEDGEHOG REGULATE THE EXTRACELLULAR MATRIX PATTERNING DURING ENTERIC NERVOUS SYSTEM DEVELOPMENT

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The enteric nervous system (ENS) is a large neural network in the wall of the intestine which is colonized by a small number of enteric neural crest cells (ENCCs). These multipotent stem cells originate from vagal level of neural tube and migrate rostrocaudally along the entire length of the gastrointestinal tract to differentiate as neurons and glial cells that form the ganglionated ENS. Incomplete migration of ENCCs leads to Hirschsprung disease, a congenital disorder characterized by the absence of enteric ganglia along variable lengths of the distal intestine. Inductive interactions between gut epithelium and mesenchyme have been suggested to regulate the migration and differentiation of ENCCs. However, little is known about the function of epithelial derived factors, such as Sonic hedgehog (Shh), how they influence the intestinal extracellular matrix expression during ENS development.

Hindgut from 6 day old chicken embryo was cultured in the presence of Shh protein or after injection of Shh overexpressing replication competent retrovirus (RCAS)-virus. In presence of Shh the hindgut is aganglionic, while in the presence of Shh inhibitor (cyclopamine) large and ectopic ganglia developed. Shh treatment strongly induced the expression of chondroitin sulphate proteoglycans (CSPGs) such as versican and collagen type IX, whereas cyclopamine reduced the expression pattern of these inhibitory matrix molecules. These results indicate that versican and collagen IX is a candidate for mediating the effects of Shh on ENCC migration. Shh also inhibited the proliferation and promoted the differentiation of ENCCs. Abnormalities of NCC migration and extracellular pattern formation are characteristic of two human intestinal disorders, Hirschsprung disease and intestinal neuronal dysplasia. Our results support an essential role for epithelial-mesenchymal interactions in these aspects of ENS development.

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P/II-4
SODIUM GLUCOSE COTRANSPORTERS AS NEW TARGETS OF RAAS INHIBITORS IN DIABETIC NEPHROPATHY

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Introduction: Chronic hyperglycemia and glucose toxicity are the leading causative factors of diabetic nephropathy (DN). In the proximal tubules sodium glucose cotransporter (SGLT) 2 is the main mediator of glucose reabsorption, while in the gut SGLT1 is responsible for glucose uptake. The renin-angiotensin-aldosteron-system (RAAS) inhibitors are the gold standard therapy in DN, but their effect on SGLT mediated glucose transport has not been tested yet.

Aim: We investigated the effect of various RAAS blockers on renal and intestinal glucose uptake mediated by SGLTs in type 1 diabetic rats.

Methods: Diabetes was induced by streptozotocin in male Wistar rats. After 5 weeks of diabetes, animals (n=6 / group) were treated in non-pressor dose either with angiotensin-converting enzyme (ACE) inhibitors (Enalapril or Ramipril), or angiotensin receptor blocker (ARB) Losartane or aldosterone antagonists (Eplerenone or Spironolactone). Healthy or untreated diabetic rats served as controls. Blood pressure and decline in renal functions were measured. Mesangial matrix expansion was evaluated on Periodic acid-Schiff (PAS) stained kidney sections. SGLT1 and 2 protein levels were determined by Western-blot.

Results: Development of DN was confirmed by increased BUN and a significant decline in GFR. Parallel to functional deterioration renal histology also showed typical structural damage of DN. RAAS inhibitors improved renal function and ameliorated mesangial matrix expansion without any effect on blood pressure. RAAS blockers showed a decreasing tendency on blood glucose levels and in parallel slightly increased glucosuria. The renal protein level of SGLT2 was enhanced in DM and the RAAS inhibitors lowered it. The level of SGLT1 in the gut was also increased in DM and decreased upon RAAS inhibition.

Conclusions: RAAS inhibitors are renoprotective independently of their action on blood pressure. This renoprotection could be attributed due to their blood-sugar lowering effect which is exerted partly through the inhibition of glucose reabsorption mediated by SGLTs.

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P/II-5
THE ROLE OF *BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)* IN DIABETES ASSOCIATED NEPHROPATHY AND COMORBID DEPRESSION

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Introduction: Comorbid depression occurring both in diabetes (DM) and chronic kidney disease (CKD) contributes to the progression of diabetic nephropathy. The level of BDNF and sigma-1 receptor (S1R) decrease in depression. Recent findings suggest a common BDNF-Sigma-1R signalling pathway in the comorbidity of depression and CKD. This pathway in the kidney has not been investigated yet.

Methods: After 5 weeks of streptozotocin induced diabetes, male Wistar rats (n=8/group) were treated diabetes *po.* with non-pressor dose of *enalapril, ramipril*, *losartan, spironolactone* and *eplerenone*. Untreated diabetic and healthy rats served as controls. Blood pressure and renal parameters were measured and the depressive behaviour was evaluated. Renal S1R and BDNF levels were analysed.

Results: Neither DM nor renin-angiotensine-aldosterone-system (RAAS) inhibitors influenced the blood pressure. Impairment of renal function and depressive behavior was observed in DM, which was improved by all RAAS-blockers. BDNF was succesfully detected in the rat kidney. Different renal expressions of the precursor and mature forms was measured in DM. S1R and mature BDNF increased while immature BDNF did not change. All RAAS inhibitors decreased both the level of S1R and mature BDNF.

Conclusions*:* These results suggest the potential role of a common, RAAS regulated S1R-BDNF pathway in the development of DM – CKD- comorbid depression thus exploring a new therapeutic horizon for RAAS inhibitors in the treatment of depression in DM and CKD.

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P/II-6
SPINAL CORD INJURY INCREASES LOCAL NORADRENALINE RELEASE IN THE RAT

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The aim of our study was to measure the changes in the release of noradrenaline following traumatic injury of the rat spinal cord. Previous observations have shown that the simulation of ischaemic conditions causes an excessive release of noradrenaline in the spinal cord *in vitro*. Thus we aimed to study how a spinal cord injury (SCI) influences the same phenomenon *in vivo*.

Methods: SCI was simulated by surgical hemisection at segment L4. ^{3}H-noradrenaline- uptake experiments, fractional release experiments and electron microscopy were performed on control and injured animals. Spinal cord segments L5-S1 were prepared 1 or 3 days following hemisection. The tissue was sliced and incubated in Krebs solution containing radioactive ^{3}H-noradrenaline. Slices were put into superfusion chambers and effluents were collected in 19 fractions. Electrical field stimuli were applied at the beginning of the 3rd and 13th fractions. Nisoxetine was added to the perfusion solution beginning from the 8th fraction. Radioactivity of the samples was determined using a liquid scintillation spectrometer.

Results:

Uptake experiments: The average uptake of radioactivity was 149 kBq/g in the control group. Surgical hemisection did not influence this uptake. Nisoxetine however decreased its value by 75%.

Fractional release experiments: Surgical hemisection caused an overall increase in the amount of ^{3}H-noradrenaline 1 and 3 days after SCI. There was an increase of 18-20% in both resting and stimulated release over untreated control. Nisoxetine successfully inhibited the release of noradrenaline but seemed to be less effective after SCI.

Electron microscopy: 3 days after hemisection many intact synapses were observed next to an overall degeneration of neurons and myelin sheath.

Conclusion: SCI increases the release of noradrenaline in the rat spinal cord after hemisection. This phemomenon may play a role in the inflammatory process and consequential loss of function following spinal cord injuries.

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P/II-7
ONE MUTATION, TWO PHENOTYPES: A SINGLE NONSENSE MUTATION OF THE *CTSC* GENE CAUSES TWO CLINICALLY DISTINCT PHENOTYPES

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Papillon-Lefévre (PLS; OMIM 245000) and Haim-Munk syndromes (HMS; OMIM 245010) are phenotypic variants of the same rare disease caused by mutations of the *cathepsin C* (*CTSC*) gene exhibiting autosomal recessive inheritance.

