

SCHOOL OF PH.D. STUDIES  
OF SEMMELWEIS UNIVERSITY

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**ALMANAC**

**7**

2011



Compiled by     Doctoral Schools of Semmelweis University

Edited by        Dr. Károly Rácz

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**ISSN 2063-2207**

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	Semmelweis Publisher
	1089 Budapest, Nagyvárad tér 4.
	<a href="http://www.semmelweiskiado.hu">www.semmelweiskiado.hu</a>

Responsible editor: Dr. László Táncos

Make-up editor: Dr. Judit Vincze

Cover design: László Táncos

SKD: 400

Printed and bound by: Mester Nyomda Kft.

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## GENERAL OVERVIEW

Semmelweis University's School of Ph.D. Studies' foundations were laid in the early 1990s, following *Act LXX of 1993 on Higher Education*, which for the first time gave individual universities the right to issue doctoral degrees.

There are hundreds of Ph.D. students enrolled in one of the more than 40 training programmes offered by the University's eight doctoral schools. These students work under the supportive guidance of the School's dedicated tutors, and can choose from among the 60-120 courses that are offered by the School each semester.

The School's professors and tutors come either from one of Semmelweis University's six faculties, or from the institutes and laboratories of various other Hungarian universities. This level of interdepartmental and interuniversity collaboration has led to the creation of new research centres that function as true melting pots.

The supportive guidance and knowledge of the School's experienced professors and talented tutors has a great impact on the research work of young candidates, whose motivation is augmented from being able to meaningfully interact with experts in their particular field. Indeed, by involving the greatest authorities from within, as well as from without the university, the School of Ph.D. Studies has, from the beginning, been able to preserve the quality and prestige of the degree.



## ORGANIZATIONAL STRUCTURE

The School of Ph.D. Studies is an autonomous educational body of Semmelweis University; its activities are subject to the decisions made by the University's Doctoral Council, which meets every second month of the academic year. The Doctoral Council determines the content of the Ph.D. programmes, the admission procedures and the admission fee. The work of the Doctoral Council is supported by the Doctoral Secretariat, which is also responsible for providing detailed information about these to the applicants.

The School of Ph.D. Studies is organised around doctoral schools, which serve as umbrellas for related branches of science and their respective programmes. Each doctoral school has its own council, which serves as its central administrative body. Nonetheless, the individual programmes continue to enjoy a considerable amount of independence.

Currently the School of Ph.D. Studies at Semmelweis University has eight doctoral schools:

1. Basic Medicine
2. Clinical Medicine
3. Pharmaceutical Sciences
4. Mental Health Sciences
5. Sport Sciences
6. Neurosciences (János Szentágothai)
7. Molecular Medicine
8. Pathological Sciences.

The School of Ph.D. Studies integrates research groups and programmes from all the faculties of Semmelweis University that are entitled to issue Ph.D. degrees. The University's largest faculty, the Faculty of Medicine, is represented in almost every doctoral school. The faculties of Dentistry and Health Sciences each have their own study programmes, while the Faculty of Pharmacy and the Faculty of Physical Education and Sport Sciences are represented by their own doctoral schools.

The basic unit of the School's complex educational system is "one student - one tutor". Together, they enjoy a high level of freedom and autonomy in conducting their research, within the limits set by the School's rules and regulations.





## PROGRAM OVERVIEW

The Ph.D. program at Semmelweis University consists of two parts: the Educational Phase (Phase I) and the Qualification Phase (Phase II).

### *Phase I: Educational Phase*

The aim of Phase I is to train students to become scientists through coursework and research activity. It is in this phase that students select the specific scientific topic that will become the core of their final dissertation. Research is conducted in collaboration with faculty members, while a qualified tutor supervises each student.

### *Phase II: Qualification Phase*

Phase II provides students with the opportunity to evaluate the results of experiments and publish them in acknowledged scientific journals. Naturally this is, or can be, an on-going activity in Phase I as well. At the end of this phase, students are required to pass a comprehensive examination and to write and defend a dissertation. Since dissertations are required to be made available to the public prior to its defence, an online database containing hundreds of full-text doctoral theses, and their respective synopses has been set up by the School, in order to facilitate this process. Although Phase II logically follows Phase I, students may choose to skip the first phase and go straight into Phase II, provided that the necessary prerequisites and requirements have been met.

### *Ph.D. Courses*

There are a number of courses announced on the School's website each semester. The list of required courses, which have to be taken during the Ph.D. training period, is finalised each year a few weeks after registration. Beginning in 2002, the doctoral schools have published a study plan for the entire training period, while a database of available courses is made accessible through the School of Ph.D. Studies' website, giving students the freedom to easily construct their own individual study plan.



## ADMISSION AND TUITION

The School of Ph.D. Studies offers three forms of education:

- Full-time, entering Phase I as students
- Part-time, entering Phase I as students
- Individual studies, entering Phase II as candidates

Both full-time and part-time students are required to meet the same admission requirements. Individuals who join the programme in Phase II are not considered students, and will not be given a record book or student identity card; rather, they are considered candidates for the doctoral degree.

### *Admission Requirements and Process*

Doctoral applicants must

- be university graduates or students registered for their final semester of university studies
- possess at least a certified C type (oral and written) state foreign-language exam or an equivalent certificate if applying admission to the Hungarian-language program. Applicants for the English-Language program must have a good command of English.

When applying to the programme, applicants are required to state the specific training programme and research topic they wish to pursue within one of the University's doctoral schools.

The admission procedure is based on evaluating the candidate's

- general knowledge and personal ability
- topic-related knowledge and academic competence
- previous scientific activity and contribution

The admission board of each doctoral school creates a ranked list of candidates which is submitted to the University's Doctoral Council. The Doctoral Council makes the final decision regarding admissions.

### *Tuition Fees*

Certain costs of education, scientific training and official procedures are covered by students and candidates. Most of the fees are equal to or close to what is ordinarily paid by undergraduate students.





## DOCTORAL COUNCIL

**President of the Doctoral Council: Dr. Károly Rácz**

### *Members of the Doctoral Council*

<b>Dr. József Tímár</b>	Vice-President
<b>Dr. Ágoston Szél</b>	Vice-Rector of Semmelweis University
<b>Dr. Miklós Tóth</b>	Vice-Rector for Scientific and International Affairs
<b>Dr. Gábor Makara</b>	President of the Educational Board
<b>Dr. János Rigó</b>	President of the Quality Control and Evaluation Board
<b>Dr. László Rosivall</b>	Basic Medicine Doctoral School
<b>Dr. Zsolt Tulassay</b>	Clinical Medicine Doctoral School
<b>Dr. Éva Szőke</b>	Pharmaceutical Sciences Doctoral School
<b>Dr. István Bitter</b>	Mental Health Sciences Doctoral School
<b>Dr. Dániel Bereczki</b>	János Szentágothai Neurosciences Doctoral School
<b>Dr. György Nagy</b>	President of the Disciplinary Procedures Committee
<b>Dr. József Mandl</b>	Molecular Medicine Doctoral School
<b>Dr. Emil Monos</b>	Basic Medicine Doctoral School
<b>Dr. József Tihanyi</b>	Sport Sciences Doctoral School
<b>Dr. György Losonczy</b>	Representative of the Faculty of Medicine
<b>Dr. Gábor Varga</b>	Representative of the Faculty of Dentistry
<b>Dr. Kálmán Magyar</b>	Representative of the Faculty of Pharmacy
<b>Dr. Péter Tamás Sótonyi</b>	Representative of Szent István University
<b>Dr. Zsolt Radák</b>	Representative of the Faculty of Physical Education and Sport Sciences
<b>Dr. István Szabolcs</b>	Representative of the Faculty of Health Sciences
<b>Dr. Sándor Békási</b>	President of the Doctoral Student's Union



## PERMANENT COMMITTEES OF THE DOCTORAL COUNCIL

### *Educational Board (EB)*

The Educational Board (EB) meets at least once in a half year. It expresses opinion on course proposals and requests for financial support for courses. If needed, the EB can alter courses. It can make proposals in the following matters: (1) the structure of teaching, (2) the co-ordination of courses, (3) the nature of the method of course registration and registration deadlines, (4) the establishment of credit points which can be given to each course and (5) the recognition of credit points.

Students receiving tuition are advised to choose those courses which are promoted by the Doctoral Council of Semmelweis University. Theoretical knowledge and skills necessary for research are obtained from the compulsory course modules. Throughout the year the Ph.D. schools organize optional courses. Some of them organize courses which are obligatory for all students who are registered in that particular school.

**President of the Educational Board: Dr. Gábor Makara**

#### *Members of the Educational Board*

<b>Dr. László Rosivall</b>	Basic Medicine Doctoral School
<b>Dr. Béla Molnár</b>	Clinical Medicine Doctoral School
<b>Dr. Éva Szőkő</b>	Pharmaceutical Sciences Doctoral School
<b>Dr. László Tringer</b>	Mental Health Sciences Doctoral School
<b>Dr. Gábor Pavlik</b>	Sport Sciences Doctoral School
<b>Dr. Emília Madarász</b>	János Szentágothai Neurosciences Doctoral School
<b>Dr. Ágota Vér</b>	Molecular Medicine Doctoral School
<b>Dr. Károly Nagy</b>	Pathological Sciences Doctoral School
<b>Tamás Sticz</b>	Representative of the Doctoral Students' Union

Members of this body debate and decide whether a candidate has a thorough grounding in academic work by examining his/her previous performance in education and research and the elected topic for research. The board decides whether the candidate will or will not be able to produce a thesis three or four years after his/her entrance into the system.

### *Quality Control and Evaluation Board (QCEB)*

The efficiency of the doctoral training is shown in the frequency of completed doctoral theses and academic publications. The standards of these works are judged by scientometric indicators. This process evaluates both the academic competence of individual Ph.D. candidates and also the academic standards of the Doctoral School.

One of the most important acts of quality control is that everybody involved in the process complies with the instructions given in the qualification phase by the Doctoral Council (DC). The importance of this issue led to the establishment of The Quality Control and Evaluation Board (In Hungarian: VMB). This first evaluating forum controls whether the submitted work fulfils the conceptual, structural and formal requirements of a doctoral thesis. Consequently, a formal opinion is released stating whether the Ph.D. candidate acquired the scientometric indicators prescribed in the Book of Regulations of the Doctoral School or not.

***President of the Quality Control and Evaluation Board: Dr. János Rigó***

***Members of the Quality Control and Evaluation Board***

<b>Dr. Tamás Ivanics</b>	Basic Medicine Doctoral School
<b>Dr. László Herszényi</b>	Clinical Medicine Doctoral School
<b>Dr. István Antal</b>	Pharmaceutical Sciences Doctoral School
<b>Dr. Katalin Hegedűs</b>	Mental Health Sciences Doctoral School
<b>Dr. Gyöngyi Szabó (Földesiné)</b>	Sport Sciences Doctoral School
<b>Dr. András Csillag</b>	János Szentágothai Neurosciences Doctoral School
<b>Dr. Miklós Csala</b>	Molecular Medicine Doctoral School
<b>Dr. Janina Kulka</b>	Pathological Sciences Doctoral School
<b>Katalin Dezső</b>	Representative of Doctoral Students' Union

Considering the proposals given by the QCRB (VMB in Hungarian) the Doctoral Council decides whether the doctoral thesis can be sent to the opponents. At a first glance this process might seem unnecessary because the control of requirements looks like a simple administrative issue. However, the process of evaluation described above - which applies the general rules (sometimes with a great deal of empathy) - is highly desirable for a number of reasons: there is a great variety of research topics, the issues discussed range from molecular biology to behavioral sciences which must be able to win academic recognition in Hungary and abroad.

Apart from works which meet all the standards there are doctoral theses which are inadequate in their content and structure and are therefore unacceptable. Candidates who do not fulfill the main requirements are advised to withdraw their dissertation prior to a detailed, expert review. We are proud that only thoroughly controlled doctoral theses are given in the hands of official opponents and reviewers. It is worth mentioning some of these requirements which doctoral candidates must take into consideration.

- (a) Only those candidates deserve scientific degrees who are able to publish their results intelligibly and based on a coherent analysis. Summarizing the content of two or three excellent publications is not equal to a doctoral dissertation.
- (b) Some articles which were published in high-rank international journals with a sophisticated title and a high impact factor are not sufficient to create the basis for Ph.D. qualification. Only those articles are potential items for recognition which are the result of real academic work. Therefore, articles summarizing the academic literature of a particular topic or commenting on the academic work of others as "letters to the editor" are not acceptable. By contrast, articles published in a journal under the latter heading could include original scientific results. But this must become clear from the presentation of scientific methods and/or from the editor's professional opinion.
- (c) The QCRB during its evaluation takes into consideration the grammatical correctness and style of the English or Hungarian language, the length as well as the external appearance of the thesis and the quality of illustrations.

These examples illustrate that the board has a high level of responsibility in defining the academic quality of Ph.D. qualifications. At the same time the board is meticulously tactful

in giving criticisms. Therefore, written judgments also include constructive suggestions for correcting the deficiencies discovered. This professional opinion is sent to both the candidate and the head of the training program. This process creates grounds for the necessary corrections and gives the possibility of legal remedies.

When this evaluation process is applied in practice, for instance, nine doctoral theses out of ten are found acceptable. The other one is rejected usually because basic requirements are not fulfilled, i.e. the shortage of sufficient acceptable publications. Furthermore, it occurs that two or three theses are rejected in form (i.e. the outward appearance and/or some of the essential requirements are missing from the package which was submitted to the QCRB). In these cases the professional review of the doctoral theses will be delayed until the corrections are completed and necessary supplements are submitted.

One of the major duties of the QCRB is to report its experience to the Doctoral Council and to suggest proposals concerning the alterations in the Rules of the Doctoral School if necessary. Apart from the duties described above the QCRB has authority over any stage of the doctoral procedure in scientific matters. Furthermore, it passes judgments on applications, looks into the matters of complaints and makes decisions concerning naturalizations (e.g. the recognition of qualifications).

Since 2000 the Quality Control and Evaluation Board has had this role of quality evaluation within the Doctoral School.

### ***Disciplinary Procedures Committee***

The activity of this committee is needed only in exceptional cases, of which plagiarism and disharmony between student and tutor have given some work to the committee in the past years.

***President of the Disciplinary Procedures Committee: Dr. György Nagy***

#### ***Members of the Disciplinary Procedures Committee***

**Lilla Fang**

Clinical Medicine Doctoral School

**Dr. István Antal**

Pharmaceutical Sciences Doctoral School

**Emese Ficsor**

Pharmaceutical Sciences Doctoral School

**Ákos Gerencsér**

Mental Health Sciences Doctoral School



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## DOCTORAL SECRETARY OFFICE

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<b>Emőke Márton</b>	Head
<b>Anna Marádi (Pintérné)</b>	Financial officer
<b>Anita Marosfalvi</b>	Adviser
<b>Tímea Rab</b>	Adviser

The administrative duties of the Doctoral School are managed by the Doctoral Secretary Office which creates a link between the Doctoral Council, the Ph.D. training programs and the Ph.D. students. It maintains permanent contact with the educational bodies outside of the university (e.g. Ministry of Education, Hungarian Accreditation Board, etc.). The Secretary is available for Ph.D. students on an office-hours basis, however, they are ready to help anytime in urgent cases. In one little room practically every major step of the degree obtaining process is handled, starting from the first inquiries and paper work of the entrance examination, all the way up to the preparation of the diplomas. (Address: H-1085 Budapest, Üllői út 26. ground floor Nr. 9.)

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## DOCTORAL STUDENTS' UNION (DSU)

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The DSU (In Hungarian: DHÖK) is a body elected by the doctoral students in order to legally represent their interests both inside and outside the university; e.g. in the Doctoral Council and the National Association of Doctoral Students. Members of the union participate in the *ad hoc* commissions dealing with matters in their interest and are responsible for organizing the Scientific Ph.D. forums. The head office of the DSU is: The Students' Office of Semmelweis University (H-1089 Budapest, Nagyvárad tér 4. ground floor Nr. 18.) Members of the Union of the Doctoral Students are also accessible through the Doctoral Secretarial Office.

***President of the Doctoral Student's Union: Sándor Békási***

### ***Members of the Doctoral Students' Union***

<b>Lilla Fang</b>	Basic Medicine Doctoral School
<b>Árpád Patai</b>	Clinical Medicine Doctoral School
<b>Emese Ficsor</b>	Pharmaceutical Sciences Doctoral School
<b>Ákos Gerencsér</b>	Mental Health Sciences Doctoral School
<b>Kinga Kiszela</b>	Sport Sciences Doctoral School
<b>Viktória Reményi</b>	János Szentágothai Neurosciences Doctoral School
<b>Sándor Békási</b>	Molecular Medicine Doctoral School
<b>Tamás Sticz</b>	Pathological Sciences Doctoral School



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## INTRANET

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**Website:** <http://www.phd.sote.hu>

The website of the Doctoral School at Semmelweis University is an essential means for organizing doctoral education. Hundreds of Ph.D. students take the courses as part of more than thirty training programs of eight doctoral schools under the supervision of hundreds of tutors in different locations. Every half year the school organizes 60 - 120 courses; the lectures and seminars are given in more than 50 locations within the university.

There are great advantages stemming from the intensity and variety of our education system. Therefore, it is a high priority to publish information which is clear-cut and accessible by everybody. The gradual augmentation of the website leads to the accumulation of information about every training program and sub-program and of every teacher and doctoral defense since 2000. Importantly, the website provides information about on-going courses and application possibilities. All application forms and documents, which are necessary for the administration of doctoral matters and the resolutions of the Doctoral Council, are also accessible on the website. Other detailed information and curricula are also available electronically. The website provides addresses, telephone numbers and e-mail addresses.

The regulations, the forms, the course and program data, the decisions of the Doctoral Council and the invitations to all defense ceremonies are accessible via the Internet. News on important conferences, university events, calls for proposals are also not missing from the repertoire.

The website opens a possibility for course leaders to put the information about their courses directly to the website. The Doctoral Secretarial staff manages and publishes all the relevant information: e. g. general news, advertisements and Ph.D. defenses without the assistance of a web supervisor.

The website has considerable web traffic according to statistical figures. The database system of presenting doctoral theses on the internet was set up. It is required that doctoral theses be available to the public before the defense so they may be accessed electronically in full through the internet simultaneously with the announcement of the Ph.D. defense. The "Dissertation Abstracts", a trademark of ProQuest, allows for the availability of each recently defended thesis all over the world. Older works are not available yet, however we try to put out as many of our precious creations as possible.



## **'VERITAS ET VIRTUS' AWARD IN MEMORY OF DR. ZSOLT FARKAS JR.**

After the tragic death of Dr. Zsolt Farkas, a Ph.D. student of the Doctoral School, his parents, Dr and Mrs Zsoltné Farkas established a foundation in memory of their late son. The aim of the foundation is to support financially research by Ph.D. candidates.

Some of the aspects of the charter are: "The aims of the Foundation are to subsidize the work of Ph.D. students under thirty-five years who are concerned primarily with physiological research in the Doctoral School of Semmelweis University. Additionally, it contributes to the realization of the aims of the Doctoral School, i.e. to improve the quality of doctoral education, to facilitate the acquisition of widely recognized scientific degrees, to provide financial support for the expansion of accredited doctoral research programs, to establish pre-doctoral scholarships and to improve scientific communication. ...". "... Those Ph.D. students are able to benefit from the payments of the foundation whose submitted work wins a public competition advertised by the trustees of the Foundation. The type of work submitted can be in the process of publication but the candidate must be its first author. Other details are defined by the committee of trustees who are responsible for both advertising and reviewing the submitted work. ...". "The awards must be transferred ceremonially to the winners every year on the Dies Academicus (first Saturday of November)."

The Office of the Foundation is: H-1085 Budapest VIII., Üllői út 26. The trustee committee is the Advisory Board of the Foundation. The president of the Advisory Board of the Foundation is always the current head of the Doctoral Council at the Semmelweis University, at present, university professor, Dr. Ágoston Szél.

### ***Recipients of 'Veritas and Virtus' Award***

<b>2011 Dorottya Csuka</b>	Basic Medicine Doctoral School
<b>Zalán Péterfi</b>	Molecular Medicine Doctoral School
<b>Ágnes Prókai</b>	Clinical Medicine Doctoral School

## **PH.D. COURSES**

Every semester there are there a number of courses (60-120) announced on the website. Previously, the Educational Board of the Doctoral school filtered down the number of courses to between sixty and seventy. The Doctoral Council of Semmelweis University took into consideration the views the Educational Board and restricted the number of courses which can be run by each departmental doctoral school in one semester to between five and seven.

Since then the following procedure has been established concerning Ph.D. courses, i.e. the Doctoral Committee of each Departmental Doctoral School proposes between five and seven courses at the beginning of each semester which are entered the database of current courses. However, the Educational Board can recognize and award credit points for participation in Ph.D. courses of the appropriate standard at other universities. In this case the Educational Board needs the recommendation of the tutor and the head of the departmental doctoral school of the student in question.

The database of available courses is accessible at the website of the Doctoral School. Consequently, students are able to access the database and construct their own individual study plan.

Molecular biological methods in clinical and basic science	2011/2012/1	Ádám Vannay
Therapeutical activity, side effects and interactions in phytotherapy	2010/2011/2	Ágnes Kéry
Information, communication and sport	2010/2011/2, 2011/2012/1	Ágnes Kokovay
Role and detection of cell junction structures and molecules. Molecular diagnostics	2011/2012/1	András Kiss
Cell adhesion molecules / FISH technique in pathology diagnostics	2010/2011/2	András Kiss
Constitutional relationships of sportlaw and its selfregulation	2010/2011/2	András Nemes
Theoretical and practical studies for succesful Ph.D. degree	2011/2012/1	Anna Blázovics
Molecular enzymology	2011/2012/1	Attila Ambrus
Medical equipments inclinal diagnosis and therapy	2011/2012/1	Attila Nemes
Semmelweis Symposium 2011 - Organ transplantation in the XXI. century	2011/2012/1	Attila Szabó
Frontiers in surgery	2010/2011/2	Attila Szijártó
Tumor progression and its prediction	2011/2012/1	Balázs Győrffy, József Tímár
Aspiration cytology in practice	2011/2012/1	Balázs Járay
Liver transplantation with special interest on hepatitis C virus	2010/2011/2	Balázs Nemes
Liver transplantation and hepatobiliary surgery	2011/2012/1	Balázs Nemes
Research in pediatrics: from idea to published paper	2011/2012/1	Barna Vásárhelyi
Introduction into drug research	2010/2011/2	Béla Noszál
Cardiometabolic risk and its therapy	2011/2012/1	Csaba Farsang
Theory of action - efficacy	2010/2011/2	Csaba Nagykáldi
Endocrinology and sport	2011/2012/1	Csaba Nyakas
Nutritional science	2010/2011/2	Csaba Nyakas
The latest question of the medical genomics	2010/2011/2	Csaba Szalai
Clinical assays in neurology and psychiatry	2011/2012/1	Dániel Bereczki, Gábor Faludi
Introduction to biometry	2011/2012/1	Elek Dinya
Clinical cardiovascular physiology - 2011	2010/2011/2	Emil Monos, Márk Kollai
In vitro cell technology	2010/2011/2	Emilia Madarász
Introduction to natural and synthetic drugs used in the treatment of diabetes mellitus	2011/2012/1	Ernest Adeghate
Physiological role of GTP-binding proteins	2011/2012/1	Erzsébet Ligeti

Phytochemistry	2011/2012/1	Éva Lemberkovics
Pharmaceutical biotechnology	2011/2012/1, 2010/2011/2	Éva Szőke
Research and innovation management training	2010/2011/2	Éva Szökő
General course on intellectual property	2011/2012/1	Éva Szökő
Neuroethics: ethical considerations in neurological/psychiatry research and therapy	2010/2011/2	Ferenc Oberfrank
Sportestetica	2010/2011/2	Ferenc Takács
History of philosophy	2010/2011/2, 2011/2012/1	Ferenc Takács
Neurobiology and therapy of mood disorders and anxiety	2010/2011/2	Gábor Faludi
In situ hybridisation techniques in pathology	2011/2012/1	Gábor Lotz
Sport physiology	2010/2011/2, 2011/2012/1	Gábor Pavlik
Hungarian and European Union financial opportunities, proposal building, project financing and management in the field of health and life sciences	2010/2011/2	Gábor Pörzse
Genetechnology in the neurosciences	2010/2011/2	Gábor Szabó
Role of inflammatory processes in the development of cardiovascular diseases	2011/2012/1	Gábor Széplaki
Modern research methods in dentistry – methodological course	2011/2012/1	Gábor Varga
Sport in contemporary society	2010/2011/2, 2011/2012/1	Gyöngyi Szabó Földesiné
Neurochemistry, pharmacology and models of behaviour	2010/2011/2	György Bagdy
Development of health-education and nursing care in hospitals and outpatient clinics	2010/2011/2	György Harmat
Signal transductional therapy and rational drug design	2010/2011/2	György Kéri
Cellular biology of asthma bronchiale	2011/2012/1	György Losonczy
Autoimmunity	2011/2012/1	György Nagy
Disturbances in coagulation and haemostasis	2010/2011/2, 2011/2012/1	Gyula Domján
Professional role changes with appearance of medical care specialist having the BSc degree	2011/2012/1	Hollós Sándor
HPLC application in pharmacology	2011/2012/1	Huba Kalász
Ophthalmology	2011/2012/1	Ildikó Süveges
Clinikai neuropsychology	2011/2012/1	Ilona Pataky
Bioanalytic methods in pharmacokinetics	2011/2012/1	Imre Klebovich
Drug in the organism (ADME): pharmacokinetics, drug metabolism	2010/2011/2	Imre Klebovich
Organogenesis	2010/2011/2	Imre Oláh
Principles of developmental biology	2011/2012/1	Imre Oláh

Industrial pharmaceutical technology	2011/2012/1	István Antal
Psychiatry I.	2011/2012/1	István Bitter
Evidence based medicine in behaviour sciences	2011/2012/1	István Mucsi
Personality at molecular level	2011/2012/1	István Peták, Zsolt Rónai
Nutrigenomics and nutrigenetics	2010/2011/2, 2011/2012/1	István Szabolcs
Deviant behaviour and sociopathology	2010/2011/2	István Vingender
Isotope use methodology and radiation protection	2010/2011/2	István Voszka
Sport pedagogy	2010/2011/2, 2011/2012/1	János Gombocz, József Bognár
Human biology	2011/2012/1	János Mészáros
Molecular psychiatry	2010/2011/2	János Réthelyi
Nano-immunotoxicology	2010/2011/2	János Szebeni
Data analysis	2010/2011/2, 2011/2012/1	József Bognár
Research methodology of pedagogy	2010/2011/2	József Bognár
Neurobiology and pharmacology of behavior	2011/2012/1	József Haller, Dóra Zelena
Neuromechanics of human movements	2010/2011/2	József Laczkó
Principles of pathobiochemistry	2011/2012/1	József Mandl
Sociological theories of deviances	2011/2012/1	József Rácz
Biomechanics of the musculoskeletal system	2010/2011/2	József Tihanyi
General pathology for biologists	2011/2012/1	József Tímár
70th Congress of Pathology	2011/2012/1	József Tímár
Methods of the structural characterization of macromolecular interactions	2011/2012/1	Judit Fidy
History of development of medicine, history science	2010/2011/2	Judit Forrai
The process of becoming a medical care provider	2011/2012/1	Judit Mészáros
Complications after stent implantation in great vessels, peripheral and coronary arteries	2010/2011/2	Kálmán Hüttl
Molecular mechanisms of obesity, insulin resistance and type 2 diabetes mellitus	2011/2012/1	Károly Cseh
Molecular virology: Human retroviruses (HIV, HTLV) and their roles in immunopathological disorders	2010/2011/2	Károly Nagy
Hormonal regulatory mechanisms in health and disease	2011/2012/1	Károly Rácz
Radiation biology: the biological basis of radiation therapy and radiation protection	2011/2012/1	Katalin Lumniczky, Géza Sáfrány
Gene therapy of malignant and other diseases	2011/2012/1	Katalin Lumniczky, Géza Sáfrány
History of sport	2010/2011/2	Katalin Szikora
Interpretations of body in philosophy and psychology	2010/2011/2, 2011/2012/1	Katalin Vermes

History of philosophy	2011/2012/1	Katalin Vermes
Theory of science I.	2011/2012/1	Katalin Vermes
Pharmacodynamics	2010/2011/2	Klára Gyires, Kornélia Tekes
Allergy	2010/2011/2, 2011/2012/1	Kristóf Nékám
Role of protein phosphorylation in the regulation of cell function	2011/2012/1	László Buday
Bio-medical applications of antibodies	2010/2011/2	László Cervenák, Zoltán Prohászka
Modern measuring and research methods in experimental and clinical medicine (selected chapters)	2011/2012/1	László Dézsi
Evidence based medicine and health technology assessment	2010/2011/2	László Gulácsi
Clinical oncology	2010/2011/2, 2011/2012/1	László Kopper
Chemotaxis: Its biological and clinical significance	2010/2011/2	László Kőhidai
Nephrology - from molecules to bedside	2011/2012/1	László Rosivall
From molecule to bedside, from cell to organism	2011/2012/1	László Rosivall
18th Budapest Nephrology School (Nephrology, hypertension, dialysis, transplantation)	2010/2011/2	László Rosivall
Nanomedicine	2011/2012/1	László Rosivall, János Szebeni
Sport psychology	2011/2012/1	László Tóth
Psychotherapy in medical practice	2011/2012/1	László Tringer
Methods of literature research	2010/2011/2, 2011/2012/1	Lívía Vasas
Bibliometrics for the efficient scientific publishing	2010/2011/2, 2011/2012/1	Lívía Vasas
Food allergy and intolerance	2010/2011/2	Mária Barna
Clinical neurogenetics	2010/2011/2	Mária Judit Molnár
Hot topics of the molecular neurosciences	2011/2012/1	Mária Judit Molnár
Future trends and perspectives of personalized medicine	2011/2012/1	Mária Judit Molnár
Basics of behavioural medicine	2010/2011/2, 2011/2012/1	Mária Koppt
Basis of molecular biology	2010/2011/2	Mária Sasvári, Szabolcs Sípek, András Váradi
Clinical aspects of developmental damages of brain circuits	2011/2012/1	Mariann Berényi, Ferenc Katona
STD- clinical characteristics, microbiology, epidemiology	2011/2012/1	Márta Marschalkó, Ferenc Rozgonyi

Oncodermatology- pathogenetic factors in malignant melanoma, basal cell carcinoma, cutaneous lymphoma	2011/2012/1	Márta Marschalkó, Norbert Wikonkál
Health economics	2010/2011/2	Márta Péntek
Structure and function of non-neuronal elements of the neural system	2010/2011/2	Mihály Kálmán, Zsuzsanna Huszti
Event marketing and event management	2010/2011/2	Mihály Nyerges
Clinical immunology and allergology	2010/2011/2, 2011/2012/1	Miklós Benczúr, Péter Gergely
Proteins and nucleic acid: in silico theory, in vitro practice	2010/2011/2	Miklós Csala, Tamás Mészáros, Zsolt Rónai
Clinical endocrinology	2010/2011/2	Miklós Góth
Molecular biomechanics	2011/2012/1	Miklós Kellermayer
Biomedical light microscopy and digital image processing	2010/2011/2	Miklós Kellermayer
System's neuroanatomy	2011/2012/1	Miklós Palkovits
Physiology and pathology of the musculoskeletal system's function	2010/2011/2	Miklós Szendrői
Biomaterials	2011/2012/1	Miklós Zrínyi
Research methods	2011/2012/1	Miklós Zsidegh
Biometrics	2010/2011/2	Miklós Zsidegh
Investigation of lipid nanovesicles with biophysical methods	2011/2012/1	Pál Gróf
Theoretical and methodological fundamentals of PE curricula	2010/2011/2	Pál Hamar
Medical professionalism in the health care	2010/2011/2	Péter Balázs
The significance of professionalism in providing health care	2011/2012/1	Péter Balázs
Networks and system stability	2010/2011/2	Péter Csermely
Roaming in the world of channels	2010/2011/2	Péter Enyedi
Metabolic bone diseases	2011/2012/1	Péter Lakatos
Gastrointestinal genetics and immunology	2011/2012/1	Péter László Lakatos
Aspects of organic and medicinal chemistry in drug research and development	2010/2011/2	Péter Mátyus
Relation between artistic and scientific experiences on the real world	2011/2012/1	Péter Rajna
Health and medical relation in Hungarian legal practice	2011/2012/1	Péter Sótónyi
Experimental animals - animal experiments	2011/2012/1	Piroska Anderlik
Pharmaceutical aspects of quality assurance	2010/2011/2	Romána Zelkó
Genetics of sex	2010/2011/2	Sára Tóth
Gender in medicine	2011/2012/1	Szilvia Ádám
Discovery of family networks in psychiatry	2011/2012/1	Tamás Kurimay
Economics and theory of organization	2010/2011/2, 2011/2012/1	Tamás Sterbencz



Hemodynamic monitoring	2010/2011/2	Tibor Gondos
Intensive care of patients with severe sepsis	2011/2012/1	Tibor Gondos
Basic neuropathology	2011/2012/1	Tibor Kovács
Evidence based medicine and health technology assessment	2011/2012/1	Valentin Brodszky
Bioenergetics in the central nervous system	2011/2012/1	Veronika Ádám-Vizi
Neurobiology of stroke	2011/2012/1	Zoltán Nagy
Neurophysiology	2011/2012/1	Zoltán Nusser
Clinical genetics	2011/2012/1	Zoltán Papp
Clinical biostatistics	2010/2011/2	Zoltán Prohászka
Biometry	2010/2011/2	Zsolt Csende
Motor control and learning	2010/2011/2	Zsolt Csende
Free radicals, exercise physiology and pathology of aging	2010/2011/2	Zsolt Radák
Molecular adaptation to exercise training	2010/2011/2	Zsolt radák
Gastroenterology	2011/2012/1	Zsolt Tulassay
Postgraduate course in gastroenterology	2010/2011/2	Zsolt Tulassay
Handling negotiations and conflicts for prospective leaders of innovative projects	2010/2011/2	Zsombor Lacza
Financing innovative projects	2010/2011/2	Zsombor Lacza
SWAN learn to market IP	2010/2011/2	Zsombor Lacza
Intellectual property exploitation: how to use your patents to make money	2011/2012/1	Zsombor Lacza
Histamine biology	2010/2011/2	Zsuzsa Darvas
Clinicopathological approach in research	2010/2011/2	Zsuzsa Schaff
Diagnostics and differential diagnostics of non-tumorous diseases	2010/2011/2	Zsuzsa Schaff
Cytopathology	2010/2011/2	Zsuzsa Schaff

## PH.D. SCIENTIFIC DAYS

The Ph.D. training program provides opportunities for every candidate to acquire practical knowledge of the methodology of presenting results gained in scientific research. Ph.D. students therefore are required to present their work regularly both among fellow workers and in a wider professional environment. The need for an overall Ph.D. conference of the Doctoral School was promoted even though the departmental doctoral schools organize scientific forums for their own Ph.D. students. The primary objective was that participants would be able to familiarize themselves with the scientific work of each program. On these occasions Ph.D. students and candidates had the opportunity to present their work in several sections with a jury. Candidates with works of a high standard gained awards in each section.

In the frame of the program of the Ph.D. Scientific Days 2011, holders of "Vilma Hugonnai Award" have been invited to give plenary lecture with great success.

***Plenary Lecturers***

2011 **Romána Zelkó**

Options for the use of positron annihilation lifetime spectroscopy  
in pharmacology

**Veronika Müller**

Cellular stress in pulmonologic disorders

The plenary speakers are carefully selected from among those who have been awarded with the distinction of the "Excellent Ph.D. Supervisors".

**EXCELLENT PH.D. SUPERVISOR AWARD**

Nominations for the Excellent Ph.D. Supervisor Award are made by the heads of individual Ph.D. Schools, and the University Doctoral Council decides on the final list of awardees. The number of awardees is limited

2011 **Ilona KOVALSZKY**  
**Péter MÁTYUS**

Pathological Sciences Doctoral School  
Pharmaceutical Sciences Doctoral School

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# SCHOOL OF PH.D. STUDIES

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## 1. BASIC MEDICINE

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***Head of the Doctoral School:***

**László ROSIVALL M.D., Ph.D., D.Sc.**

Institute of Pathophysiology

4. Nagyváradi tér, 1089 Budapest

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**General Overview:** The Doctoral School of Basic Medicine at Semmelweis University consists of five multi-disciplinary research and training Ph.D. Programs. These Programs are closely related to the physiological sciences, and are chaired by internationally recognized professors as coordinators. At first, each Program was accredited individually in 1994, then all the Ph.D. Programs were integrated into a Doctorate (Ph.D.) School in 2002.

The major aims of the Ph.D. Programs are to investigate the mechanisms of diseases with high morbidity and mortality statistics in Hungary (e.g. cardiovascular and renal diseases, hypertension, obesity), and to study those environmental effects (UV and X-Radiation) which may influence the whole society. Investigating the molecular-cellular background of physiological and pathophysiological processes, and integration of the knowledge at organ and organism levels lead us to new scientific results and discoveries which may promote the development of up-to-day methods for health prevention, diagnostics, and therapy. In addition to several basic research projects offered to the Ph.D. students, applied clinical studies are also incorporated into the Programs of the School.

### ***PROGRAM 1/1.***

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#### **PHYSIOLOGY AND CLINICS OF THE HEART AND CORONARY DISEASES**

***Coordinator:***

**Béla MERKELY M.D., Ph.D., D.Sc**

Heart Center

H-1122 Budapest, Városmajor str. 68.

Tel/fax: + 36 1 458 6840

E-mail: [titkarsag@kardio.sote.hu](mailto:titkarsag@kardio.sote.hu)

**Program Overview:** The complex program is directed to well-qualified students who are interested in cardiovascular research. The spotlight is on regulatory aspects and treatment of different cardiovascular diseases. According to the scientific interest of most of coordinators, the main problems are connected to pathophysiology (clinical physiology) of myocardial function, coronary regulation and arrhythmogenesis. (However, as the list of the topics shows, other circulatory topics are included, too.)

The program prepares students for careers in either clinical science (especially invasive and non-invasive cardiology, anesthesiology, and cardiovascular surgery) or basic sciences. Preference is given to those who are ready to study overlapping territories of these sciences. Although the individual postgraduate trainings have an overall general similarity in their logistic aspects, the main characteristic of the entire educational process is the flexibility. Consequently, that research work can be tailored to the tutor's mutual interest within the territory covered by the general aims.

### ***Titles of research projects***

### ***Supervisors***

New aspects in the non-pharmacological therapy of tachyarrhythmias	Béla Merkely
Heart failure: pathomechanisms and new methods in the pharmacological and non-pharmacological treatment	Béla Merkely
Electrophysiology of ventricular arrhythmias	Béla Merkely
Role of endogenous agents in arrhythmogenesis	Béla Merkely
Challenge in the field of interventional cardiology	Béla Merkely
Cardiovascular adaptation of elite athletes	Béla Merkely
Role of myocardial contrast echocardiography in acute coronary syndrome: diagnosis and evaluation of therapeutic success	Péter Andrásy
Interventional radiology in the treatment and follow-up of patients with vascular diseases	Viktor Bérczi
External and internal noxa-induced secondary circulatory damage: clinical symptoms and therapy	András Csókay
Causes of recurrent stenosis after carotid surgery or other vascular surgical approaches. The clinical impact of the phenotype changing of the smooth muscle cells. Researches in vascular surgery	László Entz
Role of cardiac and endothelial progenitor cells in the remodeling and regeneration of the myocardium: in vivo and in vitro studies	Gábor Földes
Clinical and experimental electrophysiology	László Gellér
Vasoactive peptides in heart diseases and their experimental models	Ferenc Horkay
Complications of interventional treatment of the vascular diseases	Kálmán Hüttl
Cardiovascular and cardioprotective effects of endogenous peptides in myocardial ischaemia: experimental and clinical studies	Violetta Kékesi
Local myocardial interactions of cardiogenic agents: experimental studies	Violetta Kékesi
Mechanism of metabolic autoregulation in the coronary circulation	Violetta Kékesi
Mechanisms of the actions of cardiovascular regulatory agents: in vitro investigations	Violetta Kékesi

Role of nitro-oxidativestress and NO-cGMP-signalling in the development and treatment of cardiovascular diseases	Tamás Radovits
Cardiovascular effects of brain death. Donor management and selection	Gábor Szabó
Heart insufficiency in the era of modern cardiac surgery	Gábor Szabó
Tissue injury during and after cardiac surgery. Novel strategies to prevent reperfusion injury and acute and chronic rejection.	Gábor Szabó
Pharmacogenomic investigations in the cardiovascular system	Zsolt Szelid
Identification of factors (metabolic, procedural and psychosocial) determining the short- and long-time mortality and morbidity of cardiac surgery; scoring system applied adult and pediatric cardiosurgical interventions	Andrea Székely
Role of inflammation mechanism in cardiovascular diseases	Gábor Széplaki
Nuclear cardiology in the diagnosis of ischemic heart disease	István Szilvási
Molecular mechanisms of cardiac hypertrophy especially in the early and decompensated phase of the disease	Miklós Tóth
Identification of site of origin and mechanism of wide QRS complex tachycardias by combined use of expert computerised ECG classification algorithm and artificial neural network	András Vereckei
Studies on pathomechanism and potentially effective therapies in heart failure with preserved ejection fraction (HFPEF)	András Vereckei
Investigation of epidemiology and mortality rates, pathophysiological, prognostic factors and intensive therapeutic strategies of diseases requiring cardiopulmonary resuscitation.	Endre Zima

**Ph.D. students**

Astrid Apor	pt (a)
Zsolt Bagyura	ft
Enikő Barnucz	ft
György Bárczi	pt(a)
Andrea Dósa	pt
Tamás Erdei	ft (a)
Péter Hegedűs	ft
Zoltán Gonda	pt
Zsigmond Máté Jenei	pt
Mihály Károlyi	ft
Máté Kerekes	ft (a)
Annamária Kosztin	ft
Kinga Lakatos	ft
Zsuzsanna Lendvai	ft
Árpád Lux	ft (a)
Mónika Moravszki	pt
Klaudia Viven Nagy	ft
Attila Oláh	ft
István Osztheimer	pt

**Supervisors**

Péter Andrassy
Béla Merkely
Gábor Szabó
Péter Andrassy
Zsolt Szelid
András Temesvári
Gábor Szabó
László Entz
Endre Zima
Béla Merkely
Violetta Kékesi,
László Dézsi
Béla Merkely
Béla Merkely
Gábor Földes
Zsolt Szelid
István Szilvási
Béla Merkely
László Gellér
László Gellér

Lívía Polgár	ft	Gábor Széplaki
Miklós Pólos	pt	Ferenc Horkay
György Szabó	pt(a)	Béla Merkely
Csaba Mihályi	ft	Violetta Kékesi
Roland Tóth	ft	Roland Tóth
Katalin Túri	ft	Violetta Kékesi
Eszter Mária Végh	ft	László Gellér

***Ph.D. candidates***

Balázs Berta	ft
Zoltán Jambrik	na
Zsolt Béla Komka	pt
Valentina Kutyifa	ft
Pál Maurovich Horváth	pt
Balázs Sax	ft
Gabriella Veress	ft

***Ph.D. graduates***

Tamás Breuer	ft
Csaba Diószeghy	na
Andrea Nagy	ft
Balázs Nemes	na

***Supervisor***

Béla Merkely
Béla Merkely
Ferenc Horkay
Béla Merkely
Béla Merkely
Violetta Kékesi
Béla Merkely

***Supervisors***

Miklós Tóth
Béla Merkely
Violetta Kékesi
Kálmán Hüttl

a, absolutorium; ft, full-time; pt, part-time; na, not affiliated;

***Abstracts of Ph.D. theses successfully defended in 2011*****TAMÁS BREUER (2011)****The relationship of natriuretic peptides and hemodynamic, parameters following heart surgery in infancy**

*Supervisor: Miklós Tóth*

Natriuretic peptide levels are good markers of cardiovascular diseases and, ventricular function. NT-proXNP, a new virtual natriuretic peptide analyte, incorporates, information about the levels of both N-terminal pro-atrial and pro-brain natriuretic, peptides (NT-proANP, NT-proBNP). We aimed to investigate the clinical applicability, of NT-proXNP in neonates and infants undergoing open heart surgery. We also aimed, to elucidate the associations of natriuretic peptide levels and postoperative, hemodynamic parameters in this population.

After approval of the institutional review board and parental informed consent, we enrolled 30 children under the age of 1 year into this prospective study. All patients, underwent elective cardiac operation with cardiopulmonary bypass to achieve complete, biventricular repair. Hemodynamic parameters assessed by transpulmonary, thermodilution and natriuretic peptide levels were recorded preoperatively, postoperatively and 12, 24, 48 and 72 hours after the arrival at the intensive care unit. Clinical and laboratory values were analyzed in the first 48 hours following surgery. The new NT-proXNP immunoassay was sensitive to the activations of both, NT-proANP and NT-proBNP.



NT-proXNP and the other natriuretic peptide levels had, strong inverse correlations with cardiac index (CI) and stroke volume index throughout, the postoperative period. There were also correlations between natriuretic peptide levels, and systemic vascular resistance, extravascular lung water and other hemodynamic, parameters, respectively. Conventionally measured parameters such as heart rate, mean, arterial pressure and pulse-pressure product exhibited weaker correlations with CI than, natriuretic peptide levels. Clinical and laboratory values, except for creatinine levels, showed no correlation with CI. Postoperative NT-proBNP and NT-proXNP levels had, good diagnostic and prognostic performance in ROC analysis for low output syndrome, and mechanical ventilation longer than 72 hours.

NT-proXNP and the natriuretic peptide levels are reliable indicators of the, circulatory state and they are useful for the follow up of neonates and infants after open, heart surgery. Elevated postoperative NT-proBNP and NT-proXNP levels are good, markers of low cardiac output and might be applicable for the prediction of, complications following surgery.

- Breuer T, Sápi E, Skoumal R, Tóth M, Ala-Kopsala M, Vuolteenaho O, Leppäluoto J, Ruskoaho H, Szatmári A, Székely A. *N-terminal pro-brain, natriuretic peptide level inversely correlates with cardiac index after arterial, switch operation in neonates. Pediatric Anesthesia 2007; 17: 782-8.*
- Breuer T, Skoumal R, Horkay F, Merkely B, Ala-Kopsala M, Leppäluoto J, Vuolteenaho O, Ruskoaho H, Tóth M., Székely A. *Strong relationship between, NT-proXNP levels and cardiac output following cardiac surgery in neonates and, infants. Acta Anaesthesiologica Scandinavica 2010; 54: 502-9.*
- Székely A, Breuer T, Sápi E, Székely E, Szatmári A, Tóth M, Hauser B, Gál J., *Transpulmonary thermodilution in neonates undergoing arterial switch surgery. ,Pediatric Cardiology 2010; doi: 10.1007/s00246-010-9828-0*

## CSABA DIÓSZEGHY (2011)

### Comparison of the Hungarian and international hand positions during cardiopulmonary resuscitation

*Supervisor: Béla Merkely*

Effective chest compressions are probably the single most important part of cardiopulmonary resuscitation. The method described originally by Kouwenhoven in 1960 has been widely accepted and adopted by the whole world ("International method"). During the past 50 years a slightly different hand position has been evolved in Hungary ("Hungarian method"). By the worldwide introduction of the Universal Guidelines for resuscitation, the availability of internationally recognised European ALS and BLS Provider Courses in Hungary and the increasing participation of Hungarian medical professionals outside the borders made it necessary to choose one of these hand positions as the single recommended method for chest compressions which then should be taught to lay persons and professionals. A set of studies designed to compare the effects of the two different hand positions during chest compressions would help to make this choice to be based on the principles of evidence based medicine. Our studies suggest that the use of the international hand position during cardiopulmonary resuscitations would have better clinical results compared to the traditional Hungarian hand position. We could not prove the benefit of the Hungarian method in any of the investigated domains (physical effects, physiological effects, effects on the rescuer and clinical efficacy). According to our studies the reasons of the higher clinical efficacy of the international method would be based on the fact that larger surface

compressed by the Hungarian hand position results a lower effective average compression force on the chest wall resulting smaller changes in the intrathoracic pressures. That would cause a somewhat weaker haemodynamic effect consequently decreasing the chance of survival compared to the chest compressions by the international method (OR: 1.53). As a conclusion of our studies we propose that the international hand position should be regarded as the single recommended method for chest compressions in the forthcoming Guidelines for Cardiopulmonary Resuscitation issued by the Hungarian Resuscitation Council as well as in the related teaching materials for basic and advanced life support.

- Diószeghy C, Kiss D, Frituz G, Szekely G, Elo G: *Comparison of effects of different hand positions during cardio pulmonary resuscitation. Resuscitation 2005; 66: 297-301.*
- Élő G, Diószeghy C, Dobos M, Andorka M: *Ethical, considerations, behind the limitation of cardiopulmonary resuscitation in Hungary the role of education and training. Resuscitation 2005; 64:71-77.*
- Diószeghy C, Fritúz G, Kiss D, Péntes I: *A nemzetközi ajánlásokban szereplő és a hagyományos magyar kéztartás összehasonlító vizsgálata újraélesztésnél végzett mellkasi kompressziók során. Újraélesztés. Resus Hung 2003; 1:39-42.*

#### ANDREA NAGY (2011)

##### **Potential influence of the pericardial space on myocardial function: Cardiac interactions of adenosine and endothelin-1**

*Supervisor: Violetta Kékesi*

The present study aimed to investigate the adenosine - endothelin-1 regulatory couple and their cardiovascular and pharmacological effects evoked from the pericardial space. The pericardial fluid contains numerous important cardioactive regulatory agents that function in an autocrine or paracrine manner in the heart and their levels were found to be several magnitude higher in the pericardial fluid than in the venous plasma. Moreover, in certain cardiovascular pathologies their pericardial levels could increase further. Therefore the pericardial fluid may reflect the levels and alterations of the compounds of myocardial interstitium. On the basis of the high pericardial concentrations of these cardioactive regulators the question arose, whether these agents may act backward towards the myocardium, by which the pericardial space could behave as a potentially active fluid compartment of the heart. The aim of the present study was to investigate the interaction and cardiovascular effects of adenine nucleosides and endothelin-1 (ET-1) evoked from the pericardial space, determine the pericardial elimination of intrapericardially applied adenosine and inosine and observe their effects on the cardiovascular function compared with their intravenous administration. The present studies were performed on *in situ* dog heart using the "closed pericardium model" worked out previously in our research laboratory. Our present data have demonstrated the significant increase of the concentrations of adenine nucleosides after intrapericardial administration of ET-1. Regarding the adenine nucleosides - ET-1 interaction, we have demonstrated ET-1 liberation provoked from the pericardial space after intrapericardial administration of adenosine and inosine. The present study confirmed the significantly slower elimination of adenine nucleosides in the pericardial space than in the systemic circulation. Thus, the same order of magnitude or even higher adenine nucleoside levels could be achieved in the pericardial space with local administration than the endogenous concentrations measured under severe myocar-

dial ischemia without adverse hemodynamic effects. In conclusion, the present study confirmed that characteristic cardiovascular effect and bi-directional interaction of adenine nucleosides and ET-1 could be provoked by and detected in the pericardial space, reflecting probably parallel changes in the interstitial fluid compartment of the heart. The low pericardial turnover rate of adenine nucleosides offers the opportunity of utilizing their multiple beneficial effects for local pharmaco-therapeutic interventions.

- Nagy A, Sax B, Entz L jr., Barát E, Toma I, Becker D, Merkely B, Kékesi V: *Comparison of elimination and cardiovascular effects of adenine nucleosides administered intrapericardially or intravenously in anesthetized dog. J Cardiovasc Pharmacol* 2009; 54:341-347.
- Nagy A, Toma I, Rusvai M, Barát E, Huszár É, Juhász-Nagy A, Kékesi V: *Intra-pericardial adenine nucleosides induce elevation of endothelin-1 concentration in the pericardial space of the dog heart. J Cardiovasc Pharmacol.* 2004; 44:S227-230.
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## BALÁZS NEMES (2011)

### New possibilities in the endovascular treatment of supraaortic vessels

*Supervisor: Kálmán Hüttl*

Cerebrovascular disease, including stroke, represents the third-leading cause of death in Hungary and a leading cause of disability among the elderly population. The majority of all strokes are ischemic, mostly secondary to thromboembolic disease of the supraaortic vessels.

We investigated new therapeutic methods in the endovascular treatment of these diseases. Surgical revascularization of supraaortic trunk stenosis is associated with high morbidity and mortality rates. Balloon angioplasty has become an increasingly accepted treatment of stenocclusive supraaortic arterial disease. Natural history data and treatment guidelines do not exist for innominate and proximal common carotid artery lesions.

We have confirmed in a large series of innominate artery angioplasties that it is a safe and effective procedure with an excellent initial success rate, with a lower complication rate than the surgical option and with a similar long-term patency rate as for surgery.

In the largest published study on transfemoral angioplasty of ostial and proximal common carotid artery stenosis we have proved that endovascular treatment has high success rate with low stroke/death rate. Carotid stenting (CAS) is an evolving alternative to surgery in the treatment of patients with carotid stenosis. Stent selection is influenced by several factors, including the carotid anatomy and lesion characteristics.

We examined the wall adaptability of a new closed-cell carotid stent (NexStent), which was designed for carotid bifurcation treatment. Data obtained from angiographic and computed tomographic images indicate that the stent provides adequate expansion and adaptation to the carotid bifurcation. There are two types of restenosis after carotid artery interventions: the early restenosis develops mainly within the first 24 months after the revascularization procedure and its

pathological background is myointimal hyperplasia; on the other hand late restenosis is rather due to progression of primary atherosclerosis and occurs more than 2 years after carotid endarterectomy (CEA). We compared the early restenosis rate in a consecutive series

of CAS versus CEA patients at a single cardiovascular institution. Our data suggest that the incidence of restenosis after stenting was less common than after surgery. Aneurysms of the extracranial internal carotid artery are extremely rare; over the past decades their treatment technique has changed. Endovascular methods have become more widespread and offer an alternative to surgery, which is often difficult in this region. Stent-graft treatment represents a less invasive approach to permanent aneurysm exclusion while maintaining the patency of the carotid artery.

We report two cases of internal carotid artery pseudoaneurysm that were treated using Wallgraft.

Our results may help vascular surgeons and interventional radiologists to consider risk versus benefit when deciding treatment options for supraaortic arterial stenosis.

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- Nemes B, Lukács L, Balázs G, Dósa E, Bérczi V, Hüttl K. *High-resolution CT and angiographic evaluation of NexStent wall adaptation. Cardiovasc Intervent Radiol* 2009; 32:436-440.

## **PROGRAM 1/2.**

### **MECHANISMS OF NORMAL AND PATHOLOGICAL FUNCTIONS OF THE CIRCULATORY SYSTEM**

#### **Coordinators:**

**Emil MONOS M.D., Ph.D., D.Sc.**

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**Program overview:** The program consists of 12 research sub-programs with several special projects completed with appropriate theoretical courses for postgraduate students. Different aspects of normal and disturbed regulatory processes of the cardiovascular system are in the focus. Each Ph.D. student is working on his/her own individual research project under the guidance of a qualified scientific supervisor. Successful completion of the project including publications in recognized international journals provides an opportunity to summarize the results in a Ph.D. thesis.

#### **Titles of research projects**

Adaptation mechanisms of vascular hemodynamics and network properties to physiological and pathological challenge

Pathophysiology of the cerebral circulation

#### **Supervisors**

Emil Monos

Zoltán Benyó

Cardiovascular adaptational mechanisms in the whole body, as well as the myocardium and the brain cortex	László Dézsi
Role of bradykinin receptors in the circulatory adaptation under normal and pathological conditions; interactions with other mechanisms affecting blood pressure	László Dézsi
Spatio-temporal correlation of coupled hemodynamics and neuronal activities in the brain	András Eke
Role of postmenopausal hormonal deficiencies in altering the fractal structuring of hemodynamic fluctuations in the brain cortex	András Eke
Impact of cerebralsclerosis in altering the fractal structuring of cerebrocortical hemodynamic fluctuations	András Eke
Effects of blood substitutes on tissue hemodynamics and oxygenation	András Eke
Regulation of calcium homeostasis in the myocardial tissue	Tamás Ivanics
Alterations of the intracellular calcium homeostasis in progressive heart failure	Tamás Ivanics
Pathophysiological processes contributing to the development of diabetic cardiomyopathy	Tamás Ivanics
Comparative evaluation of clinical and epidemiological diagnostic methods in the assessment of cardiovascular autonomic and peripheral sensory neuropathy	Péter Kempler
The mechanism of action of cell-based regenerative therapies in myocardial infarct	Levente Kiss
Investigation of vascular functions affecting the autonomous cardiovascular tone and reflex activity	Márk Kollai
Cardiovascular autonomous neural system	Márk Kollai
Tissue engineering strategies in the musculoskeletal system	Zsombor Lacza
Study of promoting and inhibiting factors in cardiovascular aging	Béla Székács
Ischemia-induced molecular-biological changes of the blood-brain barrier	Péter Sándor
The role of the female sex hormones in the regulation of the cerebral blood flow	Péter Sándor
Videomicroscopic analysis of ureteral movement pharmacological and pathological effects	György Nádasy
Alterations of the biomechanical properties of extremity arteries and veins during angiogenetic processes	György Nádasy
Adaptation of vascular hemodynamics and network properties to physiological and pathological stress	György Nádasy
Functional integrity of the cardiopulmonary system	Ildikó Horváth
Hormon-dependent cardiovascular adaptation mechanisms in normo- and hypertension in females	Szabolcs Várbíró
Congenital heart disease in adults	András Temesvári

**Ph.D. students**

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András Csepregi	pt
Katalin Fekete	ft (a)
András Hartmann	pt
András Iring	ft
Tímea Martos	ft
Anna Monori-Kiss	pt
Péter Mukli	ft
Nóra Németh	ft
Tamás Németh	ft (a)
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Ádám Domonkos Tárnoki	pt
Dávid László Tárnoki	pt

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Éva Ruisanchez	ft (a)
Miriam Leszl-Ishiguro	ft
Petra Őrsy	ft
Gabriella Váczi	ft(a)
Miklós Wessl	ft

**Ph.D. graduates**

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Gábor Lenzsér	ft
Katalin Módis	ft
Eszter Pankotai	ft
Emese Szelke	na

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**Supervisors**

Zsombor Lacza
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a, absolutorium; ft, full-time; pt, part-time; na, not affiliated

**Abstracts of Ph.D. theses successfully defended in 2011****ATTILA CSELENYÁK (2011)****Investigation of the mechanism of in vitro stem cell treatment and the role of metabolic memory in oxidative stress induced cellular injury**

*Supervisor: Zsombor Lacza*

Oxidative and nitrosative stress contributes to the development of several diseases and their complications such as ischemic heart disease or diabetes mellitus. The myocardium undergoes several metabolic changes during ischemia/reperfusion, which lead to the destruction of cardiomyocytes. Myocardial infarction can be treated using conventional and



more recently cell based therapies. Investigations, ongoing for more than a decade, showed that cell based therapies are safe but in many cases no improvement in function were found. Therefore, more detailed knowledge of the physiological and molecular mechanisms between the injured and transplanted cells is required. Our aim was to investigate the mechanism of action of the added cells and the markers of the oxidative stress in an *in vitro* ischemia/reperfusion model. The transplanted mesenchymal stem cells improved the survival of the injured cardiomyoblasts via direct cell-to-cell interactions. Nanotube formation was observed and these tubes also contained mitochondria. If the added cells contained damaged mitochondria, these cells failed to improve the survival rate of the postischemic cells. Cell fusion was observed in some cases with low frequency, which could not explain the beneficial effect of stem cells. The time frame of the experiments ruled out the impact of paracrine factors and differentiation. There was an increase in the level of LDH enzyme activity and in the concentration of malondialdehyde after ischemia, which was significantly reduced by the addition of cells.

Hyperglycemia induced oxidative stress in diabetes mellitus contributes to the development of late complications. It can be assumed that this phenomenon is driven by metabolic memory. The persistence of ROS production after high glucose incubation was investigated in an *in vitro* hyperglycemia model, which could be reduced with inhibitors but did not return to the control level. This could be explained with glycation of certain mitochondrial proteins, which continues to produce the reactive species in normal circumstances. In summary, our results provide further evidence of the role of oxidative stress in ischemic heart disease and diabetes and contribute to more efficient management of these disorders.

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## GÁBOR LENZSÉR (2011)

### Blood-brain barrier changes in hemorrhagic shock and after cerebral ischemia-reperfusion. Possible protective mechanisms.

Supervisor: Péter Sándor

In our studies we have investigated (a) the permeability of the blood brain barrier (BBB) in different hypoperfusion disorders (hemorrhagic shock, global cerebral ischemia/reperfusion), (b) the possible alterations of the structural elements of the endothelial tight junction complex, which can be responsible for the leakage of the barrier, and (c) possible protective mechanisms against the barrier disturbance by studying the effect of two different drugs.

We have found the opening of the BBB for a low molecular weight tracer during the decompensated phase of the hemorrhagic shock. At the same time, the expression of both, the tight junction protein, occludin and the adherens junction protein, cadherin significantly decreased in the walls of the cerebral microvessels. Our study revealed the first time in the literature that the blood-brain barrier disturbance in the decompensated phase of hemorrhagic shock affects mainly the paracellular route and diminished occludin and cadherin contents could be responsible for it.

We have observed increased blood-brain barrier permeability for low, as well as, for high molecular weight tracers during the early phase of reperfusion following severe global cerebral ischemia and the development of cerebral edema. After a less severe ischemia we have demonstrated delayed blood-brain barrier opening during reperfusion (24h and 48h) accompanied by considerable cerebral edema. Occludin contents were significantly reduced during late reperfusion.