Our aim was to identify the diseases causes mutations of the *CTSC* gene in two clinically distinct Hungarian patients. In order to elucidate any familiar relationship between the two investigated patients, haplotype analysis was performed.

Mutation screening and polymorphism analysis were performed by direct sequencing of the *CTSC* gene.

Mutation screening of the *CTSC* gene from the two patients revealed the presence of the same homozygous nonsense mutation (c.748C/T; p.Arg250X). However, one of the patients exhibited the PLS phenotype while the other exhibited the HMS phenotype. Although these patients were not aware of that they are related, haplotype analysis - especially the genotypes of the rs217116 and the rs217115 polymorphisms - clearly indicates that the patients are carrying the same haplotype, while the unrelated controls carrying several different haplotypes.

Our results demonstrate that PLS and HMS are phenotypic variants of the same disease, additionally, exclude the presence of a putative genetic modifier factor within the *CTSC* gene that is responsible for the development of the two phenotypes. We suggest that this putative genetic modifier factor is located outside the *CTSC* gene or alternatively, the development of the different phenotypes is the consequence of different environmental or life style factors.

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P/II-8
EFFECT OF ENKEPHALIN-CONOTOXIN HYBRID PEPTIDES ON OPIOID RECEPTORS

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Enkephalin is known as an endogenous ligand peptide for opioid receptors and conotoxin is a neurotoxic peptide isolated from the venom of the marine *cone snail*, genus *Conus* with Ca^{2+} ion channel blocker characteristic.

Our objective was to investigate the specific binding of two different enkephalin-conotoxin hybrid peptide (peptide 1 and 2)and two type of conotoxin derivative (peptide 3 and 4) towards mu, kappa and delta opioid receptors (MOR, KOR and DOR respectively) in competition binding experiments with opioid receptor specific radioactive ligands in rat brain membranes. Additionally the opioid G-protein efficacy of the observed peptides were investigated in functional [^{35}S]GTPγS binding assays in presence and absence of different opioid receptor specific antagonists, again in rat brain membranes.

Hybrids 1 and 2 effectively inhibited all three opioid receptors specific binding, where hybrid 1show the higher affinity towards KOR. Peptide 3 decreased the specific binding of KOR only in higher concentrations, while peptide 4 did not show any effect on either opioid receptor specific ligand binding. Hybrids 1 and 2 stimulated G-protein activation which was inhibited by opioid receptor antagonists, indicating these two hybrid peptides have opioid receptor activity. On the other hand conotoxin derivatives did not alter G-protein activation.

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P/II-9
STRUCTURE CHANGES OF ENTERIC NERVOUS SYSTEM IN ANIMAL MODEL OF ULCERATIVE COLITIS

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Enteric nervous system plays a major role in the functioning of gastro-intestinal tract and it is affected in inflammatory bowel diseases. The changes in the number of enteric neurons and glia are described both in humans and in animal models of IBD but the published data are fragmented and contradicting (Moynes D., 2013; Cirillo C., 2011).

Aims: to evaluate the morphological changes of enteric nervous system in the murine model of ulcerative colitis.

Methods: Adult male C56Bl/6 mice were used. Colitis was induced with 50 kDa Dextran Sulfat Soduim. Hematoxylin and eosin staining was used for pathomorphological assessment and Nissl staining – for evaluation of enteric ganglia and neurons.

Results: Mice developed severe colitis with extensive ulceration of the mucosa and inflammatory infiltration of the submucosa. Ulceration increased from proximal to distal parts of colon. In ulcerative colitis there was an increase in the overall number of myenteric ganglia and centrally sectioned myenteric neurons, due to colon shrinkage. After analyzing the cellular composition of myenteric ganglia the statistically significant decrease in hypochromic neurons and enteric glia and the increase in hyperchromic neurons were found in colitis in comparison with the control group. The overall number of myenteric neurons was unchanged. The area of centrally sectioned neurons and their nuclei was reduced. These changes of enteric nervous system may result in the altered motor and secretory function of the colon.

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P/II-10
DEVELOPMENT OF 3D TISSUE CULTURING METHOD FOR INVESTIGATION OF CIRCULATING TUMOR CELLS

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The appearance of circulating tumor cells in the blood vessels is an accentuated step during the metastasis formation. Based on the basic properties and the surface markers of the disseminated cells we can infer to the malignity of the primary tumor and monitor the disease state. However, the absence of proper molecular and immunological knowledge and the low number of isolable circulating tumor cells set back the method's clinical utility. To get to know the metastatic activity of the tumor cells we need more information about the genetical, epigenetical and immune phenotype changes taken place during the metastasis formation. Increasing evidences support that the surrounding stroma is not only a passive bystander, in the microenvironment around a tumor a diversified network is acting. Based on these considerations, the appropriate modeling of the *in vivo* tissue environment plays an important role in the course of *in vitro* investigation of the tumor spread.

Aims: We planned to develop culturing methods with circulating tumor cells isolated from breast cancer patients and to investigate the growth characteristics, the phenotype of these cells by analyzing their surface markers, cytoskeleton and viability capabilities. Our long term aim is to find relationship between the number of circulating tumor cells, the state of the disease and the effectiveness of the applied therapy.

Results: As pre-investigation of future samples from breast cancer patients we started to develop and test 3D fibrin matrices with tumorigenic and non-tumorigenic cell lines. We prepared fibrin matrix either from human plasma or using purified fibrinogen by addition of thrombin in calcium containing buffer and optimized the structure of the matrix to be suitable for cell culturing. By dint of fluorescent dyes and microscopic methods we observed the location and migration of the inoculated cells.

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P/II-11
IN VIVO AND IN VITRO STUDY ABOUT THE ANTIFUNGAL ISOTHIOCYANATES OF HORSERADISH

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The biggest horseradish harvesting country besides the USA is Hungary, firstly it is harvested as a condiment. Its lacrimatory odor and taste is occured by isothiocyanates, which made up the essential oil of the horseradish. These components are the reason for its medicinal effect. Recently several researches are made in connection with its anticarcinogen and antimicrobial effect, especially about its antibacterial activity. Altough about its antifungal effect we have only few information.

Aim: We would like to manifest the antifungal effect of horseradish (*Armoracia rusticana* Gaertn. Mey. et Scherb.) essential oils both on pathogen and apatogen species, and to make in vitro horseradish cultures, especially hairy roots, from which we would like to select that clones, which produces in optimal way the antifungal components.

***Results*:** We established the powerful effect of horseradish essential oil on four fungi species. *(Aspergillus nidulans, A. fumigatus, Saccharomyces cerevisiae* and *Candida albicans*). We made experiments with the volatile oil both in gas and liquid phase. Our aim was also to find out the mode of mechanism. Our hypothezis is that isothiocyanates act in an oxidative stress way. To produce isothiocyanates in vitro, we created callus cultures, horseradish plants regenerated from callus, and genetically transformed hairy root cultures. The identification of the isothiocyanates was made by SPME-GC/MS and GC/MS. The in vitro hairy root clones produces both the antifungal allyl and phenethyl isothiocyanate.

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P/II-12
THE EFFECTS OF ANGIOTENSIN II ON THE NMDA RECEPTORS IN TWO BRAIN STRUCTURES

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Experiments were performed on two dopaminergic structures: prefrontal cortex (PFC) involved in memory and learning, while striatum is crucial in motor coordination. Both the brain renin-angiotensin system and NMDA receptors influence these functions.

Our aim was to study the effects of angiotensin II (AngII) on NMDA receptors of pyramidal cells in PFC and medium spiny interneurons in striatum by patch clamp method.

Whole-cell voltage-clamp access was established in pyramidal cells and medium spiny interneurons of brain slices prepared from 10-12 days old rats. Cells were superfused with artificial-cerebrospinal-fluid (ACSF). NMDA (30μM) applied 3 times for 1.5 min with 10-min intervals, induced inward currents (T1-3). The effects at T3 were presented as T3/T2. More than ±15% change at T3 was considered as an effect. AngII was added 5 minutes prior to T3, antagonists were in the ACSF throughout. For statistical analysis one-way ANOVA and Bonferroni correction was applied.

Our previous results showed that AngII has dual effect on pyramidal cells: lower concentrations (0,3-1μM) enhanced, higher concentrations (1-3μM) reduced the currents in different subpopulations of cells. The stimulation was reversed by eprosartan (1μM).

Current experiments revealed that 0,001-0,1μM AngII also increased the currents. The AngII-induced enhancement was reversed by tetrodotoxin (0,5μM), Ca-free ACSF and D1-antagonist SCH-23390 (10μM), but not by D2-antagonist sulpirid (20μM). It suggests that D1 receptor-activation by dopamine released by AT1 receptor stimulation enhances NMDA currents in PFC.

Inhibitory effect of AngII wasn't affected neither by eprosartan nor by the AT2-antagonist PD123319 (5μM). AngIV (0,1μM), a shorter AngII-sequence, mimicked the inhibition, indicating an AT4-mediated action.

0,1-1μM AngII stimulated NMDA currents in striatal interneurons. Eprosartan failed to influence this effect.

Thus the mechanisms of stimulatory effects mediated by AngII are different in these brain structures. We plan further experiments to reveal the underlying mechanisms.

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P/II-13
FIBRINOGENESIS AND FIBRINOLYSIS FOLLOWED WITH NANO-THROMBELASTOGRAPHY

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Hemostasis is a complex process that relies on a sensitive balance between the formation and breakdown of the thrombus, a three-dimensional polymer network of the fibrous protein fibrin. Neither the details of the fibrinogen-fibrin transition, nor the exact mechanisms of thrombus degradation are fully understood at the molecular or supramolecular level. We investigated nanoscale changes in the viscoelasticity of the 3D-fibrin network during fibrinogenesis and streptokinase (STK)-induced fibrinolysis by using a novel, atomic-force-microscope (AFM)-based application of force spectroscopy, named nano-thrombelastography.

Clot formation was initiated by adding Ca2+ to fresh, anti-coagulated mixed human plasma droplet on a glass surface. In order to induce fibrinolysis, STK, at a final enzyme activity of up to 10,000 IU was applied in situ. For measuring the nanoscale elastic and viscous properties of the fibrin network, the tip of an AFM cantilever was immersed in the plasma droplet and oscillated vertically with a constant rate. The cantilever bending was correlated with fibrin-clot elasticity and viscosity in time. Morphological changes were followed by scanning AFM on polymerized fibrin deposited on mica surface.

Whereas the global features of the time-dependent change in cantilever deflection corresponded well to a macroscopic thrombelastogram, the underlying force spectra revealed large, sample-dependent oscillations in the range of 3-50 nN and allowed the separation of elastic and viscous components of fibrin behavior. Upon STK treatment the nano-thrombelastogram signal decayed gradually. The decay was driven by a decrease in thrombus elasticity, whereas thrombus viscosity decayed with a time delay. In scanning AFM images mature fibrin appeared as 17-nm-high and 12–196-nm-wide filaments. STK-treatment resulted in the decrease of filament height and the appearance of a surface roughness with 23.7 nm discrete steps that corresponds well to the length of a fibrinogen monomer.

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P/II-14
CLINICOPATHOLOGICAL ANALYSIS OF PREGNANCY ASSOCIATED MELANOMAS

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Background: Melanoma is the most common malignant tumor of pregnancy, with an incidence of 1/1000. Pregnancy-associated melanoma (PAM) by definition is diagnosed under pregnancy or after delivery within one year. The role of the estrogen in the development and progression of PAM is not clearly understood.

Methods: Retrospective analysis of PAM diagnosed at the Dermatology, Venereology and Dermatooncology Department of the Semmelweis University between 2003-2014 included 32 women (18-45 years). Twelve clinical data including course of PAM, melanoma risk factors, spontaneous and procured abortion, general pregnancy outcome, as well as 9 histological characteristics of the primary tumor were evaluated and compared with data of tumor stage and age matched non-pregnant female (NPAM n=32) and male (NPAM n=32) melanoma patients. For statistical analysis chi square test, Fisher's exact test and Kaplan-Meier analysis were used. All the statistic tests were two-sided and $p<0.05$ was considered statistically significant.

Results: During the eleven year study period the number of diagnosed melanoma in female patients (age 18-45) was 336 and from those 34 were diagnosed as PAM including 2 in situ melanomas. None of the 32 PAM patients developed placental or fetal metastases, and altogether 29 healthy babies were born after the PAM diagnosis. In 11,7 % of cases pregnancy was terminated by abortion. Clinicopathological data of PAM when compared with NPAM and MM did not show any significant difference. The worst prognosis was observed in a PAM patient who participated in IVF.

Conclusions: The incidence of PAM was high among women with melanoma in reproductive age. Although we could not find any significant difference in clinicopathological characteristics between PAM and age and stage matched melanoma patients, further analysis is needed to understand clearly the relation between melanoma and pregnancy.

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P/II-15
HEALTHCARE-ASSOCIATED INFECTIONS AND ANTIMICROBIAL USE IN LONG-TERM CARE FACILITIES – HUNGARY, 2013

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Healthcare-associated infections (HAI) and antimicrobial use are common among residents in long-term care facilities (LTCF). HAIs represent an important and growing challenge to the healthcare and social system.

Aims: As part of the ECDC-funded HALT-project (Healthcare-associated Infections and Antibiotic Use in European Long-term Care Facilities), we conducted a point-prevalence survey with voluntary participation to establish representative baseline rates and identify priorities for improvement.

Methods: All LTCFs were invited to participate in the HALT-project. Between April - May 2013, trained LTCF-staff completed: i) an institutional questionnaire on infection control practices (ICP) and ii) a form on each resident with HAIs and/or on antimicrobial therapy on the day of the survey. We used the ECDC definitions and protocol. We calculated prevalence of infections and antimicrobial use, using the number of all residents as the denominator and 95% confidence intervals (95% CI).

Results: 91 (23%) LTCFs with approximately 11,823 residents participated in the study. The prevalence of HAI was 2.1% (95% CI 0%-10.1%). Of 250 HAIs reported, the most common were skin/soft tissue (36.4%), respiratory (30%), and urinary infections (20.8%). Of all residents, 1.3% (95% CI 0%-7.6%) used antimicrobials. Of 155 antimicrobials reported, 97.3% were for systemic use.

Conclusions: The first baseline data indicate that HAIs and antimicrobial use constitute a relevant public health problem in LTCFs in Hungary. We recommend implementing a surveillance system specific for LTCFs to follow trends in HAIs and antimicrobial use and to identify priorities for national and local intervention measures focusing on preventing infections and prudent antimicrobial use in the LTCF residents.

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P/II-16
ATTACHMENT ANXIETY AS PREDICTOR OF RISK FOR EATING DISORDERS ON A REPRESENTATIVE HUNGARIAN ADULT SAMPLE

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Attachment can mediate between early experiences and psychiatric disorders in adulthood, also in case of eating disorders, for attachment is insecure among all types of them. Data even underline that attachment security influences the severity of eating disorders.

Aim: to determine the exact predisposing traits of attachment in the development of eating disorders and the strength of attachment's impact on the risk for classical eating disorders.

Methods: Study was based on a cross-sectional nationally representative survey called „Hungarostudy 2013" (n=2000, 46.9% males, mean age 46.9 years, SD=18.24 years). Measures: Sociodemographic and self-reported weight and height data. A short Hungarian version of Relationship Scale Questionnaire was used to determine two main factors of attachment: detachment and attachment anxiety. Eating disorders were detected with SCOFF eating disorder questionnaire. Short Hungarian version of Beck Depression Inventory to control depression.