The mitoK<sub>ATP</sub> channel opener diazoxide used in a preconditioning protocol reduced the extent of the permeability increase of the barrier and the adjacent cerebral edema. To the best of our knowledge, this is the first study in the literature in which chemical preconditioning resulted in blood-brain barrier protection.

The poly (ADP-ribose) polymerase (PARP) enzyme inhibitor PJ34 used in a pre- and post-treatment protocol reduced the barrier permeability and the brain edema seen in late reperfusion. PJ34 treatment hindered the decline of the tight junction protein occludin. The increase of protein degradation is a possible mechanism behind the decreased occludin levels deduced from the negative correlation between occludin and its byproduct in reperfusion. We have demonstrated the inhibition of inflammation after PJ34 treatment in reperfusion: the transcription of the pro-inflammatory adhesion molecule ICAM-1 and the leukocyte infiltration in the cerebral cortex were both decreased. The permeability of the blood-brain barrier proportionate to the leukocyte infiltration after reperfusion, suggesting a major contribution of the inflammation processes in the barrier disturbance. The results of our studies indicate that the activation of the PARP enzyme in ischemia/reperfusion contributes to the increased BBB opening, to the disintegration of the endothelial tight junction complex and its effect is mainly driven by the augmentation of the inflammatory pathway.

- Lenzser G, Kis B, Bari F, Busija DW: Diazoxide preconditioning attenuates global cerebral ischemia-induced blood-brain barrier permeability. *Brain Res* 2005; 27: 72-80.
- Krizbai IA, Lenzser G, Szatmari E, Farkas AE, Wilhelm I, Fekete Z, Erdos B, Bauer H, Bauer HC, Sandor P, Komjati K: Blood-brain barrier changes during compensated and decompensated hemorrhagic shock. *Shock* 2005; 24:428-33.
- Lenzser G, Kis B, Snipes JA, Gáspár T, Sándor P, Komjati K, Szabó C, Busija DW: Contribution of poly(ADP-ribose) polymerase to postischemic blood-brain barrier damage in rats. *J Cereb Blood Flow Metab* 2007; 27:1318-1326.

## KATALIN MÓDIS (2011)

### Cell-Based high throughput screening approaches for the identification of cytoprotective compounds

Supervisor: Csaba Szabó

Cell-based high throughput screening is emerging as an efficient pharmacological tool used to identify novel molecules that influence complex cellular responses and diseases-relevant pathways. The assays are set up in a way that compounds with cytotoxicity or suboptimal cell uptake are generally excluded, and the assay conditions tend to be conducive for the identification of compounds with relevant pharmacological effects and good therapeutic ratio.

In the current work, two C-HTS assays were established; *in vitro* cell-based assays to model myocardial and renal ischemia reperfusion injuries. The generic library of 1280 pharmaco-

logically active molecules (LOPAC) was screened for validating our previously established C-HTS assays and determining compounds with cytoprotective effects.

In the *in vitro* model of myocardial reperfusion injury in H9c2 rat cardiomyocytes APB hydrobromide molecules emerged with outstanding cytoprotective properties from the LOPAC library screen. We have subsequently demonstrated that the mode of APB hydrobromide's action does not include dopamine receptor. We further demonstrated that these compounds act as indirect PARP inhibitors, without their direct modulatory effect on the PARP-1 enzyme or being free radical scavengers.

In our *in vitro* cell-based assay of ATN in NRK proximal tubular cells adenosine and inosine proved to be cytoprotective in a model of severe oxygen-glucose deprivation. We demonstrated first that adenosine and inosine participate in two interrelated pathways: the pentose phosphate shunt and the adenosine kinase mediated route.

Our *in vitro* cell-based assays of myocardial and renal ischemia reperfusion injuries is applicable for cell-based high throughput screening of various additional generic or original compound libraries and can be used to identify additional compounds or molecule combinations of interest.

- Gerö D, Módis K, Nagy N, Szoleczky P, Tóth ZD, Dormán G, Szabó C: Oxidantinduced cardiomyocyte injury: identification of the cytoprotective effect of a dopamine 1 receptor agonist using a cell-based high-throughput assay. *Int J Mol Med* 2007; 20:749-761.
- Módis K, Gerö D, Nagy N, Szoleczky P, Tóth ZD, Szabó C: Cytoprotective effects of adenosine and inosine in an *in vitro* model of acute tubular necrosis. *Br J Pharmacol* 2009; 158:1565-1578.

## ESZTER PANKOTAI (2011)

### The role of mitochondria in reactive nitrogen species production and in restoring energy levels of oxidatively injured cells

Supervisor: Zsombor Lacza

Cell transplantation therapies are widely used treating several diseases – including stroke and myocardial infarction –, but in spite the completed clinical studies our understanding of the molecular mechanisms behind the regeneration process is still incomplete. The aim of the present study was to investigate the role of mitochondria in an *in vitro* model of cell transplantation after oxidative injury, and to follow molecular changes in the mitochondria as a source and target of reactive oxygen and reactive nitrogen species in oxidative injury. In our experiments we attempted to investigate the possible positive effects of the addition of healthy cells on the cell survival ratio of oxidatively injured cardiomyoblasts; and tried to outline the role of mitochondria in this beneficial effect. We found that the addition of healthy cells to oxidatively injured cardiomyoblasts can increase the number of surviving cells; while, on the contrary, mitochondria-depleted cells failed to improve the cell survival ratio. Our observation of the development of tunneling membrane bridges between healthy and oxidatively injured cells, and the finding of the traffic of mitochondria-like particles along these membrane connections between the cells, further points to the important role of mitochondria in this 'rescue' process. Mitochondria are not only important as energy sources of the cells, but also have major role in cell death signaling in oxidative and nitrosative stress. H<sub>2</sub>O<sub>2</sub> and NO-donor treatment of isolated mitochondria samples resulted in the poly (ADP-ribosyl)ation of several mitochondrial proteins, including important members of the Krebs cycle, urea cycle and the respiratory chain. Concomitant inhibition

of these proteins in oxidative injury leads to ATP depletion, membrane potential alteration, mitochondrial dysfunction, and finally cell death. We found a central role for  $\alpha$ -ketoglutarate dehydrogenase in the poly (ADP-ribosyl)ating processes in the mitochondria.  $\alpha$ -ketoglutarate dehydrogenase is inhibited by reactive oxygen and nitrogen species – such as  $H_2O_2$ , NO and  $ONOO^-$ , but it is also a source of free radicals. In search for possible NO and RNS sources in the mitochondria we could not identify the putative mtNOS, but found that mitochondria produce RNS mainly through the respiratory chain, rather than in an arginine-dependent pathway. These results indicate the important role of mitochondria in oxidative and nitrosative injury, and highlight these organelles as a source of potential candidate molecules – such as KGDH – in combat with free radicals.

- Cselenyak A, Pankotai E, Horvath EM, Kiss L, Lacza Z. *Mesenchymal stem cells rescue cardiomyoblasts from cell death in an in vitro ischemia model via direct cell-to-cell connections. BMC Cell Biol* 2010; 20:11:29.
- Pankotai E, Lacza Z, Murányi M, Szabó C. *Intra-mitochondrial poly(ADP-ribosyl)ation: potential role for alpha-ketoglutarate dehydrogenase. Mitochondrion* 2009; 9:159-164.
- Csordás A, Pankotai E, Snipes JA, Cselenyák A, Sárszegi Z, Cziráki A, Gaszner B, Papp L, Benko R, Kiss L, Kovács E, Kollai M, Szabó C, Busija DW, Lacza Z. *Human heart mitochondria do not produce physiologically relevant quantities of nitric oxide. Life Sci* 2007; 80:633-637.

## EMESE SZELKE (2011)

### Effect of female sex hormones on hypothalamic blood flow and CO<sub>2</sub>-sensitivity of hypothalamic vessels and global cerebral blood volume

Supervisor: Péter Sándor

The consequence of the absence of female sexual steroids and the effectiveness of hormone replacement therapy (HRT) are doubtful in the literature, probably because the same hormones (and their derivatives) influence life functions controversially during different circumstances.

There are only a few data about the effect of female sexual hormones on cerebral circulation and on the most important parameters of cerebrovascular bed (either in steady-state condition or in other situations), and these data are contradictory.

In our examinations -summarized in my paper- the following questions are to be answered: What is the role of female sexual hormones on steady-state regional, hypothalamic blood flow (HBF); autoregulation of regional hypothalamic blood flow and on modulation of CO<sub>2</sub>-responsiveness of hypothalamic vessels; CO<sub>2</sub>-responsiveness of global, hemispherical cerebral blood volume (CBV)?

Female Sprague-Dawley rats were bilaterally ovariectomized in our studies, and cerebral vascular parameters were investigated after (1) estrogen replacement therapy, (2) progesterone replacement therapy, (3) and combined (estrogen and progesterone) hormone replacement therapy:

Regional hypothalamic blood flow was estimated by Aukland's H<sub>2</sub>-gas clearance method during (a) steady-state conditions, (b) stepwise decrease of systemic arterial pressure (MAP) and (c) on different CO<sub>2</sub> levels.

Global hemispherical blood volume was estimated by Tomita's photoelectric method simultaneously at different CO<sub>2</sub> levels.

Results: The steady-state hypothalamic blood flow (HBF):

- decreased significantly after ovariectomy;
- estradiol monotherapy inhibited this change of HBF;0
- medroxy-progesterone monotherapy did not result similar changes, the HBF remained significantly lower.

The autoregulation of hypothalamic blood flow:

- the lower limit of hypothalamic autoregulation decreased after ovariectomy;
- estradiol monotherapy caused a restoration of the lower limit of autoregulation;
- medroxy-progesterone monotherapy caused a restoration of the lower limit of autoregulation too.

The CO<sub>2</sub>-sensitivity of the hypothalamic blood vessels and global, haemispheric cerebral blood volume:

The CO<sub>2</sub>-sensitivity of hypothalamic blood flow (HBF):

- increased significantly after ovariectomy during hypercapnia;
- estradiol monotherapy inhibited this increase;
- medroxy-progesterone monotherapy did not inhibit this increase;
- combined (estrogen+progesterone) hormone replacement did not inhibit this increase;
- the CO<sub>2</sub>-sensitivity of the hypothalamic blood vessels did not change significantly during hypocapnia.

The CO<sub>2</sub>-sensitivity of global cerebral blood volume (CBV)

- increased significantly during hypercapnia;
  - estradiol monotherapy prevented this change of CBV;
  - medroxy-progesterone-monotherapy did not prevent the changes, CBV remained significantly higher;
  - combined (estrogen+progesterone) hormone replacement prevented the increase of CBV;
  - the CO<sub>2</sub>-sensitivity of CBV did not change significantly during hypocapnia.
- Szelke E, Varbiro Sz, Mersich T, Banhidý F, Szekacs B, Sandor P, Komjati K: *Effects of estrogen and progestin on hypothalamic blood flow autoregulation J Soc Gynecol Investig* 2005; 12:604-609.
  - Szelke E, Mersich T, Szekacs B, Sandor P, Komjati K, Varbiro S: *Effects of estrogen and progestin on the CO<sub>2</sub>-sensitivity of hemispheric cerebral blood volume. Menopause* 2008; 15:346-351.

### **PROGRAM 1/3.**

## **BIOLOGICAL EFFECTS OF IONIZING AND NON-IONIZING RADIATION**

### **Coordinator:**

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**Program overview:** Biological effects, induced by different physical and chemical environmental factors (e.g. ionizing and non-ionizing radiations, pollutants) endanger the whole biosphere including humans. The conscious environmental protection and the prevention

of several human diseases due to these environmental factors can be effective only knowing and quantifying the sources (natural radiation background, nuclear disaster, solar radiation, ozone depletion, chemical pollution, etc.). In this program field and laboratory measurements of monitoring of ionizing and ultraviolet radiations are offered with particular interest to the quantification of their biological effects on global, cellular and molecular level.

### ***Titles of research projects***

Self-assembling amyloid filament systems  
 Self-organizing and nanomechanical properties of the myosin motor protein  
 Nanobiotechnology  
 Nanomechanics of nucleoprotein systems  
 Molecular biophysics of the giant muscle protein titin  
 Studies of the effects of antioxidants and photosensitizers on cell cultures and liposomes  
 Investigation of molecular interactions — lipid-lipid, lipid-drug, lipid macromolecules — by biophysical methods  
 Computational and experimental investigation of the structure, dynamics and function of ABC transporters  
 Structural and dynamical principles of functional interactions of microscopic and submicroscopic biological systems  
 Conformal exposure planning based on tomographic methods  
 Mechanism of action of photosensitizers and their application in microbial inactivation  
 Development of pharmaceutical design methods in biophysical chemistry  
 Biological and biomimetic materials; chemical foundations of nanotechnology

### ***Supervisors***

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Melinda Simon	ft
Judit Somkuti	ft

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Balázs Kiss	ft
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Csilla Ünige Murvai	ft

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**PROGRAM 1/4.****FLUID AND ELECTROLYTE BALANCE IN HEALTHY AND DISEASED  
REGULATION OF BLOOD PRESSURE AND CIRCULATION****Coordinator:****László ROSIVALL M. D., Ph.D., D.Sc.**

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**Program overview:** Our Ph.D. program in pathophysiology/nephrology received accreditation in 1993. The goal of this Program is to foster the continued development of traditionally and internationally recognized basic and clinical nephrology research in Hungary. Participating experts in this Program represent various fields of physiology, pathophysiology, internal medicine, pediatrics, transplantation and clinical nephrology, and share a complex, multidisciplinary view of nephrology research and education. In our research activities, special emphasis is placed on the control of fluid and electrolyte balance, blood pressure and regulation of kidney function. With the discipline of translational research, modern experimental techniques are used at various levels from molecule to bedside. Research topics for doctorate degree graduates in Nephrology and Hypertension (43 Ph.D.-s so far) are quite extensive. Our research team has gained international recognition and is a leading expert on the regulation of renal hemodynamics and microcirculation, the mechanisms and progression of various kidney diseases including chronic renal failure, diabetic nephropathy, fibrosis and kidney allograft rejection. We are studying intracellular signal mechanisms, cell-cell communication, TGF-beta and the renin-angiotensin system, and their interaction with the control of renal hemodynamics. By studying the morphology and function of the afferent arteriole and juxtaglomerular apparatus, we have described a novel regulatory mechanism of glomerular filtration.

***Titles of research projects******Supervisors***

Genetic factors inhibit the progressive renal fibrosis Exploration of molecular transcriptic mechanism inhibiting profibrotic effects TGF-beta

László Rosivall

Effects of VEGF, Angiotensin II, relaxin and renin (prorenin) on endothelial fenestration and permeability

László Rosivall

Dialysis therapy, biocompatibility, quality of life

László Rosivall

Characterization of leucocyte subpopulation to follow / prevent the rejection of kidney in transplanted patients

László Rosivall

Risk factors in diabetes nephropathy – analysis of the correlations among serum relaxin, vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-beta) and angiotensin II levels – Prevention of cardiovascular death

László Rosivall

Renin-angiotensin system (RAS)

László Rosivall

Intracellular signalling mechanisms of transforming growth factor-beta and angiotensin II

László Rosivall

Factors associated with outcome in kidney transplanted patients	László Rosivall
Novel concepts in the regulation of blood pressure and kidney function	László Rosivall
Dialysis therapy, biocompatibility, quality of life	István Mucsi
Diagnosis and treatment of renal osteodystrophy	István Mucsi
Obstructive sleep apnea syndrome as a cardiovascular risk factor in chronic kidney disease patients	István Mucsi
Factors associated with outcome in kidney transplanted patients	István Mucsi
Cardiovascular risk, calcium, phosphorus and bone metabolism in chronic kidney disease patients	István Mucsi
Intracellular signalling mechanisms of transforming growth factor-beta and angiotensin II	István Mucsi
Cell-cell and cell-matrix interactions in the progression of chronic renal fibrosis	István Mucsi
Cardiovascular and renal pathophysiology of aging	Zoltán Ungvári
The role and mechanisms of epithelial- mesenchymal transition during fibrosis and tumor progression	Attila Sebe
Pathophysiology of nano-medicines with particular focus on nephrology and circulation	János Szebeni
New prognostic and morphological approaches to diagnosing HIV	János Szebeni
Pathophysiology of the complement system, with particular focus on the mechanism of drug-induced acute activations, their consequences and inhibition	János Szebeni
Novel concepts in the regulation of blood pressure and kidney function	János Peti-Peterdi
Endogeneous diuretic substances in the development of cardiac hypertrophy: experimental and clinical studies	Miklós Tóth
Effect of hypertension on microcirculation	Ákos Koller
Regulation of blood circulation in metabolic diseases	Ákos Koller
Molecular mechanisms of progression of renal fibrosis	Gábor Kökény
Molecular mechanisms of podocyte damage in diabetes	Gábor Kökény
Therapeutic utilisation of RNA interference to prevent ischemia-reperfusion injury of the kidney	Péter Hamar
Investigating the dual role of TGF-beta in atherosclerosis in a double gene-modified mouse strain	Péter Hamar
Molecular mechanisms of renal allograft rejection	Péter Hamar
Cardiovascular diseases and the renal failure. Prevention of renal hyperparathyroidism and osteodystrophy in early stage renal failure	András Szabó
SPECT analysis of cerebrovascular dysfunction induced by free radicals following cerebral trauma.	Kinga Karlinger

Hypertension in pregnancy and molecular mechanisms of the toxicosis	Miklós Molnár
Malnutrition and inflammation in patients with chronic kidney disease	Miklós Zsolt Molnár
The role of zinc in the regulation of the intracellular $\text{Ca}^{2+}$ and cAMP concentrations, as well as of the transepithelial ion transport	Ákos Zsembery
Study of the receptor-ligand binding and their interactions by paramagnetic nanoparticles: binding force of epidermal growth factor (EGF) to the receptors, and the interactions in the gastrointestinal tissues.	Tivadar Zelles
Study of the paramagnetic blood components by magnetooptical spectroscopy	Tivadar Zelles
Examination and treatment of surgical pathological conditions in animal models with special attention to microcirculation and renal changes	György Weber

**Ph.D. students**

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Ghafari Seyed Mohammed Reza	ft (a)
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Csaba Mihály Rikker	pt
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Károly Varga	na

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**Supervisors**

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## ***Abstracts of Ph.D. theses successfully defended in 2011***

**TIVADAR TAMÁS DANKÓ (2011)**

### **Role of extracellular zinc in the regulation of ion transport in airway and intestinal epithelium**

*Supervisor: Ákos Zsembery*

Zinc is an important trace element that plays a fundamental role in a variety of physiological and biochemical processes. Bidirectional transport of electrolytes and water is one of the main functions of epithelial tissues in the gastrointestinal tract and in the airways. The main purpose of the present thesis was to elucidate the effect of extracellular  $\text{Zn}^{2+}$  on important epithelial transport processes, such as  $\text{Cl}^-$  secretion in cystic fibrosis (CF) airway epithelial cells and divalent metal cation transport by the intestinal  $\text{Ca}^{2+}$  transporter channel human TRPV6, respectively. Firstly, we investigated the role of  $\text{Zn}^{2+}$  in different extracellular ionic milieu on the activity of  $\text{Ca}^{2+}$ -dependent  $\text{Cl}^-$  channels in CF airway epithelial cells. Then, we tested the effect of extracellular  $\text{Zn}^{2+}$  on hTRPV6-mediated  $\text{Ca}^{2+}$  transport in transiently expressing HEK293 cells. Our results indicate that: (1)  $\text{Zn}^{2+}$  exerts a dual effect on  $\text{Ca}^{2+}$ -dependent chloride channels (CaCCs) in CF airway epithelial cells.  $\text{Zn}^{2+}$  indirectly enhanced, however directly blocked the activity of CaCCs. Nonetheless, extracellular alkalization per se could elicit  $\text{Ca}^{2+}$  entry and evoke  $\text{Ca}^{2+}$ -activated  $\text{Cl}^-$  conductance without the application of  $\text{Zn}^{2+}$ . These findings suggest that a sufficiently alkaline,  $\text{Zn}^{2+}$ -free saline aerosol might be also beneficial for CF patients; (2)  $\text{Zn}^{2+}$  modulates hTRPV6 function in a dose-dependent manner. High concentrations of zinc inhibit, whereas low concentrations enhance  $\text{Ca}^{2+}$  transport via hTRPV6 channels. These findings suggest that dietary  $\text{Zn}^{2+}$  intake might play an important role in hTRPV6 channel-mediated transepithelial  $\text{Ca}^{2+}$  transport in the intestines. Furthermore, the hTRPV6 channels are also permeable for  $\text{Zn}^{2+}$  in the absence of  $\text{Ca}^{2+}$ , representing a novel pathway for  $\text{Zn}^{2+}$  absorption under calcium-restricted conditions.

- Dankó T, Hargitai D, Pataki A, Hakim H, Molnar M, and Zsembery A: Extracellular alkalization stimulates calcium-activated chloride conductance in cystic fibrosis human airway epithelial cells. *Cell Physiol Biochem* 2011; 27:401-410.
- Kovacs G, Dankó T, Bergeron MJ, Balazs B, Suzuki Y, Zsembery A, and Hediger MA: Heavy metal cations permeate the TRPV6 epithelial cation channel. *Cell Calcium* 2011; 49:43-55.
- Hargitai D, Pataki A, Raffai G, Füzi M, Dankó T, Csernoch L, Várnai P, Szigeti GP, and Zsembery A: Calcium entry is regulated by  $\text{Zn}^{2+}$  in relation to extracellular ionic environment in human airway epithelial cells. *Respir Physiol Neurobiol* 2010; 170:67-75.

**KÁROLY VARGA (2011)**

### **Biogenesis, maturation and surface trafficking of wild-type and mutant CFTR**

*Supervisor: László Rosivall*

Here we show that a second substitution in the carboxyl-terminal tail of CFTR, I1427A, on Y1424A background more than doubles CFTR surface expression as monitored by surface biotinylation. Internalization assays indicate that enhanced surface expression of Y1424A, I1427A CFTR is caused by a 76% inhibition of endocytosis. Patch clamp recording of chlo-

ride channel activity revealed that there was a corresponding increase in chloride channel activity of Y1424A, I1427A CFTR, consistent with the elevated surface expression, and no change in CFTR channel properties. Y14124A showed an intermediate phenotype compared with the double mutation, both in terms of surface expression and chloride channel activity. Metabolic pulse-chase experiments demonstrated that the two mutations did not affect maturation efficiency or protein half-life. Taken together, our data show that there is an internalization signal in the COOH terminus of CFTR that consists of Tyr (1424)-X-X-Ile(1427) where both the tyrosine and the isoleucine are essential residues. This signal regulates CFTR surface expression but not CFTR biogenesis, degradation, or chloride channel function.

One unusual feature of this protein is that during biogenesis, approximately 75% of wild type CFTR is degraded by the endoplasmic reticulum (ER)-associated degradative (ERAD) pathway. Examining the biogenesis and structural instability of the molecule has been technically challenging due to the limited amount of CFTR expressed in epithelia. Consequently, investigators have employed heterologous overexpression systems. Based on recent results that epithelial specific factors regulate both CFTR biogenesis and function, we hypothesized that CFTR biogenesis in endogenous CFTR expressing epithelial cells may be more efficient. To test this, we compared CFTR biogenesis in two epithelial cell lines endogenously expressing CFTR (Calu-3 and T84) with two heterologous expression systems (COS-7 and HeLa). Consistent with previous reports, 20 and 35% of the newly synthesized CFTR were converted to maturely glycosylated CFTR in COS-7 and HeLa cells, respectively. In contrast, CFTR maturation was virtually 100% efficient in Calu-3 and T84 cells. Furthermore, inhibition of the proteasome had no effect on CFTR biogenesis in Calu-3 cells, whereas it stabilized the immature form of CFTR in HeLa cells. Quantitative reverse transcriptase-PCR indicated that CFTR message levels are approximately 4-fold lower in Calu-3 than HeLa cells, yet steady-state protein levels are comparable. Our results question the structural instability model of wild type CFTR and indicate that epithelial cells endogenously expressing CFTR efficiently process this protein to post-Golgi compartments.

Misfolded proteins destined for the cell surface are recognized and degraded by the ERAD [ER (endoplasmic reticulum) associated degradation] pathway. TS (temperature-sensitive) mutants at the permissive temperature escape ERAD and reach the cell surface. In this present paper, we examined a TS mutant of the CFTR [CF (cystic fibrosis) transmembrane conductance regulator], CFTR  $\Delta F508$ , and analysed its cell-surface trafficking after rescue [r $\Delta F508$  (rescued  $\Delta F508$ ) CFTR]. We show that r $\Delta F508$  CFTR endocytosis is 6-fold more rapid ( $\sim 30\%$  per 2.5 min) than WT (wild-type,  $\sim 5\%$  per 2.5 min) CFTR at 37 °C in polarized airway epithelial cells (CFBE410-). We also investigated r $\Delta F508$  CFTR endocytosis under two further conditions: in culture at the permissive temperature (27 °C) and following treatment with pharmacological chaperones. At low temperature, r $\Delta F508$  CFTR endocytosis slowed to WT rates (20% per 10 min), indicating that the cell-surface trafficking defect of r $\Delta F508$  CFTR is TS. Furthermore, r $\Delta F508$  CFTR is stabilized at the lower temperature; its half-life increases from  $<2$  h at 37 °C to  $>8$  h at 27 °C. Pharmacological chaperone treatment at 37 °C corrected the r $\Delta F508$  CFTR internalization defect, slowing endocytosis from  $\sim 30\%$  per 2.5 min to  $\sim 5\%$  per 2.5 min, and doubled  $\Delta F508$  surface half-life from 2 to 4 h. These effects are  $\Delta F508$  CFTR-specific, as pharmacological chaperones did not affect WT CFTR or transferrin receptor internalization rates. The results indicate that small molecular correctors may reproduce the effect of incubation at the permissive temperature, not only by rescuing  $\Delta F508$  CFTR from ERAD, but also by enhancing its cell-surface stability.

- Varga K, Goldstein RF, Jurkuvenaite A, Chen L, Matalon S, Sorscher EJ, Bebok Z, Collawn JF: Enhanced cell-surface stability of rescued DeltaF508 cystic fibrosis transmembrane conductance regulator (CFTR) by pharmacological chaperones. *Biochem J* 2008; 410: 555-564.
- Peter K, Varga K, Bebok Z, McNicholas-Bevensee CM, Schwiebert L, Sorscher EJ, Schwiebert EM, Collawn JF: Ablation of internalization signals in the carboxyl-terminal tail of the cystic fibrosis transmembrane conductance regulator enhances cell surface expression. *J Biol Chem* 2002; 277:49952-49957.
- Varga K, Jurkuvenaite A, Wakefield J, Hong JS, Guimbellot JS, Venglarik CJ, Niraj A, Mazur M, Sorscher EJ, Collawn JF, Bebök Z: Efficient intracellular processing of the endogenous cystic fibrosis transmembrane conductance regulator in epithelial cell lines. *J Biol Chem* 200421; 279:22578-22584.

### **PROGRAM 1/5.**

## **CLINICAL AND EXPERIMENTAL CARDIOLOGY AND ATHEROSCLEROSIS**

### **Coordinator:**

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**Program overview:** The aim of the program is to carry out experimental and clinical studies on the pathological mechanisms responsible for the cardiac and vascular disorders leading the mortality statistics. Metabolic and immune disturbances, as diabetes and systemic autoimmune diseases are important risk factors in this process—therefore they are used as models. The different approaches are given by the sub-programs.

### ***Titles of research projects***

Studies on the role of inflammation in the pathogenesis of cardiovascular, and rare vascular diseases

Studies on the role of environmental and genetic factors in the atherogenicity of lipoproteins

Studies on the role of metabolic and immunological alterations in accelerated atherosclerosis

Investigations on genetic, biomolecular and clinical interactions in multifactorial diseases

Effect of endogenons cardiovascular mediators and drugs on electrophysiological properties of isolated heart preparation

Thrombotic aspects of coronary heart disease. Prothrombotic states and their treatment in the clinical practice. The role of endothelial receptors in the atherothrombosis

Perilous thrombotic complications in ischaemic heart disease

### ***Supervisors***

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Zoltán Prohászka

Valéria Kecskeméti

Róbert Kiss

Róbert Kiss



Cellular and molecular genomic alterations of the endothelial metabolism in ischaemic heart disease	István Préda
Endocardial and body surface mapping and their clinical application	István Préda
Electrocardiological diagnostics of ischaemic heart disease in obesity	Mihály Medvegy
Endothelial cell physiology and pathophysiology	László Cervenák
Pathomechanism, clinical and therapeutic aspects of different types of angioedema	Henriette Farkas

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István Préda
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***Ph.D. graduate***

Katarina Vargova	ft
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***Supervisors***

István Préda
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***Abstract of Ph.D. thesis successfully defended in 2011*****KATARINA VARGOVA (2011)****Endothelial and systemic effects of percutaneous coronary intervention Determination of circulating endothelial cells in ischaemic heart disease**

*Supervisor: István Préda*

The endothelium represents a metabolically active tissue with several important functions. Previous data confirmed, that cardiovascular risk factors may induce endothelial dysfunction and promote atherosclerotic process manifesting later as stable angina, or

acute coronary syndrome. In patients with ischaemic heart disease, the recanalisation of occluded coronary artery is crucial for the prevention of further ischaemic myocardial damage. Over the last two decades, invasive coronary revascularization therapy has been referred as an important therapeutic strategy in patients with ischaemic heart disease. However, data regarding the oxidative stress response, and the extent of PCI induced direct/or indirect endothelial damage are still lacking. Early impairment of endothelial function caused by cardiovascular risk factors might be characterized by loss of endothelial integrity and endothelial cell detachment demonstrating as increased circulating endothelial cell count (CEC) in peripheral blood. Since the CEC number increases in conditions associated with vascular damage, the CEC count can serve as a sensitive marker of endothelial injury. The main aim of our study was to assess the endothelial effects of PCI and to evaluate the grade of systemic oxidative stress response and the reperfusion injury following invasive coronary intervention. Our further aim was to determine the endothelial effects of the cardiovascular risk factors and pharmacotherapy. In order to determine the effect of PCI, CEC count, plasma vWF and sICAM-1 were determined in ischaemic heart disease patients. In acute myocardial infarction we found significantly higher baseline CEC count and plasma vWF compared to stable angina indicating the presence of explicit endothelial damage during acute myocardial ischaemia. In our study, nor the coronarography, neither the elective PCI caused significant CEC count elevation. Moreover, the CEC count was comparable in stable angina patients undergoing PCI, or coronarography alone. In contrast to previous concepts, our results indicate that elective PCI itself (similarly to coronary angiography) performed in stable form of ischaemic heart disease does not cause explicit endothelial damage. In contrast, analyzing patients with myocardial infarction we found pronounced increase in CEC count after PCI with a significant maximum at 24 hours. Based on our results, during percutaneous coronary intervention performed in conditions of manifest myocardial ischaemia more extensive endothelial damage occurs. Our further aim was to study the direct effect of cardiovascular risk factors and cardiovascular pharmacotherapy on endothelial cells. In our study, among the cardiovascular drugs, only clopidogrel was found to significantly decrease the CEC count. We assume, that lower CEC count in patients taking clopidogrel might indicate endothelial protective effect of the P2Y<sub>12</sub> receptor blockers.

During further studies, serum hydrogenperoxide concentrations and plasma levels of the oxidative DNA adduct 8-hydroxy-2'-deoxyguanosine were determined in patients with acute myocardial infarction. Rapid significant 8OHdG serum level increase detected immediately after successful PCI provide the first clinical evidence of reperfusion DNA injury present in patients with myocardial infarction undergoing PCI.

- Vargová K, Toth-Zsomboki E, Beres BJ, Bencze J, Kerecsen G, Gulacsi-Bardos P, Kiss RG, Preda I. Circulating endothelial cell count, plasma vWF and soluble ICAM-1 levels following primary or elective percutaneous coronary intervention. *Atherosclerosis* 2008; 198:366-372.
- Tóth-Zsomboki E, Horváth E, Vargova K, Pankotai E, Murthy K, Zsengellér Z, Bárány T, Pék T, Fekete K, Kiss RG, Preda I, Lacza Z, Gerö D, Szabó C. Activation of poly(ADP-ribose) polymerase by myocardial ischemia and coronary reperfusion in human circulating leukocytes. *Mol Med* 2006; 12:221-228.

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# SCHOOL OF PH.D. STUDIES

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## 2. CLINICAL MEDICINE

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***Chairman:***

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**General Overview:** The Clinical Medicine Doctoral School has the largest number of programmes among the eight Doctoral Schools of Semmelweis University. The training and research programs offer research projects in a large number of subdisciplines of clinical and applied medicine.

### ***PROGRAM 2/1.***

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#### **OXIDATIVE STRESS AND IMMUNOLOGICAL REACTION IN LIVER DISEASES**

***Coordinator:***

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**Program Overview:** Evidence accumulates that natural (vitamins, flavonoid type molecules) and synthetic butylated hydroxytoluene, dihydro-quinolin-type molecules) antioxidants exert a preventive effect on local oxidative damage in several models in vitro and in vivo. Therefore, the aim of our Program is to investigate the role of oxidative stress and the shift in pro/antioxidant balance in the pathogenesis of several gastrointestinal and immunological diseases, metabolic disorders and drug side effects by direct and indirect methods. The ongoing experiments focus on steatosis, hepatitis, cirrhosis, hepatocellular carcinoma, gallstone formation, cholestasis, inflammatory bowel diseases, colon neoplasm and metabolic disorders (carbohydrate, lipid) as well as amiodarone toxicity.

***Titles of research projects***

Study of redox homeostasis

Neurochemical examination of neural elements innervating the gastrointestinal visceral organs

Genetic and phenotypic examinations in disorders with chronic liver disease

***Supervisors***

Anna Blázovics

Erzsébet Fehér

Gábor Firneisz

Results of onco-surgical treatment of liver tumors from the aspect of immune system functioning. Prognostics, long term follow up, quality of life	Ferenc Jakab
Pathogenesis and therapy of non-alcoholic liver disease	Gabriella Lengyel
Alcoholic liver disease	Gabriella Lengyel
Up to date treatment in hepatobiliary diseases. The effect of ursodeoxycholic acid and interferon on viral hepatitis and the oxidative stress status	Gabriella Lengyel
Food intake, lifestyle and the liver diseases	Gabriella Lengyel
The link among carbohydrate and lipid metabolism and free radical reactions and their role in the development of arteriosclerosis	Anikó Somogyi
Effect of metal complexes on the liver pathobiochemistry	Klára Szentmihályi

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Anikó Somogyi
Anna Blázovics
Gábor Firneisz

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Tímea Varga	ft
Ildikó Vastagh	na

**Supervisors**

Anikó Somogyi
Erzsébet Fehér
Anikó Somogyi
Anikó Somogyi

**Ph.D. graduates**

Ildikó Vastagh	na
----------------	----

**Supervisors**

Anikó Somogyi
---------------

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**Abstract of Ph.D. thesis successfully defended in 2011****ILDIKÓ VASTAGH (2011)****Early macrovascular complications of carbohydrate intolerance**

*Supervisor: Anikó Somogyi*

Cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality in patients with diabetes mellitus. According to the literature macroangiopathy can be observed in patients with T1DM and gestational DM (GDM), but the results are controversial. From the preventive point of view the detection of macrovascular disorders is very important. Increased intima-media thickness (IMT) of the large elastic vessels is an early marker of the atherosclerotic process. Arterial stiffness represents cardiovascular risk. In most studies only either morphological or functional parameters were examined as early signs

of atherosclerosis. In the past few years, there have been studies published examining morphological and functional characteristics, but the results are inconclusive. For clarification purposes both morphological (d, diameter; IMT; IMCSA, intima-media cross section area) and functional (D, distensibility; C, compliance; Str, circumferential strain; SI, stiffness index; Einc, incremental elastic modulus; PWV, pulse wave velocity) parameters were examined in T1DM and GDM patients comparing control subjects with normal carbohydrate-tolerance. In conclusion, significant morphological and functional alterations of large elastic vessels could be detected in young adult type 1 diabetic patients after 10 years of disease duration. There are differences in the time course of evolution of these characteristics. Age, systolic blood pressure, duration of DM and LDL-cholesterol were independent predictor of early macrovascular alterations.

Neither significant morphological nor significant functional changes of large elastic vessels could be detected in well treated GDM pregnant. Effective glycemic control in women with GDM may help to prevent early damage of large elastic arteries.

- Vastagh I, Horváth T, Nagy G, Varga T, Juhász E, Juhász V, Kollai M, Bereczki D, Somogyi A: Evolution and predictors of morphological and functional arterial changes in the course of type 1 diabetes mellitus. *Diabetes Metab Res Rev* 2010; 26:646-655.
- Vastagh I, Horváth T, Gamavölgyi Z, Rosta K, Folyovich A, Rigó J Jr, Kollai M, Bereczki D, Somogyi A: Preserved structural and functional characteristics of common carotid artery in properly treated normoglycemic women with gestational diabetes mellitus. *Acta Physiol Hung* 2011; 98:294-304.
- Vastagh I: Early macrovascular damage in diabetes mellitus. *Metabolizmus* 2011; 1: 57-60.

## **PROGRAM 2/2.**

### **FETAL AND NEONATAL MEDICINE**

#### **Coordinator**

**Zoltán PAPP M.D., Ph.D., D.Sc.**

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**Program Overview:** The Ph.D. Program is designed for medical doctors who wish to specialize in prenatal genetics and fetal medicine. Our aims are: to provide medical and science based students with comprehensive knowledge in the field of genetic and fetal medicine, to provide suitable environment for clinical or laboratory based research project, to enable students for the use of laboratory techniques such as PCR, F-PCR, RFLP, blotting techniques etc., to train students in modern prenatal diagnostic methods, like color-Doppler ultrasound, intrauterine echocardiography etc.

#### **Titles of research projects**

Fetal and neonatal developmental disorders of the heart

Pathomechanisms, early prediction and diagnosis of the great obstetrical syndromes

Clinical and embryological aspects of assisted reproduction

#### **Supervisors**

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Nándor Gábor Than

János Urbancsek

**Ph.D. candidates**

Zsófia Róna

ft

**Supervisors**

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**Ph.D. graduates**

Ákos Murber

na

**Supervisors**

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Tibor Várkonyi

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Bálint Nagy

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**Abstracts of Ph.D. theses successfully defended in 2011****ÁKOS MURBER (2011)****Impact of ovarian stimulation protocols on the success of in vitro fertilization treatments***Supervisor: Zoltán Papp*

Controlled ovarian hyperstimulation is essential part of an in vitro fertilization treatment. Efficacy of the stimulation with gonadotrophins is improved by hampering the endogenous gonadotrophin secretion by two different protocols. GnRH-agonists have been used for 25 years for pituitary desensitisation, while nowadays the use of GnRH-antagonists signifies also an approved and well-established treatment for IVF.

I have established the digital documentation of all clinical- and embryological data, as well as stimulation protocols to evaluate all IVF-treatments performed at our department.

Comparison of the stimulation protocols showed that the use of GnRH-agonists results in higher clinical pregnancy- and live birth rates compared to GnRH-antagonists. Using GnRH-antagonist cetrorelix, both of the single- and multiple dose regimen are effective in avoiding the premature LH-surge.

Several randomized controlled trials comparing different stimulation protocols have focused on clinical aspects of the ovarian stimulation only, such as length of stimulation, number of oocytes retrieved and pregnancy rates. Even though the quality of oocytes and embryos is one of the most relevant factors determining the success of an IVF treatment, there are only few evidence in the literature concerning the effects of different stimulation protocols on oocyte- and embryo quality and embryo development.

According to my results, the number and quality of oocytes are impaired using GnRH-antagonists, but the further development of the embryos is more favourable compared to GnRH-agonists. Nevertheless the stimulation with GnRH-agonists results in higher live birth rate.

Comparing different gonadotrophin preparations I noticed significantly higher proportion of embryos suitable for cryopreservation after HP-FSH stimulation, hence the expected higher cumulative pregnancy rate in this group could favour the patient.

- Murber Á, Ledó N, Fancsovits P, Tóthné GZs, Rigó J jr., Urbancsek J: *In vitro fertilizáció (IVF) kezelése során alkalmazott stimulációs protokollok hatása a petesejt- és embrióminőségére, valamint a korai embriófejlődésre. Magyar Nőorvosok Lapja 2009; 73:23-29.*
- Murber Á, Fancsovits P, Ledó N, Tóthné GZS, Rigó J, Urbancsek J: *Impact of GnRH analogues on oocyte/embryo quality and embryo development in in vitro fertilization/intracytoplasmic sperm injection cycles: a case control study. Reprod Biol Endocrinol 2009; 7:103.*
- Murber Á, Fancsovits P, Ledó N, Szakács M, Rigó J jr., Urbancsek J: *Impact of highly purified versus recombinant follicle stimulating hormone on oocyte quality and embryo development in intracytoplasmic sperm injection cycles. Acta Biol Hung 2011; 62:255-264.*



**TIBOR VÁRKONYI (2011)****Analysis of placental signaling pathways in preeclampsia and HELLP syndrome with specific respect to the leptin gene - leptin receptor gene interaction***Supervisor: Bálint Nagy*

Placental samples with HELLP syndrome were examined at the transcript level. In early-onset preeclampsia there were 350 genes and in HELLP syndrome 554 genes were found that were altered comparing controls. 224 genes were differentially expressed in both preeclampsia and HELLP syndrome. They also had the same direction in both diseases, which raises the possibility of the change of the same regulatory networks. There were leptin,  $\beta$ -hCG and  $\beta$ -LH among genes with the highest fold change rate in both pregnancy associated diseases. The expression differences of these genes were confirmed either at the RNA level by quantitative real time PCR and at protein level by tissue microarray. Network analysis showed deviation in the cytokine-cytokine signal pathway between preeclampsia and HELLP syndrome. In HELLP syndrome, the elevated leptin expression was not associated with the leptin microsatellite polymorphism on the maternal side. I examined the leptin receptor that is the main signal transducer of leptin signalling, moreover it is also part of the cytokine-cytokine system. Determining four SNPs of the leptin receptor, there were no significant correlations with HELLP syndrome.

- Nagy B, Varkonyi T, Molvarec A, Lazar L, Hupuczi P, Than NG, Rigo J Jr: *Leptin gene (TTTC)(n) microsatellite polymorphism in pre-eclampsia and HELLP syndrome. Clin Chem Lab Med* 2009; 47:1033-1037.
- Varkonyi T, Lazar L, Molvarec A, Than NG, Rigo J Jr, Nagy B: *Leptin receptor (LEPR) SNP polymorphisms in HELLP syndrome patients determined by quantitative real-time PCR and melting curve analysis. BMC Med Genet* 2010;11:25.

**PROGRAM 2/3.****PREVENTION OF CHRONIC DISEASES IN CHILDHOOD****Coordinator****Tivadar TULASSAY M.D., member of  
the Hungarian Academy of Sciences**

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**Program Overview:** The present research and doctoral program consists various topics of paediatrics, prevention creates the common basis of the program. No reliable method is available to determine the beginning of a chronic disease. In Hungary the causes of the majority of the leading fatal diseases are to be found already in childhood, although without clinical signs. Their progression gradually leads to a permanent manifest disease with expressed clinical symptoms. A fundamental precondition of preventing the development of chronic diseases is to detect the possibly existing risk factors. Getting to know the cellular and subcellular mechanisms promoting the development of a disease may be of help not only in the prevention, but also in the successful therapy and in eliminating the complications, as well. The doctoral Program is dealing with research fields having outstanding significance in adult cardiovascular morbidity and mortality and where the identification and

elimination of risk factors could prevent long-lasting impairments. In the pathogenesis of cardiovascular diseases sodium homeostasis and its cellular regulation are of utmost importance. Within the doctoral Program this question is dealt with in 3 sub-programs. The research work is aimed to study the altered activity, structural changes and genetic regulation of Na/K/ATP-ase enzyme in diseases accompanied by irregular sodium homeostasis. In insulin dependent diabetes mellitus the prevention of late complications: vascular alterations and hypertonia are of cardinal question. Two sub-programs are devoted to study genetic, metabolic and haemodynamic risk factors in animal experiments and clinical physiological examinations. The sub-program dealing with the correlation between chronic renal diseases, cardiovascular alterations as well as uraemia and bone metabolism focuses on the regulatory role of the kidney as regards vascular alterations and bone structure deformities. The pre-term birth and treatments applied involve several late complications and hazardous situations. The harmful side effects of oxygenization can be due to the multiplication of oxidative radicals. This hypothesis has been considered as a possible pathogenetic factor in several other diseases, too. The study of this theory in pre-term babies may provide explanations similarly valid in other systems, in a wider sense, as well. The investigation of postnatal body composition, the hydrodynamic changes accompanied by electrolyte movement may reveal several fundamental regularities. This sub-program offers a completely new approach by using multifrequency bioelectric impedance analysis. The additional four sub-programs seem to be heterogeneous, however, they have one common aspect, namely, all of them are aimed to detect risk factors thereby improving life's quality. The investigation of the congenital urinary tract malformations in neonates and pre-term babies, in addition to the discovery of basic facts, has directly practical significance: to determine the optimal time and technique of surgical intervention. The number of infantile atopic airway diseases shows an increase proportional with the environmental pollution pointing out the importance of getting to know the natural course and pathomechanism of the disease. The questions of paediatric gastroenterology deal with the immunologic correlation existing between food allergens and intestinal diseases. The deeper knowledge of the pathophysiology of childhood epilepsy syndromes and primary headache disorders may result in a better life quality in adulthood.

### ***Titles of research projects***

### ***Supervisors***

Role of innate immunity in immunomediated gastrointestinal disorders (coeliac disease, food allergy induced enteropathy, inflammatory bowel disease)	András Arató
Study of inflammatory mediators in pediatric migraine and epilepsy caused by limbic encephalitis	Viktor Farkas
The role of haemodynamic and genetic factors in the pathomechanism of acute and chronic allograft nephropathy	Andrea Fekete
Effect of anaesthesia and operative intervention to the immune system	István Kocsis
Role of seasonal and circadian rhythmicity in the development of chronic complication and progression of diabetes mellitus	Anna Körner
Genetic, haemodynamic and metabolic risk factors and molecular pathogenesis of the development of diabetic nephropathy	László Madácsy
Comparative study on the asthmatic children taking part regularly in swimming programs	Györgyi Mezei
Genetics of HELLP syndrome	Bálint Nagy

Diagnosis, prevention and treatment of infections following transplantation	György Reusz
Cardiovascular effects of renal failure and transplantation in childhood	György Reusz
Cardiovascular disorders and renal failure. Possibilities for the preventive options in renal hyperparathyroidism and osteodystrophy in the early phase of renal failure	András Szabó
Studying of pathomechanism, genetic background and therapy of chronic allograft nephropathy	Attila Szabó
Use of hypothermy in the treatment of hypoxic-ischemic encephalopathy of neonates	Miklós Szabó
Pediatric liver diseases. Hereditary metabolic diseases	László Szőnyi
Childhood genetic kidney diseases	Kálmán Tory
Examinations of factors influencing the morbidity and mortality of pediatric intensive care focus on the carbohydrate metabolism	Péter Tóth-Heyn
Functional immunological studies in pediatric diseases	Tivadar Tulassay
New methods in paediatrics	Tivadar Tulassay
Significance of functional genomic examinations in the early and late complications of premature babies	Barna Vásárhelyi
Molecular biological examination of the ischemic injury of the kidney	Ádám Vannay
Expressions of microRNA in pediatric patients with Crohn's disease	Gábor Veres

**Ph.D. students**

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Tamás Bense	pt
Arianna Amália Dégi	ft
Gábor Dudás	pt
Ádám Hosszú	ft
Zoltán Jenővári	pt
Ambrus Kaposi	ft
Andrea Kerti	ft
Sándor Kőszegi	ft
Petra Lakatos	ft
Gábor Marics	pt
Gergő Mészáros	ft
Krisztina Mészáros	pt
Krisztina Molnár	ft
Dorottya Nagy-Szakál	ft
Anna Ónody	ft
Krisztina Pásti	ft
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**Supervisors**

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György Reusz
László Madácsy
Attila Szabó
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**Ph.D. graduates**

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Attila György Kálmán	na
Monika Sultész	na

**Supervisors**

Gábor Veres
Tivadar Tulassay
Györgyi Mezei

a, absolutorium; pt, part-time; ft, full-time; na, not affiliated

**Abstracts of Ph.D. theses successfully defended in 2011****ÁRON CSEH (2011)****Regulatory T cells and cellular environments in pediatric immune-mediated gastrointestinal diseases**

Supervisor: Gábor Veres

**Background:** Gastrointestinal diseases affecting the childhood such as Crohn's disease, celiac disease and allergic colitis were investigated. The pathomechanism of these immunmediated diseases is not fully known. However, both the innate and adaptive immunity including regulatory T cells, the main suppressor cell type can be involved. **Aim:** To develop a flow cytometry procedure to investigate the regulatory T cells along with their cellular network in small children. To characterize immune phenotype in pediatric gastrointestinal disorders. **Results:** In newly diagnosed children with Crohn's disease the prevalence of T helper 1, activated and effector T cells increased. With conventional therapy the prevalence of activated and effector T cells decreased, while that of T helper 1 increased. Infliximab therapy also normalized the T helper 2 shifts, but increased the prevalence of effector cells. Natural killer and natural killer T cells were lower in patients than in controls. The prevalence of dendritic cells and monocytes, particularly of those expressing Toll-like receptor are increased in therapy-naïve patients, but normalized with the conventional and biological therapy. Untreated celiac patients had lower than normal CD4 lymphocyte prevalence and T helper 1 ratio; these values increased with gluten-free diet. The prevalence of T lymphocytes expressing early activation markers is increased, while that of expressing late activation markers are decreased. These abnormalities were normalized in patients on diet. In untreated celiac disease the numbers of natural killer and natural killer T cells are decreased; on therapy just the prevalence of invariant natural killer T cells is increased. The prevalence of antigen presenting dendritic cells including those expressing Toll-like receptors is increased in children with celiac disease. Allergic colitis presents with lower prevalence of regulatory T cells, and that of activated, effector and T helper 1 lymphocytes. After the cessation of symptoms the prevalence of regulatory T cells and T helper shift normalized. **Conclusions:** The adaptive immune phenotype of children with

newly diagnosed Crohn's disease is different than in adulthood. The alterations of cell prevalence values of innate and adaptive immunity are ameliorated with conventional therapy, but the nonresponding patients only infliximab therapy had an impact on immune phenotype. In untreated celiac patients the activation of innate and adaptive immune cells were detected. On gluten-free diet, the prevalence of cells responsible for adaptive immunity is normalized, but that of innate immune cells remained unaltered. Allergic colitis leading in hematochezia responds to elementary formula. In untreated patients immune phenotype resembles to that observed in allergic disorders.

- Cseh Á, Vásárhelyi B, Szalay B, Molnár K, Nagy-Szakál D, Treszl A, Vannay Á, Arató A, Tulassay T, Veres G: *Immune phenotype of children with newly diagnosed and gluten-free diet-treated celiac disease. Dig Dis Sci* 2011; 56:792-798.
- Cseh A, Molnár K, Pintér P, Szalay B, Szebeni B, Treszl A, Arató A, Vásárhelyi B, Veres G: *Regulatory T cells and T helper subsets in breast-fed infants with hematochezia caused by allergic colitis. J Pediatr Gastroenterol Nutr* 2010; 51:675-677.
- Cseh A, Vasárhelyi B, Molnár K, Szalay B, Svec P, Treszl A, Dezsöfi A, Lakatos PL, Arató A, Tulassay T, Veres G: *Immune phenotype in children with therapy-naïve, remitted and relapsed Crohn's disease. World J Gastroenterol* 2010; 16:6001-6009.

## ATTILA GYÖRGY KÁLMÁN (2011)

### Minimally invasive methods in paediatric thoracic surgery

Supervisor: Tivadar Tulassay

Intrathoracic diseases of the newborns and children are benign in the vast majority of cases. They have been operated with minimal mortality, excellent long-term outcome and quality of life for decades.

The so called standard postero-lateral thoracotomy provides very good, wide exposure for thoracic surgery, but it means great load for the patient itself and carries the risk of potential harmful long-term sequelae. Scoliosis, asymmetry of the shoulders and winged scapula are obvious consequences of thoracotomy. We can't forget the everlasting large scar either. Different muscle-sparing thoracotomies and thoracoscopic techniques have been developed for preventing these problems.

We think – based on our experience, gathered following the introduction of minimally invasive techniques – axillary skin crease incision can be used safely in more indications and in wider age-group than it is published by Bianchi. Thoracoscopy can be used safely with low conversion rate in childhood too.

Recently ¾ of all intrathoracic operations are performed using minimally invasive methods in our department.

Ravitch-operation or its modified version was used for correction of thoracic deformities traditionally. Traditional thoracoplasty may have long-term consequences, like upper thoracic over-growth, thoracic chondrodystrophy or the poor compliance of the chest.

We introduced and modified the minimally invasive repair of pectus excavatum invented by Nuss and developed a minimally invasive method for correcting pectus carinatum. We achieved the goal, providing minimally invasive surgical method for all children with pectus excavatum or carinatum, necessitating surgical correction.

- Kálmán A: *Initial results with minimally invasive repair of pectus carinatum. J Thorac Cardiovasc Surg* 2009; 138:434-438.
- Kálmán A, Verebely T: *The use of axillary skin crease incision for thoracotomies of neonates and children. Eur J Pediatr Surg* 2002; 12:226-229.

- *Pintér A, Kálmán A, Karsza L, Verebély T, Szemlédy F: Long-term outcome of congenital cystic adenomatoid malformation. Pediatr Surg Int 1999; 15:332-335.*

## MONIKA SULTÉSZ (2011)

### The epidemiology, complications and pathogenesis of childhood rhinosinusitis

*Supervisor: Györgyi Mezei*

The number of acute bacterial rhinosinusitis (ABRS) cases has been increasing continuously. Therefore early diagnosis, examination and appropriate treatment are of paramount importance to prevent the illness from becoming chronic. In addition, it helps to prevent the development of life-threatening complications. The major events predisposing to the development of ABRS are viral upper respiratory tract infections (URI) and allergic inflammation. The experience, which I gained from treating the patients of our busy ORL department and allergology outpatient consultation, served as a basis, when I assigned two main fields to study. One of them is the epidemiological study of allergic rhinitis (AR) among primary schoolchildren living in Budapest, the other is the complex procession of the complications of sinusitis.

During the rhinosinusitis study the case charts of 339 children admitted to our department between 1997 and 2006 with persistent acute bacterial rhinosinusitis who haven't recovered following conservative therapy or who had complications of acute sinusitis were subjected to a retrospective review. In our survey we examined the data of 182 children suffering from persistent acute bacterial rhinosinusitis that did not respond to conservative therapy and 157 children who were diagnosed with secondary complications of acute sinusitis.

Of the 157 children with sinusitis complications there were 150 orbital complications, 2 intracranial complications, 1 mucocoele and 4 cases of osteomyelitis.

The classification of the ABRS orbital complications is essential, because correctly interpreted and applied classification determines the therapy. I introduced Chandler's stages to classify the orbital complications of rhinosinusitis, which has not been applied to children in Hungary before. I mapped out diagnostic and therapeutic protocol based on the classification and I introduced it into the clinical practice. In my study I indicated the use of the classification in the procession of 157 cases. This method can be a practical guideline for the pediatric otorhinolaryngologists.

While surveying allergic rhinitis I was the first to determine the prevalence of AR among 6-12-year-olds and the prevalence of assumed AR based on the symptoms in the 12 months preceding the survey.

I am the first to publish the prevalence of all physician diagnosed atopic diseases, which proved to be 34%.

It has not earlier been detected in connection with children's epidemiological examinations that positive family history of atopy; frequent upper respiratory tract infections; sinusitis; antibiotics and paracetamol given in the first year of life, consumption of drinks containing preservatives or colourants; the presence of long-lasting disease before the appearance of AR symptoms proved to be an increased risk of the development of AR.

- *Sultész M, Csákányi Zs, Majoros T, Farkas Zs, Katona G: Acute bacterial rhinosinusitis and its complications in our pediatric otolaryngological department between 1997 and 2006. Int J Pediatr Otorhinolaryngol 2009; 73:1507-1512.*
- *Sultész M, Katona G, Hirschberg A, Gálffy G: Prevalence and risk factors for allergic rhinitis in primary schoolchildren in Budapest. Int J Pediatr Otorhinolaryngol 2010; 74:503-509.*



**PROGRAM 2/4.****GASTROENTEROLOGY*****Coordinator:***

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**Program Overview:** The importance of gastroenterological diseases is increasing, and because of their frequency and complications, they are considered as one of the most menacing group of diseases. This fact is confirmed by the out-patient and in-patient numeric data, as well as morbidity and mortality indices. Gastroenterology has developed such a discipline that combines the knowledge of different specialities. It includes the pathophysiological data resulted from basic research, the results of clinical research and observations. The research of the gastrointestinal diseases can be done by different approaches and different methodological possibilities. This interdisciplinary topic offers unprecedented opportunities for scientific research. The achievements of last one and half decade resulted relevant changes in several aspects of gastroenterology, and the conventional understanding of development, progression and treatment of diseases had been changed. Despite of the undoubted results several questions need to be answered and new questions are appearing. Gastroenterological diseases can be the topic of wide-spread researches that fit to the scientific basis of public health priorities.

***Titles of research projects***

Management of esophageal tumours

Improving patient safety in anesthesia and intensive care

Intensive care in postoperative and septic conditions associated with gastrointestinal disorders

Examination of proteolytic enzyme systems and cell kinetic parameters in gastrointestinal tumors and digestive diseases

Immunogenetic risk factors and prognostic factors in colorectal cancer and other malignancies

Novel factors in the development of digestive tract mucosal lesions

Pathogenesis of the *Helicobacter pylori* related diseases

Pancreas transplantation

Examination of peripheral blood mRNA expression in 52nt he 52r s patients with colorectal cancer

Link among exercise, glucose and lipid metabolism, exercisetherapy in diabetes and obesity

Effect of exercise and food intake on the normal and pathologic brain ageing cell physiological processes

***Supervisors***

Ákos Balázs

Ákos Csomós

Katalin Darvas

László Herszényi

Judit Kocsis

László Kopper

László Kopper

Róbert Langer

Béla Molnár

Csaba Nyakas

Csaba Nyakas

Pathophysiology of the alimentary system	László Rosivall
The role of pattern recognition 53nt he53r sin non-alcoholic fatty liver disease	Gyöngyi Szabó
Mechanisms of innate immune alterations in HCV infection and its modulation by alcohol use	Gyöngyi Szabó
Toll-like receptor 4-mediated signaling in alcoholic liver disease	Gyöngyi Szabó
Hypoxia-inducible factor in alcoholic liver disease	Gyöngyi Szabó
Extrahepatic complications of chronic liver diseases: hepatic osteodystrophy, autonomic neuropathy. Wilson disease gene mutations, chronic C virus hepatitis and the liver disease associated	Ferenc Szalay
Inflammatory ibowel diseases and the osteopenia	Miklós Szathmári
Investigation of microcirculation and molecular changes in surgical diseases	Attila Szijártó
Application of video-endoscopic surgical methods in gastroenterology	Tibor Tihanyi
Study of molecular factors deteremining the evolution of bone metastasis	József Tímár
Inflammatory intestine illnesses and osteopenia	Zsolt Tulassay
New factors the digestive system mucosa nt he development of laesio	Zsolt Tulassay

**Ph.D. students**

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István Fűri	ft
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László Herszényi
Attila Szijártó
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Attila Szijártó

**Ph.D. graduates**

János Osztovits†

ft

Sándor Spisák

ft

**Supervisors**

Ferenc Szalay

Béla Molnár

a, absolutorium; pt, part-time; ft, full-time; na, not affiliated

**Abstracts of Ph.D. theses successfully defended in 2011****JÁNOS OSZTOVITS† (2011)****Autonomic nervous system function in patients with chronic hepatitis C virus infection***Supervisor: Ferenc Szalay*

Chronic hepatitis C virus (HCV) infection can be associated with various extrahepatic manifestations, including peripheral and central nervous system complications. Autonomic function has not been investigated in patients with chronic HCV infection before, although impaired autonomic function has already been described in patients with chronic liver diseases from different etiologies, and has proven to be a poor prognostic indicator. In addition, the current treatment of interferon-alpha plus ribavirin is known to affect neurological manifestations in patients with chronic HCV infection.

In our first, cross-sectional study we aimed to determine cardiovagal autonomic function in patients with chronic HCV infection, comparing to healthy controls. In our second study we followed-up the patients during the course of antiviral therapy and aimed to examine the possible changes of cardiovagal autonomic function. Autonomic function was assessed in 45 treatment-naïve patients with chronic HCV infection and in 40 healthy controls by determining spontaneous baroreflex sensitivity (BRS) and heart rate variability (HRV) indices with non-invasive methods. Then, we followed up 22 patients and assessed BRS and HRV indices at the beginning of treatment and at week 12, 24 and 48 of antiviral therapy. Besides, laboratory analyses and quantitative polymerase chain reaction for serum HCV RNA level were performed. BRS and HRV indices were lower in patients with HCV infection compared to healthy controls, and independently correlated with serum ALT levels. Further, both HRV and BRS indices decreased after 12 weeks of therapy compared to pre-treatment values; then they increased significantly by week 24 and continued to improve by week 48 of therapy. These changes were independent from the presence of cryoglobulins and from the virological response. Our results suggest that impaired autonomic function is caused by chronic HCV infection. The increase of autonomic dysfunction at the beginning of the antiviral therapy may be caused by the immunomodulatory actions of interferon alfa-2. Further studies are needed, however, to understand the exact mechanisms.

- Osztovits J, Horváth E, Tax J, Csihi L, Horváth T, Littvay L, Tóth T, Abonyi M, Lakatos PL, Kollai M, Fehér J, Szalay F, Blum HE: Reversible autonomic dysfunction during antiviral treatment in patients with chronic hepatitis C virus infection. *Hepat Mon* 2011; 11: 114-118.
- Osztovits J, Horváth T, Abonyi M, Tóth T, Bekő G, Csák T, Lakatos PL, Fehér J, Littvay L, Kempler P, Kollai M, Szalay F: Chronic hepatitis C virus infection associated with autonomic dysfunction. *Liver Int* 2009; 29:1473-1478.

**SÁNDOR SPISÁK (2011)****Characteristic molecular changes during colorectal carcinogenesis and progression***Supervisor: Béla Molnár*

In the last decade, high-throughput molecular biological methods provide more and more information about the molecular processes of tumors, but there are still many questions regarding the early diagnosis, therapy and follow-up of cancers. The high incidence and not fully understood molecular and pathological background of CRC, necessitate the systemic research of this field. In my Ph.D. thesis I identified and validated biomarkers of CRC development and progression at mRNA and protein levels. I have determined methylation regulated genes based on altered gene expression, and then I have analyzed the effect of a chemopreventive agent in cell culture model. I have established that the laser micro-dissected (LCM) samples are suitable for whole genomic microarray analysis. I have identified genes with altering expression during the colorectal adenoma-carcinoma sequence progression using LCM samples. Using LCM samples, I have determined tissue specific expression of biomarkers from biopsy and surgical studies. I have demonstrated that the methylation regulated genes could be determined by the examination of gene expression. I have identified the methylation loci of the PTGDR gene and its decreasing expression at mRNA and protein level was also proved. I have assessed molecular processes in CRC carcinogenesis which can be reversed by selective COX2 inhibitor treatment.

- Galamb O, Spisák S, Sipos F, Tóth K, Solymosi N, Wichmann B, Krenács T, Valcz G, Tulassay Z, Molnár B: Reversal of gene expression changes in the colorectal normal-adenoma pathway by NS398 selective COX2 inhibitor. *Br J Cancer* 2010; 102:765-773.
- Spisák S, Galamb B, Sipos F, Galamb O, Wichmann B, Solymosi N, Nemes B, Molnár J, Tulassay Z, Molnár B: Applicability of antibody and mRNA expression microarrays for identifying diagnostic and progression markers of early and late stage colorectal cancer. *Dis Markers* 2010; 28:1-14.
- Spisák S, Guttman A: Biomedical applications of protein microarrays. *Curr Med Chem* 2009; 16:2806-2815.

**PROGRAM 2/5.****DENTAL RESEARCH****Coordinator:****Gábor VARGA M.Sc, Ph.D., D.Sc.**

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**Program Overview:** The aim of this Ph.D. program is to select open minded, self-supporting applicants who are able to acquire the knowledge of complex understanding of theoretical and clinical state of the art in the field, and are able to use this knowledge in education and research. Therefore, the Program prepares for the two different but not unconnected directions: it focuses on the better understanding of physiological and pathological processes in the oral cavity, as well as on the development and application of new therapeutic methods in all branches of dentistry.

***Titles of research project******Supervisors***

Preventive program monitoring, risk factor evaluation using laboratory and clinical epidemiological methods	Jolán Bánóczy
Examination of oral cavity manifestations using clinical and laboratory methods	Jolán Bánóczy
Biological and clinical study and development of maxillofacial soft and hard tissue surgical techniques in rehabilitation	József Barabás
Theory-designed experiments in the characterisation of dental materials at the molecular level	Gregory A. Chass
Computational design of molecules and materials	Imre G Czizmadia
Characterization of dental materials for the purpose of clinical use	Csaba Dobó Nagy
Comparison of imaging techniques	Csaba Dobó Nagy
The role of biological mediators in periodontal regenerative surgery	Ferenc Dőri
Effects of psychological-, electromagnetic- and heat stimulation on the expression and secretion of Hsp70 type stress proteins in salivary glands	Tibor Károly Fábíán
Role of vascular endothelium in the regulation of the oral circulation	Árpád Fazekas
Role of sensory and autonomic nerve fibers in the development of inflammation in the periodontium and the pulp	Árpád Fazekas
Driven periodontal tissue regeneration	István Gera
Evaluation of visual and instrumental tooth shade determination techniques	Péter Hermann
The importance of screening of the oral human papillomavirus (HPV), and the role of the extracellular matrix and the tight junction structure in the pathogenesis of tumors in the oral cavity	Péter Hermann
Diagnostic and therapeutic aspects in dentistry supporting the prevention and rehabilitation in diseases of the craniofacial region	Melinda Madléna
Assessment of xerostomia with associated sicca symptoms and evaluation of the minor salivary gland flow rates in different conditions and diseases	Krisztina Márton
Stomatological aspects of immunopathologic disorders	Gábor Nagy
Congenital dental anomalies and their orthodontic implications. Root resorption during orthodontic treatment	Noémi Katinka Rózsa
Study of the clinical progression and examination of extracellular matrix (ECM) components in oral squamous epithelial cancers and in conditions preceding oral cancers	Zsuzsanna Suba
Histological integration of bone replacement and implanted materials in the oral region	Zsuzsanna Suba
Permanent teeth injuries and care	Ildikó Tarján

Study of the molecular regulation of epithelial ion and fluid secretion

Gábor Varga

Progenitor cells of oral origin, signals and scaffolds for foundation of tissue engineering applications

Gábor Varga

A human salivary gland model to study the molecular mechanisms of epithelial differentiation and for the development of gene implantation techniques

Gábor Varga

Investigation of pediatric disease related orofacial disorders

András Végh

Laser assisted decontamination of the implant surface in the surgical treatment of peri-implantitis

Péter Windisch

Salivary gland research

Tivadar Zelles

### ***Ph.D. students***

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Edina Erőss	pt
Sándor Farkasdi	ft
Laura Ferenczi	ft
Karola Kálló	ft
Koppány Kiss	pt
Márton Kivovics	pt
Mercedes Linninger	pt (a)
Ádám Lőrincz	ft
Szilvia Mihályi	ft
Reza Mortazavi	it
Katalin Perczel-Kovács	ft
Farhad Motae Samy	it
Kata Ágnes Sasvári	pt
László György Schmideg	pt
Péter Stiedl	ft

### ***Ph.D. candidates***

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Ildikó Faragó	na
Márta Fülöp Papp	ft
Milán Gyurkovics	ft
Attila Horváth	ft
Máté Jász	pt
Bálint Molnár	pt
Krisztián Nagy	na
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### ***Supervisors***

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András Végh
Gábor Varga
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József Barabás
Zsuzsanna Suba
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György Szabó
József Barabás
Péter Hermann
István Gera

### ***Supervisors***

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Gábor Varga
Gábor Varga
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Zsuzsanna Suba



**Ph.D. graduates**

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**Supervisors**

Péter Hermann  
József Barabás

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**Abstracts of Ph.D. theses successfully defended in 2011****JUDIT BORBÉLY (2011)****Evaluation of visual and instrumental tooth shade determination techniques**

Supervisor: Péter Hermann

Correct shade determination and communication are essential to success of a restoration. Routine clinical shade match, the method of comparing the tooth with shade tabs is subjective with not always quite controlled conditions and methods. Color matching is complicated by individual differences in color perception of even those dentists with normal color vision. The frequency of red-green color vision deficiency is reported 6-14% among dentists and dental students.

Toothguide Trainer (TT) computer program and Toothguide Training Box (TTB) electro-mechanical device are part of an educational program and used as teaching-learning aid for tooth shade selection. TT and TTB were used to evaluate how gender, experience, red and green color vision deficiency and training influences color matching results. In our study, that was simultaneously performed at 15 universities located in 9 countries, among dentists and dental students with normal color vision and color vision deficiency (CVD), females achieved significantly better shade matching results than males, indicating that gender plays an important role in shade matching. The experience was not found to be significant factor in shade matching. Our preliminary study found that red-green CVD influences color matching results. To measure how individual tooth color matching results by severe red (protanopy) and green (deutanopy) vision deficiency influenced, we used a CVD simulation monitor. Severe green color deficient display mode of the monitor resulted in significantly worse color matching quality. Experience improved shade matching quality as training with TT lead to statistical significant improvement in students' shade matching results.

Screening of dental students for red-green CVD should be used on a routine basis in dental schools. CVD dentists are just as much responsible for shade match of restorations as their color vision normal colleagues. By taking advantage of combination of visual methods and technology-based instrumentation the subjectivity of visual color assessment can be minimized and accurate color analysis for restoration's shade is more easily communicated. Predictable esthetic outcome can be achieved through a well built shade matching protocol, that is using a combination of digital shade measurement techniques, visual shade match and reference photography.

- Borbély J, Varsányi B, Fejérdy P, Hermann P, Jakstat HA: Toothguide trainer tests with color vision deficiency simulation monitor. *J Dent* 2010; 38(Suppl 2):41-49.
- Haddad HJ, Jakstat HA, Arnetz G, Borbély J, Vichi A, Dumfahrt H, Renault P, Corcodel N, Pohlen B, Marada G, de Parga JA, Reshad M, Klinke TU, Hannak WB, Paravina RD: Does gender and experience influence shade matching quality? *J Dent* 2009; 37(Suppl 1):40-44.
- Bratner SR, Vichi A, Borbély J, Jakstat HA: Der Ishihara-Test als Beamprojektion zum Screening der Farbtüchtigkeit in der Zahnmedizin. *Dtsch Zahnärztl Z* 2010; 65:29-33.

**ATTILA ZSOLT SZŰCS (2011)****Biomechanical possibilities of modelling the jaws. A biomechanical and clinical study of the shape and loading of oral implants***Supervisor: József Barabás*

Based on the clinical study data were acquired concerning the quantitative characteristics of dental implants. This helps the evaluation of early loading as well as it can give a limited prognosis of unfavourable changes in osseointegration, the possible defects of prosthetic components, thus helping the prevention of complications. Implants of various geometries were examined with the photoelastic and the finite element methods. The stress transmission of step design implants and implants with various thread designs. Conclusions were drawn concerning the implant shape with favourable stress transmission characteristics. A software was developed for the finite element modelling of threads and the surrounding bone. The notion of porosity was introduced to model spongy bone by adding random holes to the finite element network. A method to ameliorate the computer based modelling of the jaws was developed. It is capable of creating the 3D finite element network based on a volume tomographic dataset. The biomechanical properties of jaw models of various ages were characterised. This method can serve as a basis for further simulation studies in oral surgery, thus for modelling various jaw defects and their surgical treatment or reconstruction devices. Creating an individual treatment and surgical plan corresponding to individual mechanical conditions will become possible in patient care. Optimizing the placement of dental implants becomes a possibility according to biomechanical points of view. To present surgical simulation methods, the effects of various techniques of removing unerupted third molars on the mandible on the stresses emerging on the jaw were analysed thus demonstrating the possibility of screening patients for an increased risk of mandibular fracture. Laboratory fatigue tests were performed and suggestions were made to choose plastic materials suitable for stress absorbent on the implants and a difference was shown between the various implant thread types. The mechanical solidity of temporary titanium implants was examined in a binding test and recommendations were made for the design of the cervical part of the implant to prevent fracture.

- Szűcs A, Divinyi T, Koppány F, Bujtár P, Veres D, Barabás J: *Fogászati implantátumok csontintegrációjának klinikai vizsgálatával szerzett tapasztalataink. Fogorv Szle 2011; 104:55-62.*
- Szűcs A, Bujtár P, Sándor GK, Barabás J: *Finite element analysis of the human mandible following third molar removal. J Can Dent Assoc 2010; 76:a72.*
- Szűcs A, Divinyi T, Bujtár I, Polgár K, Nasztanovics F, Füstös A, Lőrincz Á, Babarabás J: *Fogászati implantátumok mechanikai feszültség átadásának biomechanikai vizsgálata végelelemes analízissel. II. rész Vizsgálatok. Fogorv Szle 2009; 99:187-193.*

**PROGRAM 2/6.****CLINICAL HAEMATOLOGY****Coordinator:****Lídia SRÉTER M.D., Ph.D., D.Sc.**

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**Program Overview:** Studies about the prognostic factors and complex therapies of haematologic disorders can contribute to more efficient treatment of this patient group. The role of infectious agents and environmental factors in the etiology of malignant lymphomas is a very interesting and up to date field of research (e.g.: post-transplantation. We will study the diagnostic use of the methods of modern molecular biology and its efficiency in the follow-up control of our patients, too. The pathogenesis of the thrombosis in malignancies and the frequency of the cytokine gene-polymorphism and p53 mutations and their therapeutic importance. The pathophysiological bases of the plasma cell-dyscrasies and their therapeutic implications are also part of our research. The bone marrow transplantation was a breakthrough in the therapy of the malignant diseases. The hemopoietic stem cell transplantation can be a model of the immunotherapy, and it may be studied well. The connection of the specific immunological state after transplantation with the complications of the transplantation, with the relapse of the disease and with the survival is still subject of investigation even nowadays. The course of the development of the immunological tolerance after allogeneic transplantation is still unknown either. The investigation of the haematologic disorders can be the subject of the research, which belongs to the scientific bases of the public health priorities because of the high frequency of oncohaematological disorders.

***Titles of research project***

Clinical and molecular haemostasis research

Role of cytokine DNA polymorphisms in the pathogenesis of malignant hematological diseases

Myeloproliferative disorders and their familial aspects

Immunohaematological aspects of malignant lymphomas

Role of growth factors and their receptors in the regulation of the development and destruction of lymphoma cells

Possibilities of individualized therapy in pediatric malignancies

The possible role of neutrophil granulocytes in thrombosis associated to neoplastic diseases

Study of liver injury following allogeneic and autologous bone marrow transplantation: Role of toxic and immunological factors

Prognosis and treatment of malignant hematologic diseases

Clinical administration of hematopoietic stem cells

***Supervisors***

Imre Bodó

Judit Demeter

Judit Demeter

Judit Demeter

László Kopper

Gábor Kovács

Raymund Machovich

Tamás Masszi

Tamás Masszi

Tamás Masszi

Human stem cell-membranetransport proteins and their alterations during cell differentiation	Balázs Sarkadi
Study of structure-function linkage in human ABC membranetransport proteins	Balázs Sarkadi
Role of growth factors and their receptors in the regulation of the development and destruction of lymphoma cells	Anna Sebestyén
Role of infectious agents and environmental factors in malignant lymphoid tumors	Lídia Sréter
Role mesenchymal stem cells in the regulation of immune processes	Ferenc Uher
Mesenchymal stem cells and regenerative medicine-stem cell therapy in type 1 diabetes	Ferenc Uher

***Ph.D. students***

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Olivér Tamás Eipel	ft
Anikó Fodor	ft
Beáta Hegyi	ft
Anita Kern	pt
Naeim Naghizadeh	it
Péter Prekopp	pt
Bernadett Sági	ft
Andrea Várkonyi	pt

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Gábor Kovács
Judit Demeter
Ferenc Uher
Judit Demeter
Lídia Sréter
Lídia Sréter
Ferenc Uher
Imre Bodó

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Márta Zubreczki-Hegyi	ft
Karolina Nemes	ft
János Sinkó	na

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Tamás Masszi
Gábor Kovács
Monika Csóka
Tamás Masszi

***Ph.D. graduates***

Adrienn Mohl	na
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***Supervisors***

Imre Bodó
-----------

pt, part-time; ft, full-time; na, not affiliated

***Abstract of Ph.D. thesis successfully defended in 2011*****ADRIENN MOHL (2011)****The molecular pathogenesis of type 3 von Willebrand disease in Hungary: details of the Hungarian mutation and alloantibody formation**

*Supervisor: Imre Bodó*

We report the genetic defects of virtually the entire type 3 population in Hungary. We performed the direct DNA sequence analysis of virtually the Hungarian type 3 VWD population. In addition, detailed clinical, laboratory and genealogical data were collected. Like

previously reported populations, genetic defects of the Hungarian cohort were found to be heterogeneous, but interestingly, we found a common new large deletion. The whole deletion resulted in the loss of 35 540 bp, including VWF exons 1, 2 and 3 (delExon1-3). Five patients carried the deletion in homozygous and 2 patients in compound heterozygous form, representing 25% (12/48) of all type 3 alleles. Sequence analysis of the deletion showed Alu repetitive elements at the breakpoints. The deletion is suspected to have resulted from an illegitimate homologous recombination event between the Alu sequences. Besides, 14 novel mutations were identified in 30 alleles. Five being nonsense mutations, 4 frameshifts, 3 missense and 1 candidate splice site mutation. 6 previously described mutations were detected in 16 alleles, including c.2435delC, frequently found in several European populations, representing 12.5% (6/48) of type 3 VWD alleles. Together delExon1-3 and c.2435delC were detected in 37.5% of all type 3 alleles, offering a rational approach to genetic testing. One patient developed an inhibitor to VWF (incidence: 4.2%, 1/24), who carried the homozygous c.3622delT mutation. In contrast to several previous reports, none of the patients homozygous for the large deletion developed alloantibodies to VWF. The reason for this discrepancy is not known, but it may indicate selection bias in some of the previous reports. In addition, we report several new mutations that may open new windows on VWF biology.

- Mohl A, Boda Z, Jäger R, Losonczy H, Marosi A, Masszi T, Nagy E, Nemes L, Obser T, Oyen F, Radványi G, Schlammadinger Á, Szélessy Zs, Várkonyi A, Vezendy K, Vilimi B, Schneppenheim R, Bodó I: Common large partial VWF gene deletion does not cause alloantibody formation in the Hungarian type 3 von Willebrand disease population. *J Thromb Haemost* 2011; 9:945-952.
- Mohl A, Marschalek R, Masszi T, Nagy E, Obser T, Oyen F, Sallai K, Bodó I Schneppenheim R: An Alu-mediated novel large deletion is the most frequent cause of type 3 von Willebrand disease in Hungary. *J Thromb Haemost* 2008; 6:1729-1735.
- Gézsi A, Budde U, Deák I, Nagy E, Mohl A, Schlammadinger A, Boda Z, Masszi T, Sadler JE, Bodó I: Accelerated clearance alone explains ultra-large multimers in von Willebrand disease Vicenza. *J Thromb Haemost* 2010; 8:1273-1280.

## **PROGRAM 2/8.**

### **PHYSIOLOGY AND PATHOLOGY OF THE MUSCULO-SKELETAL SYSTEM**

#### **Coordinator:**

**Miklós SZENDRŐI M.D., Ph.D., D.Sc.**

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**Program Overview:** The Ph.D. Program is designed for medical doctors who wish to be specialized in basic science and clinical research of musculoskeletal medicine, orthopaedics, trauma surgery and rheumatology. Our aims are: to provide medical and science based students with comprehensive knowledge in the field of orthopaedics and trauma surgery, and rheumatology, and surgery of the bone and soft tissue tumors, to provide suitable environment for clinical or biomechanical laboratory based research projects, to en-

able students for the use of laboratory techniques such as classical histology, immuno-histochemistry, collagen typisation and to train students in modern biomechanical laboratory techniques, as gait analysis.

***Titles of research project Supervisors***

Articular sportinjuries of the knee	István Berkes
Development of assistive products for persons with mobility impairments	Péter Cserháti
Measurement in rehabilitation medicine	Zoltán Dénes
Application of high technology in rehabilitation	Gábor Fazekas
Role of psychosocial factors in the rehabilitation of patients with bone fracture due to osteoporosis	Gábor Fazekas
Clinical and experimental examination of treatment options in injuries of the articular loaded surface	László Hangody
Effect of orthopedic abnormalities and injuries on movement - Orthopedic movementanalysis	Rita Kiss
Migration of totaljoint replacement investigated by using radiostereophotogrammetric analysis	Jenő Kiss
Importance of secondary conditions in the physical and rehabilitation medicine process	Lajos Kullmann
Infection and autoimmunity in inflammatory diseases of the joints	Gyula Poór
Examination of synovial sarcoma SYT-SSX fusion gene products in tissue cultures and xenografts	Zoltán Sági
Clinical oncology in bone and soft tissue tumors	Miklós Szendrői
Non-surgical treatments of juvenile and aneurysmal bone cysts: Sclerotization, cyst modelling and examination of cyst remodelling	Miklós Szendrői
Quality of life after the complex therapy of bone tumors	Miklós Szendrői
Occurrence and treatment (minimal surgical interventions) of bone metastases	Miklós Szendrői
Recidival tumor forming ability, malignization in borderline bone tumors	Miklós Szendrői
Examination of prognostic factors in certain bone tumors	Miklós Szendrői
Replacement options in extensive bone defects, comparative study of massive osteochondral homografts, autografts, endoporthesis	Miklós Szendrői
Biomechanical effect of percutaneous vertebroplasty in osteoporotic vertebral fractures on the neighbouring vertebrae: clinical and laboratory investigations	István Szikora
Histological and kinetic alterations in diseases and developmental disorders of the locomotor apparatus	György Szőke



**Ph.D. students**

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György Hangody	ft
László Rudolf Hangody	ft (a)
Gergely Holnapy	pt
Nikoletta Judit Horváth	pt
Dénes Horváthy	ft
Lőrinc Ijjas	ft
Andrea Katalin Kovács	ft
Bernadett Német Kertészne	pt
Mariann Kiss-Polauf	pt (a)
Zoltán Oláh	pt
Orsolya Péter	pt
Kálmán Rábai	pt
Károly Schandl	pt
Zsolt Szövérfi	ft
Mária Takács	pt
Dóra Végyári	ft
Katalin Zsiga	pt

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Kristóf Andrónyi	pt
Sándor Berki	na
Tamás Bodzay	na
István Béla Bors	pt
Gyula Domos	ft

**Ph.D. graduates**

Tamás Lőrincz	na
---------------	----

**Supervisors**

Gyula Poór
Zoltán Sági
György Szőke
György Szőke
Rita M. Kiss
György Szőke
Zsombor Lacza
György Szőke
Zoltán Dénes
György Szőke
Jenő Kiss
Miklós Szendrői
Gábor Fazekas
Péter Cserháti
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Gábor Fazekas

**Supervisors**

Gábor Krakovits
György Szőke
László Hangody
Rita M. Kiss
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**Supervisors**

Miklós Szendrői
-----------------

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**Abstract of Ph.D. thesis successfully defended in 2011****TAMÁS LŐRINCZ (2011)****Studies on angiogenic characteristics of bone metastases of human tumours and their modelling in vivo**

*Supervisor: Miklós Szendrői*

Bone metastases are frequent manifestations of malignant tumours, causing significant clinical problems which are associated with increased mortality and decreased survival. One key element of bone metastasis formation is the development of tumour vasculature. During our work the vessel density of human breast, renal and lung cancers was determined, and we have also examined the expression of VEGF, a pro-angiogenetic factor effective in the bone metastases of breast cancers. We have demonstrated that in the bone metastases of human carcinomas the vessel density changes, the direction of change de-

depends on the histological type: correlated to the primary tumour, the vessel density characteristically decreases in the bone metastases of renal cell cancers, increases in case of pulmonary adenocarcinomas, and in case of breast cancers we have determined that these changes are also influenced by chemo/endocrine therapy. In the second part of our work we have examined the expression and gene amplification of HER2/neu oncoprotein, serving also as therapeutic targets, in human bone metastasis samples. Where it was possible, the HER2/neu oncoprotein expression and gene amplification of the bone metastasis was also compared with the primary tumour expression and gene amplification patterns. The HER2/neu expression of primary breast cancers was associated mainly with visceral metastasis formation, but we have demonstrated that the HER2/neu overexpression and/or gene amplification occurred with 10% frequency in bone metastases which draws the attention to the possibility of targeted therapy in bone manifestations. We have exhibited that in certain cases the HER2/neu overexpression phenotype and genotype mislay in the bone metastases, that could be the explanation for the resistance against the therapy for HER2/neu oncoprotein therefore the repeated diagnostic process of metastases may be reasonable. We have studied in vivo the bone colonisation ability of human tumour cells, and with the use of human bone we have established a model that is appropriate for studying the interaction between the human tumour cell and human bone in vivo.

- Lőrincz T, Tóth J, Badalian G, Tímár J, Szendrői M: *Her2/neu genotype of breast cancer may change in bone metastasis*. *Pathol Oncol Res* 2006; 12:149-152.
- Lőrincz T, Tóth J, Szendrői M, Tímár J.: *Microvascular density of breast cancer in bone metastasis: influence of therapy*. *Anticancer Res* 2005; 25:3075-3081.
- Lőrincz T, Tímár J., Szendrői M.: *Alteration of microvascular density in bone metastases of adenocarcinomas*. *Pathol Oncol Res* 2004; 10:149-153.

## **PROGRAM 2/9.**

### **PULMONOLOGY**

#### **Coordinator:**

**György LOSONCZY M.D., Ph.D., D.Sc.**

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**Program Overview:** The subject of pulmonology comprises diseases of major public health importance, ie. chronic obstructive lung disease (affecting 3-5% of the adult population), bronchial asthma (200 000 patients in Hungary), lung cancer and tuberculosis. This Program offers research opportunities and advanced training for physicians interested in pulmonological science. The 8 subprograms cover the major areas of respiratory research and students will acquire specialized clinical skills, physiology, microbiology, biochemistry and molecular biology laboratory experience. In addition, the Program offers comprehensive courses in clinical pulmonology and basic science.

#### ***Titles of research projects***

Non-invasive investigation of airway inflammation in pulmonary diseases

#### ***Supervisors***

Balázs Antus

The role of TNFX promoter polymorphism and anti Hsp 70 antibody in the development and prognosis of lung cancer	Zoltán Bártfai
Molecular immunologic characterization of BAL monocytes	András Falus
Animal experimental modelling of emphysema.	Zoltán Hantos
Study of pulmonary mechanics	Zoltán Hantos
Pharmacology and role of inhalational drugs in the treatment of diseases of airway inflammatory diseases	Gábor Horváth
Non-invasive investigation of airway inflammation in pulmonary diseases	Ildikó Horváth
The activity, role and the interaction of enzyme systems in allergic bronchospasm	Márk Kollai
Lung tumors	László Kopper
Natural killer (NK) T lymphocytes in airway inflammation	György Losonczy
Examination of novel tyrosine kinase inhibitory molecules with selective antitumoral activity, modelling of relations between structure and biological action	György Mészáros
Prognostic and predictive factors in lung cancer	Judit Moldvay
Lower respiratory tract infections	Ferenc Rozgonyi
Mechanism and clinical significance of angiogenesis and lymphangiogenesis in lung cancer	Balázs Döme
Application of molecular epidemiological methods in the clinical practice of tuberculosis	Ákos Somoskövi
Diagnosis and therapy of endobronchial diseases. Interventional pulmonology	János Strausz
Asthma in pregnancy	Lilla Tamási

**Ph.D. students**

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András Kállai	pt

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Anikó Bohács	na
János Fillinger	na
Réka Gajdócsi	na
Krisztina Gál	pt
Tamás Tompos	pt
Zsóka Weiszhár	pt

**Ph.D. graduates**

György Lang	na
Zsófia Lázár	ft
Zsuzsanna Orosz	na

**Supervisors**

Judit Moldvay
Zoltán Hantos

**Supervisors**

Ildikó Horváth
György Losonczy
Balázs Antus
Ildikó Horváth
Veronika Müller
György Losonczy
Ildikó Horváth

**Supervisors**

Balázs Döme
Ildikó Horváth
Zoltán Bártfai

pt, part-time; ft, full-time; na, not affiliated

## ***Abstracts of Ph.D. theses successfully defended in 2011***

**GYÖRGY LANG (2011)**

### **Restitution of impaired lung allograft function with extracorporeal membrane oxygenation (ECMO)**

*Supervisor: Balázs Döme*

Lung transplantation remains the only therapeutic approach for several end stage lung diseases. The main cause for perioperative mortality is PGD. Author introduced lung retrieval in Hungary, and is performing lung transplantation for Hungarian citizens in the assigned transplant centre in Vienna.

According to our clinical experience, prolonged postoperative veno-arterial (v/a) ECMO support can prevent PGD, and with the preemptive use of ECMO we have seen excellent initial graft function even with the use of very marginal donor organs. Our hypothesis was, that controlled reperfusion and sparing ventilation provided by v/a ECMO favorably contributes for recovery after lung injury.

Therefore, we decided to test the validity of the hypothesis, in a standardized experimental model of severely injured lung allografts. Lung damage in our model was caused by a long cold ischemic period in lungs that were “triggered” by brain death. Development of severe PFG becomes an inevitable consequence under conventional implantation strategies. Transplantation on v/a ECMO and prolongation of this support through a 22 hours period of reperfusion not only maintains hemodynamical and oxygenatory stability during this critical period of time, but even more, directly contributes to improved recovery after lung injury due to brain death and long ischemic time by these two factors: reduction of pulmonary artery flow and avoidance of harmful ventilator settings, and thus provides for excellent graft function.

We concluded, that the importance of reperfusion conditions after lung transplantation and the length of the critical time period have been underestimated so far. However, the exact time period needed for lung recovery due to ischemic injury remains undefined. Obviously, it clearly exceeds the always described period of the first 10 to 15 minutes after transplantation. Based on our clinical and experimental experience, this time period should be 8-12 hours, if dealing with early signs of PGF and using v/a ECMO in a pre-emptive manner, and between 24-48 hours, if treating manifest PGF. In order to avoid further damage from barotrauma and hemodynamic instability from maximal ventilatory support, v/a ECMO should be applied early in the course of lung dysfunction after transplantation.

Our results contribute to additional safety for transplantation of marginal donor lungs, and therefore might help to expand the current organ donor pool. The suggested prolonged controlled reperfusion and protective ventilation strategies provide a valuable addition to the current worldwide efforts of ex vivo reconditioning of donor lungs.

- Pereszlényi A, Lang G, Steltzer H, Hetz H, Kocher A, Neuhauser P, Wisser W, Klepetko W: Intra- and postoperatively prolonged ECMO support for LTX in patients with pulmonary hypertension. *Eur J of Cardiothorac Surg* 2002; 21:858-863.
- Aigner C, Wisser W, Taghavi S, Lang G, Jaksch P, Czyzewski D, Klepetko W: Institutional experience with extracorporeal membrane oxygenation in lung transplantation. *Eur J Cardiothorac Surg* 2007; 31:468-473.
- Lang G, Aigner C, Winkler G, Shkirdladze K, Wisser W, Dekan G, Tamura M, Heinze G, Van Raemdonck D, Klepetko W: Prolonged venoarterial extracorporeal membrane oxygenation after transplantation restores functional integrity of severely injured lung allografts and

*prevents the development of pulmonary graft failure in a pig model. J Thorac Cardiovasc Surg 2009; 137:1493-1498.*

## ZSÓFIA LÁZÁR (2011)

### The role of purinergic system in airway diseases

*Supervisor: Ildikó Horváth*

It has been suggested that extracellular ATP – as a signalling molecule – might play a role in the pathogenesis of COPD and asthma. ATP can be involved in triggering and maintaining airway inflammation, inducing bronchoconstriction, however, compelling human evidence is lacking.

The collection of exhaled breath condensate (EBC) is an easy and non-invasive mode of sampling the airways. EBC contains droplets from the airway lining fluid (ALF), and EBC analysis provides information about physiological and pathophysiological processes in the airways. ATP concentration in EBC has not been measured before. We reported a luminescent method to successfully measure EBC ATP concentration and demonstrated that ATP in the condensate fluid is mainly derived from the lower airways. No difference was found in EBC ATP concentration between patients with acute hypoxic exacerbation of COPD or stable asthma and relevant control subjects. We found that the improvement of blood oxygenation and clinical condition in COPD or the level of disease control and airway inflammation in asthma do not influence EBC ATP concentrations. The dilution of droplets from the ALF highly influences EBC ATP concentration. The calculated airway ATP concentration is similar in asthmatic patients and healthy controls, and shows a positive correlation to airway resistance.

ATP measured in EBC cannot be considered as a marker for COPD or bronchial asthma but airway ATP might be involved in the regulation of airway calibre. ATP concentration measured in EBC is in close correlation with the extent of the dilution of the airway lining fluid. Hence the assessment of respiratory droplet dilution in the condensate fluid might also be of importance for other biomarkers measured in EBC. Although our work highlights that EBC ATP cannot be used in the diagnostics of COPD and asthma, our results also imply that further methodological improvements of assessing dilution in EBC might aid better understanding of airway processes and pave the way for new perspectives in the non-invasive monitoring of airway diseases.

- Lazar Z, Cervenak L, Orosz M, Galffy G, Komlosi ZI, Bikov A, Losonczy G, Horvath I: Adenosine triphosphate concentration of exhaled breath condensate in asthma. *Chest* 2010; 138:536-542.
- Lazar Z, Huszár E, Kullmann T, Barta I, Antus B, Bikov A, Kollai M, Horvath I: Adenosine triphosphate in exhaled breath condensate of healthy subjects and patients with chronic obstructive pulmonary disease. *Infl Res* 2008; 57:367-373.

## ZSUZSANNA OROSZ (2011)

### Cigarette smoke-induced pro-inflammatory alterations in the endothelial phenotype, the protective effect of resveratrol

*Supervisor: Zoltán Bártfai*

Although the cardiovascular morbidity and mortality induced by cigarette smoking exceeds the numbers of lung cancer related death, the molecular basis of smoking-induced

vascular injury remains unclear. Epidemiological studies suggest that Mediterranean diets rich in resveratrol are associated with reduced risk of vascular diseases. To test the link between cigarette smoke, oxidative stress and vascular inflammation, rats were exposed to cigarette smoke of 5 cigarettes per day (for one week) or isolated arteries were exposed to cigarette smoke extract (CSE) in organoid culture. Carotid arteries isolated from control rats and cigarette smoke exposed rats NO-mediated flow-induced dilatation was measured by videomicroscopy. Arterial O<sub>2</sub>- was measured by lucigenin chemiluminescence and ethidium bromide fluorescence method. Arterial H<sub>2</sub>O<sub>2</sub> production was measured by C-H<sub>2</sub>DCFDA fluorescent method and modified method of Werner. The expression of proinflammatory cytokines and iNOS were assessed by quantitative RT-PCR. In separate experiments we evaluated whether resveratrol inhibits TNF- $\alpha$ -induced signal transduction in human coronary arterial endothelial cells (HCAECs). Cigarette smoke impaired acetylcholine-induced relaxations of carotid arteries, which could be improved by the inhibition of NAD(P)H oxidase. Lucigenin chemiluminescence measurements and dihydroethidine staining showed that both smoking and in vitro CSE exposure significantly increased vascular O<sub>2</sub>- production. CSE also increased vascular H<sub>2</sub>O<sub>2</sub> production. Vascular mRNA expression of the pro-inflammatory cytokines and iNOS was significantly increased by both smoking and CSE exposure, which could be prevented by inhibition of B activation and NAD(P)H. In cultured endothelial cells CSE elicited NF- $\kappa$ B increased monocyte adhesiveness, which were prevented by apocynin and catalase. In TNF- $\alpha$ -treated HCAECs, resveratrol (in the submicromolar range) significantly attenuated expression of NF- $\kappa$ B-dependent inflammatory markers like iNOS. All these changes suggest that water soluble components of cigarette smoke (that are likely to be present in the bloodstream in vivo in smokers) elicit a pro-inflammatory shift in vascular phenotype and activate the vascular NAD(P)H oxidase. NAD(P)H B leading to pro-inflammatory oxidase-derived H<sub>2</sub>O<sub>2</sub> activates NF- $\kappa$ B alterations in vascular phenotype, which likely promotes development of atherosclerosis, especially if other risk factors are also present. Resveratrol at nutritionally relevant concentrations inhibits B activation and inflammatory gene expression and  $\kappa$ TNF- $\alpha$ -induced NF- $\kappa$ B attenuates endothelial activation.

- Orosz Z, Csiszar A, Labinskyy N, Smith K, Kaminski PM, Ferdinandy P, Wolin MS, Rivera A, Ungvari Z: Cigarette smoke-induced proinflammatory alterations in the endothelial phenotype: role of NAD(P)H oxidase activation *Am J Physiol Heart Circ Physiol* 2007; 292:130-139.
- Ungvari Z, Orosz Z, Rivera A, Labinskyy N, Xiangmin Z, Olson S, Podlutzky A, Csiszar A: Resveratrol increases vascular oxidative stress resistance *Am J Physiol Heart Circ Physiol* 2007; 292:2417-2424.
- Csiszar A, Smith K, Labinskyy N, Orosz Z, Rivera A, Ungvari Z: Resveratrol attenuates TNF-alpha-induced activation of coronary arterial endothelial cells: role of NF-kappaB inhibition *Am J Physiol Heart Circ Physiol* 2006; 291:1694-1699.



**PROGRAM 2/10.****OPHTHALMOLOGY*****Coordinator:*****Ildikó SÜVEGES M.D., Ph.D., D.Sc.**

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**General Overview:** Vision is essential for human life, but not endangered by several frequent eye diseases, the treatment of which has not been completely established. The Ph.D. Program in Ophthalmology addresses the pathophysiology and pathology of the most important eye diseases. The research projects cover the diseases of the light refractive media of the eye, the biochemical and histological alterations important for vision, and the experimental models of the ocular alterations. Ocular blood flow and aqueous humour dynamics are especially important topics of the Ph.D. School. Glaucoma, one of the blinding eye diseases with the highest prevalence is investigated with special emphasis.

***Titles of research projects***

Physiology and pathophysiology of the neuroretina in certain diseases, especially in hereditary retinal diseases

Clinical - biological - imaging examinations of retinal ganglion cell apoptosis in glaucoma

Wound healing of the cornea especially in refractive surgical procedures

Biomechanical examination of the anterior lens capsule

Eye-surface in normal and pathologic conditions

Investigation of the pathophysiology of macula using imaging techniques

Physiology and pathophysiology of vision. The topics include the examination of the refractive layers of the bulb in pathologic conditions and the follow-up of lesions occurring in diseases of the eye

In vitro culturing of corneal limbal stem cells and examination of their potential in clinical application

Electrophysiology and genetics in ophthalmology

***Supervisors***

Ágnes Farkas

Gábor Holló

Zoltán Zsolt Nagy

Zoltán Zsolt Nagy

János Németh

Gábor Somfai

Ildikó Süveges

Nóra Szentmáry

Balázs Varsányi

***Ph.D. students***

Zsuzsanna Antus

pt

Mohammad Ebadi

it

Saeid Ebadi

it

Anna Énzsöly

ft

Éva Juhász

ft

Farzaneh Naghizadeh

pt

Gábor László Sándor

ft

Ágnes Ildikó Takács

ft (a)

***Supervisors***

Ildikó Süveges

Ildikó Süveges

Ildikó Süveges

János Németh

Zoltán Zsolt Nagy

Gábor Holló

Zoltán Zsolt Nagy

Zoltán Zsolt Nagy

**Ph.D. candidates**

László Imre	na
Anita Garas	ft
Krisztina Kosina-Hagyó	ft
Ákos Kusnyerik	ft
Olga Lukáts	na
Kata Miháltz	na
Miklós Schneider	na
Ágnes Ildikó Takács	ft (a)
Erika Tátrai	ft

**Supervisors**

Ildikó Süveges
Gábor Holló
János Németh
Ildikó Süveges
Zoltán Zsolt Nagy
Ildikó Süveges
Zoltán Zsolt Nagy
Gábor Márk Somfai

**Ph.D. graduates**

Mónika Ecsedy (Szabó)	na
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**Supervisors**

János Németh
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a, absolutorium; pt, part-time; ft, full-time; it, international; na, not affiliated

**Abstract of Ph.D. thesis successfully defended in 2011****MÓNIKA ECSEDY (SZABÓ) (2011)****New diagnostic and therapeutic methods in retinopathy of prematurity**

*Supervisor: János Németh*

**PURPOSE:** To find out the indications and timing of surgical intervention on eyes with aggressive posterior ROP, to improve poor outcomes of the traditional therapeutic methods. Investigation of longterm morphological and functional changes in children with a history of preterm birth, for better understanding of recently underlied subtle longterm vision in the sin letter acuity, and color vision alterations.

**METHODS:** For our retrospective review, we analysed the data of all consecutive cases (9 eyes of 7 children) with aggressive posterior ROP, that underwent early lens sparing vitrectomy in a four year period (2004-2008) in our Department.

In the prospective case-control randomised studies, patients with a history of preterm birth, 7 to 14 years of age were compared with age-matched full-term born children. Macular morphology was investigated with optical coherence tomography, and cone function with electrophysiological and psychophysical tests.

**RESULTS:** In 7 eyes vitrectomy, with gentle posterior hyaloid peeling, could stop the disease progression. In all of these eyes the operation was performed in stage 3 or 4A, two weeks earlier then in the group with unfavorable outcome (stage 4b). In the premature groups the mean values central retinal thickness were significantly graeter compared to controls. The ERG b-wave amplitudes were significantly lower in laser treated ROP eyes compared to controls, in the standard and S-cone single flash ERGs. The general estimating equation model statistics found a significant effect of prematurity on central retinal thickness and b-wave amplitudes.

**CONCLUSIONS:** Lens sparing vitrectomy with gentle posterior hyaloid peeling, in stage 4A at early postmenstrual ages (37-40 postmenstrual weeks) around the calculated delivery seems to be advantageous in infants with aggressive posterior ROP who failed previous laser treatment. In formerly preterm children a thicker foveal central region can be seen. Longterm functional deficits are also detectable in cone funtion in children with history of

preterm birth. The macular changes and the cone dysfunction affecting the inner retinal pathways, might be related mainly to prematurity and not to the severity of ROP.

- Ecsedy M, Szamosi A, Karkó C, Zubovics L, Varsányi B, Németh J, Récsán Zs: *A comparison of macular structure imaged by optical coherence tomography in preterm and full-term children. Invest Ophthalmol Vis Sci* 2007; 48:5207-5211
- Ecsedy M, Récsán Zs: *Posterior Hyaloid peeling in aggressive posterior ROP. Eur J Ophthalmol* 2011; 21:179-182.
- Ecsedy M, Varsányi B, Szigeti A, Szrnka Gy., Németh J, Récsán Zs: *Cone function in children with a history of preterm birth. Doc Ophthalmol* 2011; 122:141-148.

## **PROGRAM 2/12.**

### **CLINICAL AND EXPERIMENTAL RESEARCH IN ANGIOLOGY**

#### **Coordinator:**

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**Program Overview:** The education of clinicians and researchers having profound scientific background is the basic aim of the postgraduate Program, offering a possibility of research work on organ failures due to vascular disorders and of application of the results in the therapeutic processes. The study of the pathogenesis of the diseases of ischemic origin using the latest techniques is also part of the Program.

#### **Titles of research project**

Relations of arteriosclerosis and chronic uraemia

Overview and planning of clinical studies of therapeutic angiogenesis

Physiological and pathological adaptation of venous system in cases hemodynamical stress

Assessment, monitoring of cardiopulmonal perioperative risks and treatment options in cardiovascular surgical diseases

The role and problems of endovascular graft implantation in treatment of aneurysms

The role of genetic factors in restenosis

Complex examination of left ventricle aneurysm

Clinical use of homologous vessel transplantation and experimental research on vessel preservation

Examination of vessel structures infected by Chlamydia pneumoniae.

Molecular biological aspects of dilatative cardiomyopathy and myocarditis of viral origin

The Role of regulatory function of nociceptin in cardiovascular disease and its control.

#### **Supervisors**

György Acsády

György Acsády

György Acsády

János Gál

Kálmán Hüttl

István Karádi

Béla Merkely

Attila Nemes

Zsuzsa Schaff

Péter Sótónyi

Péter Sótónyi

Radiological investigation and geometric analysis of aortic aneurysms

Péter Sótónyi

Experimental vascular surgery - clinical application

Attila Szijártó

The cardiovascular effects of apelin

Miklós Tóth

#### ***Ph.D. students***

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Zsuzsanna Cserép	ft
Csaba Csobay-Novák	pt
Dávid Garbaisz	ft
Gergely Gósi	pt
Endre Németh	pt
Zoltán Oláh	pt

#### ***Supervisors***

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János Gál
Péter Sótónyi
Attila Szijártó
György Acsády
János Gál
György Acsády

#### ***Ph.D. candidates***

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Tamás Mirkó Paukovits	ft
Csanád Várallyay	ft

#### ***Supervisors***

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Péter Sótónyi
Attila Nemes
György Acsády
Kálmán Hüttl
Kálmán Hüttl

#### ***Ph.D. graduates***

Gábor Bíró	na
Zoltán Szeberin	pt
Gábor Viktor Szabó	pt

#### ***Supervisors***

Attila Nemes
György Acsády
György Acsády

part-time; ft, full-time; na, not affiliated

### ***Abstracts of Ph.D. theses successfully defended in 2011***

#### **GÁBOR BÍRÓ (2011)**

**The importance of biological grafts in the management of infrarenal prosthetic graft infections. Establish and operate a vascular homograft bank**

*Supervisor: Attila Nemes*

Prosthetic graft infection in the infrarenal aortoiliac and aortofemoral region is a major challenge in vascular surgery. The most common options include resection of the infected graft with oversewing of the aortic stump and extraanatomic bypass, in situ placement of an antibiotic soaked graft, deep venous reconstruction, or cryopreserved graft. Ex situ retroperitoneal aortic bypass and nonresectional strategies, such as antibiotic irrigation, are less commonly used. Recently an important issue is the long term durability and resistance to repeated infection of the various implanted graftmaterial. The objective of this work was to establish a homograft vessel bank for non-profit use and to investigate the late results of deep vein and homograft reconstructions in case of infrainguinal prosthetic graft infection. The Homograft Bank of the Semmelweis University, Department of Cardiovas-

cular Surgery procured 407 homografts. Between 01.07.1997-12.31.2008 226 grafts were implanted. Treatment indications included lack of proper veins in infrainguinal reconstructions in 106 patients, prosthetic graft infection in 51 patients, creation of A-V fistula in 8 patients, and aortocoronary bypass procedure in 11 patients. 33 patients were treated from 30.03.1994. to 01.09.2008. for aorto-femoral or iliaco-femoral prosthetic graft infections with homografts(HG) or autologous deep veins(DV). The diagnosis was based on physical signs, bacteriological tests and CT scans. We obtain cryopreserved homografts from the non-profit vessel bank; deep veins were harvested before the arterial reconstruction. Patients were followed by clinical examination and ultrasound. 45% of the infections were caused by Gram-negativ bacteria. Treatment indications included 7 aortoduodenal fistula (21.2%) and 6 septic bleedings (18.2%). There were 6 in-hospital deaths (18.2%). All the deceased patients had Gram-negativ bacteria in cultures and pluribacterial infections. No patient died with single staphylococcus, streptococcus or MRSA infection. At 3-year freedom from reinfection was 100% in DV group and 82% (CI:0.56-0.92) in the homograft group. Survival after 3 years was 71% (CI:0.48-0.88) in HG group and 79% (CI:0.49-0.94) in DV group. The difference is not significant. For infrarenal graft infection homograft replacement is as durable as deep vein implantation. The in-hospital mortality is significantly higher if Gram-negativ bacterias are involved.

- BÍRÓ G, Szeberin Z, Nemes A, Acsády Gy: Cryopreserved homograft and deep vein replacement for infrarenal aortofemoral and iliaco-femoral graft infection: Early and late results. *J Cardiovascular Surg* 2011; 52:169-176.
- BÍRÓ G, Szabó G, Fehérvári M, Münch Z, Szeberin Z, Acsády Gy: Late outcome following open surgical management of secondary aortoenteric fistula. *Langenbecks Arch Surg.* 2011; 396:1221-1229.
- Szeberin Z, BÍRÓ G, Szabó G, Százados M, Nemes B, Dzsini Cs: Aortobifemoralis graft készítése vena femoralis superficialisból. *Érbetegségek* 2007; 14:7-11.

## ZOLTÁN SZEBERIN (2011)

### Association of fetuin-A and arterial calcification in patients with peripheral vascular disease

Supervisor: György Acsády

Atherosclerosis may present with arterial calcification, which associates with increased cardiovascular morbidity and mortality. Fetuin-A (a systemic glycoprotein) plays role in the inhibition of extraosseal calcification. The low serum level of fetuin-A in end-stage renal disease patients is related to more severe arterial calcification and higher cardiovascular mortality. The aim of our study was to examine the potential role of fetuin-A in the inhibition of arterial calcification in a population with chronic, atherosclerotic peripheral disease without renal disease or infection. The presence of classic risk factors of atherosclerosis, the severity of arterial calcification and atherosclerosis assessed by ultrasound and angiography, and serum analysis was examined in a cross-sectional study of patients with carotid stenosis, aortic aneurysm and lower extremity atherosclerosis. We demonstrated that there is an inverse correlation between serum fetuin-A levels and the severity of arterial calcification in patients with chronic atherosclerotic lower extremity disease without renal disease or infection. This finding suggests that it is not end-stage renal disease and dialysis that explains the earlier reported association of low fetuin-A level and arterial calcification. The novel finding of our study was the significantly different serum fetuin-A level in patients with aortic aneurysm of different etiology (atherosclerosis and Marfan syn-

drome). The observed difference was emphasized by the results of comparing the aneurysm groups of patients with peripheral occlusive disease and healthy controls. We found that heat shock protein-70 serum levels significantly correlate with the degree of arterial calcification independently of fetuin-A and other atherosclerotic risk factors. Our results suggest that there is an association between serum fetuin-A levels and the severity of arterial calcification also in patients without renal failure. Our cross-sectional study design is not suitable for exploring the possible causative role of fetuin-A in developing arterial calcification or its potential role as a biomarker.

- Szeberin Z, Fehérvári M, Krepuska M, Apor A, Rimely E, Sarkadi H, Bíró G, Sótonyi P, Széplaki G, Prohászka Z, Szabolcs Z, Kalabay L, Acsády G: *Fetuin-A serum levels in patients with aortic aneurysms of Marfan syndrome and atherosclerosis. Eur J Clin Invest* 2011; 41:176-182.
- Krepuska M, Szeberin Z, Sótonyi P, Sarkadi H, Fehérvári M, Apor A, Rimely E, Prohászka Z, Acsády G: *Serum level of soluble Hsp70 is associated with vascular calcification. Cell Stress Chaperones* 2011; 16:257-265.

### GÁBOR VIKTOR SZABÓ (2011)

#### The role and importance of gene polymorphisms in the development of atherosclerosis

*Supervisor: György Acsády*

The development of the atherosclerosis is a multifactorial process. Except for the classical risk factors of the atherosclerosis (hypertension, lipid-metabolic disorders, diabetes, smoking) the clinical signs can be influenced by the genetic variants (polymorphisms) of the enzymes which are responsible for the endothelial cells function and for the thrombotic factors.

The purpose of the study was to examine three genetic polymorphisms playing a role in the metabolic processes.

In this examination 992 patients' data was analysed. We compared the data of 348 atherosclerotic non-diabetic patients and 260 atherosclerotic diabetic patients treated at the Cardiovascular Department of the Semmelweis University during a one- and-half-year period with the 384 healthy control samples. We analysed the frequency of myocardial infarction and stroke in the case of different polymorphisms in the atherosclerotic non-diabetic and atherosclerotic diabetic group, and it was compared to the healthy group. In this examination the planned aim was reached, positive correlations were proved in every group. It was verified that the lipid (LDL) level is higher in patients who underwent myocardial infarction than those without infarction (4,2 vs 2,7,  $p < 0,05$ ). It was also proved if the mutant TT eNOS Glu298ASP variant is present, the myocardial infarction is significantly higher than with patients carrying heterozygote GT and normal GG genotype (TT genotype: control group 5,7%, MI group 16,9%,  $p < 0,001$ , OR: 4,56). We proved that with mutant MTHFR 677CT heterozygote variant, the occurrence of myocardial infarction is significantly higher (CT allele: control group 32%, MI group 55,1%,  $p < 0,001$ , OR: 4,13) and in the relation of the 677TT homozygote variant the difference is also significant (TT variant: control group 10,9% MI group 21,2%  $p < 0,001$ , OR: 4,65). It was verified that among patients with the mutant TNF- $\alpha$  AA genotype the occurrence of cardiovascular events is significantly higher (AA allele: control group 1, 6%, MI group 10,7%,  $p < 0,005$ , OR: 8,17). Screening the endangered or genetically high risk groups is to be considered on the long run - an early detection of a susceptibility of the disease gives better chances for prevention



and treatment. Understanding the inflammatory mechanisms of the atherosclerosis gives new therapeutical targets to pharmacologists.

- Szabó GV, Kunstár A, Acsády Gy: *Methylentetrahydrofolate reductase and nitric oxid synthase polymorphysm in patients with atherosclerosis and diabetes. Pathol Oncol Res* 2009; 15:631-637.
- Szabó GV, Acsády Gy: *Tumornecrosis-factor- $\alpha$  308 GA Polymorphism in atherosclerotic patients. Pathol Oncol Res* 2011; 17:853-857.
- Hegymegi-Barakonyi B, Erős D, Szántai-Kis Cs, Breza N, Bánhegyi P, Szabó GV, Várkondi E, Peták I, Órfi L, Kéri Gy: *Tyrosine kinase inhibitors - Small molecular weight compounds inhibiting EGFR. Curr Opin Mol Ther* 2009; 11:308-321.

## **PROGRAM 2/13.**

### **HORMONAL REGULATORY SYSTEMS**

#### **Coordinator:**

**Károly RÁCZ M.D., Ph.D., D.Sc.**

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**Program overview:** There are numerous important interactions among the hormonal system and neural, immune and other regulatory mechanisms, by which hormones may influence the physiology or pathophysiology of organs or organ systems. The program includes research projects dealing with interactions between hormones and other regulatory mechanisms, such as neuroendocrine regulation of thyroid and gonadal function, and regulation of pituitary and adrenal hormone secretion. Other research projects include studies on the molecular mechanisms of hormone sensitivity, pathomechanism of metabolic bone disorders associated with endocrine disorders, hormonal disturbances associated with in-born metabolic errors, and the pathomechanisms of sporadic and hereditary adrenal and pituitary tumors.

#### ***Titles of research project***

##### ***Supervisors***

Effect of endocrine alterations on the epidemiology of certain diseases

Nándor Ács

Neurohormonal regulation of thyroid function

Csaba Balázs

Steroids as antioxidants

Gábor Békési

Neurohormonal interactions

Ida Gerendai

Functional genomic studies in the pathogenesis of adrenal tumors especially focusing on the expression of cytokines and their receptors

Péter Igaz

Micro-RNA studies in endocrine tumors

Péter Igaz

Disorders of genes encoding mitochondrial electron transport enzymes in tumors of the endocrine system

Attila Patócs

Evaluation of the role of the glucocorticoid receptor beta in gene transcription	Attila Patócs
Molecular mechanisms determining glucocorticoid sensitivity	Károly Rác
Interactions of regulatory mechanisms in diseases of the pituitary and adrenal glands	Károly Rác
The metabolism of reactive aldehydes in type 2 diabetes mellitus, and the effect of antidiabetic treatment on aldehyde metabolism	Péter Reismann
Clinical and pathophysiological studies in gynecological and reproductive endocrine disorders and in experimental models	János Rigó
The etiology and pathogenesis of endocrine diseases during pregnancy	Klára Rosta
Mechanisms of endocrine disease associated bone metabolism disorders	Miklós Tóth

**Ph.D. students**

Tamás Bence Ács	ft
Ildikó Adler	pt
Vanda Csiki	ft
Orsolya Hadarits	ft
Zoltán Kender	ft
Nikoletta Lendvai	ft
István Marczell	ft
Júlia Stark	ft
Diána Rita Szabó	ft
Zafar Ul Islam	it
Adrienn Zsippai	pt

**Ph.D. candidates**

Karolina Feldman-Kovács	ft
Márta Sereg	ft
Balázs Stenczer	ft

**Ph.D. graduates**

Belema Boyle	ft
Henriett Butz	ft
Zoltán Magyar	na
Péter Márton Szabó	ft
Ágnes Szappanos	ft
Zsófia Tömböl	ft

**Supervisors**

Attila Patócs
Gábor Békési
Nándor Ács
Klára Rosta
Péter Reismann
Attila Patócs
Gábor Békési
Gábor Békési
Péter Igaz
Gábor Békési
Péter Igaz

**Supervisors**

Attila Patócs
Miklós Tóth
János Rigó

**Supervisors**

Csaba Balázs
Károly Rác
Attila Patócs
Gábor Békési
Péter Igaz
Miklós Tóth
Péter Igaz

a, absolutorium; pt, part-time; ft, full-time; na, not affiliated

**Abstracts of Ph.D. theses successfully defended in 2011****BELEMA BOYLE (2011)****Role of glucocorticoids in certain endocrine diseases***Supervisor: Csaba Balázs*

In the first part of my work patients with Graves' orbitopathy (GO) and healthy Hungarian adults were genotyped for 4 polymorphisms of the glucocorticoid receptor (GR) gene to examine whether associations could exist between these polymorphisms and the development or clinical manifestations of GO. The carrier and allelic frequencies of the N363S, ER22/23EK, A3669G, and BclI polymorphisms were determined in 95 patients with GO and 160 healthy controls. No significant changes were found in carrier frequencies of the four polymorphisms between GO patients and healthy controls. However, when GO patients were divided into two subgroups (American Thyroid Association Committee, ATA I-II vs ATA III or greater), the frequency of the polymorphic BclI allele was significantly higher in patients with ATA I-II compared with those with ATA III or more. The significant association between the frequency of the polymorphic BclI allele and ATA stage distribution suggests that this polymorphism may affect clinical manifestations of GO, presumably due to an increased signaling of the GR. This may result in an increased sensitivity to endogenous glucocorticoids leading to a suppression of immune and inflammatory reactions. If the results will be confirmed in a larger group of patients, it is possible that BclI polymorphism will serve as a useful prognostic marker for the prediction of the severity of GO.

In the second part of my work GR $\alpha$  and GR $\beta$  mRNA expression was examined by quantitative real-time PCR in 31 adrenal tissues including 19 non-functioning adenomas, 6 cortisol-producing adenomas and 6 normal adrenocortical tissues. In addition, the presence and cellular localization of GR $\alpha$  and GR $\beta$  proteins in adrenal tissues were studied by immunohistochemistry. Compared to normal adrenocortical tissues, both GR $\alpha$  and GR $\beta$  mRNAs were significantly increased in cortisol-producing adenomas whereas GR $\alpha$ , but not GR $\beta$  mRNA expression was moderately but not significantly increased in non-functioning adenomas. The amount of GR $\alpha$  mRNA positively correlated with the amount of GR $\beta$  mRNA in both groups of adrenocortical adenoma tissues. Using anti-GR $\alpha$  antibody a strong nuclear staining was observed in non-functioning and cortisol-producing adenomas, and a less remarkable immunoreactivity was detected in some nuclei of normal adrenocortical cells. GR $\beta$  immunostaining was absent in normal adrenal tissues and non-functioning adenomas, while a strong cytoplasmic and nuclear immunoreaction was found in cortisol-producing adenomas. Altered expression of GR $\alpha$  and GR $\beta$  in cortisol-producing adenomas and that of GR $\alpha$  in non-functioning adenomas raises their possible role in the pathophysiology of these adrenal tumors, although further studies are needed to elucidate the potential significance of these findings.

- Boyle B, Korányi K, Patocs A, Liko I, Szappanos A, Bertalan R, Racz K, Balazs Cs: Polymorphisms of the glucocorticoid receptor gene in Graves' ophthalmopathy Br J Ophthalmol 2008; 92:131-134.
- Boyle B, Patócs A, Likó I, Bertalan R, Lendvai N, Szappanos Á, Butz H, Rácz K, Balázs Cs: A glukokortikoid-receptor gén polimorfizmusok szerepe autoimmun betegségekben Magyar Belorvosi Archivum 2008; 61:171-175.
- Boyle B, Butz H, Liko I, Zalatnai A, Toth M, Feldman K, Horányi J, Igaz P, Racz K, Patocs A: Expression of glucocorticoid receptor isoforms in human adrenocortical adenomas Steroids 2010; 75:695-670.

**HENRIETT BUTZ (2011)****Role of microRNAs in sporadic pituitary tumorigenesis***Supervisors: Károly Rácz, Attila Patócs*

The pathogenetic factors involved in the development of sporadic pituitary adenomas, especially in non-functioning adenomas (NFA) are poorly understood. The role of miRs in the pathomechanism of several other tumors has already been established. My Ph.D. work deals with microRNAs (miRs) that may have a role in the development of sporadic pituitary adenomas. During the course of my studies I characterized the miR expression profile of NFA samples and identified miRs which may have a pathogenetic role in these adenomas.

With the use of molecular and cell biological methods I identified two proteins (Wee1, Smad3) which are regulated by miRs in sporadic pituitary adenomas. I showed that Wee1 protein expression determined by immunohistochemistry was significantly lower in pituitary adenoma tissues compared to normal pituitary tissues, however, no difference between the two types of tissues was observed in Wee1 mRNA levels as measured by qRT-PCR. To examine the posttranscriptional regulation of Wee1 in silico target prediction experiments were performed and 5 miRs potentially targeting the Wee1 were selected for validation. Of the 5 miRs, 3 miRs targeting Wee1 3'UTR (miR-128a, 516a-3p and miR-155) were identified, and qRT-PCR analysis revealed that these miRs were overexpressed in NFA samples compared to normal pituitary tissues. Interactions between these 3 miRs and the Wee1 mRNA, as well as the exact binding sites of miRs were experimentally confirmed using dual-luciferase assay and site-directed mutagenesis. Finally, I showed that exogenous overexpression of these miRs inhibited Wee1 protein expression in HeLa cells.

With the analysis of miR expression profile of NFA tissues I was able to identify miRs whose expression correlated with the size of tumors. Using pathway analysis I showed that TGF $\beta$  signaling may have a role in the development of these adenomas. I found repressed signalling by Smad3 due to a significant underexpression of Smad3 caused by miRs in NFA samples. Overexpressed miRs which showed negative correlation with Smad3 mRNA expression and potentially targeted Smad3 3'UTR were identified. These miRs included miR-140-5p that has been already considered and experimentally validated by others to target Smad3. I conclude that miRs identified in my study may exert a regulatory role on the TGF $\beta$  pathway and this mechanism may participate in the development of pituitary adenomas.