Results: The frequency of risk for eating disorders (anorexia or bulimia nervosa) among the respondents (n=1860) was 3.9% (n=76). Attachment anxiety was significantly ($t_{(1888)}$=-3.939, p<0.001) higher in the eating disorder risk group, also significantly (OR=1.09, p=0.40) increased the risk of eating disorders after adjusting for the potential background variables such as age, gender, qualification, body mass index and depression. Detachment was not a significant predictor of eating disorder symptoms (OR=0.98, p=0.515). Younger age (OR=0.97, p<0.001), higher level of depression (OR=1.09, p<0.001) and higher body mass index (OR=1.08, p<0.001) were also significant predictors of risk for eating disorder. The explained variance of the model was 10.7%.

Conclusions: Attachment anxiety is a predisposing factor of risk for eating disorder, with a possible a therapeutic relevance. Assessment of attachment's further aspects and creating multivariable models are required for more thoroughful understanting and optimising of intervention points.

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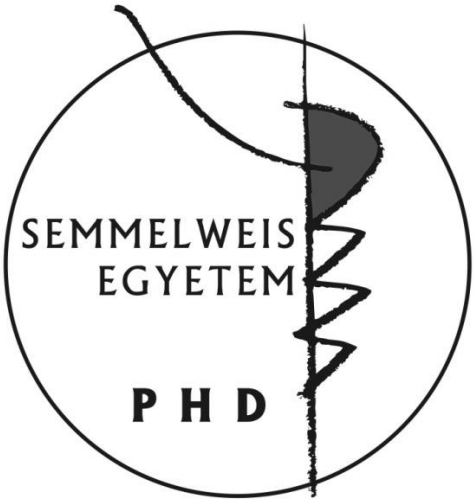

AUTHORS AND TITLES OF ABSTRACTS

(LISTED UNDER THE CORRESPONDING DOCTORAL SCHOOLS)

BASIC MEDICINE DOCTORAL SCHOOL

E/VI-1
GENE POLYMORPHISMS AS RISK FACTORS FOR PREDICTING THE CARDIOVASCULAR MANIFESTATIONS IN MARFAN SYNDROME
Kálmán Benke, Bence Ágg, Bálint Szilveszter, Balázs Odler ,Gábor Mátyás,
Tamás Radovits, István Hartyánszky, Miklós Pólos, Pál Maurovich-Horvat, Béla Merkely, Zoltán Szabolcs
Program: Cardiovascular disorders

E/VI-2
THE ROLE OF THE WHITE BLOOD CELLS IN THE RESYNCHRONIZATION THERAPY OF CHRONIC HEART FAILURE
András Mihály Boros, Péter Perge, Zsigmond Jenei, Zsolt Bagyura, Endre Zima,
Levente Molnár, Astrid Apor, Dávid Becker, László Gellér, Zoltán Prohászka, Béla Merkely, Gábor Széplaki
Program: Cardiovascular disorders: physiology and medicine of ischaemic circulatory diseases

E/VI-3
ENVIRONMENTAL OR GENETIC EFFECTS INFLUENCE THE MORPHOLOGY OF THE AORTIC ROOT? A CLASSICAL TWIN STUDY
Csilla Celeng, Tamás Horváth, Bálint Szilveszter, Ádám Levente Jermendy, Attila Kovács, Ádám Domonkos Tárnoki, Dávid László Tárnoki, György Jermendy, Béla Merkely, Pál Maurovich-Horvat
Program: Cardiovascular disorders: physiology and medicine of ischaemic circulatory diseases

E/VI-4
THE ROLE OF FRAILITY IN THE RISK STRATIFICATION FOR CARDIOVASCULAR SURGERY
Enikő Holndonner-Kirst, Dániel J. Lex
Program: Cardiovascular disorders, physiology and medicine of ischaemic circulatory diseases

E/VI-5
BLOOD LOSS REDUCING EFFICACY OF A NEW, SYNTHETIC APROTININ-ANALOGUE IN A CANINE MODEL OF CARDIOPULMONARY BYPASS
Balázs Tamás Németh, Csaba Mátyás, Attila Oláh, Henriett Biró, Christiane Miesel-Gröschel, Gergő Merkely, Tamás Radovits, Béla Merkely, Gábor Szabó
Program: Cardiovascular disorders, physiology and medicine of ischaemic circulatory diseases

E/VI-6
THE EFFECTS OF THE CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH MITRAL REGURGITATION OF VARIOUS SEVERITY
Péter Perge, Csilla Liptai, Ágnes Schneider, Astrid Apor, Klaudia Viven Nagy, Levente Molnár, Endre Zima, László Gellér, Gábor Széplaki, Béla Merkely
Programme: Cardiovascular disorders: physiology and medicine of ischaemic circulatory diseases

E/VI-7
LEFT ATRIAL THROMBUS DETECTION BEFORE CARDIOVERSION: CT VERSUS TEE
Bálint Szilveszter, Gyöngyi Major, Attila Kovács, Szabina Pataki, Kálmán Benke, Márton Kolossváry, Hajnalka Vágó, Astrid Apor, László Szidonya, Béla Merkely, Pál Maurovich-Horvat
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P/II-13
FIBRINOGENESIS AND FIBRINOLYSIS FOLLOWED WITH NANO-THROMBELASTOGRAPHY
Tímea Feller, Miklós S.Z. Kellermayer, Balázs Kiss
Program: Cellular and molecular biophysics

CLINICAL MEDICINE DOCTORAL SCHOOL

E/II-9
INCREASED ACTIVATION OF POLY(ADP-RIBOSE)POLYMERASE IN PAEDIATRIC PATIENTS WITH CROHN'S DISEASE
Nóra Judit Béres, Gergő Szabó, Rita Benkő, Katalin Borka, Apor Veres-Székely, Szabolcs Heininger, Attila Szabó, Ádám Vannay, Gábor Veres, Eszter M. Horváth
Program: Prevention of Crohnic Diseases in Childhood

E/III-1
EFFECTS OF (-)-DEPRENYL ON HUMAN DENTAL PULP STEM CELLS
Krisztián Benedek Csomó
Program: Dental Research

E/III-2
A NEW PRECLINICAL MODEL OF BONE REMODELING AROUND TITANIUM IMPLANTS
Sándor Farkasdi, Gergely Hriczó-Koperdak, Róbert Rácz, Tamás Harangozó, Szilvia Koncz, Beáta Kerémi, David Pammer, Bence Szabó, Csaba Dobó-Nagy, Frederic Cuisinier, Wu Gang, Gábor Varga
Program: Dental Research

E/III-3
TOOTH-DERIVED STEM CELL CULTURING ON AMINO-ACID BASED HYDROGELS
Orsolya Hegedűs
Program: Dentistry

E/III-4
EFFECTS OF CHLORHEXIDINE CONTAINING VARNISH ON ORAL AND DENTAL HEALTH IN HIGH RISK PATIENTS
Lídia Lipták, Adrienn Káldy, Nóra Bársony, Krisztina Szabó, Sándor Márton, Gábor Nagy, Melinda Madléna
Program: Dental Research

E/III-5
INVESTIGATION OF RELATIONSHIPS BETWEEN ORAL MICROBIAL AND DENTAL CONDITIONS AND ORAL CANCER
Károly Mensch, Júlia Pongrácz
Program: Dental Research

E/III-6
VASCULAR TOPOGRAPHIC AND DEPTH OF FIELD INVESTIGATIONS BY TRANSPARENT, TRUE 3D MICROSCOPY OF GINGIVA AND SUBMANDIBULAR SALIVARY GLAND
Izabella Nagy, Beáta Kerémi, Milán Gyurkovics, Edit Komarek, Csaba Korom, Gábor Varga, István Stuber, Zsolt Lohinai
Program: Dental Research