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- Butz H, Likó I, Czirják S, Igaz P, Munayem Khan M, Zivkovic V, Bálint K, Korbonits M, Rácz K, Patócs A: Down-regulation of Wee1 kinase by a specific subset of microRNA in human sporadic pituitary adenomas. *J Clin Endocrinol Metab* 2010; 95:E181-191.
- Butz H, Likó I, Czirják S, Igaz P, Korbonits M, Rácz K, Patócs A: Downregulation of TGF $\beta$  pathway in non-functioning, sporadic pituitary adenomas revealed by microRNA profile. *Pituitary* 2011; 14:112-24.

**ZOLTÁN MAGYAR (2011)****The investigation of menopausal hormone therapy on the histological transition of endometrial tissue and the demonstration of selected steroid hormones antioxidant effect***Supervisor: Gábor Békési*

The intracellular and secreted myeloperoxidase (MPO) of the neutrophil granulocytes has a predominant role in the cellular redox homeostasis. Estrogens and androgens have an antioxidant potential maintained by the MPO. In postmenopausal women a 40-day-long administration of combined estrogen and intermittent gestagen increased the intracellular MPO activity significantly at Day 12 and 40 compared to the baseline. The secreted MPO amount was gradually and significantly increased from the baseline to Day 12 and 40. Moreover the increase from Day 12 to 40 was also significant.

In case of a high-fat diet I have demonstrated in a rat experimental model that the treatment with dehydroepiandrosterone and its sulphate results in a significantly increased total scavenger capacity (TSC). The increased liver fat content caused by the high-fat diet could be ameliorated by these steroid hormones. According to my findings the activities of antioxidant enzymes in the local scavenger system of the liver - namely superoxid dismutase, catalase and glutathione S transferase - do not take part unambiguously in the increase of the systemic TSC change.

The menopausal hormone therapy (MHT) has a key role not only in the counterbalance of the disadvantageous vasomotor, urogenital tract, bone metabolism and mental changes but also in the control of endometrial function. Under the auspices of a Menopause Outpatient Unit with the appropriate medical training and facilities, the individualized, preventive medical care and follow-up strategy is highly necessary for avoiding the side effects of MHT and to approach the prevention and early diagnostics of breast cancer. During MHT the continuous-combined products resulted in atrophic endometrium and markedly decreased the prevalence of endometrial hyperplasia and subsequent bleeding. Proliferative and hyperplastic endometria were seen in subjects without MHT. Atypia-associated complex hyperplasia was not however simple hyperplasia was seen in subjects with MHT. Cervical polyp was seen more frequently in MHT. Based on my results the MHT can diminish the prevalence of postmenopausal vaginal bleeding and might prevent endometrial carcinoma. In summary this beneficial effect might be explained by the changes in the antioxidant status as well.

- Magyar Z, Bekesi G, Racz K, Feher J, Schaff Z, Lengyel G, Blazovics A, Illyes G, Szombath D, Hrabak A, Szekacs B, Gergics P, Marczell I, Dinya E, Rigo J Jr., Tulassay Z: Increased total scavenger capacity and decreased liver fat content in rats fed dehydroepiandrosterone and its sulphate on high-fat diet. *Gerontology* 2011; 57:343-349.
- Magyar Z, Berkes E, Csapo Z, Papp Z: Effect of hormone replacement therapy on postmenopausal endometrial bleeding. *Pathol Oncol Res* 2007; 4:351-359.
- Magyar Z, Csapó Z, Papp Z: A postmenopausal hormonpótló kezelés hatása a változó korban jelentkező vérzészavarra. *Orv Hetil* 2007; 31:1451-1459.

**PÉTER MÁRTON SZABÓ (2011)****Exploring the molecular patomechanism of adrenocortical tumors***Supervisor: Péter Igaz*

Sporadic adrenocortical tumors are common, but their pathogenesis is poorly elucidated. Herein, we present an integrative pathway meta-analysis of gene expression microarray and CGH studies performed to date on sporadic adrenocortical tumors including our own data. As immunological and inflammatory mechanisms have already been reported to be involved in adrenocortical tumorigenesis, we investigated the expression of histamine-related genes in the normal adrenal gland and adrenocortical tumours at mRNA and protein levels.

Data of four publicly available whole genome microarrays performed on two different platforms from altogether 168 tumors and 18 normal adrenal tissues were reanalyzed. Significant gene sets and cytogenetic changes from studies where genomic data were unavailable have also been examined. Our own experimental study included 10 tumor and 4 normal samples that were analyzed by parallel mRNA and comparative genome hybridization (CGH) profiling. Microarray and CGH data from altogether 22 publications were collected that included 42 normal adrenals, 350 adrenocortical adenomas and 270 carcinomas. Data were examined by GeneSpring, Gene Set Enrichment Analysis, Ingenuity Pathway Analysis and own softwares by an integrative approach searching for gene expression changes paralleling chromosome aberrations. Expression of histamine-related genes were investigated in 15 normal adrenals and 43 adrenocortical tumours by QRT-PCR, Western-blot and immunohistochemistry. Both the meta-analysis of available mRNA and CGH profiling data and pathway analysis of the results of our small experimental study revealed three major pathogenetic pathways that could be relevant in adrenocortical tumorigenesis: i. damage of cell cycle, ii. alterations of retinoic acid signaling and iii. expression changes of genes in complement system and antigen presentation machinery. We have found previously undescribed pathomechanisms in these pathways that could even represent potential drug targets. However, experimental validation of these pathways will be necessary.

We have reported the presence of histidine decarboxylase, histamine receptors and histamine-N-methyltransferase in the normal adrenal gland. Histamine content was significantly lower and the expression of histamine receptor type 3 was significantly higher in adrenocortical carcinomas compared to normal tissues and benign tumors. Our results may contribute to the better understanding of adrenocortical tumorigenesis, to the development of novel biomarkers and might even form the basis for novel treatment options.

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- Szabó PM, Wiener Z, Tömböl Z, Kovács A, Pócza P, Horányi J, Kulka J, Riesz P, Tóth M, Patócs A, Gaillard RC, Falus A, Rácz K, Igaz P: *Differences in the expression of histamine-related genes and proteins in normal human adrenal cortex and adrenocortical tumors. Virchows Arch* 2009; 455:133-142.
- Szabó PM, Tamási V, Molnár V, Andrásfalvy M, Tömböl Z, Farkas R, Kövesdi K, Patócs A, Tóth M, Szalai C, Falus A, Rácz K, Igaz P: *Meta-analysis of adrenocortical tumour genomics data: novel pathogenic pathways revealed. Oncogene* 2010; 29:3163-3172.



## ÁGNES SZAPPANOS (2011)

### Sensitivity to glucocorticoids and bone metabolism in patients with endogenous hypercortisolism

Supervisor: Miklós Tóth

The long-term consequences of prolonged glucocorticoid excess on the skeleton (glucocorticoid-induced bone disorder) and the importance of the genetic variants in the determination of glucocorticoid sensitivity, as well as clinical variability and disease severity are mostly unexplored.

Serum OC of patients with endogenous hypercortisolism showed strong negative, while  $\beta$ -CTx displayed strong positive correlation with serum cortisol. Our results confirm some previous findings regarding the uncoupling of bone formation and bone resorption in hypercortisolism and the restoration of coupled remodelling after the cure of endogenous Cushing's syndrome. Furthermore our findings suggest that serum OC reflecting the bone formation process should be considered as a sensitive biologic marker of glucocorticoid activity and perhaps disease severity in patients with endogenous Cushing's syndrome. In the time course of bone marker changes after the cure of Cushing's syndrome, serum OC increased rapidly and remained increased until the 24th postoperative month, while  $\beta$ -CTx levels failed to show differences at baseline during the 4-year follow-up period.

Investigating the clinical importance of glucocorticoid receptor gene variants in patients with endogenous Cushing's syndrome, we have shown that the BclI, N363S, ER22/23EK and A3669G polymorphisms probably do not modify the risk for the development of Cushing's disease and Cushing's syndrome. BclI polymorphism may increase the skeletal sensitivity to glucocorticoids in endogenous glucocorticoid excess states since patients carrying the BclI variant in a homozygous form had reduced BMD at femoral subregions and displayed significantly increased bone resorption.

For detection of the rs846910 and the rs846911 polymorphisms of the *HSD11B1* gene, located at the 5' regulatory region, I have planned a rapid, simple and cost-effective multiplex allele-specific PCR method. The reliability of the method was verified with direct sequencing results, showing 100% accuracy of the new method. These results suggest that this method newly developed for the combined detection of rs846910 and the rs846911 polymorphisms may also be applied in large-scale, population-based studies.

To evaluate the potential importance of gene variants of the *HSD11B1* gene in patients with endogenous hypercortisolism, I have demonstrated that the rs846910, rs846911 and the 83,557insA polymorphisms do not modify the risk for the development of endogenous Cushing's syndrome. Patients carrying the 83,557insA variant had higher serum OC and plasma ACTH concentrations and smaller adrenal tumor size. Since the intronic region containing the site of the 83,557 insA polymorphism may act as an enhancer of the *HSD11B1* expression and the presence of the 83,557insA variant results in a reduced transcriptional activity of the *HSD11B1* gene, we suggest that these results could be explained by reduced HSD11B1 enzyme activity.

- Szappanos A, Patócs A, Tóke J, Boyle B, Sereg M, Majnik J, Borgulya G, Varga I, Likó I, Rácz K, Tóth M: *BclI polymorphism of the glucocorticoid receptor gene is associated with decreased bone mineral density in patients with endogenous hypercortisolism. Clin Endocrinol* 2009; 71:636-643.
- Szappanos A\*, Tóke J\*, Lippai D, Patócs A, Igaz P, Szücs N, Fütő L, Gláz E, Rácz K, Tóth M: *Bone turnover in patients with endogenous Cushing's syndrome before and after successful treatment. Osteoporos Int* 2010; 21:637-645. \*equally contributed to this work

- Szappanos A, Patócs A, Gergics P, Bertalan R, Kerti A, Ács B, Feldmann K, Rácz K, Tóth M: The 83,557insA variant of the gene coding 11 $\beta$ -hydroxysteroid dehydrogenase type 1 enzyme associates with serum osteocalcin in patients with endogenous Cushing's syndrome. *J Steroid Biochem Mol Biol* 2010; 123:79–84.

## ZSÓFIA TÖMBÖL (2011)

### Exploring the expression patterns and pathogenic relevance of microRNAs in adrenal tumours

Supervisor: Péter Igaz

The different expression and pathogenic role of microRNAs (miRNAs) has been previously reported in several neoplastic diseases, however, there has been only a few data on their pathogenic relevance in tumors of the adrenal gland often representing diagnostic and therapeutic challenges. Therefore, it could be hypothesized that miRNAs can contribute to the classification and better diagnostics of these tumors and can help to elucidate their pathogenesis. Our aims were to study the miRNA expression patterns of different subgroups of adrenocortical tumors and pheochromocytomas, and to explore pathogenic pathways affected by altered posttranscriptional regulation.

miRNA expression profiling of adrenocortical tumors (n=36) and pheochromocytomas (sporadic and hereditary, n=33) has been performed by TaqMan Human miRNA Panel and miRNA microarray (Agilent), respectively. Results of these high-throughput methods were validated by qRT-PCR. Potential target mRNAs of the miRNAs with significant expression differences were identified by various computational target prediction algorithms. In our study on adrenocortical tumors, the number of predicted targets was reduced by an own tissue-specific target prediction approach integrating the results of the parallelly performed miRNA and mRNA expression profiling methods. Pathway analysis of the miRNA targets was carried out to reveal major pathogenic pathways in adrenal tumors affected by altered posttranscriptional regulation.

Six miRNAs among the different subgroups of adrenocortical tumours and five miRNAs in pheochromocytomas were found to be significantly differentially expressed. dCT<sub>hsa-miR-511</sub>-dCT<sub>hsa-miR-503</sub> turned out to be the most appropriate biomarker for adrenocortical malignancy, while *hsa-miR-1225-3p* has been identified as a useful marker for the recurrence of pheochromocytomas. Pathway analysis of the “in silico” predicted target mRNAs revealed the “Cell Cycle: G2/M checkpoint regulation” and the “Notch signaling” as major pathogenic pathways in adrenocortical cancer and recurring pheochromocytomas, respectively. These “in silico” identified pathways should be further experimentally validated.

Our result may contribute to the reliable classification and better diagnostics of adrenal tumors, and to a deeper understanding of their pathogenesis and may help the identification of new therapeutic targets.

- Tömböl Z, Szabó PM, Molnár V, Wiener Z, Tölgyesi G, Horányi J, Riesz P, Reismann P, Patócs A, Likó I, Gaillard RC, Falus A, Rácz K, Igaz P: Integrative molecular bioinformatics study of human adrenocortical tumors: microRNA, tissue-specific target prediction, and pathway analysis. *Endocr Relat Cancer* 2009; 16:895-906.
- Tömböl Z, Éder K, Kovács A, Szabó PM, Kulka J, Likó I, Zalatnai A, Rácz G, Tóth M, Patócs A, Falus A, Rácz K, Igaz P: MicroRNA expression profiling in benign (sporadic and hereditary) and recurring adrenal pheochromocytomas. *Mod Pathol* 2010; 23:1583-1595.
- Szabó PM, Tömböl Z, Molnár V, Falus A, Rácz K, Igaz P: MicroRNA target prediction: Problems and possible solutions. *Current Bioinformatics* 2010; 5:81-88.

**PROGRAM 2/14.****CLINICAL AND EXPERIMENTAL RESEARCH ON UROLOGICAL DISEASES****Coordinator:****Imre ROMICS M.D., Ph.D., D.Sc.**

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**Program Overview:** The program offers research on several fields of clinical and experimental urology and andrology.

***Titles of research projects******Supervisors***

Hereditary and acquired disorders of the external genital and urological tracts

Zsolt Kelemen

Diagnostic and therapeutic challenges in urine retention and evacuation diseases

Péter Nyirády

Up to date clinical experimental research of andrological diseases

Péter Nyirády

Reconstructive urology

Imre Romics

Novel diagnostic and therapeutic options in urological tumors

Imre Romics

Etiology and etiopathogenesis of urinary tract stones, challenges in drug therapy, surgical treatment and prevention

Imre Romics

Inflammatory disorders of the urinary organs

Imre Romics

Congenital anomalies of the kidney, urinary tract and external genital tract in newborn infants

Éva Görbe

***Ph.D. candidates***

Gergely Bánfi

na

András Horváth

na

István Laczkó

na

***Supervisor***

Imre Romics

Péter Nyirády

Péter Nyirády

na, not affiliated

**PROGRAM 2/15.****MOLECULAR GENETICS, PATHOMECHANISMS, AND CLINICAL ASPECTS OF METABOLIC DISORDERS****Coordinator:****Péter LAKATOS M.D., Ph.D., D.Sc.**

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**Program Overview:** The program consists of 13 research sub-programs completed with appropriate theoretical courses for postgraduate students. Molecular as well as pathological and clinical aspects of different metabolic diseases are studied including metabolic bone diseases and disturbances of calcium metabolism and lipid metabolism, disorders in onco-hematology processes, endocrine glands, diabetes mellitus and vascular diseases. Ph.D. students are working under the supervision of a qualified scientist but also participate in the work of the laboratory. Publication in peer-reviewed international journals is a requirement for a successful Ph.D. thesis.

***Titles of research projects***

Molecular genetics, pathomechanism, early diagnosis, prevention and therapy of chronic liver diseases

Regulation of endocrine functions of fat tissue and its relation to insulin resistance

Metabolic aspects of malignant hematological disorders

Investigation of disorders associated with macro- and microvascular complications and risk factors of atherothrombotic vascular diseases

Pituitary gland dysfunction: Clinical and experimental studies. Ghrelin and cell proliferation

Identification of genes participating in the stimulatory effect of ghrelin on cell proliferation

Effect of calcium and bone metabolism disorders and the drugs influencing it on mineral content, quality and mechanical properties of bone tissue

Gestational diabetes as preexisting condition for type 2 diabetes and metabolic syndrome

Investigation the pathophysiology of insulin resistance. Development of early diagnostic tools and therapeutic interventions

Thyroid disorders and their effects on bone metabolism

Molecular genetics, pathomechanism, early diagnosis, prevention and therapy of chronic liver diseases

***Supervisors***

Margit Abonyi

Károly Cseh

Judit Demeter

Csaba Farsang,  
Zoltán Jári

Miklós Góth

Miklós Góth

Csaba Horváth

Zsuzsa Kerényi

László Korányi

Péter Lakatos

Péter László Lakatos

Molecular mechanisms in bone metabolism	Attila Mócsai
Extraskeletal effects of key genes and proteins of bone metabolism	Gábor Speer
Pathophysiological aspects of normoglycemic control of diabetes mellitus	Gyula Tamás
Prevalence and incidence of diabetes and pathophysiological points of normoglycemic treatment	Gyula Tamás
Endocrinological aspects, pathomechanism and therapy of polycystic ovary syndrome	Szabolcs Várbiro

***Ph.D. students***

Örs Levente Babos	ft
Judit Dénes	ft
Csaba Halászlaki	pt
László Krivanek	ft
Rita Magenheimer	ft (a)
Mihály Vaszkó	pt (a)

***Ph.D. candidates***

Lajos Sándor Kiss	na
Magdolna Krasznai	na

***Ph.D. graduates***

El Hajd Othmane Taha	pt
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***Supervisors***

Zoltán Járai
Miklós Góth
István Takács
Csaba Farsang
Gyula Tamás
Péter Lakatos

***Supervisors***

Péter László Lakatos
Károly Cseh

***Supervisors***

Zoltán Járai
--------------

a, absolutorium; pt, part-time; ft, full-time; na, not affiliated

***Abstract of Ph.D. thesis successfully defended in 2011*****EL HADJ OTHMANE TAHA (2011)****The role of parameters of arterial stiffness to prognose cardiovascular survival in haemodialysis patients: determinants and therapeutic options**

*Supervisor: Zoltán Járai*

In end-stage renal disease (ESRD) patients, calcification of the large arteries begins early, facilitating a 20- to 30-times higher rate of cardiovascular mortality (CV) than in the age-matched general population. In ESRD patients, the prognostic value of arterial stiffness parameters (pulse wave velocity: PWV, augmentation index: AI, central pulse pressure: CPP and carotid-femoral pulse pressure amplification: AMP) in one cohort for CV survival, the effect of phosphate binder sevelamer on aortic stiffness and the validation of the oscillometric device (Arteriograph) has not previously been examined. I have performed three studies in ESRD patients; the first examined the predictive power of different stiffness parameters for CV mortality evaluated in a single cohort. The second study assessed the effect of sevelamer on aortic stiffness, and the third evaluated the validity of Arteriograph device and the predictive value of measured parameters for CV mortality, compared to those of the reference PulsePen device. The first study showed that, pre- and

postdialysis PWV and predialysis AMP values were related to CV mortality. In the second study, by the end of follow-up, PWV decreased in sevelamer-treated patients while it increased in controls. The direction of changes of AI was similar, although it did not reach the level of statistical significance. In the third study, AI values measured by the two devices showed statistically significant linear correlation, while for PWV similar correlation was not observed. Only PWV, measured by PulsePen, was related significantly to CV mortality. AI, measured by either of the devices, did not show a relationship with CV mortality. These results showed that in ESRD patients, among different stiffness parameters, PWV is consistently related to CV mortality, irrespective of the timing of measurement, predialysis AMP seems to provide additional prognostic information and that sevelamer treatment is associated with an improvement in aortic stiffness. Lack of correlation between PWV-values measured by the PulsePen and Arteriograph devices, and lack of prognostic significance of PWV measured by Arteriograph suggest limited validity of Arteriograph to determine PWV in patients on hemodialysis.

- Othmane Tel H, Bakonyi G, Egresits J, Fekete BC, Fodor E, Jarai Z, Jekkel C, Nemcsik J, Szabo A, Szabo T, Kiss I, Tislér A: *Effect of semelamer on aortic pulse wave velocity in patients on hemodialysis: A prospective observational study. Hemodial Int 2007; Suppl 3: S13-21.*
- Othmane Tel H, Nemcsik J, Fekete BC, Deák G, Egresits J, Fodor E, Logan AG, Németh ZK, Jarai Z, Szabó T, Szathmári M, Kiss I, Tislér A: *Arterial stiffness in hemodialysis: which parameter to measure to predict cardiovascular mortality? Kidney Blood Press Res 2009; 32: 250-225.*
- Nemcsik J, Egresits J, El Hadj Othmane T, Fekete BC, Fodor E, Szabó T, Jarai Z, Jekkel C, Kiss I, Tislér A: *Validation of arteriograph – A new oscillometric device to measure arterial stiffness in patients on maintenance hemodialysis. Kidney Blood Press Res 2009; 32: 223-229.*

## **PROGRAM 2/16.**

### **DERMATOLOGY AND VENEROLOGY**

#### **Coordinator:**

**Sarolta KÁRPÁTI M.D., Ph.D., D.Sc.**

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**Program Overview:** The Ph.D. program of the Department Dermatology-Venereology and Skin Oncology at Semmelweis University Ph.D. School aims to fill a gap in development of skin and venereal diseases that will provide support for scientific research, education and postdoctoral training of the specialty. The foundation of this new doctoral program stems from a sub-program that belonged to the Molecular Medicine Ph.D. School since 1998. Graduates from this sub-program have already started an independent research work. As a result of the scientific activity of the group, it gained accreditation as a joined research group of the Hungarian Academy of Sciences. The previous Ph.D. program “Basics of Human Molecular Genetics and genetic Diagnostics” under which our sub-program was listed could no longer harbor all that diverse clinical and research activities that include



venereology, STD-related microbiology, genetics, dermatologic immunology and dermatologic oncology. Our department has accumulated a very extensive dermato-venereologic clinical data that requires further research that eventually will benefit to our patients in understanding their diseases and will result in providing better healthcare. Our program is being transferred from the Molecular Medicine Ph.D. School and will continue the research of monogenic inherited skin diseases. Our department is also the home of the National Epidermolysis Bullosa Center that carries out studies in the genetics of this severe inheritable group of diseases and has established successful prenatal diagnostics in the lethal forms. Diagnostics is now provided for more than 20 genes at the moment that are responsible for epidermolysis bullosa, Darier's disease and Hailey-Hailey disease and ichthyosis. The analysis of the genotype-phenotype relation as well as macro- and micro-alterations will give further insight into the pathophysiologic events in keratinocytes. Our facilities and expertise enable us to carry out clinical as well as basic science. A close scientific partnership is reflected by the introduction of two co-program leaders on the field of stem cell research. The skin is largest organ in our body and also serves as the largest organ of our immune system. The skin is easily accessible and has great regenerating potential. The therapy of inherited, immunologic and all erosive skin diseases could benefit from a better understanding of the nature of *epidermal stem cells*. We wish to join the hot research area of stem cells with the tracking of stem cells of bone marrow transplanted recipient patients and with the use of an animal model. Our future aim, along with investigating skin differentiation and the dynamics of keratinocytes, is to explore the potential in gene therapy. In the current situation with the closing of the National Institute for Dermato-Venereology the university clinic got the obligation to further care of STD patients in form of a state center for *STD diseases* with national coverage that is based on the previous expertise from the above mentioned institution. To this area of dermatology is given special attention in our Ph.D. program. Beside the classical STD's, the altered immune reactions of HIV positive patients and opportunistic infections that frequently occur among HIV positive individuals are being investigated. This program is strongly supported by a complete microbiological laboratory, including the National Mycology Reference Laboratory, which also belongs to the department. This activity provides a diagnostic background for rare infectious diseases and also is in the process of introducing novel molecular biology diagnostic tools that yield new research data and scientific achievements. A long-lasting successful research activity on *autoimmune blistering skin diseases and gluten sensitive diseases*, like dermatitis herpetiformis and celiac disease, is well indicated by the fact, that in this field one Ph.D. work had been completed, and two further Ph.D. works are in progress. The large number of patients, the regular and careful study of circulating and tissue bound autoantibodies render good possibilities for the project. *Pharmacogenomics*, a new research area of the institute, is also based on the large number of patients with drug induced side effects on the skin. Within the planned biobanking, genetic and bioinformatic studies we started to elaborate material and data from patients with drug side effects. Our further goal is to focus to the predictivity of drug induced damages. Collecting data we plan to get important information about the pathomechanism of toxicodermas as well. With our *Pharmacogenomics* Ph.D. course we join the molecular toxicology, bioinformatics and pharmacology as well. Two years ago the Dermato-Venereology Clinic changed its name incorporating the *Skin Oncology* words as well, to underline the extended activity of the institute on the field. Scientific goal: the rapidly growing number of melanoma malignum forces us to organize extended preventive programs with organizing auto-investigation of the skin, and dermatological screening of the Hungarian population. The UV induced carcinogenesis, the development of skin tumors and its molecular biological background is

also one of our ongoing studies. The Center of the Lymphoma Group of the Hungarian Dermatological Society is also in our clinic. Clinical, immunohistochemical, therapeutical and pathological features of cutaneous lymphomas will be worked up. Epidemiology would be part of different themas: incidence of STD diseases, skin tumours: melanoma, cutaneous lymphomas is planned to be evaluated.

### ***Titles of research projects***

### ***Supervisors***

Analysis of evidence based results, metaanalysis and modelling	Valentin Brodszky
„New Public Health”:epidemiology, disease burden and disease progression, evidence based medicine, impact and cost assessment as well as analysis of policy implications.	László Gulácsi
Pharmaco-economics.	László Gulácsi
The examination of psoriasis immune pathomechanism	Péter Holló
Clinical and immunological studies in autoimmune bullous dermatological diseases	Sarolta Kárpáti
Pharmacogenomics: Pharmacogenomic investigation of molecular mechanisms in toxicoderma	Sarolta Kárpáti
Stem cell research in dermatology	Sarolta Kárpáti, Éva
Mezey	
Occurrence, prognostic and etiological factors and investigation of therapeutic modalities in ctuan lymphoma	Márta Marschalkó
Molecular genetic investigations in genodermatosis	Márta Medvecz
Microbial organisms as pathogens, cofactors and opportunistic infections in retroviral infections	József Ongrádi
Antibacterial target proteins and peptides	László Ötvös
Health related quality of life and disease burden assessment in chronic conditions, with special focus on dermatologic diseases	Márta Péntek
Do MRSA strains form a distinct subspecies in the Staphylococcus genus ?	Ferenc Rozgonyi
Prevalence, restistance to antibiotics, in vitro and in vivo pathogenic charateristics of coagulase negative staphylococci in nosocomial infections	Ferenc Rozgonyi
Application of molecular microbiological methods in the rapid microbiological diagnostics	Ferenc Rozgonyi
Molecular genetic diagnosis of Neisseria gonorrhoeae infections and resistance to antibiotics	Ferenc Rozgonyi
Molecular pathogenic and taxonomic examination of Methicillin-resistant Staphylococcus aureus (MRSA)	Ferenc Rozgonyi
Characterisation of bacterial species, molecular methods	Ferenc Rozgonyi
Antifungal susceptibility of Candida clinical strains and pathogenecity properties	Ferenc Rozgonyi
Elaboration of a prevention program to improve the early recognition of melanoma	Beáta Somlai

Allergic skin diseases	Erzsébet Temesvári
The role of environmental and meteorological factors in mortality	Klára Törő
The effects of UV light on the normal and abnormal cutaneous functions, and in the development of malignant skin tumors	Norbert Wikonkál

**Ph.D. students**

Réka Dóra Farkas	ft
Dóra Haluszka	ft
Hajnalka Jókai	ft
Orsolya Kontár	ft
Noémi Mihalik	ft
Veronika Tóth	pt (a)

**Supervisors**

Norbert Wikonkál
Norbert Wikonkál
Péter Holló
Márta Marschalkó
Márta Marschalkó
Beáta Somlai

**Ph.D. candidates**

Eszter Ostorházi	na
Edit Vereckei	na

**Supervisors**

László Ötvös
Klára Törő

**Ph.D. graduate**

Zsuzsa Szabó	ft
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**Supervisor**

Ferenc Rozgonyi
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a, absolutorium; pt, part-time; ft, full-time; na, not affiliated

**Abstract of Ph.D. thesis successfully defended in 2011****ZSUZSA SZABÓ (2011)****Identification of rare but clinically relevant yeast species and studying of their susceptibility to the newest antifungal agent**

*Supervisor: Ferenc Rozgonyi*

The frequency of invasive fungal infections has been increased dramatically during the past three decades. Some commercially available tests used for identification of yeasts (API ID 32C, API 20C AUX, API Candida) often provide uncertain or false results. The frequent emergence of *non-albicans Candida* species having primary and secondary resistance requires a correct identification of the species as well as knowledge of their antifungal profile. Using the API ID 32C and the MICRONAUT-Candida systems we made an identification of 264 yeasts. The MICRONAUT-Candida system can be used for identification at species level after a 24-hour-long incubation time without using extra tests in the case of *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, which occur very frequently. The new method can be used successfully in the identification of infrequent but clinically relevant species as well. Our studies with time-kill curves in the case of *Candida inconspicua* confirmed that Amphotericin B at clinical attainable concentration (1 mg/L) showed fungicidal effect against *C. inconspicua* isolates, thus it can be an effective in certain clinical situations. We proved that from among the three species belonging to the „*psilosis*”- group, *in vitro* the *C. metapsilosis* was the most susceptible to the caspofungin either the RPMI- 1640 or the AM3 is the applied medium. Although the MIC values of *C. orthopsilosis* are lower to caspofungin than MIC values of *C. parapsilosis sensu stricto* isolates,

the time-kill curves were similar in both species. In the studies with *C. dubliniensis* the time-kill curves showed that all triazoles inhibited the growth of *C. dubliniensis* easily even at relatively low concentrations (2-4 x MIC). Since the amphotericin B showed a good fungicidal effect even at low concentrations, in some invasive infection caused by *C. dubliniensis* amphotericin B can be proposed from the examined antifungal agents.

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## SCHOOL OF PH.D. STUDIES

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### 3. PHARMACEUTICAL AND PHARMACOLOGICAL SCIENCES

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***Chairwoman:***

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**General Overview:** The Doctoral School of Pharmaceutical and Pharmacological sciences focuses on two scientific disciplines:

- *Pharmacological research* is needed to select new active substances, to develop and use medicinal products. In addition, new scientific results and discovered relationships may help to understand functions of human living organism.
- *Pharmaceutical research* is related to drug research, development of drug delivery systems as well as it is a prerequisite to produce and apply pharmaceutical preparations. Although pharmaceutical science involves the knowledge of other disciplines (e.g. chemistry and medical science), but the evaluation of medicinal products requires specialised knowledge from the viewpoint of this interdisciplinary science.

The objective of the Doctoral School is to train qualified experts with an internationally recognized scientific degree (Ph.D.) for pharmacological and pharmaceutical research. Scientific results of the above mentioned research topics will be summarized in doctoral thesis and research papers which will be published in international journals of high impact. Research topics provide students with theoretical and practical experience in different fields of pharmaceutical and pharmacological sciences. Special problems are covered by the research projects of the educational Program:

- study of bioactive substances of plant origin in connection with phytochemical and biological evaluation as well as biotechnological production; pharmaceutical chemistry and analysis; design, manufacturing and biopharmaceutical evaluation of novel dosage forms; clinical pharmacy and pharmacoeconomics; study of organic compounds with potential bioactivity; investigation of medical and pharmaceutical aspects of biology and environmental protection;
- pharmacodynamic investigations; pharmacokinetic and drug metabolism; influence on neurochemical transmission; study of neurodegenerative and neuroprotective mechanisms; cardiovascular pharmacological investigations; separation methods and their applications; study of drugs affecting on calcium and bone metabolism; human study of cytostatic drugs; role of iontransport mechanisms controlling neurochemical transmission.

**PROGRAM 3/1.****MODERN TRENDS IN PHARMACEUTICAL SCIENCES****Coordinator:****István ANTAL M.Sc., Ph.D.**

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**Program Overview:** The scientific-education scope of the participating 15 institutes/departments provides the eligible professionals (pharmacists, medical doctors, chemists, biologists, physicists, chemical engineers) with a wide selection of topics in the fields of fundamental and specific drug-oriented research, including current problems of inorganic, organic, physical, analytical, bioinorganic, bioorganic, and coordination chemistry, biology, biophysics, biotechnology, botany, microbiology and virology.

The specific topics of drug- and pharmaceutical research are drug design and synthesis, structure-activity relationships, mechanism of action of drugs, drug-receptor binding, isolation of active compounds from natural sources, drug metabolism, biochemical toxicology, relationships between physicochemical properties and biological function, pharmacognosy, elucidation of biosynthesis of natural compounds, pharmacokinetics, drug-drug interactions, transport mechanisms, biopharmaceutics, pharmaceutical technology, physical pharmacy, chemical pharmacy and social pharmacy.

**Research topic**

MODERN TRENDS IN PHARMACEUTICAL SCIENCES

***Production of bioactive compounds by biotechnological methods***

Optimization of active substance formation by biotechnological methods (fermentation, bioregulation, gene transformation) in tissue and cell cultures of medicinal plants

Study on role of endogenous formaldehyde in C1 metabolism and biosynthesis related to C1 fragments

Research and production of bioactive lignanes of plant origin by in vitro cell cultures for therapeutical use

Study on protective response of plants induced by elicitors in case of in vivo and in vitro systems

***Phytochemical and biological evaluation of bioactive substances of plant origin***

Active ingredient content assays of medicinal plants and their preparations

**Coordinator/  
supervisor***István Antal**Éva Szőke*

*Éva Szőke*  
*László Kursinszki*

*Lehel Hullán*

*Miklós László*  
*István Gyurján*  
*Zoltán Krisztóf*

*Károly Bóka**Éva Lemberkovics*

*Éva Lemberkovics*  
*Éva Szőke*



Formation of bioactive compounds in medicinal plants	Éva Szőke Andrea Balázs
Research of plant-derived active substances for phytotherapeutical purpose	Ágnes Kéry
Symptoms of heavy metal contaminations in medicinal plants	Béla Böddi
Metals and metal ions in medicinal plants and their extracts in consideration of dosage forms	Klára Szentmihályi
Screening of antioxidant activity of plant compounds in HTS-conditions	György Tibor Balogh
<b><i>Pharmaceutical chemistry and drug analysis</i></b>	<i>Béla Noszál</i>
Microspeciation of bio- and drug molecules	Béla Noszál
Study on cyclodextrines regarding the ability to form inclusion complexes	Ágnes Barcza-Buvári
Application of chiroptical, CD/UV and NMR spectroscopy in analysis of chiral and natural compounds	András Gergely
Development and application of high resolution separation methods for analysis of bioactive molecules and drug candidates	Miklós Idei
Rational drug desing in signal transduction therapy	György Kéri
Preparation of kinase inhibitor molecules by retional drug design	György Kéri
Study on novel molecules with selective tyrosine kinase effect – modelling relationships between chemical stucture and biological effect	György Mészáros
Study on pathobiochemical processes of cancerous and inflammatory diseases regarding to role of kinases and to development of drug candidates	Tibor Vántus
Investigations of nonlinear chemical phenomena	Krisztina Csörgei- Kurin
Development of on-line enrichment procedures for determination of metal traces by atomabsorption spectrometry	
Determination of metal traces by atomabsorption spectrometry and computer modelling of binding forms to separate them by chelate-exchange method in drug matrix	Alexandra Lásztity
Role of combinatorical chemistry and informatics int he design and preparation of new drug candidates	László Órfi
Study on relationships between molecular properties and chemical structure, role of lipophilicity	Krisztina Takács- Novák
Chromatographic analysis of amino acids and amines	Miklósne Perl
Identification and quantitative determination of flavoids and lignanes of plant origin by chromatographic methods	Miklósne Perl

Analysis of drug residuals in environmental and drinking water by classical and solid phase extraction with trimethylsilyl (oxym)-ether/ester form by GC-MS method	Miklósné Perl
Development of microanalytical methods and speciation of elements for studying biological systems	Gyula Záray
<b><i>Design and preparation of modern dosage forms</i></b>	<i>István Antal</i>
Investigation of excipient systems used as drug carriers	Judit Dredán
Investigation of drug carrier systems with controlled and programmed drug release	István Antal
Study and optimization of pharmaceutical technological procedures	István Antal
Investigation of competitive interfacial processes in colloidal drug carriers	Ferenc Csempesz
<b><i>Biopharmaceutical considerations of design and evaluation of pharmaceutical preparations</i></b>	<i>Sylvia Marton</i>
Investigation of drug carrier systems with improved bioavailability	Sylvia Marton
Investigation of drug carrier systems with controlled and programmed drug release	Sylvia Marton
Analytical assay of drug carrier systems	Krisztina Ludányi
<b><i>Pharmacoeconomics and clinical pharmacy</i></b>	<i>Zoltán Vincze</i>
Pharmacoeconomical investigations	Zoltán Vincze
Studies in clinical pharmacy	Romána Zelkó
Application of novel dosage forms in the clinical pharmacy	Romána Zelkó
Health care-economics, technological analysis	Ágnes Mészáros
<b><i>Study of potentially bioactive organic compounds</i></b>	<i>Péter Mátyus</i>
Study of potentially bioactive organic, heterocyclic compounds	Péter Mátyus
Design and synthesis of potentially bioactive compounds	György Keserű
Synthesis of potentially bioactive „O” and „N”-heterocyclic compounds and investigating their effect	Sándor Antus
<b><i>Pharmaceutical considerations of biology and environmental protection</i></b>	<i>László Kőhidai</i>
Pharmacological and molecular biological investigations of histamine, its receptors responsible for action, histamine agonists and antagonists regarding the role in cell proliferation	Sára Tóth
Biological and clinical principles of chemotaxis	László Kőhidai
Study on action mechanism of pharmaceutical substances influencing membranes	Gabriella Csík

Study of molecular dynamic interactions on model membranes by spectroscopical methods		Pál Gróf
Study of glycoproteins and biomarkers by mass spectrometry		Károly Vékey
Structural bases and medical aspects of protein aggregation		Judit Fidy László Smeller
Computer study of protein dynamics – role of dynamics in ligand binding		Erika Balog
Significance of glutamaterg neuron phenotype in parvicellular and magnocellular neurosecretory systems		Ferenc Tölgyesi
Study on structural bases of functional interactions in proteins		Judit Fidy László Smeller Levente Herényi Szabolcs Osváth
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Krisztina Kurin
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Miklós Idei
Ágnes Andrea
Mészáros
Krisztina Ludányi
Zoltán Vincze
Éva Szőke
György Horvai

a, absolutorium; ft, full-time; pt, part-time; f, foreign; i, individual; CRC, Cooperation Research Centre

***Abstracts of Ph.D. theses successfully defended in 2011*****EDIT BAKA (2011)****Development and examination of solubility measurement methods for drug solubility determination**

*Supervisor: Krisztina Takács Novák*

The biggest part of my Ph.D. work was the standardization of the classical saturation shake-flask solubility method. During the experiments we examined systematically which parameters have significant influence on the solubility value and how large experimental error (standard deviation) is caused by them in the solubility method. According to our results the measured thermodynamic solubility is influenced strongly by the temperature, the time of sedimentation, the composition of buffer solution and the technique chosen for separation of solid and liquid phases. However, the amount of solid excess does not influence significantly the intrinsic thermodynamic solubility results. Based on this standardization study, we developed a new shorter (36 hours) protocol for measurements of equilibrium solubility of drug molecules. The new protocol was validated with the aid of 6 struc-

turally different compounds. The equilibrium solubility was measured by both (standard and new) protocols. The results were in good agreement, so the shorter protocol can be applied to measure the equilibrium solubility of drug compounds.

Applying the new protocol we investigated the thermodynamic solubility of 6 different compounds (5 bases and an ampholyte) at different pH values to get their pH-dependent solubility profiles. Then we accurately determined the  $pK_a$  values of these 6 compounds. With the aid of  $\log S_0$  and  $pK_a$  values we calculated the pH-dependent solubility profiles according to the HH relationships. The aim of the present work was to study the validity and the limits of the Henderson-Hasselbalch (HH) relationship in the case of structurally diverse weak bases. According to our experiences the HH relationship can be applied well to predict the pH-dependent aqueous solubility of drugs at different pHs, until the limit of salt solubility. Below pH 2 common-ion effect significantly decreased the salt solubility. Third part of my Ph.D. work was the validation of a novel potentiometric solubility method (CheqSol). During this work we measured the intrinsic solubility of 14 structurally different compounds with the classical saturation shake-flask solubility method. The solubility results were in good agreement in the most cases of the drugs. With the new validated method the intrinsic solubility of the ionisable compounds can be determined in 1-2 hours.

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- Baka E, Comer JEA, Takács-Novák K: *Study of equilibrium solubility measurement by saturation shake-flask method using hydrochlorothiazide as model compound*. *J Pharm and Biomed Anal* 2008; 46:335-341.
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## BALÁZS BALOGH (2011)

### Molecular modelling studies on $\alpha_2$ -adrenoceptors and the lysophosphatidic acid 1 receptor

*Supervisor: Péter Mátyus*

The Ph.D. work was carried out at the Department of Organic Chemistry, Semmelweis University with the aims to provide support for ongoing medicinal chemical projects of the Department relating to  $\alpha_2$ -adrenoceptor subtypes and lysophosphatidic acid (LPA) receptor 1. In both cases, the modeling work was focused on the study of the intermolecular interactions between those receptors and their ligands. As modelling tools homology modelling and docking were applied. The most important new results are summarized as follows.

1. Models at atomic level of three subtypes of the  $\alpha_2$ -adrenoceptors as well as that of lysophosphatidic acid (LPA) receptor 1, which were constructed via homology modelling procedure. Each model was validated by using statistical parameters and through its predictivity performance. Structural differences in the binding sites were identified for the three  $\alpha_2$ -adrenoceptor models. On the other hand, molecular dynamic calculations were also carried out for the complex of lysophosphatidic acid receptor 1 with its ligand to analyze their interaction.
2. Docking of known to binding sites of these models was investigated and features of the interactions between ligands and receptors were in agreement with mutagenesis data.



3. A good correlation was found between free energy of binding values calculated by AutoDock program and those derived from experimental data, by which affinity of new agonists can also be estimated.
  4. Three-dimensional structure–activity relationship studies of  $\alpha_{2A}$ -adrenoceptor agonists were carried out by Distance Comparison (DISCOthech) and Comparative Molecular Field Analysis (CoMFA) methods to define the pharmacophore and a quantitative model, respectively, of this class of compounds. The statistical validation of the CoMFA model indicates its high predictive performance for designing new  $\alpha_{2A}$ -adrenoceptor agonists.
- Balogh B, Szilágyi A, Gyires K, Bylund DB, Mátyus P: Molecular modelling of subtypes ( $\alpha_{2A}$ ,  $\alpha_{2B}$  and  $\alpha_{2C}$ ) of  $\alpha_2$ -adrenoceptors: a comparative study. *Neurochemistry International* 2009; 55:355-361.
  - Balogh B, Hetényi C, Keserű MG, Mátyus P: Structure-based calculation of binding affinities of  $\alpha_{2A}$ -adrenoceptor agonists. *Chem Med Chem* 2007; 2:801-805
  - Balogh B, Jójárt B, Wágner Z, Kovács P, Máté G, Gyires K, Zádori Z, Falkay G, Márki A, Viskolcz B, Mátyus P: 3D QSAR models for  $\alpha_{2A}$ -adrenoceptor agonists. *Neurochemistry International* 2007; 51:268-276.

#### ANDREA BÖSZÖRMÉNYI (2011)

##### Phytochemical characterization of *Salvia*, *Lavandula* and *Morus* taxa by its terpene compounds

Supervisor: Éva Lemberkovics

*Salvia officinalis* and *Lavandula angustifolia* are important herbs of Lamiaceae family. Their most important pharmaceutically active ingredient is the essential oil, which has sedative effect in lavender, and spasmolytic, antimicrobial effects in sage. The essential oil components of white- and purple-flowered and other three ornamental variants of *Salvia officinalis* (*tricolor*, *purpurascens*, *Kew Gold*), as well as three exotic sage species, *S. judaica*, *S. africana-caerulea*, and *S. mexicana* were examined. The highest essential oil content was gained from the leaves of *Salvia africana-caerulea* and of *S. officinalis* 'Kew Gold' during full flowering period. 56 volatile components were identified in sage essential oils using the GC-MS method, while the percentage-composition of those essential oils was examined by the GC-FID method. The main volatile component analysed is the  $\alpha$ -thujone in the white-blossom *Salvia officinalis*,  $\alpha$ -humulene in the purple-blossomed and cultivated samples, as well as ledol in Judean, piperitone in African, and  $\beta$ -caryophyllene in the Mexican sage. *S. africana-caerulea* was cultivated in vitro for naturalisation purposes. The essential oil production of the in vitro herbs proves to be less than of the intact herb, while their compositions do not differ significantly. Monoterpene hydrocarbons were identified in a higher ratio in SPME extracts, these extracts resemble the scent of the original herbs the most. The genetic determination of essential oil composition of *Salvia* taxa was verified by molecular and chemotaxonomic examinations based on oil compositions and RAPD markers. Molecular and chemotaxonomic examination of *Salvia* taxa based on their essential oil composition and RAPD markers reveal the genetic determination of their essential oil composition. Among *S. officinalis* taxa the *purpurascens* and *tricolor* versions, while among the external genera, *S. mexicana* and *S. africana-caerulea* show closer relationship. The essential oil content of the Hungarian harvested *Lavandula vera*, *L. vera* ssp. *pyreneica*, *L. intermedia*, *L. stoechas*, and *L. dentata* was analysed. The blossom of *L. intermedia* has the highest essential oil content. In lavender taxa 46 volatile components were

identified. Linalool is the main component of *Lavandula vera* and *L. intermedia* oil, except for the *Lavandula vera*-3 ecotype, where lavandulyl-acetate is the dominant component. Fenchone and fenchyl-acetate are the main essential oil components of *L. stoechas*, and eucalyptol is the primary component in the oil of the flower and leaf of *L. dentata*. In the SPME extract the ratio of esters to alcohols was higher. In fact, PCA analysis has proved that the Pyrenean lavender, which is often cited in the literature as a separate genus, is the subgenus of *L. vera*.

The anti-inflammatory activity of the sterol and triterpene molecules of *Morus alba* is based on the inhibition of the protein kinase-C enzyme. The extracts of *Morus alba* leaf and bark produced by organic solvents, as well as laboratory and pilot scale SFE methods, were compared. Out of the SFE purified extracts the pilot scale method has the highest yield, whereas among traditional extracts the ethanolic extraction proved to be the most effective one, but its selectivity remained low for sterol and triterpene components. An increase in the ratio of apolar contents was observed during the vegetation period from spring to fall. Using GC-MS,  $\beta$ -sitosterol, lanost-7-en-3-on,  $\alpha$ -amyrin, and lupeol were identified in *Morus* leaf extracts, and  $\beta$ -amyrin in bark extracts. Using 5- $\alpha$ -cholestane-3-on as the internal standard of the derivation-free GC-FID method the highest  $\beta$ -sitosterol content was gained in pilot scale SFE.

- Böszörményi A, Héthelyi É, Farkas Á, Horváth Gy, Papp N, Lemberkovics É, Szőke É: Chemical and genetic relationships among sage (*Salvia officinalis* L.) cultivars and Judean sage (*Salvia judaica* Boiss.). *J Agric Food Chem* 2009; 57:4663-4667.
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- Horváth Gy, Jámor N, Végh A, Böszörményi A, Lemberkovics É, Héthelyi É, Kovács K, Kocsis B: Antimicrobial activity of essential oils: the possibilities of TLC-bioautography Flavour. *Fragr J* 2010; 25(3):178-182.

## PETRA ZSÓFIA DUNKEL (2011)

### Novel extensions of the *tert*-amino effect: synthesis of azecine and oxazonine-fused ring systems

Supervisor: Péter Mátyus

The term 'tert-amino effect' was first used by Meth-Cohn and Suschitzky in 1972, to describe unusual cyclizations of *ortho*-substituted *tert*-anilines, due to an increased reactivity.

In a special subtype of *tert*-amino effect type 2 reactions a new C-C bond is formed between the  $\alpha$  carbon of the *tert*-aniline group and the  $\beta$  atom of an *ortho*-vinyl substituent, resulting in the formation of a tetrahydropyridine ring. Type 2 cyclizations have been widely used for the synthesis of various fused ring systems, but only rarely for the synthesis of medium-sized rings or macrocycles. In the course of my Ph.D. work, I took part in *tert*-amino effect related studies. We studied potential extensions of the *tert*-amino effect to bi- and triaryl systems and *via* type 2 *tert*-amino effect novel oxazonine- and azecine-fused ring systems were synthesized. In the applied model compounds, the interacting vinyl and *tert*-amino moieties were in *orthoortho'*/'*ortho*' positions on two different aromatic rings, connected *via* a third benzene or pyridazinone ring or an oxygen bridge. The aldehyde intermediates used for the synthesis of the vinyl starting compounds were prepared by the reaction of the appropriate *tert*-aminophenol and 2-fluorobenzaldehyde or *via* two subse-

quent Suzuki-couplings from dihalo starting compounds with *ortho-sec*-amino- and 2-formylphenyl boronic acids. The structures of several intermediates were determined by X-ray diffraction. Cyclization of non-conjugated biaryl ethers demonstrate, that *tert*-amino effect could operate also via direct hydride transfer, therefore, this type of reaction might be of a broader significance.

As a part of the ongoing vascular-adhesion protein-1 (VAP-1) research program in the Department of Organic Chemistry, starting from some of the intermediates used for *tert*-amino effect related studies and further biaryl aldehydes, potentially VAP-1 inhibitor derivatives were prepared.

- Dunkel P, Túrós G, Bényei A, Ludányi K, Mátyus P: *Synthesis of novel fused azecine ring systems through application of the tert-amino effect. Tetrahedron* 2010; 66:2331-2339.
- Dunkel P, Gelain A, Barlocco D, Haider N, Gyires K, Sperlággh B, Magyar K, Maccioni E, Fadda A, Mátyus P: *Semicarbazide-sensitive amine oxidase/vascular adhesion protein 1: Recent developments concerning substrates and inhibitors of a promising therapeutic target. Curr Med Chem* 2008; 15:1827-1839.

## PÉTER ERDÉLYI (2011)

### Designing, preparation and biological testing of valdecoxib analogues

Supervisor: Péter Mátyus

The developing of selective COX-2 inhibitors provided novel therapy for the physicians to treat chronic inflammation and pain. In contradiction to the traditional non steroidal anti-inflammatory drugs, coxibs are expected to offer a more favourable side-effect profile as drawn up in guidelines of their developments. The success of celecoxib having been experienced by the market, rofecoxib and valdecoxib were withdrawn because of their unforeseen and serious cardiovascular events they caused. We attempted to develop novel, but less selective COX-2 inhibitors with improved adverse-effect profile.

In the present thesis we introduced the syntheses and pre-screening of 28 close analogues of valdecoxib. Among them the *N*-hydroxy-valdecoxib, which is known as a phase I. metabolite of valdecoxib, showed significant efficacy. We were able to eliminate the instability of this compound derived from its structure by forming its stable monohydrate by means of crystallization. It was proved to possess equivalent or higher, and more favourable efficiency than that of valdecoxib by *in vivo* pharmacological assays. We concluded that *N*-hydroxy-valdecoxib metabolized to valdecoxib in rats so it is a prodrug of valdecoxib, and being an NO-release molecule it might have favourable cardiovascular side-effects.

- Erdélyi P, Fodor T, Kis-Varga Á, Czugler M, Gere A, Fischer J: *Chemical and biological investigation of N-hydroxy-valdecoxib: An active metabolite of valdecoxib. Bioorg Med Chem* 2008; 16:5322-5330.
- Havemeyer A, Grunewald S, Wahl B, Bittner F, Mendel R, Erdelyi P, Fischer J, Clement B: *Reduction of N-hydroxy-sulfonamides, including N-hydroxy-valdecoxib, by the molybdenum-containing enzyme mARC. Drug Metab Dispos* 2010; 38:1917-1921.

**ÁGOTA ANNA FÖLDI (2011)****New extension of *tert*-amino effect: Synthesis of naphthazepine- and naphthazonine ring systems***Supervisor: Péter Mátyus*

The term '*tert*-amino effect' was introduced by Meth-Cohn and Suschitzky in 1972, to describe the thermal rearrangement of *ortho*-substituted *tertiary* anilines *via* cyclization to benzofused aza-ring systems. The extensions of *tert*-amino effect to biaryl or triaryl systems were studied in our Institute, in which the *ortho*-positioned *tert*-amino and vinyl groups are situated on aryl rings that are connected directly or linked by a third aryl ring. Following this line in my Ph.D. studies, we decided to study *ortho*-fused aromatic ring systems, the prototype of which is naphthalene, possessing key functionalities in *peri*-positions. Our aim was to explore the new extension of *tert*-amino effect in the synthesis of new *ortho*- and *peri*-fused naphthazepine and naphthazonine ring systems.

The most important results could be summarized as follows. Novel straightforward syntheses of naphtho-fused azepines and benzazonine *via tert*-amino effect were observed. Starting from 1-naphthylamine 8-*N,N*-dialkylaminonaphthalene-1-carbaldehydes were obtained in three steps. The 8-(2-*N,N*-dialkylamino)-naphthalene-1-carbaldehydes were prepared by a Suzuki reaction of 8-bromonaphthalene-1-carbaldehyde with the convenient phenylboronic acid. Treatment of aldehydes with active methylene compounds afforded novel naphthazepines and benzazonine, respectively; through rearrangement of isolable vinyl intermediates or benzo[*de*]quinolinium derivatives, or without isolation of any intermediates. A mechanistic investigation supported an intramolecular hydride transfer in the rate limiting step. Our results indicate that the *tert*-amino effect provide a valuable approach to the synthesis of *ortho*- and *peri*-fused aza-ring systems. Aminomethyl azepines were prepared from dicyanoazepines for biological investigations. Two compounds have been found to exhibit significant inhibitor activity on semicarbazide sensitive amine oxydase enzyme, which forms a rational basis for further studies.

Structure of new compounds were studied by X-ray analysis to recognise interesting non-bonding interactions.

- Földi ÁA, Ludányi K, Bényei ACs, Mátyus P. *Tert-Amino effect in peri-substituted naphthalenes: Syntheses of naphthazepine and naphthazonine ring systems.* Synlett 2010; 14:2109-2113.
- Dajka-Halász B, Földi ÁA, Ludányi K, Mátyus P. *Study of tert-amino effect: The role of substituents in isomerization of 5-amino-4-vinyl-3(2H)-pyridazinones.* Arkivoc 2008; 3: 102-126.
- Mátyus P, Dajka-Halász B, Földi Á, Haider N, Barlocco D, Magyar K. *Semicarbazide-sensitive amine oxidase: Current status and perspectives.* Curr Med Chem 2004; 11: 1285-1298.

**VIKTOR HORVÁTH (2011)****Studies on the dynamical behavior and the mechanism of new oscillatory chemical systems***Supervisor: Krisztina Kurin-Csörgei*

In my thesis the results of my research work on the field of nonlinear chemical dynamics are summarized. These results are related to three areas of nonlinear chemical dynamics: my aim was to study temporal and spatial oscillations observed in chemical systems, to de-

velop mechanisms and to model known oscillators, and to produce new chemical oscillating systems based on design.

For studying the oscillations and the pattern formation the bromate – dual substrate (hypophosphite and acetone) – dual catalyst (Mn(II) and Ru(II)) system have been used. Our goal was to develop a mechanism which explains the experimentally observed temporal and spatial behavior of the system. The total system was broken up to subsystems which were separately studied. The bromate – Ru(II) – bromoacetone subsystem was identified as core oscillator which is capable of producing similar dynamics observed in the total system. The unknown rate constant of some reactions were measured and used in the mechanism. A 14-step mechanism was suggested to simulate both the dynamics of the subsystems and the oscillations observed in the total system.

A recently published design method for producing oscillations in the concentrations of ions possessing only a single stable non-zero oxidation state was used to induce oscillations in the concentration of  $F^-$  by coupling the pH dependent hydrolysis of  $Al^{3+}$  and the consecutive aluminium-fluoride complex formation to the  $BrO_3^- - SO_3^{2-} - Mn^{2+}$  pH-oscillator.

A slight modification of the original method enabled us to extend the number of cations which participate in oscillatory process. With the new version of the method, which is based on coupling a redox core-oscillator to irreversible chemical reactions, we successfully induced oscillations in the concentrations of some divalent metal ions like  $Ca^{2+}$ ,  $Cd^{2+}$ ,  $Zn^{2+}$ ,  $Co^{2+}$ ,  $Ni^{2+}$ .

- Szalai I, Kurin-Csörgei K, Horváth V, Orbán M: *New Experimental Data and Mechanistic Studies on the Bromate-Dual Substrate-Dual Catalyst Batch Oscillator*. *J Phys Chem A* 2006; 110:6067-6072.
- Kurin-Csörgei K, Horváth V, Orbán M: *Chemical origin of the sustained-like pattern formation observed in the bromate - Dual substrate - Dual catalyst oscillatory batch system* *React. Kinet Catal Lett* 2007; 90:405-411.
- Horváth V, Kurin-Csörgei K, Epstein IR, Orbán M: *Oscillations in the Concentration of Fluoride Ions Induced by a pH Oscillator*. *J Phys Chem A*, 2008; 112:4271-4276.

## MÓNIKA HUSZÁR (2011)

### Determination of optimal lipophilicity and phospholipophilicity range by different potential anti-tumor molecules and NOX inhibitors

Supervisor: Miklós Idei

In this study four molecule libraries have been characterised using “early ADME(T)” parameters, such as lipophilicity, phospholipophilicity, permeability. Out of the four molecule libraries, three were studied as potential antitumour drug molecules and one as a group of NOX-4 inhibitor candidates. Our aim was to perform a complete correlation analysis between the biological and the physico-chemical data and to study the structure-activity relationship. - Chromatographic separation was carried out on all of the four molecule libraries. Applying the performed highly effective and fast methods, geometric isomers (trans and cis isomers) could be separated and measured simultaneously.

- Linear correlation was found between the calculated and measured lipo- and phospholipophilicity values.
- Molecules having the same *CLOGP* values could also be separated chromatographically. It proves the importance of the measuring procedure compare to the calculation method.



- Two columns, such as reversed phase and immobilized artificial membrane columns were characterised using four different molecule libraries.
- Permeability, therefore the penetration ability of the potential drug molecules has also been studied applying PAMPA method.
- Our aim was to perform a method where as much ADME(T) parameters as possible are used to establish an optimal range of the biological and physico-chemical data. Using this range a general trend could be created which might be applicable to define the druglikeness behaviour of a potential drug molecule. In our study, the optimal range proved to be at middle lipo- and phospholipophilicity values for the potential anti-tumour drug compounds and at low lipo- and phospholipophilicity for the NOX-4 inhibitors.

Our results proved that the correlation analysis between the physico-chemical and biological data and generally the “early ADME(T)” characterisation is an important and efficient part of the drug discovery. It can be perfectly used to separate the effective from the non-effective, the useful from the not so promising molecules.

- Huszar M, Varga A, Horvath A, Lorand T, Agocs A, Idei M, Mandl J, Vantus T, Keri G: *Comparative characterization of experimental and calculated lipophilicity and anti-tumour activity of isochromanone derivatives. Curr Med Chem* 2010; 17:321-333.
- Huszár M, Hallgas B, Idei M, Kiss-Szikszai A, Horváth A, Patonay T: *Lipophilicity of substituted aurones and related compounds measured on immobilized artificial membrane (IAM) and conventional C8 (MOS) columns. J. Liq. Chrom. Rel. Technologies* 2008; 31: 3143-3158.

## ANDRÁS INOTAI (2011)

### **Pharmacoeconomic aspects of oral nonsteroidal anti-inflammatory drugs in rheumatoid arthritis focusing on the selective COX-2 inhibitor celecoxib**

*Supervisor: Ágnes Andrea Mészáros*

Although disease modifying antirheumatic drugs (DMARDs) gain increasing importance in the treatment of rheumatoid arthritis (RA), there are still many patients who need nonsteroidal anti-inflammatory drug (NSAID) medication. The selective Cyclooxygenase (COX)-2 inhibitors – despite their favourable gastrointestinal (GI) side effect profile – are not adequate for every patient, mainly due their cardio-vascular side effects and significant price premium. This study analyses the pharmacoeconomic aspects of oral NSAIDs in RA, focusing on the selective COX-2 inhibitor celecoxib. One of the main goals of this research was to determine the cost-effectiveness of celecoxib in average GI risk RA patients, compared to conventional NSAIDs and NSAID+PPI (proton pump inhibitor) combination therapy. We also intended to evaluate the NSAID therapy in a group of RA patients, with special focus on safety, quality of life and cost-effectiveness. The pattern of NSAID use of this study group was compared to the total consumption of the Hungarian population and other Central Eastern European countries, to depict actual regional trends of these drugs.

According to our model, combination therapy dominated celecoxib; further investigation is needed to determine the cost-effectiveness of celecoxib (possibly in combination with PPI) in high GI risk patients. In contrast, combination therapy was found to be cost-effective in average GI risk patients; consequently PPI co-prescription should be considered to a broader group of patients. In the RA study group, patients with current/previous GI events were much likely to be prescribed drugs associated with GI friendly side effect profile (meloxicam, celecoxib, etoricoxib), than patients with low GI risk. Similarly, safer NSAIDs



had higher consumption in our RA study group compared to the total Hungarian population. Our international drug utilization study showed that trends of NSAID consumption in Hungary were comparable to other countries in the region. Economic evaluations from other countries should be adopted carefully; otherwise their conclusion might be misleading due to different local settings. Consequently, results of our local technology assessment can contribute to improve the allocative efficiency of public resources in Hungary. The NSAID use in the RA study group was considered to be rational regarding safety and pharmacoeconomic aspects.