E/III-7
FUNCTIONAL MEASUREMENTS OF ION-TRANSPORTERS INVOLVED IN PH REGULATION OF AMELOBLAST CELLS
Róbert Rácz, Erzsébet Bori
Program: Dental research

E/IV-1
EVALUATION OF THICKNESS AND OPTICAL PROPERTY CHANGES OF THE MACULA LUTEA IN PATIENTS WITH MULTIPLE SCLEROSIS
Boglárka Enikő Varga, Erika Tátrai, Wei Gao, Kornélia Lenke Laurik, Magdolna Simó, Gábor Márk Somfai, Zoltán Zsolt Nagy, Delia Cabrera DeBuc
Program: Ophthalmology

E/IV-6
ELEVATED LEVELS OF POTENTIALLY *MEN1*-TARGETING MICRORNAS IN SPORADIC COMPARED TO MEN-1 SYNDROME ASSOCIATED PRIMARY HYPERPARATHYROIDISM
Vince Kornél Grolmusz, Katalin Borka, Katalin Balogh, Anna Szentpéteri, Csaba Dékány, András Kiss, Miklós Tóth, Anikó Somogyi, János Horányi, Károly Rácz, Attila Patócs
Program: Hormonal regulations

E/IV-7
PROSPECTIVE INVESTIGATION OF GENETIC ALTERATIONS IN SAMPLES COLLECTED BY FINE NEEDLE BIOPSY FROM THYROID NODULES IN HUNGARY
Csaba Halászlaki, Bálint Tóbiás, Bernadett Balla, János Kósa P., János Horányi, Eszter Bölöny, Zsolt Nagy, Gábor Speer, Balázs Járay, Eszter Székely, Roland Istók, Zsuzsanna Putz, Péter Lakatos, István Takács
Program: Molecular Genetics, Pathomechanism and Clinical Aspects of Metabolic Disorders

E/IV-8
GLUCOCORTICOID RECEPTOR AND HSD11B1 GENE POLYMORPHISMS MAY INFLUENCE THE THERAPEUTICAL DOSAGE AND THERAPY-ASSOCIATED MORBIDITIES IN PATIENTS WITH ADDISON'S DISEASE
Ágnes Molnár, Annamária Kövesdi, Nikolette Szücs, Miklós Tóth, Péter Igaz, Károly Rácz, Attila Patócs
Program: Hormonal Regulations

E/IV-9
GENE AND PROTEIN EXPRESSION PATTERN OF CYTOKINES IN DISC HERNIATION DEPEND ON TIME OF SYMPTOMS
Árpád Bozsódi, Áron Lazáry, Péter Pál Varga
Program: Physiology and Pathology of the musculoskeletal system

E/IV-10
COMPARISON OF AIRWAY AND SYSTEMIC MALONDIALDEHYDE LEVELS FOR ASSESSMENT OF OXIDATIVE STRESS IN CYSTIC FIBROSIS
Orsolya Drozdovszky, Imre Barta, Krisztina Kelemen, Balázs Antus
Program: Pulmonology

E/IV-11
NEW DIAGNOSTIC METHOD FOR PRADER - WILLI SYNDROME (PWS)
Orsolya Dóra Ács, Bálint Péterfia, Péter Hollósi, Irén Haltrich, Ágnes Sallai, Andrea Luczay, Dóra Török, Ilona Kovalszky, Karin Buiting, Bernhard Horsthemke, György Fekete, András Szabó
Program: Prevention of Chronic Diseases in Childhood

E/IV-12
SURGICAL SITE INFECTION AFTER PRIMARY DEGENERATIVE LUMBAR SPINE SURGERIES AND ITS EFFECT ON LONG-TERM OUTCOME
István Klemencsics, Áron Lázáry, Zsolt Szövérfi, Árpád Bozsódi, Péter Éltes, Péter Pál Varga
Program: Physiology and pathology of the musculoskeletal system

E/IV-13
COMPARISON OF INTRACYTOPLASMIC SPERM INJECTION (ICSI) AND CONVENTIONAL IN VITRO FERTILIZATION (IVF) OUTCOMES IN VIEW TO SEMEN QUALITY
Ádám Lehner, Zita Kaszás, Ákos Murber, János Rigó Jr, János Urbancsek, Péter Fancsovits
Program: Reproductive Medicine

E/V-9
EFFECTIVENESS OF 9-CIS RETINOIC ACID AND MITOTANE COMBINATION IN AN ADRENOCORTICAL CANCER XENOGRAFT MODEL
Zoltán Nagy, Kornélia Baghy, Ilona Kovalszky, Pál Perge, Peter M. Szabó, Attila Patócs, Károly Rácz, Péter Igaz
Program: Hormonal Regulations

E/VI-8
ACCELERATED TREATMENT STRATEGY IN INFLAMMATORY BOWEL DISEASES; IS IT ASSOCIATED WITH A CHANGE IN THE DISEASE COURSE?
Petra Anna Golovics, Zsuzsanna Végh
Program: Gastroenterology

E/VI-9
HETEROGENEOUS EFFECTS OF OVER-EXPRESSION OF GRß IN COLONIC MUCOSAL CELL LINE PARTLY REFLECTS ALTERATIONS FOUND IN IBD
Zsolt Nagy, Bence Ács, Henriett Butz, Karolina Feldman, Péter M. Szabó, István Likó, Károly Rácz, Attila Patócs
Program: Hormonal regulations

E/VI-10
LOW INCIDENCE OF VENOUS THROMBOEMBOLISM IN INFLAMMATORY BOWEL DISEASES: PREVALENCE AND PREDICTORS FROM A POPULATION-BASED INCEPTION COHORT
Zsuzsanna Végh, Petra Anna Golovics
Program: Gastroenterology

E/VI-11
INVESTIGATING THE UNDERLYING MECHANISM OF REMOTE ISCHEMIC PERCONDITIONING: THE NEURAL HYPOTHESIS
Zoltán Czigány, Zsolt Turóczi, Dénes Kleiner, Gábor Lotz, André Homeyer, László Harsányi, Attila Szijártó
Programme: Gastroenterology

E/VI-12
ALTERATIONS IN SEGMENTAL LIVER FUNCTION AFTER PORTAL VEIN LIGATION - AN EXPERIMENTAL STUDY
András Fülöp, Gábor Lotz, László Harsányi, Attila Szijártó
Program: Gastroenterology

P/II-4
SODIUM GLUCOSE COTRANSPORTERS AS NEW TARGETS OF RAAS INHIBITORS IN DIABETIC NEPHROPATHY
Dóra B. Balogh, Judit Hodrea, Lilla Lénárt, Sándor Kőszegi, Renáta Gellai, Edgar Szkibinszkij, Ádám Vannay, László J. Wagner, Attila J. Szabó, Andrea Fekete
Program: Diabetes and Renal Disorders

P/II-5
THE ROLE OF *BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)* IN DIABETES ASSOCIATED NEPHROPATHY AND COMORBID DEPRESSION
Lilla Lénárt, Judit Hodrea, Sándor Kőszegi, Renáta Gellai, Adrienn Barczi, Dóra B. Balogh, Edgar Szkibinszkij, Dóra Zelena, Ádám Vannay, László Wagner, Attila J. Szabó, Andrea Fekete
Program: Prevention of Chronic Diseases in Childhood

P/II-6
SPINAL CORD INJURY INCREASES LOCAL NORADRENALINE RELEASE IN THE RAT
Zoltán Borbély, Krisztián Benedek Csomó
Program: Dental Research

P/II-7
ONE MUTATION, TWO PHENOTYPES: A SINGLE NONSENSE MUTATION OF THE *CTSC* GENE CAUSES TWO CLINICALLY DISTINCT PHENOTYPES
Adrienn Sulák, Katalin Farkas, Kornélia Tripolszki, Nikoletta Nagy, Márta Széll
Program: Experimental and Clinical Investigation of the Rare Monogenic Disorders

P/II-9
STRUCTURE CHANGES OF ENTERIC NERVOUS SYSTEM IN ANIMAL MODEL OF ULCERATIVE COLITIS
Dmitry Khochanskiy, Olga Makarova
Program: Histology, cytology and cell technology

P/II-10
DEVELOPMENT OF 3D TISSUE CULTURING METHOD FOR INVESTIGATION OF CIRCULATING TUMOR CELLS
Csilla Kurdi, Viktória Temesfői, Tamás Kőszegi
Program: Significance of molecular pathological and laboratory investigations in the medical diagnostics and therapy

P/II-14
CLINICOPATHOLOGICAL ANALYSIS OF PREGNANCY ASSOCIATED MELANOMAS
Melinda Fábián
Program: Dermatology and Venerology

PHARMACEUTICAL SCIENCES DOCTORAL SCHOOL

E/VII-1
DETERMINATION AND QUANTIFICATION OF 2'-*O*-FUCOSYLLACTOSE AND 3-*O*-FUCOSYLLACTOSE IN HUMAN MILK BY GC-MS
Réka Balogh, Szabolcs Szarka, Szabolcs Béni
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-2
SYNTHESIS OF NOVEL FUNCTIONALIZED NEOFLAVANS AND THEIR ANALOGS VIA ELECTROPHILIC RING CLOSURE FROM MESYLATES
András Darcsi, Szabolcs Béni
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-3
ANALYSIS OF NMDA MODULATORS WITH CE-LIF IN DIFFERENT BIOLOGICAL SAMPLES
Tamás Jakó, István Vincze, Fruzsina Bagaméry, Gergely Zachar, Tamás Tábi, András Csillag, Éva Szökő
Program: Experimental and Clinical Pharmacology

E/VII-4
AMORPHOUS FAMOTIDINE STABILIZED IN ELECTROSPUN POLYMER FIBERS AS A MODEL OF ODW FORMULATION FOR ACTIVE AGENTS WITH POOR INTRAORAL SOLUBILITY
Attila Marosi, Zsombor Kristóf Nagy, Olivér Ács, Dénes Janke, Lászlóné Tóth, Zsófia Szalay, Balázs Németh, Zoltán Kazsu, Béla Noszál, György Marosi, Ádám Demeter
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-5
QUANTITATIVE SILYLATION SPECIATIONS OF PRIMARY PHENYLALKYL AMINES, INCLUDING MESCALINE, AMPHETAMINE AND 3,4-METHYLENEDIOXY-AMPHETAMINE, PRIOR TO THEIR ANALYSIS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY
Borbála Molnár, Blanka Fodor, Imre Boldizsár, Ibolya Molnár-Perl
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-6
SYNTHESIS AND CHARACTERIZATION OF NOVEL C_3 SYMMETRIC TRIPODAL TRIAZOLES
Gábor Neumajer, Gergő Tóth, Attila Marosi, Szabolcs Béni, Béla Noszál
Programme: Modern Trends in Pharmaceutical Research

E/VII-7
PREPARATION AND STABILITY STUDY OF CARVEDILOL LOADED HYDROXYPROPYL CELLULOSE MICROFIBERS AND THEIR FORMULATION TO ORODISPERSIBLE TABLETS FOR IN VITRO DISSOLUTION ENHANCEMENT
Péter Szabó, Romána Zelkó
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-8
MOUSE MODELS FOR TESTING DRUGS IN DIFFERENT SENSORINEURAL HEARING LOSS FORMS
Judit Szepesy, Viktória Humli, Gábor Polony, Réka Andó, Máté Aller, Tamás Horváth, Tamás Dienes, Andrea Harnos, László Tamás, E. Sylvester Vizi, Tibor Zelles
Program: Experimental and Clinical Pharmacology

E/VII-9
SITE- AND SPECIES-SPECIFIC HYDROLYSIS RATES OF COCAINE
Levente Szőcs, Béla Noszál
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-10
PROTECTIVE EFFECT OF RESVERATROL ON SERUM DEPRIVATION INDUCED CASPASE ACTIVATION IN NON-TRANSFORMED CELLS
Zsófia Ulakcsai, Fruzsina Bagaméry, István Vincze, Éva Szökő, Tamás Tábi
Program: Experimental and Clinical Pharmacology

E/VII-11
APPLICATION OF MITSUNOBU REACTION FOR THE SYNTHSES OF 6β-ACYLAMINOMORPHINAN COMPOUNDS
Ákos Urai, Péter Horváth, Sándor Hosztafi, Béla Noszál
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-12
COMPARABLE EVALUATION OF RP-HPLC, SFC, UPC² TECHNIQUES IN THE PARTHENOLIDE ANALYSIS OF *TANACETUM PARTHENIUM* L. SUPERCRITICAL EXTRACTS
Krisztina Végh, Ágnes Alberti, Anita Tóth, Ágnes Kéry
Program: Modern Trends in Pharmaceutical Scientific Research

E/VII-13
NEW *IN VITRO* PERMEABILITY TEST FOR TRANSDERMAL AND LOCAL THERAPEUTIC PATCHES
Gábor Vizserálek, Bálint Sinkó, Krisztina Takács-Novák
Program: Modern Trends in Pharmaceutical Scientific Research

P/II-11
IN VIVO AND IN VITRO STUDY ABOUT THE ANTIFUNGAL ISOTHIOCYANATES OF HORSERADISH
Regina Bertóti
Program: Modern Trends in Pharmaceutical Scientific Research

P/II-12
THE EFFECTS OF ANGIOTENSIN II ON THE NMDA RECEPTORS IN TWO BRAIN STRUCTURES
Adrienn Hanuska
Program: Experimental and Clinical Pharmacology

MENTAL HEALTH SCIENCES DOCTORAL SCHOOL

E/I-1
MENTAL HEALTH OUTCOMES OF PARENTS AND CHILDREN LIVING IN LARGE FAMILIES
Csaba Bálity, Bálint Duráczky
Program: Sociological and mental health approaches to resources for individuals and communities

E/I-2
CHILDREN OF THE 1989 TRANSITION: CHILDBEARING INTENTIONS
Veronika Bóné, Beáta Dávid
Program: Sociological and mental health approaches to resources for individuals and communities

E/I-3
POSTTRAUMATIC STRESS DISORDER SYMPTOM STRUCTURE IN A SAMPLE OF RWANDANS WITH GENOCIDAL TRAUMA
Kinga E. Fodor, Richard Neugebauer
Program: Psychiatry

E/I-4
THE „COST OF CARING" FOR SERIOUSLY ILL PATIENTS – COMPASSION FATIGUE OR SATISFACTION
Adrienne Kegye, Edit Révay, Ágnes Zana, Katalin Hegedűs
Program: Mental Health Sciences

E/I-5
ASSOCIATIONS BETWEEN PATTERNS OF ADULT ATTACHMENT, RELIGIOUSNESS AND RELATIONSHIP SATISFACTION
Csilla Lakatos, Tamás Martos, Katalin Horváth-Szabó
Program: Sociological and mental health approaches to resources for individuals and communities

E/I-6
VITAL EXHAUSTION, COPING STRATEGIES AND THE QUALITY OF MARITAL RELATIONSHIP RELATED TO INFERTILITY STRESS
Enikő Lakatos, Réka Cserepes, Gábor Szabó, Piroska Balog
Program: Menthal Health Sciences

E/I-7
'BONDING' OR 'BRIDGING'? – SOCIAL CAPITAL OF ROMA UNIVERSITY STUDENTS
Ágnes Lukács, Beáta Dávid
Program: Sociological and Mental Health Approaches to Resources for Individuals and Communities

E/I-8
SOCRATES' DEMON 'IN THE MIRROR OF DEATH'
Ferenc Mújdricza
Program: Sociological and Mental Health Aspects of Individual and Community Resources