Bibliographic data of the three most significant publications considered by the Ph.D. candidate:

- Inotai A, Mészáros Á. *Economic evaluation of NSAID strategies in rheumatoid arthritis. Cost-effectiveness of celecoxib in Hungary. Int J Technol Assess Health Care* 2009; 25: 190-195.
- Inotai A, Hankó B, Mészáros Á. *Trends in the non-steroidal anti-inflammatory drug market in six Central-Eastern European countries based on retail information. Pharmacoeconom Drug Saf* 2010; 19:183-190.
- Inotai A, Rojkovich B, Mészáros Á. *The assessment of oral NSAID use in patients with rheumatoid arthritis in Hungary-a cross sectional non interventional study. Acta Pharm Hung*, 2010; 80:47-54.

#### KRISTÓF MÁRIO KOVÁCS (2011)

##### **Formulation of an intravenous dosage form comprising a poorly water soluble antifungal agent**

*Supervisor: Krisztina Ludányi*

Poor water solubility of active pharmaceutical ingredients is a great issue in pharmaceutical development. This issue is prominently important in formulating a liquid dosage form and is underlined by the fact that 10-30 % of marketed drugs have solubility problems and almost 60 % of compounds coming from early preclinical development exhibit low solubility.

The need to overcome this problem led to several methods of formulating parenteral or oral medications of poorly soluble chemicals, but choosing the appropriate technique, especially in case of parenteral administration is a complicated task. In the latter case it is also very important to pay attention to the physiology of the human body, including the possible haemolysing effect of the excipients, the pH of the composition and the effect of sterilization on the formulation.

The aim of my work was to formulate an intravenous solution containing an azole type antifungal (itraconazole, ketoconazole, miconazole). The model drugs can be used to parenterally treat the ever growing number of systemic mycoses, and the formulation of the composition expanded the choice of such preparations, which are presently quite limited.

A substantial solubility enhancement was achieved with the use of pH adjusters, co-solvents, surfactants and their optimal combinations. In case of miconazole a 42 000 fold, in case of ketoconazole an 9 000 fold increase in solubility was achieved, which in both cases exceeded the therapeutically effective dose. Optimization of the concentration of the excipients in the composition was performed in such a way that the solubilizing capacity of the preparation did not deteriorate, therefore the benefit/risk ratio was increased. The effect of sterilizing the composition containing miconazole was also evaluated and it was con-

cluded that both heat sterilization and sterilizing filtration – with certain restrictions – can adequately be used for the sterilizing of the composition. The storage time of the composition was determined by performing accelerated stability tests, during which the possible structure and quantity of the impurities and formed degradation products was determined using an LC-MS/MS method.

- Kovács K, Stampf Gy, Klebovich I, Antal I, Ludányi K. Aqueous solvent system for the solubilization of azole compounds. *Eur J Pharm Sci* 2009; 36:352-358.
- Kovács K, Antal I, Stampf Gy, Klebovich I, Ludányi K. Composition optimization and stability testing of a parenteral antifungal solution based on a ternary solvent system. *AAPS Pharm Sci Tech* 2010; 11:285-293.

## CSILLA MAJOR (2011)

### Self-medication in Hungary

Supervisor: Zoltán Vincze

Increasingly, people all around the world are taking care about their health. The number of non-prescription medicaments has increased during the past decades, among other reasons, because of the regarding of numerous prescription-bound medicaments.

Advertising and selling these non-prescription drugs is moving in the direction of liberalization in more and more countries, with the result that their advertising is permitted in many countries, and some countries even allow the availability of a variety of products from pharmaceutical outlets.

In order to establish better patient-pharmacist co-operation, marketing surveys were carried out in several pharmacies on non-prescription medicaments. With questionnaire of my own I have analysed the most important questions relating to self-medication with OTC drugs.

Half of the respondents take medicaments regularly, 65% of them watched advertisements about medicaments several times a day. Those of 40% surveyed consult a professionally-qualified person about their decision before buying non-prescription medicaments. The population obtains much information from the brochures enclosed with medicaments, and almost 70% of them read these brochures. According to their opinion, when buying nonprescription drug, pharmacists always recommend other possibilities as well, and they give details about the information concerning the application of the medicaments.

The objective was to determine the habits of the surveyed population concerning nonprescription medicaments, and, as a result, to assess the effects of advertisements. On the other hand they were looking for an answer to the question as to how could and should the public be given more assistance in connection with self-medication.

Some (34.9%) respondents believed that the effects of OTC medicines are exaggerated in advertisements. According to 58.2% of professionals, members of the public are aware of the medicine that is currently being advertised, but not of other medicines with similar effects. The results of this Ph.D. thesis could be the basis of the Hungarian protocol, development.

- Major C, Vincze Z: Consumer habits and interests regarding non-prescription medications in Hungary. *Family Practice* 2010; 0:1–6 doi:10.1093/fampra/cmp105
- Major C, Vincze Z: Self-medication in Hungary from the perspective of pharmacy workers. *Acta Poloniae Pharmaceutica Drug Research*, 2010; 67:547-554
- Major C, Vincze Z, Meskó A, Balogh J, Zelkó R, Németh E: Gyógyszerelés a rendelőn kívül. *Orv Hetil* 2007; 148:291-298.

**SZABOLCS SZARKA (2011)****Studies on the thiophene metabolism in genetically transformed hairy root cultures of *Tagetes patula* L.***Supervisor: Éva Szőke*

The roots of *Tagetes patula* L. (French marigold) accumulate a wide range of sulphur-containing thiophenes having remarkable biocide effects. The purpose of our work was to produce *T. patula* hairy root clones by the *Agrobacterium rhizogenes* mediated genetic transformation and to study the biomass and special metabolite production in order to select the optimal hairy root line. A new gas chromatographic method coupled with mass spectrometric detection (GC-MS) was developed, optimized and validated for the simultaneous analysis of thiophene compounds in the complex biological matrix. Several hairy root clones formed after the genetic transformation by *A. rhizogenes*. The #TpA6 hairy root had the highest biomass formation and thiophene production among the clones studied; therefore it was selected for further experiments. The maximal  $\alpha$ -T content ( $212 \pm 58.3 \mu\text{g/g}$ ) was observed at the end of the third week, during the intensive growing period. The content of three thiophenes [BBT, BBTOAc, and BBT(OAc)<sub>2</sub>] in hairy root tissues exceeded significantly the contents in the roots of intact field-grown plants. A 2-fold increase of the  $\alpha$ -T content was observed on the MS medium with reduced nitrogen content (1/2 NMS). The selection of the optimal culture medium was followed by the study of the effects of different sulphur-sources. Increasing the MgSO<sub>4</sub>.

concentration resulted 1.5-fold increase of  $\alpha$ -T and BBTOAc contents. Cysteine increased the thiophene amounts significantly, however, considerably inhibited the biomass formation in a dose-dependent manner. Whereas, the biomass yield was not affected by the methionine added. Moreover, 1.0 mM methionine caused a 2.4-fold increase in the BBT content, and a 1.3-fold increase in the AcOCH<sub>2</sub>BBT content.

The results of our studies suggest that the *T. patula* #TpA6 hairy root tissue cultures had fairly stable biomass production and remarkable long-term biosynthetic potential. Consequently it seems to be a promising in vitro plant tissue culture system that can be used for the large-scale biotechnological production of thiophenes.

- Szarka Sz, Gyurján I, László M, Héthelyi É, Kuzovkina IN, Lemberkovics É, Szőke É. GC-MS studies of thiophenes in the supercritical fluid CO<sub>2</sub> and solvent extracts of *Tagetes patula* L. *Chromatographia*, 2010; 71:1039-1047.
- Szarka Sz, Héthelyi É, Kuzovkina IN, Lemberkovics É, Szőke É. GC-MS method development for the analyses of thiophenes from solvent extracts of *Tagetes patula* L. *Chromatographia*, 2008; 68:S63-S69.
- Szarka Sz, Héthelyi É, Lemberkovics É, Kuzovkina IN, Bányai P, Szőke É. GC and GC-MS studies on the essential oil and thiophenes from *Tagetes patula* L. *Chromatographia*, 2006; 63:S67-S73.

**BLANKA TÓTH (2011)****Chromatographic properties of molecularly imprinted polymers***Supervisor: György Horvai*

The subject of my thesis is the investigation of molecularly imprinted polymers (MIP), in particular with respect to their analytical applications.

MIPs are selective sorbents. Selective adsorption is a practically useful property, e.g., in environmental technology, in chemical industry and in analytical chemistry. This explains the wideranging interest for MIPs.

The adsorption isotherms of MIPs are usually nonlinear even down to very low concentrations. The far reaching consequences of this nonlinearity have not been fully recognized yet. Some of the important consequences are being described in my thesis.

I have created and verified a novel experimental method for detecting the nonlinear chromatographic behavior of MIP stationary phases in the concentration range of their intended application. I have proved the nonlinear chromatographic behavior of a phenytoin imprinted MIP made with methacrylic amide functional monomer in the pores of a modified silica stationary phase.

I have proved both by experiments and by computer modeling that the characterization of MIPs by chromatographic experimental parameters like  $k$ ,  $\alpha$  and the imprinting factor (IF) is not appropriate. I have discovered that these parameters, which are all based on measuring the position of the peak maximum, show an unexpected dependence on apparently irrelevant experimental data like the length or inner diameter of the chromatographic column.

I have shown experimentally and by computer modeling that competition between coinjected analytes is much less discernible in MIP HPLC than in non-transient techniques like batch competitive binding assays or sensors.

- Tóth B, László K, Horvai G: *Chromatographic behavior of silica-polymer composite molecularly imprinted materials*, *J. Chromatogr A*. 2005; 1100:60-67.
- Tóth B, Pap T, Horvath V, Horvai G: *Nonlinear adsorption isotherm as a tool for understanding and characterizing molecularly imprinted polymers*. *J Chromatogr A* 2006; 1119: 29-33.
- Tóth B, Pap T, Horvath V, Horvai C: *Which molecularly imprinted polymer is better?* *Anal Chim Acta* 2007; 591:17-21.

## **PROGRAM 3/2.**

### **EXPERIMENTAL AND CLINICAL PHARMACOLOGY**

#### **Coordinator:**

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**Program Overview:** The topic of pharmacokinetics becomes increasingly important for studying bioequivalence and planning modern drug preparations for optimal drug treatment. The study of the mechanism of drug action by pharmacodynamic tools aims at recognising new active substances and various opioid receptor types and subtypes. It is advised to get acquainted with their physiological and pathophysiological role in the development of opioid dependence or in the protection of gastric mucosa. The Program also covers the research into the metabolism of neurotransmitters in the CNS in order to elucidate the relationship between disturbances of neurotransmission and certain psychiatric disorders. Research in the field of presynaptic regulation of the neurochemical transmission in the peripheral and central nervous system is also included in the Program. Investigation of compounds affecting calcium and bone metabolism is also carried out. The mode of action

of cardiovascular drugs and endogenous substances are planned to be tested, as well as antihypertensive agents in order to find optimal treatment of the diseases. Anticancer agents are involved in the studies to improve the effectiveness of the treatment. Structure activity relationship studies, including the chirality of drugs is also part of the Program.

**Experimental and clinical pharmacology*****Drug and mechanism-oriented pharmacodynamic studies***

Central and peripheral mechanisms as potential drug targets

The role of ORL-1 receptor-mediated neuromodulation in the central autonomic control

The role of local mediators in vascular reactions, functional integrity of mucosa and the adrenomedullar-functions

Receptor-mediated protection of the gastrointestinal mucosa

Analysis of the centrally-mediated protection of the gastrointestinal mucosa

The role of opioid receptors in the cellular immunomodulation

Mechanisms of spinal and supraspinal opioidergic control of pain perception

**Kálmán Magyar*****Klára Gyires***

Zsuzsanna Fürst

András Rónai

Klára Gyires

Klára Gyires

László Köles

Julianna Kardos

Riba Pál

***Pharmacokinetic and drug metabolism studies***

Drug pharmacokinetic studies in humans, and animal experiments

Regulation of extrahepatic cytochrome P450 enzymes; the role of inhibition of drug metabolism in drug interactions

Studies on induction of cytochrome P450 enzymes

Studies on drug interactions

Studies on metabolic drug interactions

Neuropsychopharmacology, drug discovery and development

Selective detection methods in studies of xenobiotic metabolism

Pharmacometric analysis of bioequivalence studies

Application of DNA microarray technology in pharmacodynamics

Application of quantitative electroencephalography (qEEG) in drug research

Studies on drug effects on outcome of pregnancy

Analysis of teratogenic effects and circumstances of drug use during pregnancy

***Imre Klebovich***

Imre Klebovich

Károly Tihanyi

László Vereczkey

László Vereczkey

Katalin Monostory

György Lévay

István Hazai

László Tóthfalusi

László Tóthfalusi

László Tóthfalusi

Zoltán Kazy

Ferenc Bánhidó

***Modulation of neurochemical transmission by drugs; neurodegenerative and neuroprotective mechanisms***

Analysis of correlation among nociceptinerg, nocistatinerg and biogenaminerg systems

***Kornélia Tekes***

Kornélia Tekes

Biochemical basis of affective and anxiolytic disturbances	Kornélia Tekes
Animal models for studies of drugs affecting neurochemical transmission	Júlia Tímár
Studies on the effect of streptozotocin-induced diabetes on neurochemical transmission	Júlia Tímár
Neurochemistry of mental diseases	Gábor Faludy
Investigation of neuroprotective and neuroregenerative effects	Kálmán Magyar
Studies on the role of nitric oxide synthase and transcription factors in neurodegenerative and neuroprotective processes	Éva Szökő
Biochemical basis of neuropsychiatric symptoms of chronic hepatic diseases	Ferenc Szalay
New experimental approaches for studies of potential drug candidates in the treatment of stroke	Gábor Szénási
<b><i>Preclinical and clinical cardiovascular pharmacological studies</i></b>	<b><i>Valéria Kecskeméti</i></b>
Effect of cardiovascular or other drugs on cardiac parameters (mechanical, electrophysiological) on isolated cardiac preparations under physiological and pathological conditions	Valéria Kecskeméti
<b><i>Preclinical and clinical cardiovascular pharmacological studies</i></b>	<b><i>Csaba Farsang</i></b>
Possibilities of drug treatment of macro- and microvascular diseases	Zoltán Járai
The role of imidazoline receptors in haemodynamic regulation in hypertension	Judit Kapocsi
Reduction of cardiovascular risks by antihypertensive drugs in chronic renal failure patients	István Kiss
Experimental and clinical cardiovascular pharmacological studies	Csaba Farsang
<b><i>Separation methods and their applications in pharmacological studies</i></b>	<b><i>Huba Kalász</i></b>
Investigation of fate of drugs in the body and their effects by chromatographic methods	Huba Kalász
Development and application of capillary electrophoresis methods in pharmacological research	Éva Szökő
<b><i>Studies on compounds affecting calcium- and bone metabolism</i></b>	<b><i>Péter Lakatos</i></b>
Studies on molecules and drugs affecting the calcium- and bone metabolism	Péter Lakatos



The effect of diseases and drugs of calcium- and bone metabolism  
on the mineral content, quality and mechanical competence  
of the bone

Csaba Horváth

Pharmacogenetics of the calcium metabolism

István Takács

***Human trials of anticancer drugs (controlled clinical  
pharmacological studies)***

**András Telekes**

Human studies on anticancer drugs, their mechanism of action  
and rational use

András Telekes

Clinical pharmacological studies and rational use of analgesic  
drugs

András Telekes

Clinical development of anticancer drugs

Sándor Kerpel-Fronius

***The role of ion-transport mechanisms in the pre-synaptic  
regulation of neurochemical transmission***

**Tamás Török**

The role of ion-transport mechanisms in the pre-synaptic  
regulation of neurochemical transmission

Tamás Török

***Ph.D. students***

Veronika Dóczy	ft
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Péter Lakatos  
Ferenc Bánhidý  
Kornélia Tekes  
András Telekes  
Pál Riba  
Éva Szökő

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Erzsébet Lackó	ft
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Reza Honarmand	f
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***Ph. D. graduates***

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András Rónai

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Katalin Pápai	ft	Imre Klebovits
Nashwan Shujaa Aldeen	ft	Klára Gyires
Syed Muhammad Nurulain	f	Huba Kalász

a, absolutorium; ft, full-time pt, part-time; f, foreign

## ***Abstracts of Ph.D. theses successfully defended in 2011***

### **ERZSÉBET KATÓ (2011)**

**Interaction of peptidergic, biogenic amine and amino acid transmitters in the integration of central and peripheral autonomic functions. Pharmacological characterization of some opioid derivatives and of  $\alpha_{2B}$  adrenoceptor**

*Supervisor: András Rónai*

The experiments covered by my thesis were related, either directly or indirectly, to the analysis of the interaction of neuropeptides and non-peptide neurotransmitters involved in the regulation of autonomic functions. The experiments were carried out partly in rat brain slice/prism preparations, prepared from areas considered as autonomic integrative centers; these were the nucleus tractus solitarius–dorsal motor nucleus of the vagus (NTS–DVN, “dorsal vagal complex”) and the hypothalamic paraventricular-subparaventricular nucleus. In these series, my task was to explore the advantages / disadvantages of “whole” slice versus “prism” preparations and find technical/experimental conditions to obtain more complex informations in the experimental settings. I studied the stimulation-induced release of tritiated norepinephrine, D-aspartate or  $\gamma$ -amino butyric acid and the modulation of release by peptide- and non-peptide drugs and also by neonatal pre-treatment with monosodium glutamate.

The isolated organ experiments served either i) to develop a specific nociceptin antagonist which was a prerequisite for possible further experimentation at that stage or ii) to characterize pharmacologically endomorphin derivatives and possible biosynthetic precursors to *de novo* endomorphin biosynthesis and iii) to develop a specific bioassay for  $\alpha_{2B}$  adrenoceptors, which is the adrenergic receptor subtype crucially involved in the initiation of an opioid peptide-mediated gastroprotection in the NTS–DVN (Gyires et al., 2000a, 2000c).

- Kató E, Lipták L, Shujaa N, Mátyus P, Gyires K, Rónai AZ: Alpha 2B adrenoceptor agonist ST-91 antagonizes beta 2 adrenoceptor-mediated relaxation in rat mesenteric artery rings. *Eur J Pharmacol* 2008; 580:361-365.
- Rónai AZ, Kató E, Al-Khrasani M, Hajdu M, Müllner K, Elor G, Gyires K, Fürst S, Palkovits M: Age and monosodium glutamate treatment cause changes in the stimulation-induced [ $^3H$ ]-norepinephrine release from rat nucleus tractus solitarius-dorsal vagal nucleus slices. *Life Sciences* 2004; 74:1573-1580.
- Szemenyei E, Barna I, Mergl Z, Keresztes A, Darula Z, Kató E, Tóth G, Rónai AZ: Detection of a novel immunoreactive endomorphin 2-like peptide in rat brain extracts. *Regul Pept* 2008; 148:54-61.

**KORNÉL KIRÁLY (2011)****The role of dipeptidyl peptidase IV enzyme and its inhibitors in the endomorphin 2 biosynthesis***Supervisor: András Rónai*

Since the discovery of the endomorphins (EM1: Tyr-Pro-Trp-Phe-NH<sub>2</sub> and EM2: Tyr-Pro-Phe-Phe-NH<sub>2</sub>) in 1997 they are claimed to serve as the selective endogenous agonists of the  $\mu$ -opioid receptors. They are highly selective but partial agonists, which is a rare property among endogenous ligands. EM2 is the dominant endomorphin in CNS regions involved in the primary processing of nociceptive information. In acute nociceptive tests the potency of endomorphins is much lower than it would be expected from their in vitro potencies. Endomorphins are inactivated primarily by dipeptidyl peptidase IV enzyme. Neither the precursor protein(s) nor the genomic code(s) for them are identified as yet.

Our group has proposed previously the possibility of a non-ribosomal, de novo biosynthetic pathway from di- and tripeptide fragments. We have also presumed that DPP IV might be causally involved in the biosynthesis, functioning as synthase. In the present experiments in rat isolated L4-L5 dorsal root ganglia I could demonstrate that the generation of immunoreactive EM2 was increased in the presence of high concentration of Tyr-Pro dipeptide. The addition of an inhibitor of the peptidase function of DPP IV, Ile-Pro-Ile, increased further EM2 generation in a depolarisation-sensitive manner. In the presence of Ile-Pro-Ile alone there was no detectable EM2. The tissue contents stayed far below the bath contents, which raised the possibility of an extracellular synthesis.

We hypothesized that the activation of C-fibers by maintained inflammation may model the in vitro conditions in spinal dorsal horn in vivo. I tested the antihyperalgesic action of intrathecally injected DPP IV inhibitors (Ile-Pro-Ile, vildagliptin) in a hyperalgesic model created by intraplantar carrageenan injection and measuring the nociceptive threshold to pressure by the Randall-Selitto method. Both inhibitors exerted antihyperalgesic effect which could be antagonized by co-injection of EM2 antiserum or naloxone/naltrexone pretreatment. Thus, the actions were opioid receptor-mediated and could be attributed to EM2 generation. Because the co-administration of biosynthetic precursor fragments was unnecessary, it was concluded that they must have been generated endogenously. The antihyperalgesic potencies of DPP IV inhibitors were similar to that of identically administered EM2. Intrathecally injected DPP IV inhibitors were completely ineffective in an acute nociceptive test, the rat tail-flick assay. Thus, there are differences in the role of EM2 generation in spinal dorsal horn in acute- and non-acute nociceptive information processing.

- Király K, Lambeir AM, Szalai J, Szentirmay A, Luyten W, Barna I, Puskár Z, Kozsúrek M, Rónai AZ: *The dipeptidyl peptidase IV (CD26, EC 3.4.14.5) inhibitor vildagliptin is a potent antihyperalgesic in rats by promoting endomorphin-2 generation in the spinal cord.* *Eur J Pharmacol* 2011; 650:195-199.
- Király K, Szalay B, Szalai J, Barna I, Gyires K, Verbeken M, Rónai AZ: *Intrathecal injection of Ile-Pro-Ile, an inhibitor of membrane ectoenzyme dipeptidyl peptidase IV, is antihyperalgesic in rats by switching the enzyme from hydrolase to synthase functional mode to generate endomorphin 2.* *Eur J Pharmacol* 2009; 620:21-26.
- Rónai AZ, Király K, Szebeni A, Szemenyei E, Prohászka Z, Darula Z, Tóth G, Till I, Szalay B, Kató E, Barna I: *Immunoreactive endomorphin 2 is generated extracellularly in rat isolated L4,5 dorsal root ganglia by DPP-IV.* *Regul Pept.* 2009; 157:1-2.

**KATALIN PÁPAI (2011)*****In vitro* study on ciprofloxacin-food interaction***Supervisor: Imre Klebovits*

For the prediction of food-drug interactions of the more commonly used chemotherapeutic agent – ciprofloxacin (CPFX) - next to the expensive *in vivo* studies *in vitro* dissolution studies are necessary, too. During my Ph.D. work I intended to evaluate the molecular background of the CPFX-milk/dairy products interaction using *in vitro* dissolution methods. Furthermore, I aimed to compare the *in vitro* data with earlier published *in vivo* results.

In order to determine the amount of dissolved CPFX in milky media – not depending on the fat content of the media - a solid phase extraction sample preparation, without precipitation of the proteins, followed by high performance liquid chromatography coupled mass spectrometry analytical method was developed, optimized and validated. The separation of CPFX and the internal standard (aripiprazol) was carried out with gradient elution; and selected ion monitoring was applied.

During the *in vitro* dissolution tests water, low- and high-fat milk, or appropriate amounts of calcium, casein or lactose – as milk components - were added to the dissolution media. At different pH values - simulating certain parts of the GIT – the dissolution of CPFX is pH-dependent. The low pH-values increase the dissolution of CPFX. In the presence of low-fat milk the amount of dissolved CPFX is significantly lower than in case of aqueous medium. The relatively low protein content of high-fat milk – being at about 30% less than that of low-fat milk – is in connection with the ~ 30% higher free CPFX amounts measured in high-fat milky media, in comparison to the low-fat ones.

Calcium reduced the amount of free CPFX at ~ 51-92%, while the presence of lactose caused 87-98% decrease in the dissolved amount of CPFX. According to my *in vitro* data, the presence of casein can be made responsible for the decreasing effect.

Not only the milk and dairy products, but also other foods with high protein content can have an influence on the pharmacokinetic of CPFX and can lead to inefficient clinical therapy and as a consequence of it to bacterial resistance. My results highlight the importance of correct patient information.

- Pápai K, Ludányi K, Budai M, Antal I, Klebovich I: *In vitro* studies on ciprofloxacin-milk interaction using LC-MS method (in Hung.), *Acta Pharmaceutica Hungarica* 2007; 77: 33-38.
- Füredi P, Pápai K, Budai M, Ludányi K, Antal I, Klebovich I: *In vivo* effect of food on absorption of fluoroquinolones. *Acta Pharmaceutica Hungarica* 2009; 79:81-87.
- Pápai K, Budai M, Ludányi K, Antal I, Klebovich I: *Analysis of ciprofloxacin in low- and high-fat milk by high performance liquid chromatography-mass spectrometry. Acta Chromatographica* 2010; 22:115-129.

**NASHWAN SHUJAA ALDEEN (2011)****Analysis of the role of cannabinoid receptors and 2- adrenoceptor subtypes in gastrointestinal functions***Supervisor: Klára Gyires*

This work aimed to analyze the role of cannabinoid CB<sub>1</sub> receptors and their endogenous ligands in the regulation of gastric mucosal integrity and to determine the  $\alpha_2$ -adrenoceptor subtype(s) responsible for the inhibition of gastric motility. Gastric mucosal protection; gastric

mucosal damage was induced by ethanol in rats. The cannabinoid agonists inhibited ethanol induced mucosal lesions after both peripheral and central administration. The anandamide uptake inhibitor AM 404 and FAAH inhibitor URB-597 also exerted gastroprotective effect against ethanol after central administration. This gastroprotective effect was mediated by activation of central CB<sub>1</sub> receptors. The gastroprotective effect of cannabinoids was prevented by opioid antagonists and reduced by endomorphin-2 antiserum. In conclusion it was demonstrated that the activation of central CB<sub>1</sub> receptors results in gastroprotective effect, and this effect is mediated at least partly by endogenous opioids. Gastric motility; The effect of  $\alpha_2$ -adrenoceptor agonists/antagonists on electrical field stimulation (EFS) induced contractions in isolated gastric fundus strips of rats, NMRI mice and  $\alpha_{2A}$ -,  $\alpha_{2B}$ - and  $\alpha_{2C}$ -adrenoceptor deficient mice was tested. In the rat and NMRI mice, clonidine, oxymetazoline and ST-91 inhibited the EFS-evoked contractions in a concentration dependent manner. This inhibition was reversed by the non-selective  $\alpha_2$ -adrenoceptor antagonist idazoxan and  $\alpha_{2A}$ -adrenoceptor antagonist BRL 44408, but not by the  $\alpha_{2B/2C}$ -adrenoceptor antagonist ARC-239. Clonidine and ST-91 inhibited the EFS-induced gastric contractions in  $\alpha_{2B}$ - and  $\alpha_{2C}$ -adrenoceptor deficient mice, but not in  $\alpha_{2A}$ -deficient mice. In conclusion, these results demonstrated that  $\alpha_{2A}$ -adrenoceptor subtype is purely responsible for the inhibition of gastric motility.

- Shujaa N, Zadori ZS, Ronai AZ, Barna I, Mergl Z, Mozes MM, Gyires K: *Analysis of the effect of neuropeptides and cannabinoids in gastric mucosal defense initiated centrally in the rat. J Physiol Pharmacol* 2009; 60(Suppl):93-100.
- Shujaa N, Al-Khrasani M, Zádori ZS, Rossi M, Mátyus P, Hein L, Gyires K:  *$\alpha_2A$ -adrenoceptor agonists-induced inhibition of gastric motor activity is mediated by  $\alpha_2A$ -adrenoceptor subtype in the mouse. Neurochem Int* 2011; 58:708-713.
- Zádori ZS, Shujaa N, Fülöp K, Dunkel P, Gyires K: *Pre- and postsynaptic mechanisms in the clonidine- and oxymetazoline-induced inhibition of gastric motility in the rat. Neurochem Int* 2007; 51:297-305.

#### SYED MUHAMMAD NURULAIN (2011)

##### ***In vivo* efficacy of eight new bisquaternary k-oximes in comparison to 2-pam and obidoxime against rat with paraoxon and dfp intoxication**

*Supervisor: Huba Kalász*

There are diversified groups of organophosphorus compounds ranging from moderate toxic insecticides to deadly poison nerve agents but all have same mechanism of action that is inhibition of AChE. Oximes are the compounds used to reactivate the inhibited AChE. The present study was undertaken to evaluate the *in vivo* death preventing efficacy of eight new oximes (K-oximes). Paraoxon and diisopropylfluorophosphate were used as OP AChE inhibitor. The efficacy was compared with two therapeutically available oximes, pralidoxime and obidoxime whose efficacy has been controversial in clinical use. Intrinsic lethal effect of oximes in terms of LD<sub>50</sub> and LD<sub>01</sub> was also determined. Moreover, the *in vivo* results were compared with the *in vitro* findings of the same compounds to predict whether *in vitro* system is sufficient to translate the result for therapeutic use. LogP values of the oximes were also calculated by software.

The *in vivo* efficacy data shows that established oximes 2-PAM is poor in efficacy against both paraoxon and DFP. Obidoxime is good for DFP but not for paraoxon. Among the eight new K-oximes, K-027 was found to be the superior to all the tested oximes (established and experimental) against both paraoxon and DFP. The order of efficacy of the oximes against

paraoxon was K-027 > K-048 > K-075 > K-053 > K-074 > Obidoxime > K-107 > K108 > 2-PAM > K-113 and against DFP was K-027 > Obidoxime > K-053 > K-048 > K-075 > K-074 > 2-PAM > K-113. Paraoxon induced toxicity data did not reveal correlation with comparable *in vitro* parameters but DFP data revealed showed moderate to strong correlation, suggesting that the mechanism of action of oximes include some other physiological processes, in addition to AChE reactivation.

The calculated LogP result shows that all the tested oximes were hydrophilic, suggesting that oximes do not cross the blood brain barrier by simple passive diffusion. Conclusively, it is suggested that K-027 appears to be a promising oxime and may be a candidate for future clinical oxime. However, more study is needed to translate the work for human use.

- Nurulain SM, Lorke DE, Hasan MY, Shafiullah M, Kuca K, Musilek K: *Efficacy of eight experimental bispyridinium oximes against paraoxon induced mortality: Comparison with the conventional oximes pralidoxime and obidoxime. Neurotox Res* 2009; 16:60-67.
- Lorke DE, Hasan MY, Nurulain SM, Kuca K, Schmitt A, Petroianu G: *Efficacy of two new assymetrical bispyridinium oximes(K-27 and K-48) in rats exposed to diisopropylphosphate comparison with pralidoxime, obidoxime, trimedoxime, methoxime, and HI-6. Toxicol Mech Methods* 2009; 19:327-333.
- Lorke DE, Nurulain SM, Hasan MY, Kuca K, Musilek K, Petroianu GA: *Eight new bispyridinium oximes in comparison with the conventional oximes pralidoxime and obidoxime: in vivo efficacy to protect from diisopropylfluorophosphate toxicity. J Appl Toxicol* 2008; 28:920-928.



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## SCHOOL OF PH.D. STUDIES

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### 4. MENTAL HEALTH SCIENCES

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**Chairman:**

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**General overview:** The Ph.D. training and research programs of the Mental Health Sciences Doctoral School of Semmelweis University aim to offer research areas and methodological training for those interested in conducting research in *psychiatry, behavioural and mental health sciences as well as in community and social mental health*. The school promotes initiatives relating to preventative medicine. One of its goals is to facilitate the Ph.D. candidates' skills for promoting their research topic in public and provides feedback on their academic competence during the Ph.D. training period.

Our research projects highlight the interactions between clinical neurosciences, social sciences, mental health and in various other helping professions. Our school is proud to have a history of promoting interdisciplinary research.

We offer insight into research areas and the methodology of social sciences for all the Ph.D. students of Semmelweis University who are interested in attending our courses. Furthermore, the inter-disciplinary feature of our doctoral school manifests itself in the basic principle of its training philosophy; i.e. Ph.D. students with state scholarships and Ph.D. candidates entering into the qualification phase (without training) should become familiar with the theoretical terminology and methodology of both the natural and social sciences. However, our school is prepared to welcome only such titles of research projects which can be researched and evaluated by the principles of natural sciences.

Our school promotes methods which facilitate this process (e.g. methods of epidemiology, representative surveys, comparative studies etc.).

### **PROGRAM 4/1.**

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#### **PSYCHIATRY**

**Coordinator:**

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**Program overview:** This program offers education and research possibilities for medical doctors, psychologists and other eligible persons in behavioural sciences, clinical psychology and in neurobiological, psychosocial, diagnostic and treatment aspects of psychiatric disorders. The research profile of the program has considerably widened in the last few

years. New research topics include psychiatry, genetics and psychophysiology, as well as cognitive neuropsychology and social cognition in several psychiatric diseases, including psychotic disorders and adult ADHD. Another important area covers methodological research in the field of clinical psychopharmacology in cooperation with genetics, biochemistry and bioinformatics.

### ***Titles of research projects***

Genetic factors and gene and environment interactions in psychiatric disorders: The NEWMOOD study  
 Psychiatric disorders in children and adolescents  
 Clinical psychopharmacology  
 Psychophysiological and neuropsychological mechanisms of psychiatric disorders  
 Common neuropsychological mechanisms of psychiatric disorders  
 Survey of electroconvulsive therapy's clinical use  
 Emidemiology, clinical and psychosocial characteristics of the addictive diseases  
 Mental deficits in the developmental psychopathology  
 Intermediate phenotypes of depression: a functional magnetic resonance brain imaging (fMRI) study  
 The application of neuro-cognitive tests in psychiatric disorders  
 Family pathology and communication  
 Sleep disorders in patients with chronic kidney diseases  
 The research of factors relating to the quality of life of patients with organ transplant  
 The psycho-social aspects of chronic diseases  
 Sleep disorders among chronic kidney diseases patients  
 Experimental behavioural physiology and pharmacology  
 The role of the disturbed circadian rhythm in the development and procession of comorbid psychiatric disorders and conditions of internal medicine  
 The research of energetic aspects of mental health by the use of actigraphy  
 Clinical and biological aspects of affective disorders  
 Molecular psychiatry: genetic, epigenetic, genomic and proteomic studies of psychiatric disorders  
 Virtual Reality therapy  
 The recognition and expression of emotions in psychiatric disorders  
 Biological aspects of some sleep disorders  
 Measurement of affective temperaments among patients with chronic illnesses (hypertension, diabetes, obesity)

### ***Supervisors***

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 Lajos Simon  
  
 Lajos Simon  
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Psychotherapy in the medical practice  
Epidemiology of eating disorders

László Tringer  
Ferenc Túry

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Zsuzsanna Somlai	pt
Johanna Takács	pt
László Tombor	pt

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István Bitter

### ***Supervisor***

Lajos Simon

ft, full-time; pt, part-time; na, not affiliated

## ***Abstract of successfully defended Ph.D. thesis***

**ERIKA SZILY (2011)**

### **Cognitive and genetic aspects of emotional reactions in depression**

*Supervisor: Lajos Simon*

**Aims:** We investigated two aspects of emotion regulation dysfunctions of mood disorders and vulnerability. First, we addressed the relationship between the polymorphism of the serotonin transporter and emotion appraisal in healthy volunteers. In the second study, we

investigated the recognition of complex social emotions in patients with major depressive disorder, taking into consideration the presence or absence of basic symptoms of psychotic experiences. *Methods:* In our first study, we genotyped the 5-HTTLPR gene of 114 healthy individuals (s-carriers: 79, non-carriers: 35). Genotyping was performed at the University of Szeged and the Rutgers University, according to the methods of Lesch et al (1996). Emotion appraisal was assessed using Scherer's appraisal questionnaire. We compared emotion appraisal profiles in the case of negative (fear and sadness) and positive (joy) emotions as a function of serotonin transporter gene allelic variations. In the second study, participants were 68 young persons with major depressive disorder. Twenty-six patients also met the criteria of attenuated or brief limited intermittent psychotic symptoms according to the Comprehensive Assessment of At Risk Mental States (CAARMS) criteria. The healthy control group included 50 volunteers. Patients were assessed with the CAARMS instrument to evaluate psychosis risk. Subjective experiences were assessed with the BSABS scale. Recognition of complex social emotions and mental states was assessed using the 'Reading the Mind in the Eyes' test. The dependent measure was the percentage of correctly identified mental states. *Results:* In study 1, in the case of fear and sadness, there was a significant two-way interaction between genotype and appraisal ( $p < 0.0001$ ). The post-hoc tests revealed that s-carriers achieved higher scores than non-carriers for unpleasantness ( $p < 0.05$ ) and goal-hindrance ( $p < 0.01$ ). In contrast, s-carriers achieved lower scores than non-carriers for coping ( $p < 0.05$ ). Finally, in the case of joy, there was no interaction between genotype and appraisal ( $F < 1$ ,  $p > 0.1$ ). In study 2, depressed patients without psychosis risk were able to recognize fewer negative social emotions ( $p = 0.02$ ), whereas there were no significant differences for positive social and cognitive expressions ( $p > 0.1$ ). Patients with psychosis risk were also impaired on the recognition of negative social emotions ( $p = 0.004$ ), and they displayed additional deficits in the case of cognitive expressions ( $p = 0.009$ ). In the healthy control group and in patients without psychosis risk, there was no significant correlation between BSABS and RME scores ( $R < 0.2$ ,  $p > 0.1$ ). In the high-risk group, only self-disorder showed a significant correlation with RME scores. *Discussion:* In study 1, our data demonstrate that participants with the s-variant experience negative emotions more unpleasant, more influential and disruptive on personal goals, and feel less able to cope with these emotions. These results are consistent with previous findings suggesting that the s-variant of the serotonin transporter gene is associated with anxiety- and depression-related traits, poorer problem-solving strategies and less efficient coping in stressful situations. In study 2, depressed patients with high psychosis risk showed impaired recognition of cognitive expressions, which was not observed in patients without psychosis risk. This is especially interesting, because it has been suggested that depressed patients show social perception and 'theory of mind' disabilities. Our data indicate that theory of mind impairments are confined to negative social expressions in depression.

- Szily E, Kéri S: Anomalous subjective experience and psychosis risk in young depressed patients. *Psychopathology* 2009; 42:229-235.
- Szily E, Bowen J, Unoka Z, Simon L, Kéri S.: Emotion appraisal is modulated by the genetic polymorphism of the serotonin transporter. *J Neural Transm* 2008; 115:819-822.
- Szily E, Kéri S. Emotion-related brain regions. *Ideggyogy Sz* 2008; 6:77-86.

**PROGRAM 4/2.****BEHAVIOURAL SCIENCES****Coordinator:****Mária KOPP M.D., Ph.D., D.Sc. †**

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**Program Overview:** The behavioural sciences constitute an integrative field which bridge the paradigms of natural and social sciences. They study human behaviour in a biological, psychological and social perspective, and provide an opportunity for establishing and analysing the components of healthy behaviour, the psychological and social risk factors of diseases, as well as investigating the background of self-destructive conduct and the development of attitudes to protect health. They examine the regularities and the possibilities of developing human behaviour from an interdisciplinary and integrative perspective relying on achievements of Medicine, Psychology, Sociology, Anthropology, Bioethics, Neuroanatomy and Neurophysiology. At the present time, the prevention and successful treatment of diseases which impact on public health cannot rely entirely on a biomedical approach since the behavioural risk factors are highly influenced by psychological and social factors. The professional Program follows the analogue one of Johns Hopkins University (Baltimore, Maryland, USA).

***Titles of research projects***

Psychosocial and inherited factors in depression and addiction  
 Examination of relationships and causal contexts of chronic stress (conjugal, work-related, social) and depressive, distressful symptoms and cardio-vascular diseases  
 Possible methods for measuring and assessing health care, services and deliveries in Hungary  
 The relationships between sleep, cognitive activity and affective processes  
 The function and significance of the social capital in the healthcare system  
 Development of early attachment: Stress reactivity and parental care  
 Genetic and environmental influences on infant temperament and attachment  
 Relationships between health condition and personality traits among adolescents and young adults with special regard to suicidal behaviour  
 Mental health aspects of death, dying and bereavement  
 Behaviour redress and health psychology  
 Health and bioethics

***Supervisors***

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 Judit Gervai  
 Judit Gervai  
 Ágnes Hajnal  
 Katalin Hegedűs  
 Mária Kopp  
 József Kovács

Mental health, disorders and quality of life. Issues of intervention and prevention with special focus on elderly	Erika Mónika Kovács
Medical anthropology: cultural and intercultural aspects of diseases and their treatment	Imre Lázár
Questions of efficiency in curative and preventive communication	Erzsébet Németh
The social and health significance of disorders in sleep and awake state	Márta Novák
Gender differences in the disorders in sleep and awake state	Márta Novák
The significance of mood and anxiety disorders in patients suffering from chronic diseases	Márta Novák
Post-traumatic stress disorder (PTSD), trauma research	Dóra Perczel-Forintos
Suicide prevention	Dóra Perczel-Forintos
Study of youth's problem behaviour and mental health based on the risk and protective theory	Bettina Pikó
Study of youth's problem behaviour and mental health based on the risk and protective theory	Adrienn Stauder
Eating disorders and obesity- clinical aspects and prevention	Irena Szumska
Psychological assessment of eating disorders	Ferenc Túri

**Ph.D. students**

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Zoltán Cserhádi	ft
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Márta Novák
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Mária Kopp
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Mária Kopp
Katalin Hegedűs
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***Supervisors***

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Katalin Hegedűs
Márta Novák
József Kovács

ft, full-time, pt; part-time, na; not affiliated

***Abstracts of successfully defended Ph.D. theses in 2011*****MÁRIA ESZTER CZIRA (2011)****Assessment of the malnutrition-inflammation complex syndrome and its association with depression and mortality in patients after kidney transplantation**

*Supervisor: Márta Novák*

Protein-energy wasting and chronic inflammation are in a complex, multidimensional relationship, which can be often observed in chronic kidney disease patients. The recognition of this link lead to the description of a new syndrome, the malnutrition-inflammation complex syndrome (MICS). MICS is associated with several clinical conditions (erythropoietin resistance, endothelial dysfunction), and individual cardiovascular risk factor in dialyzed patients. Moreover, both the clinical symptoms and the potential pathophysiological pathways of MICS overlap with those of depression, which is one of the most common psychological disorders in patients with chronic kidney disease. To offset difficulties related to the measurement of MICS in clinical practice, recently a semi-quantitative scoring system, the Malnutrition-Inflammation Score (MIS) has been developed. In dialyzed patients the MIS showed independent association with depressive symptoms and predicted mortality. However, to date the MIS has not been used and the MICS was not assessed in kidney transplanted patients. In this study we adapted the MIS to kidney transplanted population, and examined for the first time its relationships with nutritional and inflammatory status in a cross-sectional design. According to our results the MIS reflects

both malnutrition and inflammation in this patient population, which renders MIS a reliable tool to assess MICS in kidney transplant recipients. In our cross-sectional analysis the MIS remained independently associated with the severity of depressive symptoms even after adjustment for several clinical and socio-demographic co-variables. Of all nutritional and inflammatory parameters the MIS showed the strongest and most robust association with depression. In the prospective part of our study we followed the patients and assessed the association between MIS and negative clinical outcome. In time-dependent, competing risks regression analysis the MIS was independent predictor of both mortality and return to dialysis even after correction for other risk factors. Our results call the attention to this inexpensive, easy-to-use tool that could be used for risk assessment in epidemiologic studies, and also in everyday clinical practice. Further studies are needed to assess if improvement of nutritional-inflammatory state would reduce the prevalence of depressive symptoms and risk of mortality in this patient population.

- Czira ME, Lindner AV, Szeifert L, Molnar MZ, Fornadi K, Kelemen A, Laszlo G, Mucsi I, Keszei AP, Kennedy SH, Novak M: Association between the malnutrition-inflammation score and depressive symptoms in kidney transplanted patients. *Gen Hosp Psychiatry*. 2011; 33:157-165.
- Molnar MZ, Keszei A, Czira ME, Rudas A, Ujszaszi A, Haromszeki B, Kosa JP, Lakatos P, Sarvary E, Beko G, Fornadi K, Kiss I, Rempert A, Novak M, Kalantar-Zadeh K, Kovesdy CP, Mucsi I: Evaluation of the Malnutrition-inflammation score in kidney transplant recipients. *Am J Kidney Dis* 2010; 56:102-111.
- Molnar MZ, Czira ME, Rudas A, Ujszaszi A, Lindner A, Fornadi K, Kiss I, Rempert A, Novak M, Kennedy SH, Rosivall L, Kovesdy CP, Mucsi I: Association of the malnutrition-inflammation score with clinical outcomes in kidney transplant recipients. *Am J Kidney Dis* 2011; 58:101-108.

## GYÖNGYVÉR HORVÁTHNÉ SALAVECZ (2011)

### The Association between work stress and health on national and international samples

*Supervisor: Adrienne Stauder*

Besides physical and chemical hazards, psychosocial stressors at work were shown to adversely affect the health of working people. The evidence linking psychosocial work stress with poor health is strong in Western societies but little is known about the effect of work stress in the post communist countries in Central-Eastern Europe. In this thesis we reported results of two researches with data of six nations' workers from four large scale epidemiological studies (N=18494). The first report investigated the association of work stress and health and well-being among Hungarian employees. The Effort-Reward Imbalance (ERI) model was predictive for various psychological health outcomes and well-being measures among Hungarian workers derived from the HEP 2006 Study. The components of the model, ERI and over commitment proved to be determinants of depression, psychological well-being, general happiness, self-reported health, severity of somatic symptoms, alcohol use disorders and BMI. The low degree of job security and social support at work were found to increase the risk of adverse health outcomes and well-being among Hungarian employees but further studies need to be clarified the role of control at work in health of Hungarian workers. The second investigation provides evidence of a strong association of components of ERI with poor self-rated health in working populations in Western European and Central-Eastern European countries. We did not find support one of our hypothesis, that the effect of work stress is stronger in the post-communist countries. These effects

were significant but weaker in Russia and Poland compared to Hungary, Czech Republic, Germany and the United Kingdom. The studies reported in this thesis demonstrate that the ERI model provides important measures for the evaluation of an adverse working environment. It is recommended that instrument based on ERI model is applied to screen risk factors and improve workplace conditions in the region of Western and Central-Eastern Europe also.

- Salavecz Gy, Chandola T, Pikhart H, Dragano N, Siegrist J, Jöckel K-H, Erbel R, Pajak A, Malyutina, Kubinova R, Marmot M, Bobak M, Kopp M: *Work stress and health in Western European and post-communist countries: an East–West comparison study. J Epidemiol Community Health* 2010; 64:57-62.
- László KD, Pikhart H, Kopp MS, Bobak M, Pajak A, Malyutina S, Salavecz Gy, Marmot M: *Job insecurity and health: A study of 16 European countries. Soc Sci Med* 2010; 70: 867-874.
- Kopp MS, Konkoly Thege B, Balog P, Stauder A, Salavecz Gy, Rózsa S, Purebl Gy, Ádám Sz: *Measures of stress in epidemiological research. J Psychosom Res* 2010; 69:211-225.
- Salavecz, G: *Munkahelyi Stressz és Egészség. In: Kopp Mária (szerk.): Magyar lelkiállapot. Semmelweis Kiadó, Budapest, 2008. pp. 288-298.*

#### ÁGNES ZSÓFIA KOVÁCS (2011)

##### **Factors associated with health-related quality of life in patients with chronic kidney disease**

*Supervisor: Márta Novák*

The research of health-related quality of life (thereafter quality of life) in chronic kidney disease (CKD) populations is getting more attention as the conventional clinical outcomes are not expected to improve significantly in the near future. Furthermore, the renal replacement therapies, such as dialysis or kidney transplant also influence the quality of life of the patients. In my first analysis among dialysis patients I studied illness intrusiveness which is postulated to mediate between the disease, its treatment and quality of life. First we translated the Illness Intrusiveness Rating Scale (IIRS), which is a valid reliable tool and tested the basic psychometric parameters of the Hungarian version. This analysis demonstrated good reliability and validity parameters. Subsequently we compared results obtained with the IIRS in North-American versus Hungarian dialysis patients. In this simultaneous confirmatory factor analysis we demonstrated factor invariance and 'very good' factor fit for the Hungarian version. In my next cross sectional study I investigated the relationship between sleep disorders and quality of life in a large group of CKD patients on chronic dialysis. We used standard, validated self-administered scales to assess the prevalence of restless legs syndrome (RLS), obstructive apnea and insomnia and health-related quality of life. We demonstrated that the presence of RLS was associated with worse quality of life even after adjusting for important socio-demographic and clinical parameters. In multivariate linear regression models, after adjustment for insomnia, we showed that the impact of RLS on quality of life is in part independent of sleep-related issues. This suggests that other symptoms of RLS (like paresthesias, restless, discomfort) also play a role in the negative relationship of RLS with quality of life. In my last cross-sectional study I compared the quality of life of waitlisted dialysis patients (WL) versus kidney transplant recipients (Tx) using a modular quality of life instrument. Tx patients had better quality of life on most of the generic and kidney specific domains. My results, however, indicate that the strongest relationship between the modality of renal replacement therapy and quality of life

is seen on the kidney disease specific domains. My results suggest that the quality of life of patients with chronic kidney disease treated with different treatment modalities is mainly determined by psycho-social variables.

- Kovács AZ, Molnar MZ, Szeifert L, Szentkiralyi A, Ambrus C, Molnar-Varga M, Mucsi I, Novak M: *Sleep disorders, depressive symptoms and health-related quality of life – a cross-sectional comparison between kidney transplant recipients and waitlisted patients on maintenance dialysis.* *Nephrol Dial Transplant* 2011; 26:1058-1065.
- Mucsi I, Kovacs AZ, Molnar MZ, Novak M: *Co-morbidity and quality of life in chronic kidney disease patients.* *J Nephrol*, 212008; (Suppl 13):S84-91.
- Molnar MZ, Novak M, Ambrus C, Szeifert L, Kovacs A, Pap J, Remport A, Mucsi I: *Restless legs syndrome in patients after renal transplantation.* *Am J Kid Dis* 2005; 45:388-396.

## MARIANN TANDARI-KOVACS (2011)

### Emotional strain, burnout among health care workers

Supervisor: Katalin Hegedűs

The psychological syndrome of burnout was conceptualized in prolonged response to chronic interpersonal and emotional stressors. Both situational and individual factors can lead to burnout. The aim of our studies was to explore the burnout syndrome among health care professionals since they are prone to burnout. Our first research as a pilot study (N=70) revealed that the prevalence of burnout is quite high in the sample of our study, and highlighted the importance of the emotional aspect of the relationship between health care professional and client. Therefore dealing with emotional aspect of client interaction was suggested. Thus we decided to investigate emotion work, but no validated instrument for measuring the concept of emotion work was available in Hungarian. Our second study focused on the adaptation of the Frankfurt Emotion Work Scale in Hungary (N=327). This instrument has helped us to identify the impact of displayed emotions on burnout. The psychometric properties of the scales tapping from the Hungarian factor analysis were satisfactory; however, some cultural differences occurred between the original and the Hungarian versions. The main aim of our third study (N=199) was to reveal the prevalence of burnout, emotion work, especially emotional dissonance and to explore the relationship between coping, social support and burnout. The differences between the groups of nurses and physicians and between the groups working in different areas of health care (psychiatry/psychotherapeutic settings, oncology-hospice settings and other) were analysed. Similarly to the international and national literature our results showed that socio-demographic factors (age, education) and job characteristics (number of clients, health care setting, working experience) influence burnout. According to our present knowledge no study in Hungary addressed emotion work measured with a valid instrument. Introducing the concept of emotion work in connection with burnout to high relief was suggested. Emotional regulation requirements, regulation possibilities and regulation problem had a great impact on burnout syndrome. Among the addressed variables emotion work had the highest value of the explained variance of burnout. Emotional dissonance was the best predictor of emotional exhaustion, while displaying negative emotions had the greatest impact on depersonalization. Moreover, displaying positive emotions predicted personal accomplishment. The results clearly showed that different aspect of emotion work was diverse between the groups examined. The non-adaptive emotion focused coping influenced the emotional exhaustion component of burnout, while the frequent application of problem focused coping failed to protect health care workers from emotional exhaustion and deper-

sonalization. We also found differences regarding coping between the groups examined. Social support as coping strategy indicated that perceived social support from co-workers can be postulated as a protective factor. Our findings illuminate that health care setting and job characteristics are important factors when elaborating prevention or training programmes. The characteristics of the client interaction should be brought into focus in education. Especially the emotional aspect of the client interaction should be displayed as the source of stress and job satisfaction.

- Kovács M, Kovács E, Hegedus K.: *Is emotional dissonance more prevalent in oncology care? Emotion work, burnout and coping, Psycho-Oncology 2010; 19:855-862.*
- Kovács M, Kovács E, Hegedus K. *Emotion work and burnout: A cross-sectional study of nurses and physicians in Hungary. Croatian Medical Journal 2010; 51:432-442.*

### MÁRTA VARGÁNÉ MOLNÁR (2011)

#### **Factors associated with health-related quality of life and psychosocial functioning in kidney transplanted children and adult patients**

*Supervisor: Novák Márta*

Several factors modulate health related quality of life of kidney transplant recipients. In our sample patients with better health related quality of life at the beginning have significantly better chance for survival even after adjusting for several important co-variables such as clinical parameters and depression. Kidney transplant recipients have significantly better health related quality of life compared to waitlisted dialysis patients, especially at the kidney disease targeted sub-scales. Potential explanation of this difference may be related to psychosocial parameters strongly modulating quality of life. The life prospects of kidney transplant children are determined by several factors such as intelligence or psychosocial parameters. The disease specific parameters of these factors are related to cognitive functions. The maternal education level might predict the level of cognitive skills and psychological status of kidney transplant children. Depressive symptoms of mothers show strong correlation with children' mood and behaviour; which disorders are more frequently in kidney transplant patients comparing to normal control children.

- Molnár-Varga M, Molnár MZ, Szeifert L, Kovács AZ, Kelemen A, Becze A, László G, Szentkirályi A, Czira ME, Mucsi I, Novák M: *Health related quality of life and clinical outcomes in kidney transplanted recipients. Am J Kidney Dis. 2011; 58:444-452.*
- Kovács AZ, Molnár MZ, Szeifert L, Ambrus C, Molnár-Varga M, Szentkirályi A, Mucsi I, Novák M: *Sleep disorders, depressive symptoms and health related quality of life – a cross-sectional comparison between kidney transplant recipients and waitlisted patients on maintenance dialysis. Nephrol Dial Transplant 2010; 26:1058-1065.*

### LÁSZLÓ ZUBEK (2011)

#### **End of life decisions in intensive care units - Ethical and legal aspects of patient autonomy and therapy restriction**

*Supervisor: József Kovács*

Based on literature data within countries possessing developed healthcare systems, only a fraction of patients receive complete medical treatment that corresponds to nationally accessible scientific state of the art therapy, with the majority of patients deceased in intensive care units having received some kind of therapy restriction. Currently therapy restric-



tion is the major ethical and legal issue that affects the most patients and physicians throughout the world. Several important problems arise during therapy restriction. Despite its rich literature background, the definition of end of life decisions is not uniform, with the ethical and legal context surrounding end of life decisions varying from country to country. Based on multicentre studies with high numbers of patients, only approximately 5% of intensive care unit patients possess clear awareness, and hence the autonomy of the rest of the patients is likely to suffer distortions. If the patient is not autonomous and previous will is lacking then who is entitled to make end of life decisions? Providing insufficient information for patients and relatives is also a major issue; the content and form of communication is not uniform, although the primary step towards patient autonomy could be ensured through the appropriate flow of information. Our research group investigated the status of end of life decisions and patient autonomy status in Hungary through two separate studies. The first searched for reasons underlying end of life decisions, the mechanisms of decision making and the specific frequencies of therapy restriction types via analytical questionnaires sent out to intensive care unit physicians. During the second study we have assessed informed consent-related issues through the analysis of anaesthesiology informed consent forms. Based on our studies it is of note that patient autonomy can be severely impaired in Hungary primarily due to the lack of sufficient information provided. Making end-of-life decisions is also part of everyday routine in Hungary, but the process is paternalistic; the physician makes decisions alone and therapy restriction is not discussed with the patient's relatives, treating physicians or assistants prior to decision making. We have also found that the types and methods of therapy restriction in Hungary are rather different compared to the data of other European studies. Based on our experience we have defined a new classification method that may be helpful during the process of making end-of-life decisions in intensive care units.

- Zubek L, Szabó L, Diószeghy Cs, Gál J, Élő G: *End-of-life decisions in Hungarian intensive care units. Anaesth Intens Care* 2011; 39:116-121
- Zubek L, Szabó L, Gál J, Öllös Á, Élő G: *A kezeléskorlátozás gyakorlata a hazai intenzív osztályokon. Orvosi Hetilap* 2010; 151:1530-1536.
- Zubek L, Tókey B, Szabó L, Élő G: *Jogos védelem: a tájékozott beleegyezés jogi és etikai problémái. Orvosi Hetilap* 2007; 148:1155-1162.

## GROUP OF RESEARCH TOPICS OF MENTAL HEALTH SCIENCES

### **Coordinator:**

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The application of a sociological program (entitled: *Sociological and mental health aspects of individual and community resources*) has been submitted to the Hungarian Accreditation Board.



***Titles of research projects***

Analysis of the supportive and developmental effects of family and community  
 Methodology of measuring mental health characteristics; effectivity testing of educational programs and curricula  
 The impact of Postmodernity on community models of leadership training  
 Social and religious theories in the dimensions of normal and pathological phenomena  
 Lifelong learning and its worldview-related aspects  
 Multidisciplinary approaches to mental health and illnesses  
 New religious, youth, and self-help community movements  
 Social and mental health aspects of preventive health protection  
 Value, action research, human/organizational resources development

***Supervisors***

Katalin Horváth-Szabó  
 András Ittész  
 Gábor Ittész  
 Endre Nagy  
 Dávid Németh  
 Teodóra Tomcsányi  
 Péter Török  
 Szabolcs Török  
 Károly Varga

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Júlia Eszter Andrási-Stahl                      pt  
 Eszter Szőcs-Sabade                              ft

***Supervisors***

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 András Ittész

***Ph.D. candidates***

Gábor Török    pt (a)  
 Apollónia Noémi Kulcsár                              pt

***Supervisors***

Dávid Németh  
 Teodóra Tomcsányi

a, absolutorium; pt, part-time; ft, full-time

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## SCHOOL OF PH.D. STUDIES

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### 5. SPORT SCIENCES

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***Chairman:***

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**General Overview:** Doctoral courses embrace the whole field of sports science. Naturally, the specific topics reflect the orientation of the tutors, and respectively, the technical facilities of the laboratories. It is the Faculty of Physical Education and Sport Science that manages the doctoral courses, but other institutions, above all, the National Institute for Sports Medicine, extend the facilities available in the institutes and chairs, both in regard to educational staff and technical equipment. The other faculties and institutes of Semmelweis University are considered the basis of further development in this respect.

#### ***PROGRAM 5/1.***

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#### **TRAINING AND ADAPTATION**

***Coordinator:***

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**Program Overview:** Different stress factors exert considerable impact on normal functions and pathological processes throughout the whole life span. An adequate intensity of regular physical training positively influences the whole metabolism, and thus presumably plays a beneficial role in compensating against the harmful effects of stress. In our earlier studies we extensively examined the effects of stress and stress hormones on the development of the brain and neuroendocrine system, as well as on adaptive behavior. Recently we aimed at examining the metabolic impact of prenatal stress and its role in the development of obesity. Regular training during pregnancy might counteract the negative effects of stress by influencing the development of the hypophysis-pituitary-adrenal (HPA) axis. Regular physical training in early postnatal life also could influence brain development by acting on trophic factor production, such as NGF and BDNF. Training might enhance resistance against harmful neonatal risk factors such as hypoxia, NMD A and ethanol toxicity. Chronic stress produces disturbances in neuroendocrine regulation and in adaptive behavior. The possible protective effects of dietary factors and physical training are also examined. Stress has a cardinal role in the development and maintenance of drug addiction. The beneficial effects of regular training can be evaluated with behavioral studies (reinforce-

ment, sensitization, anxiety) as well as with biochemical examinations (glucocorticoid hormones and receptors, neuropeptides: CRF, neurotensin). The projects use several different scientific techniques such as hormonal, immunocytochemical and behavioral examinations. Perinatal age requires special new methodology to develop with respect to surgical, immunocytochemical and behavioral procedures.

### ***Titles of research topics***

The role of physical training in the neurobiology of stress response

The impact of physical training and dietary factors on neurobiology of stress response at different ages

In vivo biomechanical study of neuro-musculo-skeletal system with motion analysis and its adaptation for professional athletes and patients with orthopaedic diseases

The role of physical activity and nutrition in cardiovascular diseases

The importance of non-invasive cardiovascular examinations in the establishment of performance ability

Genetical aspects of physical exercise

### ***Supervisors***

Klára Felszeghy

Klára Felszeghy

Rita Kiss

Éva Martos

Gábor Pavlik

József Pucsok

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Zsuzsanna Major ft

Anna Udvardy ft

### ***Supervisors***

Gábor Pavlik

Gábor Pavlik

József Pucsok

### ***Ph.D. candidates***

Judit G. Noé pt

Álmos Zalán Gógl ft

Irén Kalabiska pt

Noémi Szakács pt

Szabolcs Tóth pt

Barbara Varga-Pintér ft

### ***Supervisors***

Gábor Pavlik

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Gábor Pavlik

Rita M. Kiss

Gábor Pavlik

Gábor Pavlik

ft, full-time; pt, part-time

**PROGRAM 5/2.****PHYSICAL TRAINING, REGULATION AND METABOLIC TRANSPORT****Coordinator:****Zsolt RADÁK Ph.D., D.Sc.**

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**Program overview:** The current program focuses on the physiological, biomechanical, and biochemical effects of acute and regular exercise on humans and laboratory animals. In addition, sport-associated injuries and the science behind regeneration are also investigated. Human gait motions, model and individual techniques in various sport events are studied in the laboratory of biomechanics with the close collaboration of the institute of biophysics. One of the key topics of this program is the complex mechanism of the effects of exercise on aging and the role of oxidative stress in adaptive response. The effects of exercise on the function, molecular physiology of skeletal muscle and brain serve as an exciting challenge for students and professors as well. The laboratories, animal house and core facilities of Semmelweis University, along with the expertise of the program's professors provide unique support for excellent research in sport science.

***Titles of research projects***

Sports injuries of the knee

Computer simulation of limb movements and mathematical modeling of their neural control

Somatic development of 7 to 18-year-old school children

Influence of physical activity and nutrition on cellular processes of normal and pathological brain aging

Interactions between physical activity, glucose and lipid metabolism. Movement therapy of obesity and diabetes

Exercise-induced adaptation to oxidative stress and aging

In vivo biomechanical study of the neuro-musculo-skeletal system and its mechanical, hormonal and genetic adaptation to strength exercises

The physiological, anatomical, biochemical, performance-physiological and cultural-anthropological unity of horse and rider

Physiologic, proteomic, and genetic characteristics of physical exercise, and cardiovascular and metabolic risk

The effect of lower education on somatic development

***Supervisors***

István Berkes

József Laczkó

János Mészáros†

Csaba Nyakas

Csaba Nyakas

Zsolt Radák

József Tihanyi

Miklós Tóth

Miklós Tóth

Márta Wilhelm

***Ph.D. students***

Edit Bosnyák

ft

Edit Dömötör Jankóné

pt

***Supervisors***

Miklós Tóth

Zsolt Radák

Réka Feszthammer	pt	István Berkes
Renátó Gál	ft	József Tihanyi
Vera Gál	pt	Zsolt Radák
Réka Karádi	ft	Miklós Tóth
Péter Katona	ft	József Laczkó
Krisztina Marosi	ft	Csaba Nyakas
Orsolya Marton	ft	Zsolt Radák
Enikő Nagy	ft	Zsolt Radák
Zalán Négele	pt (a)	Csaba Nyakas
János Négyesi	ft	József Tihanyi
Krisztián Gusztáv Papp	pt	Zsolt Radák
Anna Protzner	ft	Miklós Tóth
Kata Sótonyi	ft	Miklós Tóth
Emese Trájer	ft	Miklós Tóth
Zsófia Tróznia	pt	Csaba Nyakas
Mohammad Mosaferi Ziaaldini	it	Zsolt Radák

***Ph.D. candidates***

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Anni Andrea Ember	ft
Nikolett Hart	ft
Anna Kacsándi	ft
Bence Kopper	pt
Ágnes Mayer	pt
Pampakas Polydoros	it
Márta Zsuzsa Ránky	ft
Sándor Sáfár	ft
Linda Sárga	ft
Dóra Ureczky	ft
Szabolcs Zsigri	pt

***Ph.D. graduates***

Erika Koltai	ft
Zsófia Mészáros	ft
Gergely Pánics	na

***Supervisors***

Zsolt Radák
Márta Wilhelm
Zsolt Radák
Csaba Nyakas
József Tihanyi
József Tihanyi
János Mészáros†
Csaba Nyakas
József Tihanyi
Zsolt Radák
József Tihanyi
Csaba Nyakas

***Supervisors***

Zsolt Radák
János Mészáros†
István Berkes

a, absolutorium; ft, full-time; pt, part-time; it, international, na, not affiliated

***Abstracts of Ph.D. theses successfully defended in 2011*****ERIKA KOLTAI (2011)****The effect of IGF-1 and regular exercise on molecular mechanisms of aging: role of sirtuins**

*Supervisor: Zsolt Radák*

Aging is associated with a decline in the physiological function in brain, skeletal muscle and other organs as well. Silent information regulators are potent NAD<sup>+</sup>-dependent pro-

tein deacetylases, which have been shown to regulate the aging process. Here, changes in the level and activity of sirtuin 1 (SIRT1) in response to 6 weeks of exercise in groups of young (3 mo.) and old (26 mo.) rats were studied in the gastrocnemius muscle. There was an age-related increase in SIRT1 level, while exercise training significantly increased the relative activity of SIRT1. Aging did not significantly increase the level of DNA damage, which was in line with the activity of 8-oxoguanin DNA glykoziláz. Regular exercise decelerates the deleterious effects of the aging process via SIRT1-dependent pathways through the stimulation of NAD<sup>+</sup> biosynthesis by NAMPT.

In addition, we have investigated the effects of two weeks of IGF-1 supplementation (5 µg/kg/day) and exercise training on neurogenesis. Exercise improved the spatial memory of the old group, but IGF-1 supplementation eliminated this effect. An aging associated decrease in neurogenesis was attenuated by exercise and IGF-1 treatment. Aging increased the level of 8-oxoG and Ku70 content, indicating the role of DNA damage in age related neuropathology. Acetylation of 8-oxoguanine DNA glycosylase (OGG1) was detected for the first time *in vivo*, and this decreased with aging. Data revealed that the age-associated increase in 8-oxoG level is due to decreased acetylation of OGG1. However, in young groups, exercise and IGF-1 treatment increased AcOGG1 level. SIRT1 and SIRT3, as DNA damage associated lysine deacetylases, were measured, and SIRT1 level decreased with aging, resulting in a large increase in acetylated lysine residues in the hippocampus. Age associated decreases in SIRT1 and the associated increase in lysine acetylation in the hippocampus could have a significant impact on function and could suggest a therapeutic target. The present study reveals that the effects of exercise on DNA repair and on sirtuins with IGF-1 are involved in the neuroprotective roles of exercise and IGF-1.

- Koltai E, Szabo Z, Atalay M, Boldogh I, Naito H, Goto S, Nyakas C, Radak Z: Exercise alters SIRT1, SIRT6, NAD and NAMPT levels in skeletal muscle of aged rats. *Mech Ageing Dev* 2010; 131:21-28.
- Koltai E, Zhao Z, Lacza L, Cselenyak A, Vacz G, Nyakas C, Boldogh I, Ichinoseki-Sekine N, Radak Z: Combined exercise and IGF-1 supplementation induces neurogenesis in old rats, but do not attenuate age-associated DNA damage. *Rejuvenation Res* 2011; 14:585-596.
- Radak Z, Chung HY, Koltai E, Taylor AW, Goto S: Exercise, oxidative stress and hormesis. *Ageing Res Rev* 2007; 7:34-42.

## ZSÓFIA MÉSZÁROS (2011)

### Changes of somatic development, body composition and motor performance in lower elementary schoolboys

Supervisor: József Mészáros †

The aim of the longitudinal study was to compare the effects of regular physical activity and long-lasting relative malnutrition by using those variables which describe the children's somatic development, estimate their body composition and reliably and numerically qualify their motor abilities and performance.

The kinanthropometric data collections were carried out eight times in 400 lower elementary schoolboys between the years of 2005 and 2008. The total sample was divided into three subgroups. Namely: subgroup 1 (G1), normal sample (n = 175); those children who took part in a special physical education curriculum program were classified into subgroup 2 (G2; n = 115); subgroup 3 (G3) contains those boys whose family had a share in regular governmental social support. The used kinanthropometric techniques are accepted by the international literature.



It was found that preliminary selection before the organisation the schooling in-to the PE classes did not have an effect on the height and slope of increase. Relative body fat content of G2 boys was lower and their lean body mass was higher than those of their hypoactive peers. The mean depot fat in G1 and G3 was critically high; these boys in this respect can be evaluated as being near to a health risk. The initial differences between the physique characteristics of hypoactive and more active samples are the consequences of preliminary selection; however, the lower speed of increase of relative body linearity in the PE pupils can be related to the effects of their greater habitual physical activity. The mean motor performance of the studied boys represents a significantly lower quality if they are compared to the characteristic values some decades ago. The physical performance of PE children did not provide an exception in this respect. The lag is the greatest in the distance endurance estimated by the distance in Cooper test. Expressing the delay in decimal years of G1 and G2 boys provided a value of more than 1 year.

Corresponding with the respective literature, the high body fat and low cardio-respiratory endurance indicate an increased health risk. Both of the mentioned conditions are environmental effects.

Somatic and motor development of PE children was more balanced and faster than in the hypoactive samples. The long lasting hypo-activity results in somatic retardation. Hypo-activity and relative malnutrition separated the G3 boys from their peers in this comparison.

- Mészáros Zs, Vajda I, Mészáros J, Polydoros P, Sziva Á, Osváth P, Zsidegh M Korai gyermekfejlődés: a szocio-ökonómiai státus hatásai. *Magyar Sporttudományi Szemle* 2007; 8:8-13.
- Mészáros Zs, Mészáros J, Szmodis BM, Polydoros P, Osváth P, Völgyi E: Primary school child development – issues of socio-economic status. *Kinesiology* 2008; 40:153-161.
- Mészáros Zs, Kiss K, Szmodis MB, Zsidegh M, Mavroudes M, Mészáros J: Effects of attending elevated level school physical education in 7-to-11-year-old boys. *Acta Physiologica Hungarica* 2009; 96:349-357.

## GERGELY PÁNICS (2011)

### Role of proprioception training in the prevention of knee injuries

Supervisor: István Berkes

My study was the first in Hungary to explore the epidemiology of athletes' injuries that were treated in our department. According to the profile of the Department of Sports surgery, I paid special attention to explore the circumstances of knee injuries. I examine the injuries of athletes ranging from the hobby to high levels (I paid special attention to elite female handball players' injuries). I concluded that the most frequent knee injury was the lesion of the ACL, which was more often reconstructed operatively.

I explore the injury epidemiology among the students of the first Hungarian football academy. I was the first in Hungary to examine injury incidence among adolescent football players. Most injuries affected the lower limb and occurred in February and November.

I was one of the first authors domestically and internationally to prove the efficacy of proprioceptive training on joint position sense of the knee. With evidence on the improvement of joint position sense, I provided further support to the investigation of the proprioceptive receptor system. I gained useful information for the practice by determining that there was no improvement in joint position sense after 4 months. I proved the importance of the broad use of proprioceptive training in the prevention.

- Panics G, Tallay A, Dobos J, Berkes I: *Élvonalbeli női kézilabdázók súlyos térd sérülésének retropektív vizsgálata. Sportorvosi Szemle 2003; 122-130.*
- Panics G, Tallay A, Pavlik A, Berkes I: *The effect of proprioception training on knee joint position sense in female team handball players. Br J Sports Med 2008; 42:472-476.*
- Kynsburg Á, Pánics G, Halasi T: *Long term neuromuscular training and ankle joint position sense. Acta Physiologica Hungarica 2010; 97:183-191.*

### PROGRAM 5/3.

## SPORT AND SOCIAL SCIENCES

### **Coordinator:**

**Gyöngyi SZABÓ FÖLDESINÉ Ph.D., D.Sc.**

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**Program overview:** As in the political, economic, social, and cultural spheres, the tendency towards globalization has become more powerful in the sport subsystem. Although global growth has been beneficial for sport in many ways, its impact is regarded as contradictory. The fact that sport has become global in scope produced sweeping changes both on the international and national scenes, and sport institutions have had to face new challenges to which answers are expected on the basis of scientific results. The major objective of the program "Sport and Social Sciences" is to contribute to the understanding and explanation of the impact of globalization on sport as a social phenomenon, and of the mutual relationship between sport and society. The program embraces most areas of sport sciences dealing with various social issues related to sport from the perspectives of sport philosophy, sport history, sport politics, sport economy, sport sociology, sport psychology, sport pedagogy, sport management, sport marketing, and sport law. Theoretical backgrounds and methods used in the research of the different topics should satisfy the requirements of the individual disciplines, notwithstanding the promotion of a multidisciplinary approach. The program includes the study of physical education and all traditional fields of sport, that is, school sport, university sport, sport for all, elite sport, and sport for people with special needs. In addition, the investigation of new areas of contemporary sport (recreation, sport tourism, extreme sport, risk sport, etc.) as well as comparative and cross cultural studies from the aspect of social sciences is also welcomed.

### **Titles of research projects**

Sport geography, sport tourism

Quality of life, physical activity and value orientation of adult and the elderly

Activity structure and career development of PE teachers and sport coaches

Exploration of the organic background of learning and behavioral difficulties from a neuropsychological perspective (Developmental neuropsychology)

### **Supervisors**

Miklós Bánhidi

József Bognár

József Bognár

Rita Fodorné Földi

Sport in modern society	Gyöngyi Földesiné Szabó
The situation and the role of sport among transformed political, economic and social relations	Andrea Gál Gáldiné
Education work of sport coaches	János Gombocz
Theoretical and methodological fundamentals of physical education curricula	Pál Hamar
Scientific basics of living standards (recreation)	László Jakabházy
The application possibilities of new didactic methods at the different sport education	Katalin Keresztesi
Links between information, communication and sport	Ágnes Kokovay
Personality characteristics of athletes, developmental effect on personality and applications in pedagogy	Csaba Nagykáldi
Content and organizational modernization of sport-professional training in Hungary with regards to EU integration and legal harmonization	András Nemes
Motor performance diagnosis and its methodological basis	Károly Ozsváth
Objective analyses of elite handball team performance by diagnosis program	Csaba Ökrös
Psychometric examination of anxiety, coping with stress, and self-efficacy	Kornél Sipos
Application of autogenic training in sports and at school.	Kornél Sipos
Comparison of the mood-improving effects of various sports and physical exercises	Attila Szabó
The role of musical styles in aerobic training	Attila Szabó
The impact of tai chi or yoga on the acute response to stress and electrocardiographic QT interval	Attila Szabó
The social impact of physical education and sport and their relation to Hungarian society's special issues in the first half of the 20th century	Sándor Szakály
The effect of school physical education and student sport on averting and limiting the health damaging risk factors appearing in students' conduct	Piroska Szalay
Relations of society, physical education and sport, from ancient times to present time – lessons of social history	Katalin Szikora
Effects of values and culture on lifestyle	Tímea Tibor
The examination of the motor and psychological development in the sensitive period of the personality development, motor learning and motor development	László Tóth
Body interpretations and body awareness	Katalin Vermes

**Ph.D. students**

Anna Zsófia Alliquander	pt
Borbála Abonyi Bácskayné	pt

**Supervisors**

Tímea Tibori
Kornél Sipos

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Mariann Bardocz-Bencsik	pt	András Nemes
Franciska Bartus Sontráné	pt	Ágnes Kokovay
Piroska Béki	pt	Gál Andrea Gáldiné
Barbara Bútor Majorné	pt	Ágnes Kokovay
István Csáki	ft	József Bognár
Mónika Csüllög	pt	Katalin Vermes
Orsolya Czeglédi	ft	Mihály Nyerges
Diána Déri	pt	Mihály Nyerges
Károly Dobos	pt (a)	Csaba Nagykáldi
Eszter Gál	pt	Katalin Vermes
István Gergely	pt	Zsolt Radák
Judit Gombás	ft	Gál Andrea Gáldiné
Mária Gosztola	pt	Pál Hamar
Dóra Görögh	ft	Csaba Ökrös
Erika Gulyás	pt	Mihály Nyerges
Noémi Gyömbér	pt (a)	Kornél Sipos
Katalin Szilvia Hájas	pt	János Gombocz
Csaba Halmos	pt	Gál Andrea Gáldiné
Tamás Horváth	pt	László Tóth
István Attila Király	pt	Andrea Gál Gáldiné
Dóra Lasztovicza	ft	Andrea Gál Gáldiné
Hamidreza Mirsafian	it	Gyöngyi Szabó
		Földesiné
Azadeh Mohamadinejad	it	András Nemes
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Andrea Olajos Adorjáné	pt	Hál Hamar
Ákos Patócs	pt	Csaba Nagykáldi
Orsolya Savella	pt	
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Zsófia Tróznai	pt	Csaba Nyakas
Dániel Varga	pt	János Gombocz
Anikó Versics	pt	Pál Hamar
Dávid Péter Zalai	pt	Károly Osváth
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Zsuzsanna Balogh Olvasztóné	pt	József Bognár
István Barthalos	pt	József Bognár
Ottó Benczenleitner	pt	József Bognár
Szabolcs Levente Bertók	pt	Károly Ozsváth
Sándor Bollók	pt	Kornél Sipos
Betti Barthel	pt	Földi Rita Fodorné
Efstathios Christodoulides	it	Gyöngyi Szabó
		Földesiné

Beáta Dobay	pt	Miklós Bánhidi
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László Dorogi	na	József Bognár
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Zoltán Jókay	pt	József Bognár
Zsuzsa Kalmár	pt	Pál Hamar
Csaba Konczos	pt	Károly Ozsváth
Judit Plachy Kopkáné	pt	József Bognár
Magdolna Kovách Vécseyné	pt	József Bognár
István Kun	na	László Tóth
Gyöngyvér Lacza	na	László Jakabházy
Judit Lakó Herpainé	pt	János Gombocz
Dániel Lőkös	pt	Kornél Sipos
István Munkácsi	pt	Pál Hamar
Eleonóra Murányi	ft	Pál Hamar
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Katalin Rácz	ft	Rita Földi Fodorné
Panayiotis Shippy	it	Gyöngyi Szabó
		Földesiné
Katalin Starhon Gaálné	pt	Miklós Bánhidi
Ágnes Sztankovics Törökné	pt	János Gombocz
Bence Ervin Takács	ft	Sándor Szakály
Éva Thiry Pólusné	pt	Tímea Tibori
Attila Velencei	pt	Gyöngyi Szabó
		Földesiné
Orphanos Yiannakis	it	Gyöngyi Szabó
		Földesiné
<b><i>Ph.D. graduates</i></b>		<b><i>Supervisors</i></b>
Diana Christodoulou	it	Gyöngyi Szabó
		Földesiné
Tamács Dóczi	ft	Gyöngyi Szabó
		Földesiné
András Péter Killyéni	pt	Katalin Szikora

a. absolutorium; ft, full-time; pt, part-time; it, international, na, not affiliated

### ***Abstracts of Ph.D. theses successfully defended in 2011***

**DIANA CHRISTODOULOU (2011)**

#### **Social status of qualified physical education teachers in Cyprus**

*Supervisor: Gyöngyi Szabó Földesiné*

There is scientific evidence in many countries that PE is characterized as having a low status and providing inadequate teaching, and therefore, the work of physical education

teachers is considered non-essential. These phenomena have not been investigated by anyone in Cyprus from a sociological perspective. The author wanted to discover the social status of qualified Cypriot PE teachers regardless of their actual occupation. The aim of the research was to give answers to the following main questions: What is the status of PE in Cypriot schools? What are the actual occupations of qualified PE teachers? To what degree are qualified PE teachers satisfied with their job and their position in the Cypriot labour market, and is their status crystallized? What are their opinions regarding the governmental employment policy and social capital in relation to their employment? And finally, what are their attitudes towards sporting activities and healthy lifestyle? The basic method of the research was the survey method, which was complemented by in-depth interviews and the analysis of documents. The survey was conducted with the entire population of qualified Cypriot PE teachers (N=1880) regardless of their actual job. The researched population (n=531) was classified into 3 distinct groups: 1) active public school PE teachers; 2) those who are engaged in sport-related jobs; and 3) those engaged in other jobs unrelated to sport. The results revealed that PE is not highly appreciated and that PE teachers are not respected by the wider Cypriot public. The status of active PE teachers is crystallized and they are the most satisfied with their job. The participants whose jobs are related to PE and sports can be admired by youngsters in terms of their healthy lifestyle. The subjects who are still waiting for employment at public schools tend to believe that the governmental employment policy is unfair. Moreover, there was a consensus among the subjects regarding the great influence of social capital in their employment. Last but not least, decision makers should ensure that the subject of PE is taught properly by specialized PE teachers so as to retain its importance at schools. They also need to reconsider the governmental employment policy and the influence that social capital exerts in every sector of Cypriot society.

- Christodoulou D: *The status of physical education in Cypriot schools. Phys Cult Sport Stud Res* 2011; 50:110-117.
- Christodoulou D: *Health Awareness and sporting behaviour of qualified Cypriot physical education teachers. Biom Hum Kins (formally called Physical Education and Sport)* 2010; 2:54-57.
- Christodoulou D: *Cypriot PE teachers' opinions on occupational prestige and social capital. Phys Cult Sport Stud Res* 2009; 46:116-122.

### TAMÁS DÓCZI (2011)

#### **The impact of the 1989-1990 transition and globalization on national identity and sport in Hungary at the beginning of the 21st century**

*Supervisor: Gyöngyi Szabó Földesiné*

The present Ph.D. thesis focuses on the relations of social change and sport, and in a narrower context, the impact of the recent and current socio-economic changes on world sport, Hungary's situation and opportunities in the global sport arena. Owing to the process of globalization in sport, its nation-building function, which was a defining one in the 20<sup>th</sup> century, has become a field of special interest for the sociology of sport. The objective of the dissertation is to explore the relationship of sport and national identity through the examination of Hungarian sport politics, sport media and the views of the Hungarian public, since, despite the wide range of international literature, Hungary's case has not been dealt with in this respect, and the issue of sport and national identity has only been marginally touched upon. During the research work, both qualitative (analysis of sport politi-



cal documents, content analysis of sports newspapers and supporters' views, case study) and quantitative methods (survey of a representative sample of the Hungarian adult population, n=1027) were applied in order to analyze the relationship of sport and national identity more thoroughly. The research results indicate that the impact of elite sport success on national pride is taken for granted by politicians, the media and the population as well; however, in the public discourse, the negative effects of failure and the identity-building potential of other areas of sport are largely overlooked. During the 2008 Beijing Olympics, it could be observed that political and media actors, building up the discourse of a 'sport nation', were in a difficult position during the assessment of the results. The data also underline that the majority of Hungarians identify with sporting success, yet, in the case of disappointing results, the identification decreases both among citizens and journalists. Elite sport can only boost national pride if it remains prolific, however, it is more difficult to be successful in the global sport arena today than it used to be in the bipolar world; therefore, in order to strengthen the community of the nation, the integrative power of sport should also be recognized in other areas less related to competition. For this, the influence of politics ought to decrease, and civil society should come into the forefront both in the operation of sport as a social subsystem and in the formation of national identity.

- Dóczi T: *Gold Fever (?) Sport and national identity – the Hungarian case. Int Rev Soc Sport* 2012; 2:165-182.
- Dóczi T: *Magyar sport és nemzeti identitás a globális sportszíntéren. Magy Sporttud Szemle* 2008; 4:3-7.
- Dóczi T: *Sport és globalizáció: a 21. század kihívásai. Kalogathia* 2007; 1-2:5-13.

## ANDRÁS PÉTER KILLYÉNI (2011)

### The cultural history of sports in Kolozsvár before Trianon (1868-1920)

*Supervisor: Katalin Szikora*

The study of the beginning of sporting life in Kolozsvár, the recording of the sporting events which took place there, and the publishing of these papers are final steps in closing the chapter on the history of its local sporting life as well as Hungarian sports history. Our local history and the values of the Hungarian minority from outside the borders of Hungary are endangered by devastation and forgetting. This work tries to immortalize this chapter of our past worth remembering, and therefore it can be considered a starting point for future studies about sporting life in Kolozsvár. The period between the two world wars, as well as the era of Hungarian rule between 1940 and 1944 are also endangered from the point of view of minority culture. Thus, studies about these periods are more than a necessity; they are an obligation to anyone who is interested in keeping the culture of our ethnic group alive.

Since the time of the Hungarian-Austrian Compromise in 1867, local sporting life has had a solid background, and by the twentieth century, this had grown to a national level. The sportsmen from Kolozsvár were well-known throughout the nation, and athletes from the whole country participated in sports competitions organized in our town. Among the local athletes, István Somodi was the most popular: he was internationally famous, and his Olympic silver medal served as stimulation and inspiration for athletes of the next generation.

The documents and records of the given period were preserved in different heritages, and the coverage of sporting life in Cluj by the local sports press of the time made it possible to

replace the missing data and fill in the gaps. Studying these articles, we can re-create an accurate picture of the sports competitions, organizers, names of the participants, winners and their results.

The study of the almanacs of the local high schools, academies and universities also has an important historical value, since they contain the chronicles of sporting life in these renowned institutions. At the same time, these studies can be very useful in similar researches as well. Today, as in the past, the press is considered to be the reflection of civil life, so it can provide us with a true picture of the events of the given age.

In the past few years many researches have been carried out in the vast field of sport, and several outcomes of these studies have already been published. Aside from this, in the last two years a small collection of sports documents, photos and cups belonging to Ferencz László, one of the most outstanding sports reporters in our town during the 20-21<sup>st</sup> century, has been compiled by the Minerva Cultural Association under the name: *László Ferenc Sport Collection*. This collection serves as a basis for the preservation of other sport heritages. In addition, several sports exhibitions have been organized, the digitalization of the photos has started, and the sports library is continuously expanding, so the conditions for similar researches have been created. We strongly believe that there will always be people who will consider carrying on this work as their duty.

- Killyéni A: *István Somodi - High jumper, innovator of Hungarian athletics. Role model of the all-round sportsmen in the first decades of the 20th century. Int J Hist Sportv 2011 14:1968-1986.*
- Killyéni A: *Elfelejtett örökségünk. Kolozsvár sportlétesítményei az első világháború előtt. A szerző magánkiadása, 2010 Kolozsvár, 90.*
- Killyéni A: *Sportélet a kolozsvári Kereskedelmi Akadémián. Kalokagathia 2010; 140-154.*

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## SCHOOL OF PH.D. STUDIES

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### 6. JÁNOS SZENTÁGOTHAÍ NEUROSCIENCES

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***Chairman:***

**Dániel BERECKZI M.D. Ph.D. D.Sc.**

Department of Neurology

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**General Overview:** The Neuroscience School of Ph.D. Studies blends the theoretical and clinical neuroscience research topics, treats the basic questions of the structure and function of the nervous system in a synthetic view as well as the normal and pathological functioning of the human brain as observed by the clinicians. The research topics as listed below and arranged in three basic science and three clinical research Programs witness the large array and variation of supply.

#### ***PROGRAM 6/1.***

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#### **NEUROMORPHOLOGY AND CELL BIOLOGY**

***Coordinator:***

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**Program Overview:** This basic research program of the Neuroscience Doctoral School covers a broad spectrum of the examinations on the central nervous system – from the function and differentiation of the individual neurons up to higher cortical activities. The large variety of topics shares the methodology (neuromorphology, neurochemistry, molecular cell biology, synaptology), the functional view of the topics, and the use of the rich selection of functional neuromorphological techniques. The program includes research areas intended to better understanding of the organization of the neural tissues, the neural differentiation, and the plasticity of the central nervous system. Within the program research areas cover molecular genetics, experimental neuromorphology, and the studies of normal and pathological (neurodegenerative diseases) human brains. Cytological, neuromorphological and neurochemical (immunohistochemical) areas of the program are tightly connected both with the regulatory mechanisms of the autonomous nervous system (stress, pain, food uptake, thermoregulation) and with topics evaluating the higher order functions of the central nervous system (information processing, emotion, motivation, learning and memory).

***Titles of the research projects******Supervisors***

Localization of trigeminal pain-induced stress pathways (trigemino-hypothalamic pathway)	Miklós Palkovits
Neuroanatomical and neurochemical characterization of bidirectional neuronal pathways between the nucleus accumbens and the lateral hypothalamus	Miklós Palkovits
Development and functional organization of the extracellular matrix in the central nervous system of the chicken and the rat	Alán Alpár
Morphological and functional analysis of a novel inhibitory pathway from the brainstem to the thalamus	László Acsády
Comparative neuroanatomical basis of addictive behaviour in avian and mammalian model systems.	András Csillag
Transforming growth factor beta proteins in the central nervous system	Árpád Dobolyi
Roles of TIP39 and the PTH2 receptor neuromodulator-system in the central neural regulation of maternal adaptations	Árpád Dobolyi
Central amylin as a novel maternal neuropeptide	Árpád Dobolyi
How network activity is generated from the interaction of neurons: study of in vitro hippocampal slices during state-transitions	Attila Gulyás
Junctions between astroglia and connective tissue in the central nervous system	Mihály Kálmán
The dystrophin-dystroglycan complex in the pineal body, the pituitary gland and in the circumventricular organs	Mihály Kálmán
Position and function of G protein-coupled receptors in neuronal networks	István Katona
Neural cell differentiation. Developmental capabilities of neural stem cells of different origin	Emilia Madarász
The role of somatosensory cortical inhibition in tactile functions	László Négyessy
A new role for the tissue non-specific alkaline phosphatase (TNAP): regulation and pathology of cerebral cortical functions	László Négyessy
Functional anatomy of pre- and postsynaptic receptors and their neurotransmitters in the hippocampus	Gábor Nyíri
Study of synaptic plasticity in the rat spinal cord in normal state and following inflammation and nerve injury.	Gábor Gerber
Development regulatory role of GABA	Gábor Szabó
Transgenic mouse models for studying the functions and diseases of the CNS	Gábor Szabó
Role of prolactin-releasing peptide in the central nervous system	Zsuzsanna Tóth

**Ph.D. students**

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Melinda Cservenák	ft
Barna Dudok	ft
János Hanics	pt
Georgina Gáti	ft
Mária Rita Karlócai	ft
Margit Katalin Kerti	ft
Tekla Kirizs	ft
Tímea Kőhidi	ft
Katalin Könczöl	ft
Dávid Lendvai	pt(a)
Murali Kuramasamy	ft
Guillaume Lourmet	pt(a)
Máté Neubrandt	ft
Viktor Plattner	ft
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Csilla Vincze	pt

**Ph.D. candidates**

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György Attila Bagó dr.	na
Tamás László Balázs	ft
Nóra Hádinger	a
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Barbara Orsolits	ft
Rege Sugárka Papp	ft(a)
Éva Renner (Dobolyiné)	ft
Eszter Szabadits	ft
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Zsófia Maglóczky
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Zsuzsanna Tóth
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***Abstracts of Ph.D. theses successfully defended in 2011*****ÁGOTA ÁDÁM (2011)****Striatal pathways in relation to learning and motivation***Supervisor: András Csillag*

The present work focuses on reward-related issues of the avian and mammalian striatum. We investigated a striatal pathway instrumental in passive avoidance learning in day-old domestic chicks, and the role of the endocannabinoid system in reward-related behaviors in avian and mammalian systems. The putative role of L-aspartate (Asp) as a neurotransmitter in the arcopallial-medial striatal pathway - which is known to be involved in passive avoidance learning in domestic chicks - was investigated. Double immunocytochemistry against Asp and L-glutamate (Glu) was performed at both light and electron microscopic levels. Asp and Glu immunoreactive neurons in the arcopallium were identified and counted using the confocal laser scanning microscope. Although both transmitter amino acids were co-localized in the majority of labeled neurons of arcopallium, the percentage of single-labeled Asp immunopositive cells was 14.99%, as opposed to the percentage counted in the neighboring telencephalic region, nidopallium (5.34%). Immunoelectronmicroscopy confirmed that Asp was present in axon terminals in the medial striatum, with clear and round vesicles and asymmetric junctions. The majority of boutons (80%) were double labeled. Axon terminals single labeled against Asp or Glu as percent of total amounted to 15% or 5%, respectively. In addition, selected neuronal perikarya and 23.8% of all dendritic profiles appeared to be labeled specifically with Asp but not Glu. The results indicate that Asp may play a specific role (as distinct from that of Glu) in the intrinsic and extrinsic circuits instrumental in avian learning and memory. We evaluated the role of cannabinoid (CB1) receptors in acute alcohol-induced dopamine (DA) release in the nucleus accumbens (Ac), using mice that lack the CB1 receptor gene (CB1<sup>-/-</sup>). CB1<sup>-/-</sup> mice exhibited lack of alcohol-induced DA release in the Ac, as compared to wild-type mice. The acute alcohol-induced increase in DA in Ac dialysates in wild-type mice was completely abolished by pretreatment with the specific CB1 receptor antagonist rimonabant. These results strongly suggest that the CB1 receptor system plays an important role in regulating the positive reinforcing properties of alcohol. We investigated the effect of the CB1 receptor antagonist rimonabant upon the acquisition and consolidation of memory in young domestic chicks, using the passive avoidance paradigm. Systemic administration of rimonabant in a dose of 1 mg/bwkg 30 minutes before the training failed to affect learning, but a similar treatment 30 minutes before the recall (5.5 h after training) attenuated the retention in 60 % of animals. The observed effect was dose-dependent. Our results suggest that CB1-receptors have a mediating role in the consolidation of memory in the passive avoidance task in day-old chicks.

- Ádám ÁS, Wenger T, Csillag A: *The cannabinoid CB1 receptor antagonist rimonabant dosedependently inhibits memory recall in the passive avoidance task in domestic chicks (Gallus domesticus)*. *Brain Res Bull* 2008; 76:272-274.
- Ádám ÁS, Csillag A: *Differential distribution of L-aspartate- and L-glutamate-immunoreactive structures in the arcopallium and medial striatum of the domestic chick (Gallus domesticus)*. *J Comp Neurol* 2006; 10:266-276.
- Hungund BL, Szakáll I, Ádám Á, Basavarajappa BS, Vadász C: *Cannabinoid CB1 receptor knockout mice exhibit markedly reduced voluntary alcohol consumption and lack alcohol-induced dopamine release in the nucleus accumbens*. *J Neurochem* 2003; 84:698-704.



**ANIKÓ LUDÁNYI (2011)****Neurobiological characterization of the endocannabinoid signaling in postmortem and epileptic human hippocampus***Supervisor: István Katona*

Clinical and experimental evidences demonstrate that endocannabinoid system is implicated in many neurological disorders by modulation of synaptic transmission. The molecular architecture of the endocannabinoid signaling machinery in the human brain remains elusive, therefore we investigated the synaptic distribution of its molecular elements in the postmortem human hippocampus using neuroanatomical approaches. Immunostaining for CB<sub>1</sub> receptor, diacylglycerol lipase- $\alpha$  (DGL- $\alpha$ ) and monoacylglycerol lipase (MGL) enzymes, responsible for synthesis and degradation of 2-AG, respectively, highlighted the laminar organization of human hippocampus corresponding to glutamatergic pathways. At higher magnification, immunopositive puncta showing the localization of CB<sub>1</sub>, DGL- $\alpha$  or MGL were distributed throughout the neuropil. Electron microscopic analysis of DGL- $\alpha$  immunostaining revealed the accumulation of DGL- $\alpha$  in dendritic spine heads, however CB<sub>1</sub> and MGL were enriched in axon terminals at the ultrastructural level. Thus, the molecular architecture of the endocannabinoid system indicates that 2-AG's physiological role as a negative feed-back signaling molecule is an evolutionarily conserved feature of excitatory synapses.

Perturbation of the endocannabinoid system leads to development of epileptic seizures indicating that endocannabinoids are able to suppress pathologic neuronal excitability. To elucidate whether long-term reorganization of endocannabinoid signaling occurs in temporal lobe epileptic patients, we performed expression profiling in control post-mortem and epileptic human hippocampal tissue. qPCR measurements revealed that CB<sub>1</sub> receptor mRNA was downregulated in epileptic hippocampi, and likewise, DGL- $\alpha$  and cannabinoid receptor-interacting protein-1a (CRIP1a) mRNA was decreased in sclerotic epileptic hippocampi. However, mRNA levels of CRIP1b, DGL- $\alpha$ , MGL and enzymes responsible for anandamide synthesis and degradation were unaltered. Density of CB<sub>1</sub> immunolabeling was also decreased in the epileptic hippocampus, where electron microscopic analysis revealed significant changes in the ratio of CB<sub>1</sub>-positive glutamatergic boutons, but not in CB<sub>1</sub>-positive GABAergic axon terminals. These findings show that molecular machinery of endocannabinoid system is impaired in the epileptic human hippocampus and imply that downregulation of CB<sub>1</sub> receptors may facilitate the deleterious effects of increased network excitability.

- Ludányi A, Erőss L, Czirják S, Vajda J, Halász P, Watanabe M, Palkovits M, Maglóczy Z, Freund Z, Katona I: Down-regulation of the CB<sub>1</sub> cannabinoid receptor and related molecular elements of the endocannabinoid system in epileptic human hippocampus *J Neurosci* 2008; 28:2976-90.
- Ludányi A, Hu SS-J, Yamazaki M, Tanimura A, Piomelli D, Watanabe M, Kano M, Sakimura K, Maglóczy Z, Mackie K, Freund T, Katona I: Complementary synaptic distribution of enzymes responsible for synthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in the human hippocampus *Neuroscience* 2011; 174:50-63.
- Szabadits E, Cserép C, Ludányi A, Katona I, Gracia-Llanes J, Freund T, Nyíri G: Hippocampal GABAergic synapses possess the molecular machinery for retrograde nitric oxide signaling *The Journal of Neuroscience* 2007; 27:8101-8111.

**ANITA ZÁDORI (2011)****Environment-dependent fate of implanted neural stem cells in the brain***Supervisor: Emília Madarász*

Data obtained from in vitro and in vivo studies on NE-4C neuroectodermal stem cells and on sub-clones expressing histological markers demonstrated that the intracerebral fate of implanted neural stem cells is governed by the actual state of the host environment.

- Non-induced stem cells do not survive in, and can not integrate into the intact adult brain parenchyma. In contrast, implanted stem cells survive for long (>60 days) time in damaged brain cortices and can repopulate lesioned zones. The implanted neural stem cells, however, do not differentiate to neurons either in lesioned or in intact adult brain (Zádori, Ágoston et al., *Neuropathol Appl Neurobiol.* 2007 Oct;33(5):510-22).
- NE-4C neural stem cells can survive inside of some glioma-type neoplastic tissues, but can not „find” the tumors inside the brain indicating that the investigated tumours do not produce (enough) chemotactic signals to attract stem cells (Demeter et al., *Neurosci Res.* 2005 53(3):331-42).
- Neural precursors at early stages of in vitro induced neuronal differentiation did not show improved tissue-integration or in situ neuron formation in comparison to non-committed stem cells.
- In vitro, non-induced stem cells grow readily at low (1%) oxygen concentration and, apparently, are not damaged by hypoxia. Committed neural precursors, on the other hand, display increased sensitivity to hypoxia. At defined stages of neural differentiation, low O<sub>2</sub>-tension reduces the rates of neuron-production, markedly.
- The hypoxic environment in lesioned cortices seems to inhibit local neuron-production, but does not prevent the proliferation of the implanted stem cells. Hyperbaric oxygen therapy reduces both, the intracerebral cell proliferation and apoptosis at the lesion site, and makes the environment more permissive for formation of neurons. (Zádori et al. 2010, *submitted*)

Our studies proved, that the fate of implanted neural stem cells is determined by the host environment. The intracerebral neuron-formation was not improved by implanting committed progenitors at early phase of neural commitment. Among the parameters of the host environment, oxygen tension is one of the essential regulators of the stem cell fate.

- Zádori A, Ágoston VA, Demeter K, Hádinger N, Várady L, Góbl A, Nagy Z, Madarász E: *Survival and differentiation of neural stem cells at different oxygen levels. Exp Neurol* 2011; 227:136-148.
- Zádori A\*, Ágoston VA\*, Demeter K, Nagy Z, Madarász E: *Different behaviour of implanted stem cells in intact and lesioned forebrain cortices. Neuropathol Appl Neurobiol* 2007; 33:510-522. \*Equal contribution.
- Demeter K, Zádori A, Ágoston VA, Madarász E. *Studies on the use of NE-4C embryonic neuroectodermal stem cells for targeting brain tumour. Neurosci Res* 2005; 53:331-342.

**PROGRAM 6/2.****NEUROENDOCRINOLOGY*****Coordinator:*****Zsolt LIPOSITS M.D., Ph.D., D.Sc.**

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**Program Overview:** The course gives a deep insight into the structural organization and functional properties of neuroendocrine brain centres controlling the operation of the endocrine system. It presents the classical breakthroughs and well-established results of the discipline and also provides information on contemporary research trends and discoveries in the field of neuroendocrinology. Special attention is paid to the most recently developed research methods exploring the frontline topics of the field at molecular, cellular and system levels. The course focuses on the effects of neuroendocrine brain centres upon the pituitary-endocrine axes and vice versa, the wide scale genomic and non-genomic actions of peripheral hormones modulating the performance of the nervous system. The main topics of the course include 1. The functional neuroanatomy of the hypothalamo-hypophyseal system; 2. The organization and functional characteristics of the magno- and parvicellular neurosecretory systems; 3. The physiology of reproduction; 4. The mechanisms of thyroid hormone actions; 5. The neurobiology of stress and adaptation; 6. The central regulation of feeding and energy homeostasis; 7. Regulation of neuroendocrine rhythms and 8. The behavioural neurobiology of endocrine events. The course also focuses on the translational aspects of endocrine/neuroendocrine research, highlights inventions and novelties in the diagnosis and therapy of endocrine diseases. The course is in harmony with the educational and research mission of the International Neuroendocrine Federation.

***Titles of the research projects******Supervisors***

Neuronal and hormonal control of hypothalamic regulatory mechanisms

Zsolt Liposits

Examination of the central regulatory mechanisms involved in the development of the “low T3 syndrome”

Csaba Fekete

Examination of neuronal circuits involved in the development of satiety during refeeding

Csaba Fekete

Investigation of molecular regulation of thyroid hormone metabolism in the nervous system

Balázs Gereben

Neurobiological mechanisms underlying externalization disorders

József Halász

Integrating role of cannabinoids in trauma-induced behavioral deficits

József Haller

Hormonal, autonomic and neural background of early social deprivation-induced abnormal aggression

József Haller

Role of glutamatergic neuronal phenotype in the regulation of parvicellular and magnocellular neurosecretory systems	Erik Hrabovszky
Molecular and neuroanatomical studies of estrogen target cells in the hypothalamus	Erik Hrabovszky
Functional and morphological studies on target cells of steroid hormones in the CNS.	Imre Kalló
Studies on the neuronal connections and function of RF-amide peptide-producing neurons in the CNS.	Imre Kalló
Role of glia in homeostatic regulation.	Krisztina Kovács
Regulation of neuropeptide gene expression: -miRNA and gene silencing.	Krisztina Kovács
Neuroendocrine, paracrine and autocrine regulatory mechanisms in the regulation of adenohypophyseal hormone secretion	György M. Nagy
Investigation of the metabolism of dopamine and norepinephrine in sympathetically innervated peripheral organs (like liver, spleen or salivary gland).	György M. Nagy
The role of new signaling mechanism(s) in the regulation of pituitary function	György M. Nagy
The role of new signaling mechanism(s) in the dopaminergic regulation of pituitary prolactin secretion	György M. Nagy
Investigation of the interaction between salsolinol and different addictive drugs (like amphetamine)	György M. Nagy
Pathologic aggression and vasopressin.	Dóra Zelena
The role of vasopressin in stress in connection with stress-related psychiatric disorders (anxiety and depression)	Dóra Zelena

**Ph.D. students**

Manó Aliczki	ft
Péter Egri	ft
Andrea Kádár	ft
Bernadett Pintér Küblerné	pt
Csilla Molnár	ft
Viktória Reinthoffer	ft
Ádám Tulogdi	ft
János Varga	ft
Györgyi Zséli	ft

**Ph.D. candidates**

Ágnes Judit Domokos	ft
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**Ph.D. graduates**

Boglárka Barsy	ft
Andrea Heinzlmann	pt
Márk Oláh	ft

f; full-time; pt, part-time

**Supervisors**

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Csaba Fekete
Krisztina Kovács
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György Nagy
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**Supervisors**

Dóra Zelena
-------------

**Supervisors**

József Haller
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György Nagy

***Abstracts of Ph.D. theses successfully defended in 2011*****BOGLÁRKA BARSY (2011)****Investigation of anxiolytic-like effects of distinct stressors and their co-morbidity with drug abuse in experimental animal models***Supervisor: József Haller*

The physiological response to aversive stimuli – the stress response – becomes a pathological risk factor when it is long-lasting, is frequently repeated or is excessively strong. Continuous stress exposure or excessively strong stressors are relatively scarce, and occur in specific situations only. In contrast, repeated exposures to stressors are part of everyday life, the effects of which can accumulate and lead to various psychopathologies including anxiety. Given the strong association between stress responses and anxiety, one can hypothesize that the complexities of the former are reflected by a similarly complex stress-anxiety relationship; i.e. the similarity between the stressful situation and the testing environment should have an impact on stress-induced anxiety. In the present dissertation, thus, one of our aims was to investigate the content-dependence of different stressors [a chronic non-social (immobilisation), a chronic social (aggressive encounter) and an acute traumatic stressor (electrical footshock)] via their anxiolytic-like effects in animal models. Our results clearly demonstrated that the formation of anxiety in rats was highly depended on the test situations: whether it was homolog to the conditions of the stress situation or not. Chronic social stress caused anxiety only under social behavioural challenges but not in a non-social condition, and its chronic effect was shown by the increased adrenal weight. In contrast, a non-social stressor caused anxiety-like behaviour only in non-social environment. Traumatic experience did not provoke abnormal behaviour in any experimental situations except in trauma-like condition. However, incidental effects of trauma can be developed in heterogeneous condition, which is indicated by its comorbidity with drug abuse. Thus, we also investigated the effect of traumatic stress on craving and tolerance. Our data showed that shock exposure dramatically prolonged the drug-seeking behaviour of rats in morphine-induced place preference. Furthermore, using biotelemetric approach we found that electrical footshock accelerated the tolerance to the effects of morphine.

Taken together, our results indicated that anxiety-related effects of distinct stressors were context-dependent, however, non-anxiolytic effects – i.e. drug seeking behaviour – could be increased caused by traumatic stress exposure. The latter suggests that traumatic experience has a major impact on drug abuse in conjunction with the development of post-traumatic stress disorder-like behavioral dysfunctions.

- Barsy B, Mikics É, Barsvári B, Haller J: *The long-term impact of footshock stress on addiction-related behaviors in rats. Neuropharmacology 2011; 60:267-273.*
- Barsy B, Leveleki C, Zelena D, Haller J: *The context specificity of anxiety responses induced by chronic psychosocial stress in rats: a shift from anxiety to social phobia? Stress 2010; 13:230-7.*

**ANDREA HEINZLMANN (2011)****The role of the ovarian steroids in the regulation of the hypophyseal trop-hormones***Supervisor: Katalin Köves*

In the clinical practice estrogen (E), progesterone (P) or their combination are used not only for contraception, but to relief the symptoms caused by menopause, disturbed ovarian cyclicity, surgical removal of ovaries and uterus. The mentioned conditions result in hormone deficiency. In men E is frequently chosen as adjuvant to treat prostate cancer. In the abovementioned diseases these preparations may be administered for years.

In our experiments we tried to imitate the chronic treatments likewise in clinical practices. Twenty-five-day old Sprague-Dawley female and male rats were used for our experiments. Silastic capsule containing diethylstilboestrol (DES), progesterone (P) or their combination were implanted under the skin of the neck. After two or five month survival the following parameters were investigated. 1. The effect of a long-term DES treatment on the opening of the vaginal membrane, the vaginal smears, the weight of anterior pituitary, gonads and seminal vesicles, the distribution of LH, FSH, PRL, GH, VIP, PACAP and S-100 immunoreactive folliculostellate cells in the anterior pituitary, and the basal plasma hormone levels. 2. It was also investigated whether the P is able to influence the changes caused by DES in the opening of the vaginal membrane, vaginal smears, the weight of the above-mentioned organs, in the distribution of the hormone producing and VIP, PACAP and S-100 immunoreactive cells, and in the basal plasma hormone levels. 3. Finally we studied that, after removing of DES capsule, these parameters are able to return to the control levels.

We have received the following results. 1. Upon steroid treatments the opening of the vaginal membrane was significantly advanced. DES resulted in persistent estrus. DES+P and P did not interrupt the cyclicity but it was irregular and metestrus predominated. 2. DES treatment diminished the body weight, body length in both sexes. In five months P attenuated the effect of DES on the body length and body weight of females and the body weight of males. 3. DES enhanced the weight of the anterior pituitaries and diminished the weight of gonads and seminal vesicles. P blunted the effect of DES on the weight of the above-mentioned organs. Two months after the removal of DES capsule the weight of anterior pituitaries, ovaries and seminal vesicles returned to the control level; however, the weight of testes gradually neared to, but not reached the control level. 4. Except of PRL there was a sexual dimorphism in the changes of tropic hormone levels upon the treatments. The effect of DES treatments on PRL levels was the same in both genders, the basal PRL levels extremely enhanced and prolactinomas developed, it was accompanied by the enhancement in the weight of anterior pituitaries. P in the case of twomonth treatment attenuated, and in the case of five-month treatment prevented the effect of DES. The changes was reversible. After the removal of DES capsule the PRL levels and the weight of anterior pituitaries returned to control level. The changes in the basal LH and FSH levels showed sexual dimorphism. Basal LH and FSH levels declined only in male rats upon DES and DES+P treatment. After the removal of DES capsule the FSH levels and the weight of testes remained low; however, the LH levels and the weight of seminal vesicles normalized by the end of the second month. The reduced weight of ovaries caused by DES treatment also normalized because after the removal of DES the ovulation returned and the corpora lutea appeared. There was a mild sexual dimorphism in the GH levels. In the case of two-month treatment DES depressed the GH level in females but did not influenced it in males; however, the body length and body weight were lower in both male and females than in their control groups. In the case of five-month DES+P treatment P could partially attenuate the loss of body weight of of both sexes and prevented the decrease in body length of females.



In the case of the removal of DES the body weight remained lower in males than in the control group, in females it came nearer the control level. 5. We have found correlation between the immunohistochemistry and the basal plasma hormone levels. DES extremely depressed the number of LH and FSH cells, although the number of PRL cells enhanced, in the case of five-month survival prolactinomas developed. GH cells were evenly distributed but they were not present in the prolactinomas. Prevented the above-mentioned changes. Two months after the removal of DES capsule the immunohistochemical appearance of LH, FSH, PRL and GH cells were similar to that of the control animals. 6. The number of VIP immunoreactive cells enhanced upon DES treatment in both sexes. In the case of five-month survival VIP-omas developed. P prevented the effect of DES. 7. In both sexes the different treatments did not cause the occurrence of PACAP immunoreactive cells in the anterior pituitary. 8. The S-100 immunoreactive folliculostellate cells embraced the prolactinomas, but inside them they rarely appeared.

It was concluded that there was a sexual dimorphism in the effect of steroid treatments on the basal plasma LH and FSH levels, the body length and body weight, and the weight of gonads and seminal vesicles; however, the steroid treatments similarly influenced the PRL levels, the weight of pituitaries, the number and distribution of VIP and folliculostellate cells in both sexes.

On the bases of our unpublished data and those available in the literature we suppose that DES and P affects the pituitary hormone secretion through specific receptors present in the anterior pituitary itself.

- Heinzlmann A, Köves K: *The characteristic change in the distribution of S-100 immunoreactive folliculostellate cells in rat anterior pituitary upon long-term estrogen treatment is prevented by progesterone.* *Endocrine* 2008, 33:342-348.
- Heinzlmann A, Kirilly E, Meltzer K, Szabó E, Baba A, Hashimoto H, Köves K. *PACAP is transiently expressed in anterior pituitary gland of rats. In situ hybridization and cell immunoblot assay studies.* *Peptides* 2008, 29:571-577.
- Heinzlmann A, Köves K, György M. Nagy MG: *Effect of concomitant progesterone administration or the effect of removal of estrogen capsule on changes caused by long-term estrogen treatment in pituitary VIP immunoreactivities.* *Endocrine* 2010; 37:396-402.

MÁRK OLÁH (2011)

### **New hypothalamo-hypophyseal regulatory mechanism in the control of pituitary hormone secretion**

*Supervisor: György Nagy*

Prolactin (PRL) is a polypeptide hormone secreted by the lactotroph cells of the anterior lobe (AL) of pituitary gland. Together with the adrenocorticotroph hormone (ACTH) of pituitary and with the corticosterone of the adrenal gland they play a pivotal role in the initiation and maintenance of milk synthesis and lactation. The major physiological regulator of PRL release is the dopamine (DA) secreted in the tuberoinfundibular subdivision of the neuroendocrine dopaminergic (NEDA) neurons and is transported through long portal vessels from median eminence to the AL. Further subdivisions of the NEDA neurons innervate the intermediate lobe (IL) of the pituitary and negatively regulate the secretion of alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH) cleaved from pro-opio-melanocortin (POMC). Using animal models we have investigated the followings in our study: 1. what type of new regulational mechanisms can be responsible for the altered ACTH secretion during lactation, 2. what is the role of DA D<sub>2</sub>-receptors and NEDA system in the suckling-induced

ACTH release, 3. which molecular mechanisms and signaling pathways could be associated with the altered DA responsiveness, namely the diminution of tonic DAergic inhibition during lactation. We have investigated the changes in plasma concentration of PRL, ACTH and  $\alpha$ -MSH and activity of different signaling cascades (Akt, MAPK, cAMP) following physiological, surgical and pharmacological manipulations of the NEDA system. It can be declared that the regulation of ACTH secretion and release shows different properties during lactation period compared to ovariectomized female or male rats and the phenomenon is thought to be due to altered D<sub>2</sub> DA receptor expression, sensitivity and/or altered pro-opio-melanocortin (POMC) cleavage in the AL and IL of pituitary gland. The NEDA neurons control ACTH secretion in the lactation as well. This signaling switch from one hypothalamic mechanism to another one allows a higher ACTH, corticosterone and PRL levels in the same time. We have demonstrated that suckling stimulus, similarly to DA depletion can cease tonic DAergic inhibition of D<sub>2</sub>-receptors through activation of  $\beta$ -arrestin-dependent and G-protein-independent signaling pathways.

- Fehér P, Oláh M, Bodnár I, Hechtel D, Bácskay I, Juhász B, Nagy GM, Vecsernyés M: Dephosphorylation/inactivation of tyrosine hydroxylase at the median eminence of the hypothalamus is required for suckling-induced prolactin and adrenocorticotrop hormone responses. *Brain Res Bull*, 2010; 82:141-145.
- Oláh M, Fehér P, Ihm Z, Bácskay I, Kiss T, Freeman ME, Nagy GM, Vecsernyés M. Dopamine-regulated adrenocorticotrop hormone secretion in lactating rats: functional plasticity of melanotropes. *Neuroendocrinology*, 2009; 90:391-401.
- Bodnár I, Hechtel D, Székács D, Oláh M, Nagy GM. Effect of local (intracerebral and intracerebroventricular) administration of tyrosine hydroxylase inhibitor on the neuroendocrine dopaminergic neurons and prolactin release. *Ideggyogy Sz*, 2009; 60:177-181.

### **PROGRAM 6/3.**

#### **FUNCTIONAL NEUROSCIENCE**

##### **Coordinator:**

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**Program Overview:** The doctoral program mainly covers training and research in the application of neuropharmacological, neurochemical and neurophysiological methods to approach the function of neuronal networks mainly from the functional point of view. The major direction of neuropharmacological research is the study of the non-synaptic model of the brain, which not only defines a new mechanism of chemical transmission of nerve impulses but also explains the mechanism of action of some medications with effect on the central nervous system, and may also suggest new targets for the treatment of neuropsychiatric disorders. A further research priority is the study of the less well known connection between the nervous system and the immune system, and the identification of new neurotransmitters and modulators in the central nervous system. The neurochemical re-

search focuses on pathological processes following hypoxia and oxidative stress in the neurons of the central nervous system, with major interest in  $\text{Na}^+$  and  $\text{Ca}^{2+}$  homeostasis, in *in situ* mitochondrial function and in changes of excitability. Neurophysiological studies are performed mostly in the area of cognitive psychophysiology, and aim to understand the central nervous system mechanisms of higher level neuronal functions with the analysis of event related cerebral potential changes.

### ***Titles of research projects***

Function of ion channels and ionotropic receptors as revealed by nonlinearoptical imaging and electrophysiological methods  
 Models of brain diseases established by drug-induced alterations in neuronal networks of the peripheral and central nervous system  
 Mechanisms in neurodegeneration and neuroprotection  
 Mechanism of free radicals production by mitochondrial alpha-ketoglutarate enzyme complex: structure – function relations  
 Effects of receptors and ion-channels on integrative functions of neurons through investigations on temporal and spatial patterns of calcium dynamics and membrane potential.  
 Molecular mechanisms of drug action on ion channels  
 Three dimensional two-photon imaging of dendritic integration in neuronal networks in vivo.  
 The role of ATP- and adenosine-mediated signalling in the nervous system  
 Thy synaptical structure of the mossy fiber tract of the hippocampus  
 The bioenergetics of the central nervous system, the role of mitochondria  
 Electrophysiological analysis of evoked, spontaneous oscillations and pathological signs  
 Advanced mitochondriology  
 In vitro electrophysiological studies on synchronous population activities  
 Mechanisms of cellular damage in the central nervous- and sensory systems; potential pharmacological targets

### ***Supervisors***

E. Sylvester Vizi  
 E. Sylvester Vizi  
 Veronika Ádám  
 Attila Ambrus  
 Balázs Lendvai  
 Árpád Mike  
 Balázs Rózsa  
 Beáta Sperlág  
 János Szabadics  
 László Tretter  
 István Ulbert  
 Christos Chinopoulos  
 Lucia Wittner  
 Tibor Zelles

### ***Ph.D. students***

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János Brunner	pt
Balázs Chiovini	ft
Richárd Fiáth	ft
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 Christos Chinopoulos

Csaba Konrád	ft	Christos Chinopoulos
Gergely Márton	ft	István Ulbert
Orsolya Papp	ft	Norbert Hájos
Klaudia Spitzer	ft	Balázs Rózsa
Anett Szabó	ft	Árpád Mike
Gergely Szabó	ft	Norbert Hájos
Nikoletta Diána	ft	László Tretter
Judit Veres	ft	Norbert Hájos

***Ph.D. candidates***

Cecília Csölle	ft
Attila Heinrich	pt
Attila Kaszás	ft

Zsófia Komáry	pt
Miklós Mándi	pt
Flóra Szabó	pt

***Ph.D. graduates***

Richard Csercsa	ft
Róbert Károly	ft
Nóra Lenkey	ft
Rita Zemankovics	ft

***Supervisors***

Beáta Sperlág
Beáta Sperlág
E. Sylvester Vizi,
Balázs Rózsa
Veronika Ádám
Veronika Ádám
Katalin Köves

***Supervisors***

István Ulbert
Árpád Mike
Árpád Mike
Norbert Hájos

ft, full-time; pt, part-time

***Abstracts of Ph.D. theses successfully defended in 2011*****RICHARD CSERCSA (2011)****Laminar analysis of the slow wave activity in humans***Supervisor: István Ulbert*

The cortical slow wave activity emerging during the deepest stages of non-rapid eye movement sleep is thought to underlie essential restorative processes and facilitate the consolidation of declarative memories. In animals the slow oscillation consists of two rhythmically recurring phases: one of them is characterized by widespread, increased cellular and synaptic activity, referred to as active- or up-state, followed by cellular and synaptic inactivation, referred to as silent- or down-state. However, its neural mechanisms in humans are poorly understood since the traditional intracellular techniques used in animals are inappropriate for investigating the cellular and synaptic/trans-membrane events in humans. For the examination of the neuronal properties of the sleep slow oscillation, we recorded intracortical laminar local field potential gradient, multiple and single unit activities with laminar multichannel microelectrodes and simultaneous surface potentials with subdural grid electrodes chronically implanted into the cortex of patients with drug resistant focal epilepsy undergoing cortical mapping for seizure focus localization. We also analyzed the current source density and spectral features of the recorded signals. We found that slow

wave activity in humans reflects a rhythmic oscillation (0.6–2 Hz) between neuronal activation and silence. Similar to animal studies, cortical activation was demonstrated as increased wideband (0.3–200 Hz) spectral power, increased multiple and single unit activity, and powerful inward transmembrane currents, all mainly localized to the supragranular layers. Neuronal firing was sparse and the average discharge rate of single cells was less than expected from animal studies. The latency of firing at up-state onset across all layers was in the range of 10 ms, suggesting close inter-laminar coupling at up-state onset.

Here we provide strong direct experimental evidences that slow wave activity in humans is characterized by hyperpolarizing currents associated with suppressed cell firing, alternating with high levels of oscillatory synaptic activity associated with increased cell firing. Our results emphasize the major involvement of supragranular layers in the genesis of slow wave activity.

- Csercsa R, Dombovári B, Fabó D, Wittner L, Erőss L, Entz L, Sólyom A, Rásonyi Gy, Szűcs A, Kelemen A, Jakus R, Juhos V, Grand L, Magony A, Halász P, Freund TF, Maglóczky Zs, Cash SS, Papp L, Karmos Gy, Halgren E, Ulbert I: *Laminar analysis of the slow wave activity in humans*. *Brain* 2010; 133:2514-2515.
- Cash SS, Halgren E, Dehghani N, Rossetti A, Thesen T, Wang C, Devinsky O, Kuzniecky R, Doyle W, Madsen JR, Bromfield E, Erőss L, Halász P, Karmos Gy, Csercsa R, Wittner L, Ulbert I: *The human K-complex represents an isolated cortical down-state*. *Science* 2009; 324:1084-1087.
- Grand L, Wittner L, Herwik S, Göthelid E, Ruther P, Oscarsson S, Neves H, Dombovári B, Csercsa R, Karmos G, Ulbert I, *Short and long term biocompatibility of NeuroProbes silicon probes*. *J Neurosci Methods* 2010; 189:216-229.

## RÓBERT KÁROLY (2011)

### Application of kinetic modeling in drug research

Supervisor: Árpád Mike

State-dependent binding of a ligand (agonist, antagonist, modulator, etc.) to a receptor or ion channel necessarily involves modulation of gating transitions between states. The reciprocal interactions between binding and gating (the extent of binding is dependent on the distribution of states, while the distribution of states is dependent on binding of the ligand) produces a complex network of interrelated transitions, in which questions cannot always be correctly answered by mere speculation.