E/I-9
INVESTIGATION OF THE PSYCHOLOGICAL ASPECTS OF DRY EYE DISEASE
Ildikó Szakáts, Margit Sebestyén, Emma Birkás, György Purebl
Program: Mental Health Sciences

E/I-10
THE ROLE OF INTERPARENTAL CONFLICTS IN CHILDREN'S ANXIETY AND DEPRESSIVE SYMPTOMS
Mária Szepes, Piroska Balog
Program: Mental Health Sciences

E/I-11
READING DISABILITY SPECTRUM EARLY AND LATE RECOGNITION SUBTRESHOLD AND FULL COMORBIDIT
Krisztina Törő, Judit Balázs
Program: *Clinical Psychology and Psychiatry*

E/I-12
CHALLENGES FOR CARERS OF ELDERLY FAMILY MEMBERS
Anett Mária Tróbert
Program: *Sociological and mental health approaches to resources for individuals and communities*

E/I-13
INDIVIDUAL AND SOCIAL-LEVEL PSYCHOLOGICAL FACTORS IN THE BACKGROUND OF HUNGARIAN HIGH SCHOOL STUDENTS' HEALTH RISK BEHAVIOR
Szabolcs Varga, Bettina Pikó
Program: *Mental Health Sciences*

P/I-1
VISUALLY IMPAIRED CHILD IN THE FAMILY: CHARACTERISTICS OF FAMILY FUNCTIONING IN FAMILIES RAISING VISUALLY IMPAIRED CHILDREN
Erika Kiss
Program: *Sociological and mental health approaches to resources for individuals and communities*

P/I-2
ELEMENTARY SENSORY DEFICITS IN SCHIZOPHRENIA INDEXED BY IMPAIRED VISUAL MISMATCH NEGATIVITY
Kinga Farkas, Gábor Stefanics, Csilla Marosi, Gábor Csukly
Program: *Clinical Psychology and Psychiatry*

P/I-3
THE EFFECTS OF FOLATE PATHWAY GENES *MTHFR* AND *MTHFD1L* ON DEPRESSIVE RUMINATION IN TWO EUROPEAN WHITE POPULATIONS
Nóra Eszlári, Dávid Kovács, Péter Petschner, Dorottya Pap, Rebecca Elliott, Ian Muir Anderson, John Francis William Deakin, György Bagdy, Gabriella Juhász
Program: *Clinical psychology and psychiatry*

P/I-4
THE EXPERIENCES OF BREAST CANCER PATIENS AND THE ROLE OF PURPOSE IN COPING – A QUALITATIVE ANALYSIS
Judit Désfalvi, Tamás Martos
Program: *Sociological and mental health approaches to resources for individuals and communities*

P/I-5
STUDY OF SOCIAL CAPITAL AND SELECTION OF UNIVERSITY PROFESSIONAL RELATIONSHIP AT SEMMELWEIS UNIVERSITY FOUR FACULTIES
Mariann Dinyane Szabó
Program: Sociological and Mental Health Approaches to Resources for Individuals and Communities

P/I-6
RELATIONSHIP BETWEEN BURNOUT AND ORGANIZATIONAL FACTORS AMONG HUNGARIAN UNIVERSITY HOSPITAL PHYSICIANS, THE HOUPE STUDY
Anikó Nistor, Katalin Nistor, Lise Tevik Løvseth, Ann Fridner, Szilvia Ádám
Program: Mental Health Sciences

P/I-7
IMPROVEMENT OF THE CONSENSUS RORSCHACH TEST'S PROCESSOMETRIC EVALUATION SYSTEM
Rita Tóth-Vajna, Tamás Martos
Doctoral School: Mental Health Sciences
Program: Sociological and mental health approaches to resources for individuals and communities

P/I-8
FACIAL EMOTION EXPRESSION DURING A FACIAL EMOTION RECOGNITION TASK IN A CLINICAL SAMPLE OF ADOLESCENTS WITH PEER PROBLEMS
Péter Vida, Nikoletta Áspán, Dóra Szentiványi, Lili Olga Horváth, Ágnes Keresztény, Mónika Miklósi, Judit Balázs, József Halász
Program: Psychiatry

P/I-9
SCREENING OF AMNESTIC MILD COGNITIVE IMPAIRMENT
Sirály Enikő, Fodor Zsuzsa, Szabó Ádám, Kovács Vivienne, Csibri Éva, Hidasi Zoltán, Salacz Pál, Csukly Gábor
Program: Clinical Psyhology and Psychiatry

P/I-10
GENDER DIFFERENCES - ADOLESCENTS KNOWLEDGE ABOUT MEDICINE AND MEDICINE USE
Máté A. Balázs, Bettina F. Pikó
Program: Sociological and mental health approaches to resources for individuals and communities

P/I-11
THE TOPOGRAPHICAL DISTRIBUTION OF DELTA POWER: CAN THE CAUDO-ROSTRAL SHIFT OF BRAIN MATURATION BE SPOTTED IN THE AGE RANGE OF 4 TO 8 YEARS?
Sára Szakadát, Piroska Sándor, Róbert Bódizs
Program: Mental Health Sciences

P/I-12
FACTORS OF THERAPY CHOICE
A MEDICAL ANTHROPOLOGICAL ANALYSIS OF INTERACTING BIOMEDICAL AND ALTERNATIVE EXPLANATORY MODELS OF ILLNESS
Szilvia Zörgő
Program: Mental Health Sciences

P/II-16
ATTACHMENT ANXIETY AS PREDICTOR OF RISK FOR EATING DISORDERS ON A REPRESENTATIVE HUNGARIAN ADULT SAMPLE
Tamás Dömötör Szalai, Edit Czeglédi
Program name: Mental Health Sciences

„JÁNOS SZENTÁGOTHAI" NEUROSCIENCES DOCTORAL SCHOOL

E/II-2
THE EFFECT OF GENETICALLY ABLATING THE ATP-FORMING SUBUNIT OF SUCCINYL-COA LIGASE ON MITOCHONDRIAL BIOENGERETIC PARAMETERS
Dóra Ravasz, Gergely Kacsó
Program: Functional Neurosciences

E/IV-4
COMPARISONS OF INTRINSIC AND ASSOCIATIVE CONNECTIONS OF THE PRIMATE SOMATOSENSORY CORTEX
Emese Pálfi, Mária Ashaber, László Zalányi, Cory Palmer, Robert Friedman, Orsolya Kántor, Anna W. Roe, László Négyessy
Program: Neuromorphology and Cell Biology

E/IV-5
SCREENING OF MONOGENIC AUTISM FORMS IN HUNGARIAN COHORT USING THE NEXT GENERATION SEQUENCING (NGS)
Ágnes Noémi Varga, Klára Pentelényi, Péter Balicza, Viven Hársfalvi, Viktória Reményi, Csilla Prekop, Szilvia Magyarósi, Judit Mária Molnár
Program: Clinical Neurosciences

P/I-13
THE EFFECT OF MATERNAL BONDING AND THE CHRNB2 GENE ON SMOKING-RELATED DEPRESSIVE SYMPTOMS
Irén Csala, Luca Egervári, Péter Döme, Gábor Faludi, Judit Lazáry
Program: Biological Psychiatry

MOLECULAR MEDICINE DOCTORAL SCHOOL

E/II-3
***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/II-4
ACTIVATION OF ATMPK9 THROUGH AUTOPHOSPHORYLATION INDEPENDENTLY OF THE CANONICAL MAPK CASCADES
Szilvia K. Nagy, Zsuzsanna Darula, Brigitta M. Kállai, László Bögre, Gábor Bánhegyi, Katalin F. Medzihradszky, Gábor V. Horváth, Tamás Mészáros
Program: Pathobiochemistry