Modeling is an excellent approach to handle such complex systems of interactions. Using simple rules, a model can be constructed which is able to reproduce experimental findings. The investigation of model behavior can reveal interactions which remain hidden during a standard analysis of experimental data, and can help to comprehend operation of the system.

Using electrophysiology experiments and modeling, we investigated two different topics: state selectivity of sodium channel inhibitors, and desensitization mechanisms of P2X3 receptors. The two problems, nevertheless, were very similar, because both involved understanding a complex system of interactions between binding and gating transitions. From our experiments and simulations with sodium channel inhibitors we concluded that protocols, which are commonly used to identify state preference, are totally unreliable, and cause misinterpretation of drug modes of action. We propose that several drugs which are assumed to be slow-inactivated-state-selective inhibitors based on results of these protocols are incorrectly diagnosed as such, and probably act by a different mode of action.

From our experiments and simulations with P2X<sub>3</sub> receptors we concluded that activation of the receptor is possible with only two bound agonist molecules, while a single bound agonist molecule is able to desensitize it. This is the basis of the puzzling observation that agonists are able to induce an activation-dependent high affinity desensitization process at concentrations more than 10 000 fold lower than the EC<sub>50</sub>. We proposed a mechanism for this paradoxical phenomenon by uncovering agonist exchange dynamics. The proposed mechanism may be the theoretical basis for developing a novel type of analgesic drugs.

- Karoly R, Lenkey N, Juhasz AO, Vizi ES, Mike A: *Fast or slow inactivated state preference of Na<sup>+</sup> channel inhibitors: a simulation and experimental study*. *PLoS Comput Biol* 2010; 6:e1000818.
- Karoly R, Mike A, Illes P, Gerevich Z: *The unusual state-dependent affinity of P2X<sub>3</sub> receptors can be explained by an allosteric two open-state model*. *Mol Pharmacol* 2008; 73:224-234.

## NÓRA LENKEY (2011)

### A comparative study of sodium channel inhibitors using electrophysiology and cheminformatics

Supervisor: Árpád Mike

There is only one established drug binding site on sodium channels. However, drug binding of sodium channels shows extreme promiscuity: in a recent screening study 25% of all investigated drugs potentially inhibit sodium channels. The structural diversity of these molecules suggests that they may not share the binding site, and/or the mode of action. To test this hypothesis we first performed a detailed patch-clamp study on the mode of action of two antidepressants: fluoxetine and desipramine. They showed a mode of action (slow inactivated state preference or slow association) that is different from the one observed using carbamazepine, phenytoin and lidocaine. Next, we performed a comparative electrophysiological study of 35 compounds (anticonvulsants, class I antiarrhythmics, local anesthetics, antidepressants, antipsychotics and neuroprotective agents) using rNav1.2 expressing HEK-293 cells and the QPatch automatic patch-clamp instrument. We used two simple voltage protocols, but optimized analysis of the data, so that multiple properties of inhibition could be extracted: resting and inactivated affinity, potency, reversibility, time constants of onset and offset, use-dependence and state-dependence. In the multidimensional space defined by the properties of inhibition at least three distinct types of inhibition could be identified; these probably reflect distinct modes of action. Drugs of the same therapeutic indication typically belonged to the same type. The compounds were clustered similarly in the multi-dimensional space defined by relevant chemical properties, including measures of lipophilicity, aromaticity, molecular size, polarity and electric charge. We identified chemical properties, which were important in determining specific properties of inhibition: e.g. the therapeutically important state-dependence correlated with lipophilicity, the ratio of the neutral form of molecules, and aromaticity. By recording multiple parameters of inhibition, we could extract more information without increasing cost, or time demand of the measurements. This allowed us to identify distinct inhibition types, and to identify chemical properties which determine specific properties of inhibition.

- Lenkey N, Karoly R, Kiss JP, Szasz BK, Vizi ES and Mike A. *The mechanism of activity-dependent sodium channel inhibition by the antidepressants fluoxetine and desipramine*. *Mol Pharmacol* 2006; 70:2052-2063.
- Karoly R, Lenkey N, Juhasz AO, Vizi ES, Mike A. *Fast- or slow inactivated state preference of Na<sup>+</sup> channel inhibitors: a simulation and experimental study*. *PLoS Comput Biol* 2010; 6:e1000818.



- Lenkey N, Karoly R, Lukacs P, Vizi ES, Sunesen M, Fodor L, Mike A: *Classification of drugs based on properties of sodium channel inhibition: a comparative automated patch-clamp study. PLoS One 2010; 5:e15568.*
- Lenkey N, Karoly R, Epresi N, Vizi ES, Mike A: *Binding of sodium channel inhibitors to hyperpolarized and depolarized conformations of the channel. Neuropharmacology 2011; 60:191-200.*

## PROGRAM 6/4.

### CLINICAL NEUROSCIENCE

#### **Coordinator:**

**Zoltán NAGY M.D., Ph.D., D.Sc.**

Department of Cardiovascular Surgery

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**Program Overview:** The Clinical Neuroscience Program within the Neuroscience Doctoral School focuses on the research of mechanisms of neuropsychiatric disorders. Laboratories in the program apply cell biological, molecular biological, pharmacological and electrophysiological methods involving Ph.D. students. Of the three research groups the vascular neurological group (head Prof. Dr. Zoltán Nagy) performs studies using permanent or transient ischemic animal models and PC12 and endothelial cell cultures applying cell biological and neuronal apoptotic studies. The epilepsy group (head: Prof. Dr. Péter Halász) studies the mechanism of spike-and-wave epilepsy, the relationship of sleep and epilepsy, and the relationship + between epileptic mechanisms and cognitive function, the temporal spike activity and memory. The pharmacological group (head: Prof. Dr. György Bagdy) studies the pharmacology of serotonin, and the relationship between serotonin and sleep disorders.

#### ***Titles of research projects***

Regulation of sleep and circadian rhythm by neurotransmitters, neuropeptides and their receptors

Neuronal damage induced by ecstasy (MDMA): morphological and functional studies

The role of spontaneous and evoked slow oscillation in organisation of sleep and restoration of frontal cognitive functions

Interrelationship of sleep and epilepsy

Genomic biomarker research for the improvement of the neurological personalized medicine

The development of new diagnostic and therapeutic modalities in mitochondrial disorders

Genomic and epigenomic investigations in Parkinson disease

#### ***Supervisors***

György Bagdy

György Bagdy

Péter Halász

Péter Halász

Mária Judit Molnár

Mária Judit Molnár

Mária Judit Molnár

Relationship of patent foramen ovale and cryptogenic stroke in the secondary prevention of stroke	Géza Szilágyi
Characterization of primary and immortalized human cerebral microvessel endothel under hyperbaric oxygen conditions	Judit Skopál
Studies on post-stroke brain plasticity by bioelectric imaging (hpEEG) techniques	Zoltán Nagy
Bone marrow mesenchymal stem cell transplantation in brains affected by transient MCA occlusion in rats (monitoring plasticity markers)	Zoltán Nagy
MRI and histological comparative studies on BBB opening in rats using colloidal iron containing tracer.	Zoltán Nagy

***Ph.D. students***

Magdolna Dombóvári	pt
Beáta Horváth	ft
Gabriella Inczédy-Farkas	ft
Szilvia Vas Kalmár	ft
István Kapás	pt(a)
Sándor Nardai	pt(a)
Viktória Reményi	ft
Léna Szabó	ft(a)

***Supervisors***

Zoltán Nagy
György Bagdy
Mária Judit Molnár
György Bagdy
Gábor Kovács
Zoltán Nagy
Mária Judit Molnár
András Fogarasi

***Ph.D. candidates***

László Entz	ft
Zita Klára Kátai	ft
Tamás Kitka	ft

***Supervisors***

Péter Halász
György Bagdy
György Bagdy

a, absolutorium; ft, full-time; pt, part-time;

***PROGRAM 6/5.*****CLINICAL NEUROLOGICAL INVESTIGATIONS*****Coordinator:*****Imre SZIRMAI M.D., Ph.D., D.Sc.**

Department of Neurology

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E-mail: [szirmaiimre@gmail.com](mailto:szirmaiimre@gmail.com)

**Program Overview:** This doctoral (Ph.D.) program includes clinical research projects in neurology. *Full time* participation in clinical research can be applied by medical students from the Hungarian, English and German faculties who accomplished their fifth year training, furthermore young doctors with certain research experience in neuroscience. *Part-time participation* is possible for young neurologists before their neurology special exam. *Participants* who are *not affiliated*, working on any subspecialties of neuroscience, could join to the subprograms if their topic may be suited to the clinical neurology. The

clinical research program includes partially laboratory work, the research activity of participants may concern to investigate clinical patients and statistical evaluation of clinical and laboratory information. The advertised programs contain mostly unsolved questions of the clinical neurology.

Research of cerebro-vascular diseases includes clinico-pathological evaluation and classification of leukoaraiosis comparing clinical symptoms and brain imaging findings. Analysis of clinical picture and outcome of neurological deficits of elderly patients who suffered ischemic insults caused by lacunar infarctions is available. By the help of the clinical register clinical and epidemiological investigations of cerebrovascular disorders is advertised.

The pathomechanism of the primary headaches is unknown. To study the biochemical and physiological causes of headaches in a clinical working group is in progress. Physiological studies involve the noninvasive measurement of blood flow velocity in the intracerebral arteries. With the help of statistical software EEG activity and Doppler flow data can be analyzed simultaneously. Neuropsychologic tests, and electrophysiological measurements can be used in patients with degenerative dementias and aphasia. Research on the movement disorders especially Parkinson disease is a prominent scientific field of the department. Projects for the research of movement and coordination will start in 2012. Many aspects of phenomenology, medical and surgical treatment are under investigation; furthermore neurosurgical research field was opened in 2011. Additionally other neurosurgical programs are also available. Psychometric methods, tremorometry and electrophysiology help the differential diagnosis of movement disorders. New program for the investigation of the basic mechanism of epilepsy was just opened. Topographic aspect and mechanism of human tremor is unknown. Subprograms provide to join to the tremor-research group. Subprogram for neuropathology is ready for the investigation of dementias and cerebrovascular diseases. Learning the instrumental diagnostic technics by the aim to improve the topography of lesions of roots and nerves and scientific analysis of the underlying diseases of peripheral nerves is possible. Research topic for the investigation of optokinetic nystagmus was planned for the approach of brainstem's pathology.

### ***Titles of research projects***

Examination of the characteristics of lacunar cerebral infarcts  
 Investigations of cognitive functions in multiple sclerosis –  
 Clinico-morphological correlations.  
 Disturbances of cognition, behavior and speech in  
 cerebrovascular diseases  
 Investigations of optokinetic nystagmus and saccades in cortical  
 and subcortical lesions.  
 Investigation of the cognition by the help of transcranial  
 Doppler and EEG  
 EEG analysis of recall and working memory  
 Studies of neuropathies with high resolution ultrasonography  
 and comparison of results with electrophysiological findings  
 Examination of the clinical characteristics, diagnostic  
 possibilities and pathomechanism of primary headaches.  
 Examination of event related desynchronisation, tremor and  
 coordination in Parkinson's disease

### ***Supervisors***

Dániel Bereczki  
 Imre Szirmai  
 Imre Szirmai  
 Imre Szirmai  
 Imre Szirmai  
 Imre Szirmai  
 Zsuzsanna Arányi  
 Csaba Ertsey  
 Anita Kamondi

Pre-, intra and postoperative examination of tremor in Parkinson and essential tremor patient treated with deep brain stimulation	Anita Kamondi
Examination of cerebellar tremor	Anita Kamondi
Complex tremoromery in various tremor syndromes	Anita Kamondi
Examination of tremorgenezis using transcranial magnetic stimulation	Anita Kamondi
Examination of motor control using combined EEG and transcranial magnetic stimulation methods	Anita Kamondi
Complex tremoromery in primary degenerative nervous system disorders	Anita Kamondi
Clinico-morphological correlations in degenerative diseases of the central nervous system	Tibor Kovács
Neuropathological investigations in vascular diseases of the central nervous system	Tibor Kovács
The pre- and postoperative electrodiagnosis of radiculopathies, the predictive value of different electrophysiological methods.	Péter Banczerowski
Modern neurosurgical treatment opportunities in case of central nervous system pathologies	Péter Banczerowski

***Ph.D. students***

Bence Barna Gunda	ft
Nóra Manhalter	pt

***Supervisors***

Dániel Bereczki
Dániel Bereczki

***Ph.D. candidates***

Attila Álmos Balogh	i
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***Supervisor***

Péter Banczerowski
--------------------

***Ph.D. graduates***

Róbert Debreczeni	i
István Valálik	i

***Supervisors***

Imre Szirmai
Anita Kamondi

ft, full-time; pt, part-time; i, individual

***Abstracts of Ph.D. theses successfully defended in 2011*****RÓBERT DEBRECZENI (2011)****Polygraphic investigation of the control of cerebral circulation**

*Supervisor: Imre Szirmai*

Change of cerebral blood flow is proportional with the cerebral blood flow velocity (BFV). Cognitive effort enhances the cerebral circulation and leads to activation of autonomic variables. We investigated 16 right-handed volunteers during verbal fluency (VF) and mental arithmetic (MA) tests. BFV was recorded by transcranial Doppler (TCD) in both MCAs. Heart rate (H), arterial blood pressure (ABP), end tidal P<sub>CO2</sub> (ETP<sub>CO2</sub>) and respiration

rate (Rr) was monitored and cerebral vascular resistance (CVR) was calculated. During MA and VF tests the left-minus-right (L-R) BFV-difference elevated significantly with ABP and HR in all subjects. Rr increased in all subjects during cognitive effort. Between CVR and  $ETP_{CO_2}$  negative correlation was observed. We assume that local neuronal activation of the vascular bed during cognition is capable to counteract the global effect of hypocapnia. Laterality index (Li) of central frequency (CF) correlated with handedness in 9 out of 12 subjects in the VF, and in 6 out of 12 subjects in the MA test. The correlation between CF and BFV during mental activity suggests a short latency global regulation of CBF and a long latency regional regulation by vasoneuronal coupling.

To clarify the causes of the orthostatic intolerance in Parkinson's disease the regulation of cerebral circulation (AR) was investigated by polygraphic method in 17 parkinsonian patients (PP) and 8 age-matched controls (C). On a tilt table BFV was recorded in MCAs, simultaneously with ABP, and  $ETP_{CO_2}$  during supine and in tilted positions. The decrease of ABP in PP was significantly lower than in the controls when supine position was restored from 70°, which suggests a damage of sympathetic cardiovascular system. This could be explained by the damage to the postganglionic structures in Parkinson's disease. Our tilt-table experiments suggested, that the cerebral blood flow in Parkinson-patients is more "pressure dependent" than in healthy controls. These results explain the frequent orthostatic intolerance of PP-s despite of normal blood pressure.

- Debreczeni R, Amrein I, Kollai M, Lénárd Z, Pálvölgyi L, Takáts A, Tamás G, Szirmai I: Az agyi autoreguláció vizsgálata Parkinson-betegségben. *Ideggyogy Sz* 2005 20:245-52.
- Szirmai I, Amrein I, Pálvölgyi L, Debreczeni R, Kamondi A. Correlation between blood flow velocity in the middle cerebral artery and EEG during cognitive effort. *Brain Res Cogn Brain Res* 2005; 24:33-40.
- Debreczeni R, Amrein I, Kamondi A, Szirmai I. Hypocapnia induced by involuntary hyperventilation during mental arithmetic reduces cerebral blood flow velocity. *Tohoku J Exp Med*. 2009; 217:147-54.

## ISTVÁN VALÁLIK (2011)

### CT-guided stereotactic thermolesion and deep brain stimulation in the treatment of patients with Parkinson's disease

*Supervisor: Anita Kamondi*

The dissertation presents my 15-year experience in the surgical treatment of Parkinson's disease. A targeting technique, based on individual MRI anatomy and CT-guided coordinate determination with self-developed planning software provided a proper accuracy for surgery. In most of the cases, intraoperative stimulation testing was sufficient in target optimisation, micro-recording can be optional.

The developed method for tremor analysis and the software for motion and voice analysis, which is based on open source and published algorithms, along with evaluation scales allowed quantified assessment of the results of surgery.

Unilateral thermolesion in the thalamus and GPi and unilateral or bilateral DBS in the thalamus, GPi and STN can be used in the treatment of Parkinson's disease with a low risk and high effectiveness. Thalamotomy and pallidotomy are nowadays replaced with DBS and mainly used in cases of raised risk of inflammation, financial reasons and upon patient's decision. Thalamotomy improves the quality of life and has a lasting effect up to 7 years mainly in unilateral tremordominant forms for alleviation of tremor and rigidity. Pallidotomy is a safe procedure, and, in short-term, it improves the OFF symptoms, and, in

long-term, it reduces dyskinesia. Taking the higher risk of side effects into consideration, bilateral procedures are preferred in patients who do not pass the selection criteria for DBS.

In patients without marked cognitive decline, and with feasible postoperative follow-up DBS is the first choice surgical procedure. STN-DBS improves the L-dopa responsive symptoms of Parkinson's disease, and if there are no exclusion criteria in advanced stage with „on-off” fluctuations, it is the most effective surgical procedure. As Vim-DBS has less adverse effects and better tolerated than STN-DBS, it is the first option for tremordominant patients. In patients with severe dyskinesia, in the case of whom, due to cognitive decline or reduced L-dopa responsiveness, STN-DBS is abandoned, in a cognitive aspect safe GPi-DBS by dyskinesia reduction and improvement of axial symptoms may result a substantial improvement of condition.

The changes in quality of life are markedly influenced by patient selection, the adjustment of drug therapy and careful postoperative follow-up made by neurologists.

- Valálik I, Sági S, Solymosi D, Julow J. CT-guided unilateral thalamotomy with macro-electrode mapping for the treatment of Parkinson's disease. *Acta Neurochirurgica (Wien)* 2001; 143:1019-1030.
- Valálik I, Emri M, Lengyel Zs, Mikecz P, Trón L, Csókay A, Márián T. Pallidal deep brain stimulation and L-dopa. effect on PET motor activation in advanced Parkinson's disease. *J Neuroimaging* 2009; 19:253-258.
- Valálik I, Smehák Gy, Bognár L, Csókay A. Voice acoustic changes during bilateral sub-thalamic stimulation in patients with parkinson's disease. *Clinical Neurology and Neurosurgery* 2010; 113:118-195.

## PROGRAM 6/6.

### BIOLOGICAL PSYCHIATRY

#### **Coordinator:**

**Gábor FALUDI M.D., Ph.D., D.Sc.**

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**Program Overview:** The aim of the “Biological Psychiatry” program is to study the theoretical and practical aspects of brain and mental sciences, utilising and integrating knowledge from different disciplines in understanding pathopsychological functions and therapeutic response, and to contribute with its results to everyday practice in mental hygiene and psychiatry. One challenge for biological psychiatry is to integrate our psychopathological knowledge about brain functional changes with our present knowledge about the relationship between brain and behavior and brain structure. Research in the Biological Psychiatry program targets psychiatric disorders from neurobiological, neurochemical, genetic and neurocognitive aspects, building on knowledge from cooperation with other disciplines and experience from clinical observation and effective treatment of patients. Presently the program includes 7 Ph.D. themes offering the study of neurobiological, clinical and therapeutic aspects of adult and geriatric psychiatric disorders. The tutors are well-known and internationally acknowledged theoretical and clinical experts.



***Titles of research projects***

Neurobiology and therapy of affective and mood disorders  
Genetic correlates and behavioural endophenotypes of major depression  
Genetic and clinical aspects of bipolar disorders with special regards of suicide behaviour  
Role of the dopaminergic and serotonergic systems in mood and anxiety disorders  
Genetic and pharmacogenomic investigation of affective disorders and comorbid substance abuse disorders in a multifactorial model

***Supervisors***

Gábor Faludi  
Xénia Gonda  
Zoltán Rihmer  
Anna Székely  
Judit Lazáry

***Ph.D. student***

Zsuzsa Halmai ft

***Supervisor***

Anna Székely

***Ph.D. candidates***

Péter Döme i  
Zoltán Makkos i

***Supervisors***

Zoltán Rihmer  
Gábor Faludi

f, full-time; i, individual

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## SCHOOL OF PH.D. STUDIES

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### 7. MOLECULAR MEDICINE

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***Chairman:***

**József MANDL M.D., member of the Hungarian Academy of Sciences**

Department of Medical Chemistry,  
Molecular Biology and Pathobiochemistry  
37-47 Tűzoltó u. Budapest H-1094  
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**General Overview:** The postgraduate school of molecular medical sciences serves for both biomedical basic research and primary training of researchers starting their careers in the fields of clinical research. One of the major drawbacks of biomedical research is that there is no efficient connection between the basic and clinical research. Therefore, five main Programs involve applied theoretical knowledge together with clinical research.

#### ***PROGRAM 7/1.***

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#### **CELLULAR AND MOLECULAR PHYSIOLOGY**

***Coordinator:***

**Erzsébet LIGETI M.D., member of the Hungarian Academy of Sciences**

Department of Physiology  
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E-mail: [erzsebet.ligeti@eok.sote.hu](mailto:erzsebet.ligeti@eok.sote.hu)

**Program Overview:** The Program provides opportunity to receive training in the field of physiology. The professors of the Program offer courses and individual training for the Ph.D. students on their respective scientific research areas. Training courses include continuous basic methodical and scientific training for small groups of students. Individual training focuses on research under the supervision of training advisors aimed at understanding physiological regulatory mechanisms at the cellular level using electrophysiological, molecular biological, biochemical, cell biological and physiological methods.

***Titles of research projects***

Investigation of two-pore domain potassium channels  
Molecular chaperones and biological networks  
Receptor mediated regulation of 2P type potassium channels

***Supervisors***

Gábor Czirják  
Péter Csermely  
Péter Enyedi

Investigation of reactive oxygen producing enzymes in mammalian cells	Miklós Geiszt
Charge compensation mechanisms of reactive oxygen species forming enzymes	Miklós Geiszt
Regulation of G protein-coupled receptors	László Hunyady
Molecular basis of angiotensin receptor function	László Hunyady
Molecular basis of regulation of circadian rhythm	Krisztina Káldi
Role and regulation of Rho family GTPase activating proteins (GAPs)	Erzsébet Ligeti
Role of NADPH oxidase in antibacterial defense	Erzsébet Ligeti
Investigation of proteins involved in the differentiation and function of osteoclasts	Attila Mócsai
Role of oxygen radicals in the physiological effect of angiotensin II and other $\text{Ca}^{2+}$ mobilizing hormones	András Spät
The molecular and physiological role of inositol lipids	Péter Várnai
Investigation of the structure-function relationship of TrpM2 cation channels	László Csanády
The role of positional information (position along the body-axes) in the early differentiation of neural cells	Emilia Madarász

**Ph.D. students**

Krisztina Ella	ft
László Sándor Erdélyi	ft
László Fülöp	ft
Pál Gyombolai	ft (a)
Kata Kenesei	ft
István Kovács	ft
Márton Ákos Lőrincz	ft
Bence Szalai	ft
Csaba István Timár	ft
Dániel Tóth	ft (a)
József Tóth	ft
Melinda Zana	ft
Enikő Lázár	ft

**Ph.D. candidates**

Roland Csépanyi-Kömi	pt
Dávid Sándor Győri	ft
Péter Koncz	pt
Miklós Kovács	ft
Tamás Németh	ft
Robin Dezső Palotai	ft
Zalán Péterfi	ft
Balázs Tóth	ft

**Supervisors**

Krisztina Káldi
László Hunyady
Erzsébet Ligeti
László Hunyady
Emilia Madarász
Miklós Geiszt
Erzsébet Ligeti
László Hunyady
Erzsébet Ligeti
Péter Várnai
Péter Várnai
Miklós Geiszt
Miklós Geiszt

**Supervisors**

Erzsébet Ligeti
Attila Mócsai
András Spät
Attila Mócsai
Attila Mócsai
Péter Csermely
Miklós Geiszt
László Csanády

**Ph.D. graduates**

Balázs Enyedi	ft
Norbert Gyöngyösi	ft
Zsuzsanna Kertész	ft
Gergő Szanda	ft

**Supervisors**

Miklós Geiszt
Krisztina Káldi
Attila Mócsai
András Spät

a, absolutorium; f, full-time; pt, part-time

**Abstracts of Ph.D. theses successfully defended in 2011****BALÁZS ENYEDI (2011)****Novel methods for studying hydrogen peroxide-producing mechanisms in mammalian cells**

*Supervisor: Miklós Geiszt*

Hydrogen peroxide ( $H_2O_2$ ) is a reactive oxygen species of various functions in our cells. It plays important roles in fundamental biological processes such as host defense, hormone biosynthesis, regulation of vascular tone, apoptosis or fertilization. It is produced for example during mitochondrial respiration, the activation of NADPH oxidase enzymes or oxidative protein folding in the endoplasmic reticulum. Numerous aspects of its intracellular role are still of debate, such as details of its spatial and temporal production or its concentration within different cellular compartments. Our goal was to map the intracellular level of  $H_2O_2$  at different subcellular sites with a recently described protein-based sensor, HyPer. We measured the highest  $[H_2O_2]$  within the ER, and the enzyme Ero1L- $\alpha$  was demonstrated to play an important role in its production. Its amount also depends on the concentration of calcium within the ER, alterations of the  $[Ca^{2+}]_{ER}$  leads to parallel changes in the level of  $[H_2O_2]_{ER}$ . The potential role of  $H_2O_2$  in regulating cellular calcium homeostasis was investigated by characterizing the calcium signal in urothelial cells prepared from wild-type and DUOX1 knockout mice. The DUOX1-formed  $H_2O_2$ , however, did not influence the level of calcium in these cells. We developed novel measuring techniques for  $H_2O_2$ , and thereby broadened the array of methods for the detection of ROS. With our fluorescence resonance energy transfer (FRET) based OxyFRET and PerFRET probes we can follow the subcellular production of  $H_2O_2$  with high sensitivity and specificity. The probes have proven to be capable of reporting the  $H_2O_2$  production of NOX2 and DUOX1 enzymes. Our experiments characterize for the first time the  $H_2O_2$  production of NADPH oxidase enzymes with genetically encoded probes. Our results confirm previous observations claiming that NOX2 produces higher amounts of  $H_2O_2$  than the DUOX1 enzyme. Furthermore, we have characterized the extent of  $H_2O_2$  diffusion within and between the cells, and we observed that DUOX1-derived  $H_2O_2$  reaches the cytoplasm of both the producing and the surrounding cells, on the other hand, it doesn't significantly increase the  $[H_2O_2]$  measured in the mitochondrial matrix of the producing cells. Our results confirm with direct experiments for the first time the previously proposed role of  $H_2O_2$  as being a potential paracrine mediator molecule.

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**NORBERT GYÖNGYÖSI (2011)****Long-term effects of 3,4-methylenedioxymethamphetamine (MDMA) on 5-HT<sub>1B</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor functions in the control of vigilance and motor activity 6 months after treatment with neurotoxic dose of MDMA***Supervisor: Krisztina Káldi*

The recreational drug „ecstasy” (3,4-methylenedioxymethamphetamine, MDMA) belongs to the popular group of the amphetamine derivatives, and has become second in popularity to cannabis in Hungary. Although the long-term effects of MDMA on serotonergic system is well known, the consequences on the functions of serotonin receptors are still remained to be elucidated. Aim of our study was to reveal whether a single dose of MDMA (15 mg/kg, i.p.) is able to cause long-term effects on the serotonergic control of the vigilance and movement by 5-HT<sub>1B</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors 6 months after MDMA pre-treatment. Male Dark Agouti rats, the model organisms of the human population of „MDMA poor metabolisers” were treated intraperitoneally with the selective 5-HT<sub>1B</sub> agonist 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrlo[3,2-b]pyridine (CP-94,253), or the 5-HT<sub>2A/2B/2C</sub> agonist 2,5-dimethoxy-4-iodoamphetamine (DOI), or the selective 5-HT<sub>3</sub> agonist m-chlorophenylbiguanide (mCPBG) 6 months after MDMA pretreatment. 24 hour-long polysomnographic recordings and motor activity measurements were performed after the acute treatment. In addition, the effects of the selective 5-HT<sub>2C</sub> antagonist 6-chloro-5-methyl-N-{6-[(2-methylpyridin-3-yl)oxy]pyridin-3-yl}indoline-1-carboxamide (SB-242084) were studied in doses of 0,1-1 mg/kg (i.p.) on the vigilance and motor activity. The selective 5-HT<sub>1B</sub> agonist, CP-94,253 increased active and passive wake, and decreased the time spent in light slow-wave sleep, deep slow-wave sleep, and paradoxical sleep in control rats. Moreover, the 5-HT<sub>1B</sub> agonist treatment altered the parameters of the diurnal rhythm: shifted the timing of the passive vigilance states to a later time point, and advanced the wakefulness to earlier time. Generally, the effects of CP-94,253 were unaltered in MDMA pretreated rats, the only exception was the active wake, where the MDMA pre-treatment abolished the effect of the selective 5-HT<sub>1B</sub> agonist. The selective 5-HT<sub>2</sub> agonist DOI increased active and passive wake, and decreased the time spent in sleep stages. In addition, diurnal rhythms of the analysed vigilance states were also altered. The effect of DOI on active wake decreased in rats pretreated with MDMA compared to control animals. Moreover, the MDMA pre-treatment 6 months earlier caused slight, but significant alterations on the effect of DOI in deep slow wave sleep and paradoxical sleep. The selective 5-HT<sub>2C</sub> antagonist SB-242084 increased wakefulness and light slow wave sleep, and decreased the time spent in deep slow wave sleep in the dose of 1 mg/kg. Based on our data, we can suggest that activation of 5-HT<sub>2C</sub> receptors contributes to the effect of the non-subtype selective 5-HT<sub>2A/2B/2C</sub> agonist DOI on light slow-wave sleep in contrast to effects of DOI on other vigilance states. The selective 5-HT<sub>3</sub> agonist mCPBG (1 mg/kg, i.p.) increased the time spent in active wake, and decreased light slow-wave sleep. The effect of mCPBG on active wake was absent in the rats pretreated with MDMA 6 months earlier. Our results give evidence that a single dose of MDMA is able to cause long-term alterations in the 5-HT<sub>1B</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor functions in the control of sleep-wake cycle and movement, and suggest a danger of long-term functional alterations in human ecstasy users.

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## ZSUZSANNA KERTÉSZ (2011)

### Studying the role of PLC $\gamma$ 2 and p190RhoGAP proteins in osteoclast development and bone metabolism

Supervisor: Attila Mócsai

Osteoclasts are multinucleated phagocyte cells that are formed from haematopoietic stem cells. Development of mature osteoclasts is directed by M-CSF and RANKL cytokines and adhesive signals. Previous studies suggested that PLC $\gamma$ 2 and p190RhoGAP proteins may have a role in osteoclastogenesis which was tested by using mice genetically deficient of PLC $\gamma$ 2 and p190RhoGAP isoforms. During our experiments, bone marrow cells lacking PLC $\gamma$ 2, p190-A or p190-B were cultured under osteoclastogenic conditions and the development and resorptive function of osteoclasts was tested. We also tested the role of PLC $\gamma$ 2 in basal and ovariectomy-induced bone resorption by micro-CT and histomorphometric analyses of the trabecular architecture of long bone metaphyses. Postmenopausal osteoporosis was modeled by surgical ovariectomy. *In vitro* cultures of PLC $\gamma$ 2 $^{-/-}$  bone marrow cells revealed that PLC $\gamma$ 2 was required for the development of multinucleated osteoclasts and for the resorption of artificial bone surface. PLC $\gamma$ 2 was activated upon adhesion of the cells but not by stimulation with M-CSF or RANKL in suspension. PLC $\gamma$ 2 was phosphorylated in a Src-family-dependent manner upon adhesion but not upon stimulation by M-CSF or RANKL. These results indicate that PLC $\gamma$ 2 plays a critical role in the development and function of osteoclasts and PLC $\gamma$ 2 likely participates in adhesion-receptor signaling. PLC $\gamma$ 2 $^{-/-}$  mice had significantly higher trabecular bone mass under basal conditions than wild type mice. Surprisingly, ovariectomy-induced bone resorption in PLC $\gamma$ 2 $^{-/-}$  mice was similar to, or even more robust than, that in wild type animals. Taken together, PLC $\gamma$ 2 is required for bone resorption under basal conditions but it does not play a major role in ovariectomy-induced bone loss. These results suggest that basal and estrogen deficiency-induced bone resorption utilizes different signaling pathways. Using bone marrow cells lacking the p190-A or the p190-B isoform of p190RhoGAPs, we were able to show that neither isoform alone is dispensable for osteoclast differentiation and function. Taken together, these results indicate that the p190-A and p190-B proteins do not have any non-redundant functions in osteoclasts.

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**GERGŐ SZANDA (2011)****Feed-forward control of mitochondrial  $\text{Ca}^{2+}$  uptake***Supervisor: András Spät*

Mitochondrial  $\text{Ca}^{2+}$  uptake modifies cytosolic  $\text{Ca}^{2+}$  signal and regulates oxidative phosphorylation, generation of ROS, steroid-synthesis and apoptosis. Mitochondrial  $\text{Ca}^{2+}$  uptake is generally accepted to be a low affinity process occurring only when  $[\text{Ca}^{2+}]$  attains several micromoles in the so-called high  $\text{Ca}^{2+}$  perimitochondrial microdomains (HCMD). However, some data do not support this idea.

We examined the possibility of a HCMD-independent mitochondrial  $\text{Ca}^{2+}$  uptake in cells in which there is HCMD-dependent  $\text{Ca}^{2+}$  uptake. We have shown in human adrenocortical H295R cells that whereas the  $\text{Ca}^{2+}$  mobilizing agonist angiotensin II induces mitochondrial  $\text{Ca}^{2+}$  signal in a HCMD-dependent manner, mitochondrial  $\text{Ca}^{2+}$  uptake during  $\text{K}^{+}$ -evoked  $\text{Ca}^{2+}$  influx occurs without the formation of HCMDs. We have also found that angiotensin II, parallel with the mobilisation of  $\text{Ca}^{2+}$ , activates p38 MAPK and a novel-type protein kinase C isoform. Simultaneous activation of these kinases attenuates mitochondrial  $\text{Ca}^{2+}$  uptake probably by reducing the  $\text{Ca}^{2+}$  permeability of the outer mitochondrial membrane. The kinase-mediated inhibition is partially responsible for the strong correlation between  $\text{Ca}^{2+}$  uptake and ER-mitochondrion distance during  $\text{Ca}^{2+}$  mobilization whereas lack of kinase activation enables a HCMD-independent mitochondrial  $\text{Ca}^{2+}$  uptake during  $\text{Ca}^{2+}$  influx. Similarly, we have shown the existence of HCMD-independent  $\text{Ca}^{2+}$  uptake also in COS-7 cells.  $\text{Mg}^{2+}$  in supraphysiological concentration is a well-known inhibitor of  $\text{Ca}^{2+}$  uptake into suspended mitochondria. We have found in permeabilized HEK-293T cells that  $\text{Mg}^{2+}$  reduces  $\text{Ca}^{2+}$  uptake of mitochondria also in the concentration-range typical for *intact* cells. In HEK-293T and H295R cells we described a fast cytosolic  $\text{Mg}^{2+}$  signal that accompanies the  $\text{Ca}^{2+}$  signal and that is in concentration-range effectively attenuating  $\text{Ca}^{2+}$  uptake into mitochondria. The two major sources of cytosolic  $\text{Mg}^{2+}$  signal are displacement of  $\text{Mg}^{2+}$  (by  $\text{Ca}^{2+}$ ) from cytosolic binding sites and IP3-induced  $\text{Mg}^{2+}$  release from internal stores. These novel mechanisms can be regarded as negative feed-forward regulation of mitochondrial  $\text{Ca}^{2+}$  uptake and may protect the cell against apoptosis during  $\text{Ca}^{2+}$  overload.

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**PROGRAM 7/2.****PATHOBIOCHEMISTRY****Coordinator:****József MANDL M.D., member of the Hungarian Academy of Sciences**Department of Medical Chemistry,  
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**Program Overview:** Pathobiochemistry showed a remarkably dynamic progress in the past decades. The Program has two roles: a.) it outlines the aetiology and pathogenesis of different pathological conditions, b.) it aims to help the detailed knowledge of certain important fields of pathology. In planning the program the following viewpoints were considered: in diseases different mechanisms of pathological regulation can develop, reflecting changes in extracellular signals or signal transduction.

***Titles of research projects***

The comparative examination of gene polymorphisms in clinical pictures

Interaction of inherited and acquired genetic lesions in the  
Pathomechanism of haematological and immunological disordersStudy of genetic variation in the development of drug addiction  
and other psychiatric disorders

Transport systems in the endoplasmic reticulum

Neuronal scaffold proteins

Small G-proteins in cell function

Investigation of signalling pathways of receptor tyrosine kinases

Fate of glucuronides in the hepatic endoplasmic reticulum

Redox metabolism in the endoplasmic reticulum

Protein processing and quality control in the endoplasmic  
reticulumMolecular mechanisms of learning and memory formation:  
network and experimental approaches

Characteristics of calcium transporters

Genetical and immunological factors in rheumathological  
conditionsHigh efficiency separation methods for proteomics based  
biomarker discoveryApplication of the specialities of separation techniques in QSAR  
studies***Supervisors***

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Study of transporter-drug interactions in human and rat hepatocytes	Katalin Jemnitz
The genetic background of gynaecological clinical pictures	József Gábor Joó
Effects of anti-cancer and anti-inflammatory peptides – signal transduction therapy	György Kéri
Rational drug design of kinase inhibitor agents	György Kéri
Cellular signalling therapy with kinase inhibitors	György Kéri
Cell dependent thrombolysis	Kraszimir Kolev
Study of calcium transport systems in various cancer cells	Tünde Kovács
The role of pathobiochemical factors in the development and progression of inflammatory bowel diseases	Péter László Lakatos
Role of leukocytes in fibrinolysis	Raymund Machovich
Molecular mechanisms of endoplasmic reticulum stress	József Mandl
Determination of hydrophobicity of the new selective tyrosine kinase inhibitor molecules. Modelling the relationship between structure and biological activity	György Mészáros
Selection and application of protein specific aptamers	Tamás Mészáros
Genetic polymorphisms in monoamine neurotransmitter systems: association analyses and functional study	Zsófia Nemoda
Design, synthesis and structure- biological activity correlation studies of anticancer and antimicrobial agents	László Őrfi
The molecular pharmacology of the signal transmission therapies affecting the regulation of the cell death and following molecular farmacodiagnostic	István Peták
Analysis of small and large scale copy-number variations	Zsolt Rónai
Pathobiochemistry of pancreatic digestive enzymes	Miklós Sahin-Tóth
Membrane transporter proteins of human stem cells and their changes during cell differentiation	Balázs Sarkadi
Association between the structure and function of human ABC transporter proteins	Balázs Sarkadi
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The role of protein denaturation and stress response in aging	Csaba Sőti
Simultaneous application of quantitative molecular genetic measurements and high capacity cell sorting in malignant disorders of the myeloid system	Attila Tordai
Characterization of ABCG-type transporters	András Váradi
The role of NAK ATPase in the pathomechanism of diabetes mellitus	Ágota Vér
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## ***Abstracts of Ph.D. theses successfully defended in 2011***

### **EDINA KOMLÓDI-PÁSZTOR (2011)**

#### **The importance of intracellular trafficking in cancer cells and in treatment**

*Supervisor: András Váradi*

Intracellular trafficking of p53 on microtubules is followed by its nuclear translocation that is mediated via nuclear localization signal-I (NLS-I). By screening the KB-3.1 human cervical carcinoma cell line and its drug resistant sublines, we found a unique p53 mutation in the oxaliplatin resistant cell lines. This mutation resulted in a frame-shift and a protein of 420 amino acids (p53<sup>420</sup>). Additional studies showed that p53<sup>420</sup> was sequestered in the cytoplasm. We demonstrated that p53<sup>420</sup> was able to tetramerize, bind to dynein, and that cytoplasmic sequestration of p53<sup>420</sup> is due to impaired nuclear import. We also showed that p53<sup>420</sup> was able to trans-activate a target gene. This behavior of p53<sup>420</sup> underscores the necessity of its cytoplasmic sequestration so that it can contribute to the survival advantage of the cancer cell that harbors it. In addition, we demonstrated that neither NLS II nor NLS III plays a role in p53 nuclear translocation and we suggest dropping nomenclature that assigns a nuclear transport function to these regions of the protein. Like p53, many other proteins traffic on the microtubules from the site of production to the site of function. Impaired trafficking, for example due to treatment with a microtubule-targeting agent, seriously interferes with the function of these proteins and in turn the viability of the cell. Based on preclinical studies, microtubule-targeting agents were proposed to be clinically successful by causing mitotic arrest. Indeed it was the success of microtubule-targeting agents, and the attribution of this to mitotic arrest, that led to the search for more mitosis-specific drugs, and to the development of mitosis kinase inhibitors. The expectation was that mitotic kinase inhibitors would be as good as if not better than microtubule-targeting agents but without neurotoxicity. Following responses seen in pre-clinical models, clinical trials did not deliver on this expectation. In their disappointment, however, we now have data that validate a paradigm for how microtubule targeting agents kill cancer cells in patients – principally by interfering with the function of interphase microtubules, for example intracellular trafficking – not by disrupting mitosis. We believe that the steady presence and constant physiological role of microtubules are responsible for the overall success of microtubule-targeting agents. While mitosis-specific inhibitors are effective on only a small fraction of the tumor mass (dividing cells), microtubule-targeting agents target microtubules directly or by associating with its tubulin subunits, and thus interfere with a protein that has crucial roles in both mitotic and non-mitotic cells.

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## ÉVA JUDIT MAGYAR (2011)

### Effect of tea flavanols on protein processing and quality control in the endoplasmic reticulum

Supervisor: Miklós Csala

The advantageous health effects of tea consumption are primarily attributed to the polyphenols abundant in tea. EGCG, the most widely studied representative of these compounds, has been shown to reduce the risk of tumor development and hinder tumor growth. This is due to remarkable antioxidant properties, inhibition of cell proliferation and vascularization as well as stimulation of apoptosis. The antitumor activity of EGCG is particularly interesting from medical point of view, and its mechanism has not been fully elucidated. Since proapoptotic signals can also be initiated in the endoplasmic reticulum, we hypothesized that altered function of this organelle might play a role in the enhancement of apoptosis by EGCG. Hepa1c1c7 hepatoma cells and liver microsomes were used in this study. Morphology of the endoplasmic reticulum and the state of its calcium store were investigated by using fluorescent microscopy. Alterations in the protein levels indicating the activation of UPR were detected by Western blot technique. Activity of glucosidase II was measured by photometric and fluorimetric methods. The biological membranes were permeabilized by alamethicin. EGCG treatment induced endoplasmic reticulum stress in the hepatoma cells, which was well indicated by the morphological changes of the organelle. Although the activated partial UPR did not involve the induction of major endoplasmic reticulum chaperones and foldases but the most important proapoptotic elements (CHOP-induction, caspase-12 cleavage, slow depletion of endoplasmic reticulum calcium stores) as well as the enhanced phosphorylation of eIF2 $\alpha$  were all detectable. The treatment also induced apoptosis in the hepatoma cells, which therefore was – at least partly – of endoplasmic reticulum origin. It can serve as an explanation for the organelle stress that EGCG inhibited glucosidase II enzyme, which plays a key role in glycoprotein processing and quality control. The presence of gallate moiety and an appropriate configuration of the gallo group were shown to be necessary for the inhibitory effect on glucosidase II. The IC<sub>50</sub> and K<sub>i</sub> values of the most efficient tea flavanol (GCG) were similar to those of the known glucosidase inhibitor, NBDJ. Our results collectively lead us to the conclusion that EGCG interferes with protein maturation and quality control in the endoplasmic reticulum lumen by inhibiting glucosidase II enzyme. This causes a stress in the organelle, and the consequently triggered partial UPR contributes to apoptosis. The phenomenon described in this study has a dual importance. On the one hand, it may play a significant role in the well-known antitumor effect of polyphenols. On the other hand, it raises a novel approach in tumor therapy, i.e. it provides endoplasmic reticulum and the components of the local protein processing machinery as potential drug-targets.

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## POLETT SZENTIRMAINÉ RIBICZEY (2011)

### Expression of plasma membrane $\text{Ca}^{2+}$ ATPases during gastric and colon cancer cell differentiation

Supervisor: Tünde Kovács

Plasma membrane  $\text{Ca}^{2+}$  ATPases (PMCA) are essential for maintaining a low cytoplasmic  $\text{Ca}^{2+}$  concentration, and play a key role in the regulation of global and local  $\text{Ca}^{2+}$  signalling, therefore controlling  $\text{Ca}^{2+}$ -dependent cell functions. Investigating PMCA expression in gastric and colon cancer cells we found PMCA1b as the major isoform in non-differentiated cancer cells, whereas the expression level of PMCA4b was significantly lower. Post-confluent differentiation of colon cancer cells, as well as maturation of gastric and colon cancer cells initiated with histone deacetylase inhibitors (e.g. butyrate and valerate) resulted in a marked upregulation of PMCA4b protein expression. In contrast, PMCA1b levels were not affected or only moderately changed. We detected upregulated PMCA4b expression during either enterocyte-like or goblet cell-like colon cancer cell differentiation. Using a novel eccPCR (external cell control quantitative RT-PCR) method we confirmed that induction in PMCA4b protein expression during gastric and colon cancer cell differentiation is mainly the consequence of upmodulated PMCA4b mRNA expression.  $1,25\text{-(OH)}_2\text{-D}_3$  is known to induce differentiation of various tumor cell types, therefore we investigated its effect on the maturation and PMCA expression of colon cancer cells. We demonstrated that  $1,25\text{-(OH)}_2\text{-D}_3$  neither induced the differentiation of pre-confluent nor potentiated the maturation of early post-confluent Caco-2 cells. We also showed that in contrast to differentiation inducing protocols,  $1,25\text{-(OH)}_2\text{-D}_3$  treatment had no effect on the expression of the PMCA4b protein. However, these treatments resulted in upregulated PMCA1b expression in enterocyte-like colon tumor cells. Confocal immunofluorescence analysis of PMCA1b and 4b proteins showed that they localize in the basolateral plasma membrane of the small intestinal enterocyte-like differentiated Caco-2 cells. Therefore, the  $1,25\text{-(OH)}_2\text{-D}_3$ -modulated PMCA1b expression is likely to have important role in  $1,25\text{-(OH)}_2\text{-D}_3$ -induced intestinal  $\text{Ca}^{2+}$  absorption. We suggest that in gastric and colon epithelial cells the housekeeping PMCA1b is essential for cell survival, whereas the elevated expression of PMCA4b may also be needed for the normal regulation of specific cellular functions, such as proliferation or differentiation. As dysregulation of these cellular events is a main step of carcinogenesis, PMCA4b may become a potential drug target in the therapy of human gastrointestinal malignancy.

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- Bors A\*, Ribiczey P\*, Köblös G\*, Brózik A, Ujjfaludi Z, Magócsi M, Váradi A, Tordai A, Kovács T, Arányi T: External cell control polymerase chain reaction: replacing internal standards with an unbiased strategy for quantitative polymerase chain reaction normalization. *Anal Biochem* 2008; 372: 261-263. (\*equally contributed to this work)

**ANNA TANKA-SALAMON (2011)****Contribution of von Willebrand factor and free fatty acids to thrombolytic resistance.***Supervisor: Krasimir Kolev*

The medical treatment of patients with arterial thrombosis is partially based on the enzymatic dissolution of the thrombi. Thrombolytic agents activate endogenous plasminogen to plasmin, which cleaves both fibrinogen and fibrin to soluble degradation products. The efficiency of thrombolysis, in vivo, might be modified by components of thrombi, that have been shown to interfere with the fibrinolytic system in vitro. In the present study, the modulation of plasmin activity by the crucial molecular adhesive von Willebrand factor (VWF) and the most abundant free fatty acids of arterial thrombi were characterized. According to the dissociation constants for the binding of plasminogen, plasmin, and active siteblocked plasmin onto immobilized VWF, an allosteric site might be the primary binding site of their interaction. The progressive loss of clottability and generation of degradation products during fibrinogen digestion with plasmin were delayed in the presence of VWF, while fibrin dissolution was not affected. The  $K_m$  values for fibrinogen degradation by plasmin, miniplasmin and microplasmin were not modified, whereas  $k_{cat}$  values decreased with increasing VWF, following the kinetic model of non-competitive inhibition. Inhibitory constants for VWF (5,4  $\mu\text{g/ml}$ ; 5,7  $\mu\text{g/ml}$  and 10,0  $\mu\text{g/ml}$  for plasmin, miniplasmin and microplasmin, respectively) suggested a modulating role of kringle 5 domain in the interaction between VWF and plasmin. All studied fatty acids caused a 10-20-fold increase in the  $K_m$  on a low molecular weight synthetic peptide substrate of plasmin. The  $k_{cat}$  decreased in the presence of arachidonate and oleate (mixed-type inhibitors), but increased in the presence of stearate (apparent activation). Digestion of fibrinogen and fibrin were also delayed in the presence of unsaturated fatty acids. Based on the  $k_{cat}/K_m$  ratio, all three fatty acids acted as inhibitors of plasmin, and their effects required the presence of kringle 5 of the protease (miniplasmin was as sensitive to fatty acids as plasmin, whereas the activity of microplasmin was not affected). Our data suggest that VWF and unsaturated fatty acids protect fibrinogen against degradation by plasmin, preserving its adhesive role, and contributing to thrombolytic resistance of arterial thrombi, whereas effect of saturated stearic acid is unusual: the weak inhibitor turns to be an activator at saturating substrate concentrations.

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- Tanka-Salamon A, Kolev K, Machovich R, Komorowicz E: Proteolytic resistance conferred to fibrinogen by von Willebrand factor. *Thromb Haemost* 2010; 103:291-298.
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**GÁBOR VIKTOR SZABÓ (2011)****The role and importance of gene polymorphisms in the development of atherosclerosis***Supervisor: György Acsády*

The development of the atherosclerosis is a multifactorial process. Except for the classical risk factors of the atherosclerosis (hypertension, lipid-metabolic disorders, diabetes, smoking) the clinical signs can be influenced by the genetic variants (polymorphisms) of the en-

zymes which are responsible for the endothelial cells function and for the thrombotic factors. The purpose of the study was to examine three genetic polymorphisms playing a role in the metabolic processes. In this examination 992 patients' data was analysed. We compared the data of 348 atherosclerotic non-diabetic patients and 260 atherosclerotic diabetic patients treated at the Cardiovascular Department of the Semmelweis University during a one- and-half-year period with the 384 healthy control samples. We analysed the frequency of myocardial infarction and stroke in the case of different polymorphisms in the atherosclerotic non-diabetic and atherosclerotic diabetic group, and it was compared to the healthy group. In this examination the planned aim was reached, positive correlations were proved in every group. It was verified that the lipid (LDL) level is higher in patients who underwent myocardial infarction than those without infarction (4,2 vs 2,7,  $p < 0,05$ ). It was also proved if the mutant TT eNOS Glu298ASP variant is present, the myocardial infarction is significantly higher than with patients carrying heterozygote GT and normal GG genotype (TT genotype: control group 5,7%, MI group 16,9%,  $p < 0,001$ , OR: 4,56). We proved that with mutant MTHFR 677CT heterozygote variant, the occurrence of myocardial infarction is significantly higher (CT allele: control group 32%, MI group 55,1%,  $p < 0,001$ , OR: 4,13) and in the relation of the 677TT homozygote variant the difference is also significant (TT variant: control group 10,9% MI group 21,2%  $p < 0,001$ , OR: 4,65). It was verified that among patients with the mutant TNF- $\alpha$  AA genotype the occurrence of cardiovascular events is significantly higher (AA allele: control group 1, 6%, MI group 10,7%,  $p < 0,005$ , OR: 8,17). Screening the endangered or genetically high risk groups is to be considered on the long run - an early detection of a susceptibility of the disease gives better chances for prevention and treatment. Understanding the inflammatory mechanisms of the atherosclerosis gives new therapeutical targets to pharmacologists.

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## NIKOLETT WOHNER (2011)

### Role of cellular elements in thrombosis formation and thrombolysis

Supervisor: Krasimir Kolev

Diseases related to thrombosis and haemostasis such as ischemic heart disease and stroke are leading causes of death around the world. Research in this field is especially important, as understanding the way thrombi develop and finding new ways of thrombolysis could improve the therapy of these illnesses. Although the main pathomechanism of thrombus formation and lysis is well established, fine regulatory mechanisms are still being explored. My research focused on the role of cellular elements in haemostasis.

The first aspect of the reported work is the effect of haemostatic (plasmin, thrombin) and neutrophil granulocyte-derived (neutrophil elastase, matrix metalloproteinase-8 and -9) enzymes on the arterial wall structure and the von Willebrand factor (VWF)-dependent platelet adhesion which takes place at high shear rate in small arteries and arterioles. According to our findings leukocytes promote platelet adhesion to the injured vessel wall, especially to the media layer through removing proteoglycans by proteolysis and increasing the availability of collagen fibres for VWF and platelets. The second aspect of our studies was the degradation of VWF by the enzymes mentioned above. Limited proteolysis of VWF may influence platelet-collagen interaction in thrombi by regulating the size of VWF

multimers. Under static conditions the presence of platelets inhibited, while under flow conditions it increased the proteolytic sensitivity of VWF. VWF can be effectively degraded by plasmin, neutrophil elastase and thrombin, but not by matrix metalloproteinases-8 and -9 originating from neutrophil granulocytes.

Cellular elements are also important components of thrombi. Red blood cells, leukocytes and platelets are entrapped within the fibrin meshwork in the course of thrombus formation. Our measurements on the rate of fibrinolysis in artificial thrombi containing different amount of red blood cells showed that increasing number of these cells causes fibrinolytic resistance that can be partially reversed by an integrin receptor inhibitor (eptifibatide) that abolishes red blood cell-fibrinogen interactions.

- *Wohner N, Keresztes Z, Sótónyi P, Szabó L, Komorowicz E, Machovich R, Kolev K: Neutrophil granulocyte-dependent proteolysis enhances platelet adhesion to the arterial wall under high-shear flow. Journal of Thrombosis and Haemostasis 2010; 8:1624-1631.*
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## ZSUZSANNA ESZTER WOLF (2011)

### Membrane microdomains and their role in human disease: a novel strategy for characterization disease specific alteration

*Supervisor: László Romics*

Lipid rafts resemble cholesterol- and glycosphingolipid-enriched, liquid-ordered plasma membrane microdomains, allowing specific interactions that modulate signal transduction, membrane trafficking and pathogen entry. Recently, lipid rafts have been also implicated in a range of monocyte/macrophage functions, including endotoxin-mediated activation, scavenging and recycling of atherogenic lipoproteins, cellular cholesterol influx/efflux and trafficking. Due to their tightly ordered lipid phase, membrane microdomains show a relative resistance to nonionic detergents (classically to Triton X-100) providing an easy analytical tool to study them.

The aim of the thesis was to analyze specific antigens of lipid microdomains in monocytes that establish the raft-associated, ligand induce CD14-dependent specific activation of these cells. The studies established and applied a rapid flow cytometric detergent resistance-based (FCDR) assay to investigate microdomain association of proteins on circulating monocytes from whole blood samples. By using FCDR assay, constitutive and activation-induced detergent resistant membrane (DRM) associations of certain antigen were demonstrated upon *in vitro* LPS stimulation. Characteristic alterations and different patterns of CD14-dependent receptor co-assembly within microdomains could be detected *ex vivo* in different disease states, such as inflammatory response (SIRS/sepsis and CAD/myocardial infarction) or disorder affecting cellular cholesterol trafficking (Niemann-Pick type C disease). Moreover, we provided evidence that this assay is capable to detect effects of therapeutic agents affecting membrane microdomains structure and/or function, such as ezetimib a lipid lowering drug.

Our results demonstrate that flow cytometric analysis of short time *in situ* detergent extraction provides a powerful tool for rapid examination of blood monocyte DRMs. This may contribute to screen patients with potential microdomain abnormalities or monitor ef-

fects of therapeutic agents on membrane constituents. In addition, multi-color analysis allows the possibility to explore parallel different surface antigens on different cell populations without the need to purify them by physical separation.

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- Wolf Zs, Orsó E, Werner T, Klünemann HH, Schmitz G: *Human blood monocyte cholesterol homeostasis correlates with the presence of detergent resistant membrane microdomains Cytometry A. 2007; 71:486-494.*

### **PROGRAM 7/3.**

## **EMBRYOLOGY, THEORETICAL, EXPERIMENTAL AND CLINICAL DEVELOPMENTAL BIOLOGY**

### **Coordinator:**

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**Program Overview:** The program deals with the progressive changes of the vertebrate organisms from the primordial germ cells through the fertilization up to the organogenesis. During this progressive development primary tissues (epithelial, supporting, muscle and nervous tissues) are formed from different stem cells or progenitors, what is timely and spatially strictly regulated at both genetic and molecular levels. The Program focuses on the early formation of lymphoid organs including the epithelio-mesenchymal interactions (thymus and bursa of Fabricii), formation of hemopoetic sites, cardiac anlage, accessory dendritic cells of the immune system and the effect of different environmental agents on the ontogeny. The ontogeny of the visual system and its relationship with the circadian rhythms (pineal body) is a significant and progressive topic of the Program. The endocytosis by the monocyte-macrophage system is also a rapidly expanding area of the Program. Finally, characterization of the accessory cells of the MALT in avian species and human completes the series of scientific topics. The methods used by the Program incorporate a wide range of different techniques like light- and electron microscopy, immunocytochemistry, immunofluorescence combined with confocal microscopy, monoclonal antibody production, tissue culture, embryo manipulation (ablation and transplantation of embryonic organ rudiments, chimaerism, parabiosis) and Western blotting.

### ***Titles of research projects***

Role of caveolae and caveolin isoforms in various function of the cells

### ***Supervisors***

Anna L. Kiss

In vitro organotypic retinal cultures to study cone differentiation in mammals

Ákos Lukáts

Developmental biology of the hemopoietic organs

Nándor Nagy

Development of lympho-myeloid organs and supporting tissue

Imre Oláh

Photosensitive molecules and photoreceptors in the vertebrate retina and pineal gland

Ágoston Szél

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Ákos Lukáts
Nándor Nagy
Zsuzsanna Fürts
Nándor Nagy
Ákos Lukáts

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Zoltán Hajdú	ft

#### ***Supervisors***

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Imre Oláh

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### ***PROGRAM 7/4.***

## **BASIS OF HUMAN MOLECULAR GENETICS AND GENE DIAGNOSTICS**

#### ***Coordinator:***

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**Program Overview:** To provide an overview on various fields of human medical and molecular genetics, genomics, including theory and methodology.

#### ***Titles of research projects***

Molecular investigation in oncohaematology
Molecular investigation in coagulopathology
Studies on the pathomechanism of rheumatology diseases

#### ***Supervisors***

Imre Bodó
Imre Bodó
Edit Buzás



Regulation of histidine decarboxylase (HDC) gene expression in physiological and pathological processes	Zsuzsanna Darvas
Study on the inflammation agents and regulator molecules of the acute-phase response	András Falus
Molecular immunological characterization of BAL monocytes	András Falus
Molecular genetic analysis of adhesion protein family	András Falus
Diagnostic methods of gene analysis in clinical paediatrics	György Fekete
The examination of the influences of genetical and immunological factors in rheumatological conditions	Pál Géher, György Nagy
Molecular biological methods in examining patients with muscular dystrophies	Veronika Karcagi
Chemotaxis - Its biological and clinical significance	László Kőhidai
Role of histamine in antigen presentation and cell differentiation	Valéria László
Cell cycle-specific expression changes of Waf-1/p53/PCNA/ciclins/ cdk-s in cell cultures studied by Northern, Western and rt-PCR techniques	Zoltán Marcsek
The introduction of systems biology in the research of the diagnosis, prevention and therapy of neurological and psychiatric disorders	Mária Judit Molnár
Genetical and immunological factors in rheumatological conditions	György Nagy, Pál Géher
The active immunologic relationship between foetus and mother means fetal antigen presentation, maternal antigen recognition and immunologic response	Erna Pap
Molecular biology methods in the prenatal diagnosis	Zoltán Papp
Studies on the genomic background of haematological malignancies	Éva Pállinger
Forensic aspects of the DNA investigation	Péter Sótonyi
Study on the pathomechanism of asthma with molecular genetic methods	Csaba Szalai
Evaluation of medical biology data	Csaba Szalai
ALL genomics	Csaba Szalai
Analysis of cardiac functions in histamine-free transgenic murine model	Sára Tóth
Simple nucleotid polymorphisms in the development of paradontal disease and missing tooth-germs	Gábor Varga
Isolation and characterization of dental postnatal stem cells	Gábor Varga
The human MRP1, ABC-transporter examination of the nucleotide-binding protein domens and study of the catalytic cycle	András Váradi

The significance of genetic polymorphism studies in systemic mastocytosis

Judit Várkonyi

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Gábor Varga
Sarolta Kárpáti
Mária Judit Molnár

a, absolutum; f, full-time; pt, part-time; na, not affiliated

***Abstracts of Ph.D. theses successfully defended in 2011***

**ANNA FÖLDES (2011)**

**Metabolic and endocrine alterations in histamine-deficient HDC-KO mice**

*Supervisor: Gábor Varga*

We studied the role of histamine in the regulation of food intake and energy metabolism in wild-type (WT) mice and in histidine decarboxylase knock-out (HDC<sup>-/-</sup>) mice incapable of histamine synthesis.