E/II-5
NUCLEASE RESISTANT OLIGONUCLEOTIDE RECEPTOR FOR TROPONIN DIAGNOSTICS
Zsuzsanna Szeitner, Anna Doleschall, Gergely Lautner, Katalin Keltai, Róbert Gyurcsányi, Tamás Mészáros
Program: Pathobiochemistry, Selection and application of protein specific aptamers

E/II-6
LIVER METABOLIC ALTERATIONS INFLUENCE PXE-LIKE PHENOTYPE
Borbála Vető, Caroline Bacquet, Hugues de Boussac, Attila Horváth, Endre Barta, Dávid Jónás, László Buday, Bálint L. Bálint, László Nagy, András Váradi, Tamás Arányi
Program: Pathobiochemistry

E/II-7
EVIDENCE FOR THE CYTOSOLIC LOCATION OF NAD(P)H CYTOCHROME B5 OXIDOREDUCTASE
Veronika Zámbó, Éva Kereszturi, Mónika Tóth, Gábor Lotz, Miklós Csala
Program: Pathobiochemistry

E/II-8
THE ROLE OF B-ARRESTINS IN THE HETEROLOG REGULATION OF TYPE 1 ANGIOTENSIN RECEPTOR
András Tóth, Dávid Laczkó
Program: Cellular Physiology

E/II-10
LOCAL MUCOSA INSTRUCTS MURINE CD8+ RESIDENT MEMORY T CELLS TO DEVELOPUNIQUE PHENOTYPES MEETING LOCAL NEEDS
Nikolett Lupsa, Barbara Érsek, Péter Pócza, Eszter Sarzsinszky, Anett Tóth, Bence Bagita, András Bencsik, Hargita Hegyesi, András Matolcsy, Edit Buzás, Zoltán Pós
Program: Basis of Human Molecular Genetics and Gene Diagnostics

E/IV-3
RESPONSE TO SOCIAL CHALLENGES: THE ROLE OF 2-ARACHIDONOYLGLYCEROL SIGNALING
Zoltán Balogh, Zoltán Kristóf Varga, Manó Aliczki, József Haller
Program: Neuroendocrinology

E/V-10
IMPACT OF *GRIA1* POLYMORPHISMS ON ASPARAGINASE HYPERSENSITIVITY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA
Nóra Kutszegi, Ágnes Félné Semsei, Viktória Nagy, Judit Sági, András Gézsi, Katalin Csordás, Krisztina Míta Gábor, Zsuzsanna Jakab, Orsolya Lautner-Csorba, Csaba Szalai, Gábor Kovács, Dániel Erdélyi
Program: Basis of Human Molecular Genetics and Gene Diagnostics

P/II-3
ENDODERM DERIVED SONIC HEDGEHOG REGULATE THE EXTRACELLULAR MATRIX PATTERNING DURING ENTERIC NERVOUS SYSTEM DEVELOPMENT
Csilla Barad
Program: Embryology, Theoretical, Experimental and Clinical Developmental Biology

PATHOLOGICAL SCIENCES DOCTORAL SCHOOL

E/II-1
SYNDECAN-1 IN LIVER FIBROSIS AND REGENERATION
Eszter Regő
Program: Oncology

E/V-1
DIGITAL IMAGE-ANALYSIS PROCESSES TO DETERMINE KI-67 PROLIFERATION INDEX IN BREAST CANCER
Balázs Ács, Zsuzsanna Bodor
Program: Alteration of cell, extracellular matrix, fiber system in cardiovascular and certain neoplastic diseases.
Experimental and diagnostic pathomorphological examinations.

E/V-2
THE PROGNOSTIC IMPACT OF TERT PROMOTER MUTATION AND POLYMORPHISM IN MALIGNANT PLEURAL MESOTHELIOMA
Ágnes Bilecz, Christine Pirker, Mir Ali Reza Hoda, Bahil Ghanim, Thomas Klikovits, Ildikó Szirtes, Balázs Döme, Rajiv Kumar, Walter Berger, Balázs Hegedűs
Program: Oncology

E/V-3
ALTERATION OF BIOENERGETIC PATHWAYS DETECTED BY MASS SPECTROMETRIC METHODS AND MTOR ACTIVITY RELATED PROTEINS IN TUMOR CELLS
Zoltán Hujber, András Jeney, Júlia Oláh, Anna Sebestyén, Ágnes Márk, Noémi Nagy, Gézáné Csorba, Gábor Petővári, Károly Vékey, Norbert Szoboszlai
Program: Oncology

E/V-4
CONVERGENCE OF SOMATIC MUTATIONS WITHIN THE JAK-STAT SIGNALLING PATHWAY IN A NOVEL *RUNX1*-MUTATED PEDIGREE
Péter Attila Király, Kiran Tawana
Program: Oncology

E/V-5
THE ROLE OF CD49D EXPRESSION IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS
Csilla Kriston, Márk Plander, Ágnes Márk, Orsolya Szabó, András Matolcsy, Gábor Barna
Program: Experimental Oncology

E/V-6
MTOR INHIBITOR TREATMENT REDUCES THE PROLIFERATION IN HL CELL LINES WITH CONSTITUTIVELY ACTIVE NOTCH1
Noémi Nagy, Ágnes Márk, Zoltán Hujber, Anna Molnár; Mónika Tóth, Titanilla Dankó, Gábor Petővári, Melinda Hajdu, Péter Attila Király, László Kopper, Anna Sebestyén
Program: Experimental Oncology

E/V-7
THE INFLUENCE OF GLIVEC ON LIVER REGENERATION IN MOUSE
András Rókusz
Program: Oncology

E/V-8
FDG-PET/CT AND DIFFERENT RESPONSE CRITERIA AFTER PRIMARY SYSTEMIC THERAPY IN BREAST CANCER

Tímea Tőkés, Gyöngyvér Szentmártoni, Kornélia Kajáry, Zsolt Lengyel, Tamás Györke, László Torgyík, Krisztián Somlai, Anna-Mária Tőkés, Janina Kulka, Magdolna Dank
Program: Oncology

E/V-11
TESTING OF ELECTRO-HYPERTHERMIA INDUCED PROGRAMMED CELL DEATH MECHANISM IN A COLORECTAL ALLOGRAFT MODELL
Tamás Vancsik, Éva Kiss, Csaba Kővágó
Program: Experimental Oncology

P/II-1
DISCRIMINATING COLON CANCER SUBTYPES BASED ON MICROARRAY GENE EXPRESSION
Zsófia Sztupinszki, Balázs Győrffy
Program: Oncology

P/II-2
EFFECTS OF TARGETED THERAPY ON INTRATUMOR HETEROGENEITY IN RENAL CELL CARCINOMA PATIENTS
Pongor Lőrinc Sándor, Sztupinszki Zsófia, Győrffy Balázs
Program: Oncology

P/II-15
HEALTHCARE-ASSOCIATED INFECTIONS AND ANTIMICROBIAL USE IN LONG-TERM CARE FACILITIES – HUNGARY, 2013
Rita Szabó
Program: Research in Public Health and Health Science

SPORT SCIENCES, UNIVERSITY OF PHYSICAL EDUCATION, BUDAPEST

E/IV-2
EFFECTS OF INTERVAL TRAINING AND PROBIOTIC SUPPLEMENTATION ON COGNITIVE FUNCTION IN A TRANSGENIC MICE MODEL OF ALZHEIMER'S DISEASE
Dóra Ábrahám, Klára Felszeghy, János Fehér, Zsolt Radák
Program: Physical Training, Regulation, Metabolism

MEDICAL UNIVERSITY OF SZEGED

P/II-8
EFFECT OF ENKEPHALIN-CONOTOXIN HYBRID PEPTIDES ON OPIOID RECEPTORS
Reza Samavati, Ferenc Zádor, Adriano Mollica, Anna Borsodi, Sándor Benyhe
Program: Using novel compounds in pain management