We observed that histamine deficient mice grow fat with age. The amount of visceral adipose tissue increases, blood leptin concentration is high, blood glucose regulation is perturbed, and mice are not capable of appropriate energy mobilization in cold environment. High blood leptin concentration may be due to an increase in leptin expression in the adipose tissue, therefore we measured leptin mRNA abundance by real-time PCR in different (epididymal, subcutaneous and brown) adipose tissue samples in WT and HDC<sup>-/-</sup> mice. There was no significant difference between WT and HDC<sup>-/-</sup> animals. Hence, higher leptin level is explained by the presence of more adipose tissue and not by a change in leptin expression. Since obesity in humans is associated with higher leptin concentrations as well as leptin resistance, we studied the expression of the signaling form of leptin receptor in the hypothalamus of mice. There was no difference between WT and histamine deficient animals. We studied the effects of leptin receptor activation on the amount of phosphorylated STAT, an important signaling component, in the central nervous system. In nucleus arcuatus there was no difference in the amount of phosphorylated STAT between the two genotypes. However, in the brainstem, within the dorsal vagal complex of HDC<sup>-/-</sup> mice, there were no immunopositive cells. Therefore, presumably these cells are responsible for mediating defective leptin action.

As a great number of histaminergic synapses are present near the orexigenic (NPY, orexin) and anorexigenic (POMC) neurons of nucleus arcuatus, we used in situ hybridization to study whether the expression of these neuropeptides was under histaminergic regulation. We found no difference between the two genotypes in the expression pattern of neuropeptides in the hypothalamus.

In addition, HDC<sup>-/-</sup> mice had reduced fertility and reproduction, elevated testosterone levels, and Leydig cells had ultrastructural alterations.

Our observations contribute to a better understanding of the homeostatic role of the histamine system and of the development of obesity.

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## KRISZTIÁN NÉMETH (2011)

### Contribution of hematopoietic stem cells to the homeostasis and regeneration of the uterine epithelium and the epidermis

*Supervisor: Sarolta Kárpáti*

In the last couple of years it became evident that bone marrow hematopoietic stem cells - besides producing blood lineages- are also capable to differentiate into a large number of none-hematopoietic cell types. The rate at which this transdifferentiation occurs is still debated. The seemingly contradictory data most likely stem from technical issues and grant further investigation utilizing newer animal models and more complex analytic tools. To address this controversy we decided to assess the contribution of HSCs to two rapidly re-

newing epithelial tissues: the uterine epithelium in mice and the skin epidermis in human. In order to circumvent technical issues presented by bone marrow transplantation we developed a mouse model that can aid transdifferentiation studies focusing on the plasticity of hematopoietic stem cells. Utilizing the Cre/lox technology we generated double transgenic mice engineered to show permanent GFP expression in all cells that ever expressed CD45, an antigen found exclusively on hematopoietic cells (hematopoietic stem cells, progenitors and mature white blood cells). Evaluation of the mice showed strong expression of GFP in all blood leukocytes, and a time and use dependent expression in the uterine epithelium, one of the tissues with the highest turnover rate in mice. To compare this newly developed system with the traditional bone marrow transplantation model, we transplanted GFP expressing bone marrow cells into wild-type mice and found a similar GFP expression pattern in the uterus epithelium several months after the infusion of tagged donor cells. In conclusion: we created a functional animal model system that can serve as a new tool for bone marrow transdifferentiation studies without the need of in vitro manipulation of donor stem cells, or toxic preconditioning of the recipient organism. Since preconditioning regimens frequently cause permanent sterility in the recipient organism, avoidance of these agents enabled us to assess bone marrow contribution to the pregnant uterus. To our surprise we found that the overwhelming majority of the pregnant uterus epithelium was composed of bone marrow derived cells, which suggest that bone marrow stem cells play an important role in the development and maintenance of the pregnant uterine epithelium. Also, our data indirectly support the hypothesis that endometriosis (ectopic presence of endometrial tissue) stems from the opportunistic planting and transdifferentiation of HSCs in various organs. The epidermis stood in the center of our human studies. Transdifferentiation of bone marrow cells into skin keratinocytes has been proven and also disproven by several research groups. To address these seemingly controversial results we analyzed skin biopsy samples from female patients who underwent bone marrow transplantation and received donor marrow stem cells from a male donor. Using a combination of immunostaining and in situ hybridization we detected donor derived keratinocytes in the patients' epidermis in the non-hairy back skin as well as in the hairy occipital area. Our results show that bone marrow derived keratinocytes can be found in greater number in the scalp area as compared to the back skin, they tend to appear in patches which suggest clonal origin for their presence, and they are able to actively divide within the epidermis. These observations point to the clinical potential of HSCs in epidermal injury settings where enhanced regeneration is needed (using the patient's own HSCs as an autologous stem cells source), or in genetic skin diseases where missing epidermal proteins could be replaced by the HSC derived keratinocytes (using HSCs from third party donors as an allogeneic stem cell source).

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- Bratincsák A, Brownstein MJ, Cassiani-Ingoni R, Pastorino S, Szalayova I, Tóth ZE, Key S, Németh K, Pickel J, Mezey E: CD45-positive blood cells give rise to uterine epithelial cells in mice. *Stem Cells* 2007; 25:2820-2826.

**ZSUZSANNA PÁL (2011)****The investigation of mechanisms underlying antibody diversification and studies on the immunological and genetic background of an antibody mediated disease, myasthenia gravis***Supervisor: Mária Judit Molnár*

In this thesis we focused on two major aspects of B-cell immunology. In the first part of the dissertation we investigated the role of a poorly defined transcription factor, homeobox C4 (Hox C4) in antibody diversification, a physiological characteristic of germinal centre B-cells. Using Hox C4 knock-out mice, we showed that Hox C4 plays a vital role in both somatic hypermutation and isotype switching via the regulation of activation induced cytidine deaminase, the key enzyme of antibody diversification.

In the second part of the dissertation we focused on a pathological condition of antibody production, and examined two factors which could potentially influence the pathomechanism of autoimmune myasthenia gravis (MG). For this purpose we established a biobank consisting of 170 MG patients.

First we examined the presence of natural autoantibodies reactive with carbohydrates and glucosaminoglycans found in skeletal muscle and thymus tissue in sera of patients with MG. We showed that the serum levels of chondroitin-sulphate A, C and heparane sulphate IgM as well as chondroitin-sulphate C IgG are significantly higher in patients with MG compared to age and gender matched healthy controls. We also found that in patients who harbour anti-AChR antibodies, there is a significant difference in the anti-carbohydrate antibody profile compared to healthy controls, the levels of anti- $\alpha$ -mannose IgG antibodies are higher.

Secondly we investigated the genetic background of myasthenia by the investigation of association of various non-HLA genes.

1. We found that two intronic polymorphisms of the *ER $\alpha$*  gene previously shown to be associated with multiple autoimmune diseases, were not associated with MG in women.
  2. We showed that from the examined three functional polymorphisms of the *IL4R $\alpha$*  gene, the rare GG genotype of the I75V polymorphism, which influences signal transduction, is associated with MG.
  3. We are the first to describe the association of a *galectin-1* polymorphism with human disease. The haplotype of the rs4820293 *galectin-1* polymorphism, and the rs743777 *IL2R $\beta$*  polymorphism shows strong association with MG, and causes a 2,3 fold increase in the risk for developing the disease.
  4. We are also the first to describe the disease association of a polymorphism of the *galectin-8* gene. The described polymorphism is functional; it alters carbohydrate binding of galectin-8.
- Pál Z, Antal P, Srivastava SK, Hullám G, Semsei AF, Gál J, Szalai C, Gabius H-J, Molnár MJ, Falus A, Buzás EI: A novel galectin-8 single nucleotide polymorphism is associated with rheumatoid arthritis and myasthenia gravis in the Caucasian population. *J Neuroimmunol*, 2010; 229:107-111.
  - Pál Z, Varga Z, Semsei A, Falus A, Buzás EI, Molnár M: Interleukin-4 receptor alpha polymorphisms in autoimmune myasthenia gravis in a Caucasian population. *Hum Immunol*, 2011; 73:193-195.
  - Pál Z, Antal P, Millinghoffer A, Hullám G, Pálóczi K, Tóth S, Gabius HJ, Molnár MJ, Falus A, Buzás EI: A novel galectin-1 and interleukin 2 receptor  $\alpha$  haplotype is associated with autoimmune myasthenia gravis. *J Neuroimmunol*, 2010; 229:107-111.

**PROGRAM 7/5.****IMMUNOLOGY****Coordinator:****Péter GERGELY M.D., D.Sc.**

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**General overview:** The recognition of immunology as an independent scientific discipline is recent, therefore, in many universities immunological research is carried out in various (e.g. biochemical etc) departments. Qualified immunologists are greatly demanded in many areas, including clinical science. This project, completing the curriculum of undergraduate training, yields a perspective to qualify in several areas of immunology. The purpose of this Ph.D. Program is to train independent, reliable and competent research scientists. The Program emphasizes the importance of studying basic immunology and laboratory methods, both being prerequisites of any work in experimental and clinical immunology.

***Titles of research projects***

Expression of proto-oncogenes and tumor suppressor genes in gestational trophoblastic tumors and normal pregnancy

Study of the disease associations with the major histocompatibility complex (MHC)

Regulation of immune reactions and role of cytokines in the pathomechanism of autoimmune diseases.

Acute phase proteins in clinical diagnostics

The effects of immunological and environmental factors in various inflammatory and/or malignant cellular proliferations

Study of calcium transport systems in various cancer cells

Signal transduction and membrane transport process in the immune system

Effect of bacterial product of progression of HIV infection

Infection and autoimmunity in inflammatory diseases

Investigation of molecular mechanisms in rheumatic, immunological and bone disorder

***Supervisors***

Vilmos Fülöp,  
László Kopper

György Füst

Péter Gergely  
László Kalabay

Beatrix Kotlán  
Tünde Kovács

Erzsébet Ligeti,  
Balázs Sarkadi

Károly Nagy  
Gyula Poór

Gyula Poór

***Ph.D. students***

Judit Czúcz ft (a)

Ivanics Rita Margit pt

Péter Juhász

Krisztián Vörös pt (a)

***Supervisors***

György Füst  
Vilmos Fülöp  
Gyula Poór  
László Kalabay



**Ph.D. candidates**

István Aladzsity	ft
Zsófia Bánlaki	ft
Veronika Makó	ft

**Supervisors**

Zoltán Prohászka
György Füst
Zoltán Prohászka

**Ph.D. graduate**

Márton Keszei	na
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**Supervisor**

Csaba Szalai
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a, absolutorium; f, full-time; pt, part-time; na, not affiliated

**Abstract of Ph.D thesis successfully defended in 2011**

**MÁRTON KESZEI (2011)**

**Immunogenetics of asthma and systemic lupus erythematosus**

*Supervisor: Csaba Szalai*

Complex or multifactorial genetic diseases are a major cause of mortality globally and are caused by the interaction between several disease susceptibility loci and environmental factors.

My studies focused on two multifactorial immunopathologies: asthma and the autoimmune disorder Systemic Lupus Erythematosus (SLE). Allergic asthma is triggered by an external antigen, while SLE is characterized by autoantibody production against internal (nuclear) epitopes. Despite seeming like two entirely disparate conditions, both diseases involve exaggerated humoral immune responses in the host. Association studies of candidate genes, linkage analysis and genome-wide association studies indicate that both asthma and SLE pathogenesis are primarily dependent on alterations in cytokines, cell-surface receptors and the connected intracellular signaling molecules.

In our asthma studies, we were examining genetic association between polymorphisms of several candidate genes (MCP-1, RANTES, TNF and mannose binding lectin) with childhood asthma. We found that among these polymorphisms, only the MCP-1 -2518A/G biallelic variant had a significant genetic association with asthma and demonstrated that serum MCP-1 levels were significantly lower in asthmatic children. Atopy or elevated serum IgE was associated with a further reduction in MCP-1 levels compared to the non-atopic patients. However, there was no significant association between the MCP-1 -2518 genotype and MCP-1 serum concentration in asthmatic children.

My subsequent work involved elucidating the contribution of the SLAM-family (*SLAMF*) of co-stimulatory receptors in the pathogenesis of SLE using gene-targeted knockout and transgenic mouse models. Genome-wide linkage scans of SLE patients and studies of murine congenic mouse strains consistently demonstrated the presence of a lupus susceptibility locus on chromosome 1 (1q23) and on the syntenic mouse region. Interestingly, these regions include seven *SLAMF* (*Slamf* in mice) genes. The systematic analysis of lupus prone congenic mouse strains suggests a role for two isoforms of the *Slamf6* (*Ly108*) receptor in the pathogenesis of the disease. We demonstrated that *Ly108* is involved in the pathogenesis of a lupus-like autoimmunity in mice by comparing the SLE phenotype in *Slamf1*, *Slamf2*, *Slamf3* and *Ly108* congenic knock-out strains. In addition, using transgenesis, we determined that *Ly108-1*, a known lupus candidate gene, is able to drive spontaneous lupus. More importantly, we identified a third protein isoform, *Ly108-H1*,

which is absent in two lupus prone congenic animals. Introduction of a Ly108-H1 expressing transgene markedly diminishes T cell dependent autoimmunity in congenic *B6.Sle1b* mice. Taken together, we demonstrate here for the first time that the Ly108-1 and Ly108-H1 isoforms are able to regulate T cell intrinsic SLE phenotypes in a reciprocal manner.

- Keszei M, Nagy A, Kozma GT, Radosits K, Tolgyesi G, Falus A, Szalai C: Pediatric asthmatic patients have low serum levels of monocyte chemoattractant protein-1. *J Asthma* 2006; 43:399-404.
- Keszei M, Latchman YE, Vanguri VK, Brown DK, Detre C, Morra M, Arancibia CV, Paul E, Calpe S, Castro W, Wang N, Terhorst C, Sharpe AH: Autoantibody production and glomerulonephritis in congenic *Slamf1*<sup>-/-</sup> and *Slamf2*<sup>-/-</sup> [B6.129], but not in *Slamf1*<sup>-/-</sup> and *Slamf2*<sup>-/-</sup> [BALB/c.129] mice. *Int Immunol* 2010; 23:149-158.
- Keszei M, Detre C, Rietdijk ST, Muñoz P, Romero X, Berger SB, Calpe S, Liao G, Castro W, Julien A, Wu Y, Shin D, Sancho J, Zubiaur M, Morse HC, Morel L, Engel P, Wang N, Terhorst C: A novel isoform of the Ly108 gene ameliorates murine lupus. *J Exp Med* 2011; 208:811-22.

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# SCHOOL OF PH.D. STUDIES

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## 8. PATHOLOGICAL SCIENCES

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***Chairman:***

**László KOPPER M.D., Ph.D., D.Sc**

1st. Department of Pathology and  
Experimental Cancer Research

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**General Overview:** The Doctoral School of Pathology includes six postgraduate teaching Programs as follows: Oncology, Pathomorphology, Microbiology, Transplantation studies, Health Sciences, Public Health. Consequently, the training covers a rather broad area of medical sciences involving both the etiopathogenesis, diagnostic and therapeutic activities of the most common human diseases and health education. The training concentrates on individual research work guided by the tutors who makes proposal for the topic of the research, provides the facilities, warrant the technical/intellectual up-to-dateness and the progress of study. At present 38 Ph.D. students with diploma in medicine, pharmacy, or biology are holders of fellowship, in addition 42 medical doctors as corresponding Ph.D. students are preparing their dissertation. The Ph.D. degree has been awarded to 13 students trained in the frame of Doctorate School of Pathology in this year.

### ***PROGRAM 8/1.***

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#### **ONCOLOGY**

***Coordinator:***

**László KOPPER M.D., Ph.D., D.Sc.**

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Research

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**Program Overview:** The Program invites those who intended to learn and study tumor biology as well as experimental and clinical oncology. The Ph.D. students are also trained in updated techniques in cell biology, pathology, biochemistry and recombinant gene technology. Following courses are organized by the program: Experimental Oncology, Clinical Oncology, Molecular Oncology.

***Titles of research projects***

Markers of efficacy in therapy of against urological cancer

Predictive and prognostic factors in moderate tumours

***Supervisors***

István Bodrogi

Magdolna Dank

Pregnancy breast cancer	Magdolna Dank
Pediatric oncology	Miklós Garami
System biological modelling of chemoresistance	Balázs Győrffy
In vitro examination of pediatric malignancies	Péter Hauser
Investigation of ionizing radiation induced molecular changes in normal fibroblasts and tumor cells	Hargita Hegyesi
Oncogenic and angiogenic signaling in tumor progression	Balázs Hegedűs
Experimental modelling, characterization and chemotherapeutic response in osteosarcoma	András Jeney
Biomarkers of melanoma progression (with particular reference to cell cycle regulation)	Tibor Krenács
Regulation of cell proliferation and cell death	László Kopper
Role of extracellular matrix elements in the regulation of liver behavior	Ilona Kovalszky
Role of proteoglycans in carcinogenesis	Ilona Kovalszky
Gene defects related to malignancy	Ilona Kovalszky
Epidermal growth factor receptor (EGFR) in giant cell bone tumors	Tibor Krenács
Defects of direct cell-cell communication in malignant melanoma due to failures in connexin junctions	Tibor Krenács
Studying bioelectromagnetic effects in tumor models	Tibor Krenács
Tumor immunology - tumor infiltrating immunocells in human tumors and immunological parameters in sentinel lymph nodes	Andrea Ladányi
The effect of ionizing radiation on the immune system and its role in the modulation of antitumor immune response	Katalin Lumniczky
Molecular genetics in genesis and progression of lymphomas	András Matolcsy
Signalling pathways directed by receptors and metabolism in cell death and their pharmacological characterization	Rudolf Mihalik
Role of liver stem cells in hepatic disorders and tumors	Péter Nagy
Tumor induced angiogenesis	Sándor Paku
Morphological study on the biliary tract and its vascular network during regeneration and carcinogenesis	Sándor Paku
Host and tumor factors in metastatization (mainly in melanomas)	Erzsébet Rásó
The examination of individual beam sensitivity in radiation therapy patients, the identification of genes is responsible for the beam sensitivity	Géza Sáfrány
The increase of the sensitivity of tumours for radiotherapy with gene therapy procedures	Géza Sáfrány
The examination of the late genetic effects of the ionising radiation	Géza Sáfrány
Chromosomal instability in giant cell bone tumors	Zoltán Sági
Death receptor signalling as target for tumor therapy	István Peták

The model of carcinogenesis in synovial sarcoma	Zoltán Sági
INI1 suppressor gene investigation in epithelioid sarcoma	Zoltán Sági
Repair of the function of proapoptotic regulators to increase the effect of chemotherapy	Anna Sebestyén
Clinical progression and ECM components in oral precancerosis and squamous cell cc	Zsuzsanna Suba
Role of microRNA in the pathogenesis of non-Hodgkin lymphomas	Ágota Szepesi
Gene expression maps to predict individual behavior and response of tumors	József Tímár
Metastization and angiogenesis	József Tímár
Modelling and regulation of the movement of human tumor cells	József Tóvári

**Ph.D. students**

Houman Ahmadbebahani	it
Eszter Balázsne Persa	pt
Péter Balla	ft
Tamás Barbai	ft
Mansour Bassel	it
Edina Bugyik	ft
Chang Chien Yi-Che	ft
Katalin Dobos (Dömötörné)	ft
Siamak Eftekhari	it
Alexandra Fullár	ft
Tamás Márton Garay	ft
Zita Hegedűs	ft
Eleonóra Imrédi	ft
Navid Kabiri	it
Katalin Kiss	ft
Gergő Kiszner	ft
András Lőrincz	ft
Nóra Meggyesházi	pt
Orsolya Németh	pt (a)
Zoltán Órfi	crc
Gergő Papp	ft
Zsófia Pénzváltó	ft
Tímea Pócza	ft
Krisztián Somlai	pt
Tamás Sticz	ft
Balázs Szabó	pt (a)
Gyöngyvér Szentmártoni	pt
József Virág	ft (a)
Ivett Zsakovics	ft

**Ph.D. candidates**

Helga Barti-Juhász	ft
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**Supervisors**

Ilona Kovalszky
Lumniczky Katalin
Tibor Krenács
Erzsébet Rásó
István Bodrogi
Sándor Paku
Zoltán Sági
Ilona Kovalszky
Zsuzsanna Suba
Ilona Kovalszky
József Tímár
József Tímár
József Tímár
Ilona Kovalszky
Ilona Kovalszky
Tibor Krenács
István Peták
Tibor Krenács
Miklós Garami
István Peták
Zoltán Sági
Balázs Györffy
Péter Hauser
Magdolna Dank
László Kopper
József Tóvári
Magdolna Dank
Miklós Garami
Tibor Krenács

**Supervisors**

István Peták
--------------

Katalin Dezső	ft	Péter Nagy
Zsuzsanna Dunai	ft	Rudolf Mihalik
Tibor Fekete	na	Balázs Győrfy
Lajos Viktor Komlósi	ft	Judit Kralovánszky
Éva Gagy	ft	András Matolcsy
Tamás Márton Garay	ft	József Tímár
Ágnes Márk	ft	Anna Sebestyén
Gyöngyi Cecilia Munkácsy	ft	Balázs Győrfy
Orsolya Németh	pt	Miklós Garami
Veronika Papp	ft	Sándor Paku
Bálint Péterfia	ft	Ilona Kovalszky
Eszter Turányi	na	Péter Nagy
Márk Plander	na	András Matolcsy
Hajnalka Rajnai	ft	András Matolcsy
Dániel Takács	ft	József Tímár
Bálint Tegze	ft	Balázs Győrfy
<b>Ph.D. graduates</b>		<b>Supervisors</b>
Kornélia Baghy	ft	Péter Nagy
Linda Moskovszky	ft	Zoltán Sági

a, absolutorium; pt, part-time; ft, full-time; it, international; crc, Cooperation Research Centre; na, not affiliated

## ***Abstracts of Ph.D. theses successfully defended in 2011***

### **KORNÉLIA BAGHY (2011)**

#### **The role of decorin in liver fibrogenesis and hepatocarcinogenesis**

*Supervisor: Péter Nagy*

Liver cirrhosis and liver cancer are widespread diseases in the world. Decorin, a small leucine-rich proteoglycan, regulates collagen fibrillogenesis, and by directly blocking the bioactivity of transforming growth factor- $\beta$ 1 (TGF $\beta$ 1), it exerts a protective effect against fibrosis. Decorin was proved to bind different receptor tyrosine kinases resulting in inhibition of cell proliferation. However, no in vivo investigations on the role of decorin in liver fibrosis and hepatocarcinogenesis have been performed before. In our study decorin-null (Dcn $^{-/-}$ ) and wild type mice served as model animals. Not only the extent of fibrosis was more severe in Dcn $^{-/-}$  animals, but also the healing process was delayed vs. wild type mice. Expressions of collagens in Dcn $^{-/-}$  livers were higher than those of wild type livers only in the first 2 months, but no difference was seen after 4 months of treatment, suggesting that the elevation of these proteins reflects an impairment of their degradation. Indeed, we found decreased MMP activity and higher expression of TIMP-1 and PAI-1 in Dcn $^{-/-}$  livers. In contrast, at the end of the recovery phase increased production rather than impaired degradation was found to be responsible for the excessive connective tissue deposition in Dcn $^{-/-}$  mice. Higher expression of TGF $\beta$ 1-inducible early responsive gene in Dcn $^{-/-}$  livers indicated enhanced activity of TGF $\beta$ 1. Moreover, the lack of decorin led to increased activation Erk1/2 and Smad3, members of TGF $\beta$ 1 signaling pathways, whereas it had no effect



on the phospho-Smad2 levels. Tumors induced by TA and DEN showed different phenotypes. The former displays tumor cells with rich in cytoplasm and eosinophil staining; in the latter narrow cytoplasm and basophil staining were typical. Dcn<sup>-/-</sup> mice developed more tumors with cirrhotic surrounding, while no significant difference between the two genotypes after DEN exposure could be revealed, despite of the higher tumor prevalence seen in knockout animals. In Dcn<sup>-/-</sup> tumors members of Ras/MAPK pathways were found to be more active. Furthermore the lack of decorin decreased the p21<sup>Waf1/Cip1</sup> level leading to the activation of CDK4/6-cyclinD1 complex that finally phosphorylates retinoblastoma and triggers the cell cycle. Our results indicate that the lack of decorin favors liver fibrosis, attenuates its subsequent healing process, and promotes hepatocarcinogenesis. Thus, decorin could be a useful tool to improve the management of liver fibrosis and cancer.

- Baghy K, Dezső K, László V, Fullár A, Péterfia B, Paku S, Nagy P, Schaff Z, Iozzo RV, Kovalszky I: Ablation of the decorin gene enhances experimental hepatic fibrosis and impairs hepatic healing in mice. *Lab Invest* 2011; 91:439-51.
- Kovalszky I, Baghy K, Tátrai P, Schaff Z: A májfibrogenézis patomechanizmusa. *Orvosi Hetilap* 2006; 147:1593-1599.
- Füle T, Baghy K, Tátrai P, Péterfia B, Kovalszky I: A stroma szerepe a daganatok biológiai viselkedésében (Role of stroma in the neoplastic growth.) *Orvosképzés* 2006; 81:193-197.

## LINDA MOSKOVSKY (2011)

### Chromosomal instability in giant cell tumour of bone

Supervisor: Zoltán Sági

Considering that no reliable clinical, biological and histopathological features have been identified so far to predict the clinical behaviour and help reducing radical surgical interventions in GCTB, our aim was to characterise the natural history of genetic instability in the selected CD68-negative cell population by using a combination of DNA cytometry, interphase FISH and array-CGH and to correlate our findings with the clinical progression of the disease. We could conclude that CD68-positive histiocytes showed no significant numerical chromosome and telomeric alterations, therefore they are only reactive passengers of the tumour. Recurrent tumours showed higher aneusomy rates than non-recurrent ones, and malignant cases had higher frequencies than recurrent cases. Our findings suggest that the increased individual-cell aneusomy both in diploid and tetraploid tumours predicts a recurrence, whereas tumours with eusomic polysomy are unlikely to recur. Array-CGH and FISH showed clonal aberrations almost exclusively in the malignant group. Mechanisms that generate chromosomal instability in giant cell tumour of bone are poorly understood. One possible cause of chromosomal instability is an error in mitotic segregation due to numeric and/or functional abnormalities of centrosomes. We found a correlation between the frequency of centrosome amplification and the clinical behaviour of GCTB. However, at the single cell level no association revealed between chromosome number alteration and centrosome amplification, which suggests that alternative causative mechanisms generate CIN in GCTB.

In conclusion, we tried to reveal the natural history of genetic instability in GCTB and found an association between the level of random aneusomy and the clinical behaviour. Centrosome amplification also correlates with the clinical behaviour, but doesn't mean the generating mechanism of genetic instability in GCTB. Our results suggest that the ploidy determination combined with FISH analysis and centrosome immunohistochemistry can predict the recurrence of GCTB.

- Moskovszky L, Szuhai K, Krenács T, Hogendoorn PC, Szendrői M, Serena Benassi M, Kopper L, Füle T, Sápi Z: Genomic instability in giant cell tumor of bone. A study of 52 cases using DNA ploidy, relocalization FISH, and array-CGH analysis *Genes, Chromosomes and Cancer* 2009; 48:468-479.
- Moskovszky L, Dezső K, Athanasou N, Szendrői M, Kopper L, Kliskey K, Picci P, Sápi Z: Centrosome Abnormalities in Giant Cell Tumour of Bone: Possible Association with Chromosomal Instability *Mod Pathol* 2010; 23:359-366 .
- Balla P, Moskovszky L, Sápi Z, Forsyth R, Knowles H, Athanasou, Szendrői M, Kopper L, Rajnai H, Pintér F, Peták I, Benassi MS, Pizzi P, Krenács T: Epidermal growth factor receptor signaling contributes to osteoblastic stromal cell proliferation, osteoclastogenesis and disease progression in giant cell tumor of bone. *Histopathology* 2011; 59:376-89.

## **PROGRAM 8/2.**

### **ALTERATIONS OF CELLS, FIBRES AND EXTRACELLULAR MATRIX. DIAGNOSTIC PATHOMORPHOLOGICAL STUDIES IN THE COURSE OF HEART AND VASCULAR DISEASES AND IN CERTAIN TUMOURS. EXPERIMENTAL AND DIAGNOSTIC PATHOMORPHOLOGICAL STUDIES**

#### **Coordinator:**

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**Program overview:** Leading causes of morbidity and mortality in Hungary are the cardiovascular, gastrointestinal, hepatic, pancreatic diseases and malignant tumors. The Program offers a multi faceted analysis of the above diseases, completed with the development of liver diseases including liver, breast and pancreatic tumors. The research studies apply various pathohistological approaches with the extension of clinical retrospective and prospective studies. The project is dealing mostly with human materials, though experimental models are also induced. Several modern molecular pathological methods have been introduced in the well equipped laboratories. Recent studies focuses on the significance of microRNAs in chronic inflammations and human tumors and alterations of cell adhesion molecules during carcinogenesis.

#### **Titles of research projects**

Prognostic factors and locoregional staging

Molecular genetic analysis of adhesion proteins

Pathology of vascular network

Exogenous restrictive pulmonary diseases

#### **Supervisors**

Gábor Cserni

András Falus

Anna Kádár

Tibor Kerényi

Adhesion proteins and cell-connecting structures in viral hepatitis	András Kiss
Claudins in breast cancer	Janina Kulka
Prognostic factors in breast cancer	Janina Kulka
Effect of hepatotrop viruses and other hepatotoxins on the metabolism of liver cells and related disorders	Gábor Lotz
Factors in the development of liver diseases	Zsuzsa Schaff
Role of extracellular matrix in chronic liver diseases	Zsuzsa Schaff
Diagnostic and pathophysiological significance of alterations of cell surface and extracellular matrix molecules in gastrointestinal tumors	Péter Tátrai

**Ph.D. students**

Zsuzsanna Baranyák	pt
Benedek Ond Gyöngyösi	ft
Mónika Gyugos	ft
Orsolya Kiss	ft
Anna Korompay	ft(a)
Krisztina Schlachter	ft
Borbála Székely	ft
Éva Antónia Végh	pt
Rita Bérczes	ft

**Supervisors**

Janina Kulka
András Kiss
Zsuzsa Schaff
Janina Kulka
Zsuzsa Schaff
Zsuzsa Schaff
Janina Kulka
Zsuzsa Schaff
Zsuzsa Schaff

**Ph.D. candidates**

Attila Patonai	ft
Áron Somorácz	ft
Attila Marcell Szász	ft
Eszter Judit Székely	na
Péter Törzsök	ft

**Supervisors**

Zsuzsa Schaff
Péter Tátrai
Janina Kulka
József Tímár
András Kiss

**Ph.D. graduate**

Áron Somorácz	ft
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**Supervisor**

Péter Tátrai
--------------

a, absolutorium; pt, part-time; ft, full-time; na, not affiliated

**Abstract of Ph.D. thesis successfully defended in 2011**

**ÁRON SOMORÁCZ (2011)**

**The Significance of Agrin and Heparan Sulfate Degrading Enzymes in Liver Tumors**

*Supervisor: Péter Tátrai*

Differential diagnosis of liver tumors poses many challenges for the pathologist. Especially, distinguishing a well-differentiated hepatocellular cancer (HCC) from a hepatocellular adenoma (HCA), or establishing the primary versus metastatic origin of a hepatic adenocarcinoma, can be problematic. In our previous work, we demonstrated that agrin, a heparan sulfate proteoglycan (HSPG), selectively accumulates in the vascular network of HCCs; moreover, the tumorous basement membranes of cholangiocellular carcinomas also

showed strong agrin immunopositivity. In the present study, we examined a total of 25 HCC, 30 HCA, 10 focal nodular hyperplasia, 25 cirrhosis (containing 8 large regenerative nodules, 23 low-grade and 7 high-grade dysplastic nodules, as well as 8 small HCCs), 16 intrahepatic CCC, 20 colorectal cancer metastasis, and 18 pancreatic ductal adenocarcinoma metastasis samples to clarify whether detection of agrin could help resolve diagnostic difficulties. By both qualitative and quantitative evaluation of immunoreactions, agrin immunohistochemistry could discriminate between HCCs and HCAs, as well as the dubious nodules of cirrhotic liver, with a sensitivity of 94% and a specificity of 93%. This specificity was achieved by combining the results of agrin and CD34 immunohistochemistry. Strong agrin immunostaining of tumorous basement membranes characteristic of CCCs was markedly less intense in metastatic cancers; thus, agrin is a useful marker for the determination of primary versus metastatic origin of liver adenocarcinomas, too. Beyond these descriptive studies, we tried to reveal the possible role of agrin in cholangiocarcinogenesis by performing in vitro experiments with MzCha2 cell line. siRNA silencing of agrin had no significant effect on migration; however, proliferation was either accelerated or inhibited depending on serum concentration. Further experiments are needed to explain this dual phenomenon. The functions of HSPGs can be profoundly influenced by heparan sulfate degrading enzymes. We investigated the expression of sulfatase-1 (SULF1), -2 (SULF2), and heparanase in HCCs, CCCs, as well as in control livers at both mRNA and protein level. A subset of HCCs showed SULF1, SULF2, and heparanase overexpression, while increased expression of SULF1 could be detected in CCCs. Based on immunofluorescence labeling, SULF2 is produced by the tumor cells in HCCs, whereas it is expressed by stromal cells in CCCs.

- Somorácz Á\*, Tátrai P\*, Horváth G, Kiss A, Kupcsulik P, Kovalszky I, Schaff Zs: *Agrin immunohistochemistry facilitates the determination of primary versus metastatic origin of liver carcinomas. Hum Pathol 2010; 41:1310-9. (equal contributors)*
- Tátrai P\*, Somorácz Á\*, Batmunkh E, Schirmacher P, Kiss A, Schaff Zs, Nagy P, Kovalszky I: *Agrin and CD34 immunohistochemistry for the discrimination of benign versus malignant hepatocellular lesions. Am J Surg Pathol 2009; 33:874-85. (equal contributors)*
- Tátrai P, Egedi K, Somorácz Á, van Kuppevelt TH, Ten Dam G, Lyon M, Deakin JA, Kiss A, Schaff Zs, Kovalszky I: *Quantitative and qualitative alterations of heparan sulfate in fibrogenic liver diseases and hepatocellular cancer. J Histochem Cytochem 2010; 58: 429-41.*

### **PROGRAM 8/3.**

#### **STUDY OF THE IMMUNBIOLOGICAL EFFECTS OF MICRO-ORGANISMS AND OF THEIR COMPONENTS AT MOLECULAR AND CELLULAR LEVEL AND IN THE MICROORGANISMS**

##### **Coordinator:**

**Károly NAGY M.D., Ph.D.,**

*Department of Medical Microbiology*

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**Program Overview:** Infections caused by bacteria, viruses, parasites and fungi have shown significant leading roles in morbidity, mortality and health economy all over the world in-

cluding Hungary. This Program has offered a variety of studying the causative agents, pathomechanisms, pathogenesis, transmission, epidemiology, control, rapid diagnosis and prevention of most frequent infections in Hungary from molecular to host level. Outstanding parts of the Program have been the *in vitro* and *in vivo* pathomechanism and pathogenesis of natural and nosocomial infections including the pheno- and genotypical features of infectious agents with special regard to the presence and expression of genes responsible for toxin production, cell-surface properties, and resistance to different antimicrobial groups. It has been extended to investigate the structure and function of adenovirus epitopes, the interaction between virus and host cell the origin and spread of hepatitis viruses, the regulation of viral oncogen expression. Most recently the effects of infections on the quality of life as well as on health care economy have been involved in the Program. Molecular mechanisms of the virus-cell interaction of human retroviruses, such as HTLV and the AIDS virus HIV, as well as the analysis of drug resistance of and the effect of antiretrovirals on HIV were added to the program as new fields

### ***Titles of research projects***

Differential diagnostics of viral respiratory

Pathogenicity and antibioticum resistancy of streptococcus and enterococcus

Molecular biology of the resistancy against Gram-negative bacterias

Role of chlamydias in the pathomechanism of chronic diseases (atherosclerosis, infertility)

Host dependent methylation pattern of latent Epstein-Barr viral genomes with automatic fluorescent genomic hybridization

Regulation of expression of latent oncogenes in cells carrying latent Epstein-Barr viral genomes

Molecular study on human retroviruses and their role in immunopathological diseases

Epidemiology of adenoviruses in immunosuppressive conditions. Adenoviral therapy

Antibiotic resistancy in Gram-negative bacterias

Mechanism of resistance against Gram negative non fermenting bacterias

Resistant microorganisms in nosocomial infections

Molecular study on hepatitis virus carrying individuals in order to identify origin and spreading of agents

Several important aspects of the development of influenza vaccines

### ***Supervisors***

György Berencsi

Orsolya Dobay

Miklós Füzi

Éva Gönczöl

János Minárovits

János Minárovits

Károly Nagy

József Ongrády

Dóra Szabó

Dóra Szabó

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Mária Takács

Éva Gönczöl

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pt

Máté Sándor Szász

ft(a)

### ***Supervisors***

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Miklós Füzi  
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Katalin Glatz na

**Supervisors**

Miklós Füzi  
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**Ph.D graduates**

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Ákos Tóth pt

**Supervisors**

László Gulácsi  
Miklós Füzi

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***Abstracts of Ph.D. theses successfully defended in 2011 and 2012***

**TAMÁS ANDRÁS KONCZ (2011)**

**Clinical and pharmacoeconomic impact of patient medication adherence**

*Supervisor: László Gulácsi*

This thesis addresses what is considered to be an important, yet often neglected aspect of pharmacoeconomic analyses: patient adherence with pharmacotherapy. The objective of this thesis was to provide evidence that patient medication adherence is suboptimal which has implications on the effectiveness and economics of pharmacotherapy. The hypothesis was that patient adherence was suboptimal and this would decrease the clinical effectiveness of pharmacotherapy and would increase overall health care resource utilization. The thesis reviewed the definitions, measurements, and epidemiology of non-adherence and its clinical and economic consequences. In achieving the first goal a systematic literature review on adherence with biologic DMARDs in RA therapy found decreased compliance and persistence rates. To address the second goal, the literature review on the impact of non-adherence on results of pharmacoeconomic evaluations showed that medication adherence was rarely incorporated into such evaluations, and when it was, there was a wide variation in the definitions and methods used. For the third goal it was shown in a large retrospective study that lower levels of gastro-protective (GPA) co-therapy with nsNSAIDs, used as a proxy for adherence with GPA co-therapy, were associated with increasing rates of gastrointestinal-related hospitalization, hence greater health care resource utilization. These findings supported the hypothesis that patient adherence is suboptimal and it decreases the clinical effectiveness of pharmacotherapy and increases overall health care resource utilization. The thesis calls for a standardization of definitions and an improvement in measurement methods so that findings of studies analyzing medication adherence can be compared. The thesis also provides recommendations on how to incorporate adherence in pharmacoeconomic evaluations. This will eventually allow for designing interventions to improve patient adherence which will allow for better clinical and economic outcomes with pharmacotherapy.

- Koncz T, Pentek M, Brodsky V, Ersek K, Orlewska E, Gulacsi L: Adherence with biologic DMARDs in Rheumatoid Arthritis. *Exp Opin Biol Ther* 2010; 10:1367-1378.
- Koncz TA, Lister SP, Makinson GT: Gastroprotection in patients prescribed non-selective NSAIDs, and the risk of related hospitalization. *Curr Med Res Opin* 2008; 24:3405-3412.
- Hughes D, Cowell W, Koncz T, Cramer: Methods for Integrating Medication Compliance and Persistence in Pharmacoeconomic Evaluations. *Value in Health* 2007; 10:498-509.



## ÁKOS TÓTH (2011)

**Molecular characterization of extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae strains***Supervisor: Miklós Füzi*

Enterobacteriaceae have become one of the most important causes of for the increasing number of nosocomial infections caused by SHV-type ESBL-producing pathogens in Hungary between 2002-2003.

In case of outbreak-causing ESBL-producing *K. pneumoniae* strains two different situations were observed: i, the seven investigated outbreaks in Neonatal Intensive Care Units were caused by 10 epidemiologically unrelated epidemic clones carrying closely related epidemic R-plasmids encoded blaSHV-5 or blaSHV-2a; ii, the nationwide dissemination of CTX-M-15 in adult hospital wards was the consequence of expansion of only three ciprofloxacin resistant, ESBL-producing *K. pneumoniae* epidemic clones.

We described the occurrence and incidence of ESBL-producing *S. enterica* strains in Hungary. No similarity was found between SHV-5 and CTX-M-15 harbouring plasmids nosocomial and community acquired infections. Beta-lactams (mainly expanded-spectrum cephalosporins and carbapenems) and fluoroquinolones constitute the main therapeutic choices to treat infections caused by these microorganisms. However, resistance to these compounds has been reported more and more frequently in the past years. Acquired resistance to expanded-spectrum cephalosporins is mainly mediated by extended-spectrum  $\beta$ -lactamases (ESBLs). Since the ESBL-producing organisms frequently also carry genes encoding resistance to other antibiotic classes, the therapeutic options are seriously reduced in these cases. The spread of mobile genetic elements, mainly conjugative plasmids, and the dispersion of specific clones (e.g. *E. coli* O25-ST131/B2) have been responsible for the increase in ESBL-producing isolates and for the spread of TEM-52, SHV-12 and CTX-M-15 in particular. The main objectives of our study were survey of occurrence and geographical distribution of different ESBLs among Enterobacteriaceae strains in Hungary, and to investigate the genetic background and molecular epidemiology of these strains. It was found that primarily two SHV genes (SHV-5 and SHV-2a) have been responsible from *S. enterica* and those isolated from ESBL-producing *K. pneumoniae* strains involved in investigated nosocomial outbreaks. Molecular typing results suggest the possibility that a CTX-M (-5, -15)-producing *S. Typhimurium* clone was disseminated across Eastern and Central Europe.

The ciprofloxacin-resistant CTX-M-15-producing *E. coli* O25-ST131/B2 and O15/D strains of human origin proved to be widespread among Hungarian healthcare facilities. CTX-M-1, CTX-M-32 and SHV-2 ESBL genes were found in the ESBL-producing *E. coli* strains of animal origin, which are present in animal strains in the other European countries as well. According to results of PFGE no clonal relationship was found between human and animal strains.

- Tóth Á, Gacs M, Márialigeti K, Cech G, Füzi M: Occurrence and regional distribution of SHV-type extended-spectrum  $\beta$ -lactamases in Hungary. *Eur J Clin Microbiol Infect Dis*, 2005; 24:284-287.
- Tóth Á, Nógrády N, Fekete P, Pászti J, Füzi M: Extended-spectrum  $\beta$ -lactamase producing *Salmonella enterica* strains isolated from humans in Hungary, between 2000-2004. *J Antimicrob Chemother* 2007; 59:579-582.
- Damjanova I, Tóth Á, Pászti J, Hajbel-Vékony G, Jakab M, Berta J, Milch H, Füzi M: Expansion and countrywide dissemination of ST11, ST15 and ST147 ciprofloxacin-resistant CTX-M-15-type  $\beta$ -lactamase-producing *Klebsiella pneumoniae* epidemic clones in Hungary in 2005 - the new 'MRSAs'? *J Antimicrob Chemother* 2008; 62:978-985.

**PROGRAM 8/4.****PUBLIC HEALTH*****Coordinator:***

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**Program Overview:** The program includes issues and joint areas of public health, forensic medicine, hygiene and dietetics. The various subprograms sum up knowledge in the fields of organ damages caused by environmental injuries, endocrinological diseases and virology. A special Program deals with topics of health education and nursing. The various Programs have a common basic and following the branching-off there is an opportunity to select a special subjects.

***Titles of research projects***

Importance of medical informatics research in healthcare

Health history

Carcinogenicity of environmental chemicals, biological markers

Investigation of the risk for HIV and HCV infection among Hungarian injecting drug users

Death caused by drugs (opiat and dopaminerg systems in heroin taking)

Role of antioxidants in prevention of certain diseases

Epidemiology of adenoviruses in immunosuppressive conditions. Adenoviral therapy

Health impacts of climate change. The use of geographical information system in public health

Science-, research-, and innovation politics and management, financing systems and their practical applications in Hungary and in European Union

Toxic injury of the myocardium

Health and medical relation in hungarian legal practice

Effect of globalization on the onset of diseases

Health informatics

***Supervisors***

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Péter Sótonyi

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Diána Kaldau

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Ildikó Rákóczi

pt(a)

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pt

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Elek Dinya

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Péter Balázs

Judit Forrai

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Gábor Ormos	na
Marcel Marius Pop	pt
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***Supervisors***

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Péter Balázs
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Istvánné Németh	pt
Annamária Pakai (Karamánné)	pt
Erzsébet Pálfi	pt
Márta Bálint (Veresné)	pt

***Supervisors***

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Abstracts of Ph.D. theses successfully defended in 2011

**ERZSÉBET MÁK (2011)****Development of a dietary menu planning and counselling software with artificial intelligence**

*Supervisor: István Szabolcs*

An artificial intelligence-based dietary counselling system has been created with the amalgamation of a number of disciplines. Our objective was to develop a counselling system which takes the needs of the users into account with unprecedented accuracy, follows up-to-date dietary guidelines and also produces common sense output menus. We have tried to overcome the shortcomings of dietary expert systems developed so far by a new interpretation of the possible aspects of menu planning, an extension of the raw material data base, partial automation of the recipe data base, a conceptual interpretation of technological operations and a formulation and systematisation of harmonising rules. In order for us to achieve these endeavours, new concepts and systematisation methods had to be developed, such as the concept of component, the application of the so called “knight’s move” rule, organoleptic index, and the technological concept. In order to implement all these and to make them usable, new IT methods have been developed as needed.

In addition, we wanted to create a marketable software which can achieve a high level of user satisfaction. For this purpose, we have been first to survey the demands of non-infectious chronic patients, and on the basis on their responses, we have worked out our expert system, which could counsel patients, lay users, doctors, nurses, etc. and also support the work of dietitians. We have analysed our hypotheses according to sex, age, disease group and form of use in 6 points (form of use, requirement for depth of information, degree of willingness to pay for use, guarantee of authenticity, time devoted to fill in medical history,

waiting time accepted for obtaining a response). We have concluded that sex, age and the selected form of use (Web, CD, via professional staff) do not significantly influence the use of the counselling system. The patient's profession (the type of work the patients does) and especially his/her disease, however, have a significant impact on use.

- Mák E, Veresné Bálint M, Pálfi E, Németh I, Lichthammer A, Gaál B, Karamánné PA, Szabolcs I: *Improving the quality of life of the population through the Internet by surveying demand for the use of diet planning software*. *New Medicine* 2010; 15:99-101.
- Mák E, Tóth T, Karamánné P, Fehér F: *Az ételcsoportosítás új rendszere*, *Új Diéta* 2010; 17: 30-31.
- Mák E, Gaál B, Vassányi I, Karamánné Pakai A, Szabolcs I: *Egészségügyi szoftverek mesterséges intelligenciával – étlendtervez\_szoftver*; *Magyar Orvos* 2008; 16:36-38.

### ISTVÁNNÉ NÉMETH (2011)

#### Analysis of dietetics training programmes

*Supervisor: Mária Barna*

One of the objectives of the Bologna Declaration of 1999 is the adoption of a system of easily readable and comparable degrees, and the promotion of mobility of students and teachers in order to promote European citizens employability in a common European labour market. This means reforms of European higher education. This study presents the results of a research made in seven European higher educational institutions of dietician training. The objective was on the one hand to determine whether the national dietician training which has a past of almost a hundred years is compatible with the expectations of the Bologna Declaration and the EFAD recommendations, and on the other hand, to assess the career orientation ideas and intention on international mobility. As a result of the research we can state that with respect to the competence correspondence, the time of the training (four years), the credit requirement (240 ECTS) and the three cycles of education (BSc, MSc, Ph.D.) the Hungarian dietician training does not only meet the European expectations, but excels them. This way it enables the Hungarian dietician training institution to become a leading centre in Europe – as long as language training and possibly the teaching of courses in foreign language (mainly English) is introduced, and thus more foreign students would be attracted to the training program in Budapest. This possibility has not been taken into consideration but it could provide a great opportunity for both Semmelweis University and Hungary.

An online survey was conducted among the students of the abovementioned institutions about their career orientation and international mobility intentions, and students could express their opinion about their expectations from the training to facilitate the mobility. There is no *significant difference* between the Hungarian and foreign students' answers; they plan to use a wide variety of options (media, research, food industry and trade, tourism, etc.). The most attractive are prevention and counselling, clinical dietician and sports nutrition. Similarly, there is no palpable difference between the intentions on mobility, although the motivations are different. Gaining professional experience, a wish to learn language and hope for financial possibilities are the three main motivating factors. Out of these, Hungarian students rank financials to the first place, while for foreign students the first is gaining experience. Two thirds of the students (64.15%) feel professionally prepared for working abroad but more than half have doubts about their foreign language skills. Among the suggestions about facilitating mobilization we find more effective professional foreign language teaching, preparation for dieticians' task of foreign countries, and the widening of student exchange programs.

- Németh I, Veresné BM, Hajdú G, Barna M, Horváth Z, Pálfi E, Mák E, Szabolcs I, Wlodarek D: *Career orientation plans of dietetics students from different member states of the European Union. New Medicine*, 2010; 4:138-141.
- Németh I, Horváth Z, Csajbók R, Mák E, Lichthammer A, Barna M: *Dietetikus képzési programok elemzése, Új Diéta*, 2011; 18:22-25.
- Krasznai A, Lichthammer A, Veresné BM, Németh I: *Dietetikusok szerepe az alapellátásban, avagy mi dolgunk lehet a háziorvosokkal? Miért volna fontos az együttműködés? Új Diéta*, 2010; 17:24-27.
- Mák E, Veresné BM, Pálfi E, Németh I, Tóth T, Fehér F, Gaál B, Szabolcs I: *Improving the quality of life the population through the Internet by surveying demand for use of diet planning software New Medicine*, 2010; 3:98-101.

### ANNAMÁRIA PAKAI (KARAMÁNNÉ) (2011)

#### Study of women's motivation for non-utilization of cervix cancer screening

Supervisor: Péter Balázs

The occurrence of cervix cancer is outstandingly high in Zala County situated in the Western Transdanubian region of Hungary. Cervix cancer screening based on personal invitation was launched within the framework of the National Programme in Hungary in 2003. The aim of our study was to reveal why women do not take the opportunity offered by the state and what reasons there are for the non-attendance of screenings. Using a cross-sectional approach, we accomplished our study on women between the ages of 18 and 60 without any medical qualifications, and among nurses of the Hungarian Zala County Hospital, in the Australian Queensland North Arm City Hospital and in the German "Stralsund Nursing Service" coupled with the Frankfurt Diakonia Clinic and the Bethania Hospital. The results of our study revealed that 13.8% of women participating in our research program have never been to a gynaecological cancer screening. Concerning this fact, the following groups deserve greater attention: 15-19 year-olds, those only with basic school qualifications, the unmarried and the unemployed. The women, who think they did not appear on the screening because they had not received a specific appointment, have almost a four times greater chance to stay away from the cervix cancer screenings. Those women, who stated to be ashamed of such a screening, have a 2.21 times greater chance never to have attended a gynaecological screening before. Those not willing to sacrifice their free time have a 2.5 times greater chance not to have attended a gynaecological screening at all before. 89.4% of the nurses have already been to a cytological screening at least once in their lives. A significant difference can be experienced among the nursing groups related to the frequency of screening attended. The majority of Hungarian and German nurses are utilizing annually the screening, whereas 50% of the Australian sample do it every second year, nevertheless it fits exactly to the recommendation of the Australian National Programme. In order to improve our national mortality indexes it is necessary to continue the cancer screenings in a well motivated target population. Achieving this in cervix cancer screening, there are available conception and infrastructure alike provided by the health administration. The weakness of the system is the low participation rate of the population. Although, it cannot be forgotten that the major share of those participated in the screening programs feel responsible for their own state of health.

- Pakai A, Dér A, Kriszbacher I, Németh K, Zsigmond E, Balázs P: *Why don't Hungarian women take part in organized cervical screening? New Medicine* 2010; 1:27-30.

- Karamánné Pakai A, Németh K, Dér A, Kriszbacher I, Mák E, Mészáros L, Lampek K, Oláh A, Balázs P: Investigating the reasons why Hungarian women avoid organized screening for cervical cancer. *Bulletin of Medical Sciences* 2008; 81:271-275.
- Karamánné Pakai A, Németh K, Kriszbacher I, Dér A, Lampek K, Mészáros L, Betlehem J, Balázs P: Examination of the reasons of non-attendance at organised cervix cancer screening between women in the West Transdanubian Region. *Hungarian Epidemiology*, 2009; 6:9-20.

### ERZSÉBET PÁLFI (2011)

#### **The research for complex treatment of food allergies has been carried out through multi-criteria interview method**

*Supervisor: Mária Barna*

The prevalence of food allergy has been estimated to be around 1% in adults and 4-6% in children in Europe. The treatment of the food allergy is the allergen elimination diet that should be feasible only with dietetic management and information about allergen content. The safe allergen free diet is difficult, because the allergens are most diverse in foods and the avoidance diet affects the quality of life of food allergic patients. The safe allergen avoidance diet includes dietetic counselling and the patients' management that concentrated in the health system. However, the further follow-up and management are affected beyond the health system. The information about 'allergen free' products is part of the food safety, the consumer protection area.

The aims of research were finding the best intervention strategies in the management of food allergy. Furthermore, this study tried to develop a complex view of key stakeholders from different sectors connected to food allergy in Hungary. We used a computer based, multi- criteria interview technique to provide an integrative and comparative analysis of the differing perspectives of key stakeholders on a broad range of possible types of interventions in food allergy management. The interview contains twenty ahead defined options and some viewpoints of their evaluation. These twenty options showed the complex situation of management of food allergy in Hungary. We compared the viewpoints of key stakeholders, in this manner developing comprehensive and multidisciplinary opinion spectrum. The interview consisted four parts built upon each other and the stakeholders took written commentaries that completed the interview.

The result of this study the multi criteria method is workable to find the strategies in food allergy management. The key stakeholders suggested that the education of consumers is the most relevant intervention point. On the grounds of opinion spectrum of most stakeholders we could say the standardised allergen labelling as intervention point was also preferred and it was considered a good one in terms of the expense efficiency. Consequently, the representatives found both allergen labelling and consumer education good treatment strategies in food allergy management.

- Pálfi E, Barna M: Food allergen labelling – it's role in the food safety of food allergic consumers. *Journal on Processing and Energy in Agriculture* 2010; 14:19-22.
- Pálfi E, Barna M: A táplálékallergia és táplálékintolerancia komplex kezelése helyzetének kutatása Magyarországon MCM módszerrel. *Allergológia és Klinikai Immunológia* 2009; 11:34-38.
- Pálfi E: Dietetikai szempontok a táplálékallergiák kezelésében. In: Czirják L (szerk.): *Klinikai Immunológia*. Budapest, Medicina Könyvkiadó 2006. pp.490-494.



**VERESNÉ BÁLINT MÁRTA (2011)****Analysis of nutritional status, dietary routines, nutrient intake values and food consumption frequency in the hungarian elderly***Supervisor: István Szabolcs*

In my study I investigated voluntary elderly people over the age of 55. It is positive that data were obtained by dietetics students, and anthropometric data were calculated based on measured values. In my study both malnutrition ( $BMI < 20 \text{ kg/m}^2$ ) and obesity ( $BMI > 30 \text{ kg/m}^2$ ) are frequent. Average energy intake is below recommended value, nevertheless, a third of the participants are obese (31,19%). Comparing BMI, MNA and waist/hip ratio more detailed anthropometric data were available for me. As a new finding I found that there is a discrepancy between the three methods. I maintain that MNA validated for the elderly is more informative and more successful method than BMI. According to their waist/hip ratio a very high percent (73,39%) of the elderly belong to visceral fat mass, high risk group (man  $> 0,95$ ; woman  $> 0,8$ ), which emphasises that even those with normal BMI can be concerned. I found significant correlation between the nutrient intake values and life style factors (gender, residence, family background, qualification, age group). The fat E% is lower among elderly people with higher qualifications. Vitamin B12 and C intake are better for people living in their homes. On the other hand, their sugar and vitamin D intakes are lower than for those living in institutions. During the analysis of nutrient content, the low level of E% of added sugar, low cholesterol intake and sufficient protein intake are favourable. High fat E%, low dietary fibre intake, carbohydrate E% and insufficient liquid consumption are all unfavourable. Excessive sodium intake is also unwanted, which is accompanied by insufficient potassium intake, thus sodium-potassium rate is multiple of the recommended value. It is also unfavourable that calcium intake is insufficient in both genders, excessive phosphorus as well as calcium and intake rates are both far from ideal. It is novelty, that the dietician students was in possession of the menu of the given day during 24 hour recall so they did not rely only on the memory of the interviewee and the documentation of the consumed food was made easier. My study proved that elderly people stick to their well-known tastes since white bread of poor-nutrient content, traditional pasta, potato or hulled rice were all popular. Only 10-14% consumes several servings of vegetables and fruit on a daily basis, fish is eaten monthly or even rarer and they do not prefer light margarine or butter. However, they accept low-fat milk and liked lean meat. It is a good result that 'consumer products' consumption is at a tolerable level. It is also favourable that the elderly have their meals at regular times, at least three times a day, and rarely have snacks. Significant differences can be found in the national guidelines for the elderly and nutrient intake reference values in different countries, which renders comparative studies of data difficult. Thus I conclude that it is necessary to standardise the methodology of nutrition and nutrient intake analysis.

- Békési K, Veresné Bálint M, Kiss A: Tápláltsági állapot és tápanyag-ellátottság időskorban. *Új diéta* 2007; 1:10-11.
- Veresné Bálint M, Lichthammer A, Pálfi E, Szabolcs I: Malnutrition and nutrient intake values in the Hungarian elderly. *New Medicine* 2010; 4:133-137.
- Veresné Bálint M, Prikkné Nagy Á: Idősek tápláltsági állapotának és étel- és táplálékfogyasztási szokásainak felmérése. *Új Diéta* 2010; 2:12-13.

**PROGRAM 8/5.****CLINICAL AND EXPERIMENTAL TRANSPLANTATION****Coordinator:****Róbert LANGER M.D., Ph.D.**

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**Program overview:** The Ph.D. School for Transplantation was founded in 2007. Transplantation represents an interdisciplinary area of medicine, which is a quite young discipline. It was only 50 years ago that the first successful operations were performed and the number of these was quite low at the beginning. The surgical technique has not change much since then, but our knowledge of immunology and the evolution of intensive care changed the scenery enormously. The introduction of new immunosuppressive drugs and problems of the follow-up of the immunosuppressed patient represent a big everyday challenge. The background for these challenges is unimaginable without the laboratory work, the experimental and large clinical studies and the dialogue between basic science and clinical science. Our Ph.D. School is the answer for these question and gives possibility for the academically interested professionals.

***Titles of research projects***

Isotope diagnostics in transplanted patients

Significance of renal transplantation from living donors  
in HungaryAnatomical and chirurgical basis of partial liver transplantation  
from living donorDiagnostic method to study drugmetabolizing capacity in  
transplanted patients - the future of individual  
immunosuppression

Tolerance after renal transplantation

Hepatitis C before and after liver transplantation

Monitoring redox-homeostasis, graft function and therapeutic  
drug level in transplanted patientsComplications after renal transplantation with special attention  
to malignant diseasesComplications of infectious origin after transplantation with  
special attention to viral diseasesThe concerns of organ transplant and the immunsupressiv  
oncology treatment (experimental and/or clinical research)***Supervisors***

Gabriella Dabasi

Jenő Járay

László Kóbori

László Kóbori

Róbert Langer

Balázs Nemes

Enikő Sárváry

Éva Toronyi

Marina Varga

Gyula Végső

***Ph.D. students***

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Fanni Gelley ft

***Supervisors***

Róbert Langer

Balázs Nemes

András Kiss

Mátyás Kiss	pt	László Kóbori
Zsolt Mészáros	ft	Róbert Langer
Károly Németh	ft	László Kóbori
Hidas Tamás	ft	Éva Toronyi

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Gergely Zádori	ft

***Supervisors***

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László Kóbori
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***Ph.D. graduates***

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László Kóbori

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## ***Abstracts of Ph.D. theses successfully defended in 2011***

### **MATTHIAS HEUER (2011)**

#### **Prognostic factors of liver injury in abdominal trauma: is transplantation a valuable option?**

*Supervisor: László Kóbori*

**Backgrounds** Prognosis of patients with abdominal injuries is limited mainly by severe haemorrhage. Although, mechanisms of altered immune response have been intensively investigated, little is known about the relevance of liver injury as an independent predictive outcome factor in these patients. Because of these poor requirements and organ shortage, especially liver injury due to trauma is a rare indication for transplantation and is occasionally described as “waste of organs”, however based on insufficient data. Our studies aimed to report our experience, outcome and to critically question the indication of transplantation in these patients.

**Methods** 10,469 patients from the DGU Trauma Registry (1993-2005) were retrospectively analyzed. Primarily admitted patients with an injury severity score  $\geq 16$ , without isolated head injury were included. Patients were analyzed according to the injury pattern as liver injury (AIS abdomen  $<3$  and AIS liver 2-5;  $n=321$ ), non-liver abdominal trauma (AIS abdomen 2-5 or AIS liver  $<3$ ;  $n=574$ ) and control group without abdominal injuries (AIS abdomen or liver  $<3$ ;  $n=9,574$ ). Of them, 6 transplants were performed due to motor-vehicle accidents which caused uncontrollable acute liver trauma in 4 patients. The patients' peri-operative course, short- and long-term outcomes were analyzed.

**Results** Severe liver injury is associated with excessive demands for volume resuscitation and induces a significantly increased risk for sepsis and MOF compared to both other groups (sepsis 19.9% vs. 11.0%; MOF 32.7% vs. 16.6%). Furthermore, deleterious outcome is more frequently associated with severe liver trauma (mortality 34.9%) compared to severe abdominal trauma (12.0%). In our department, five deceased-donor liver transplantations (4 full size, 1 split) and 1 living donor (right) transplantation were performed due to liver trauma. The median GCS score was 9/15; the median MELD score was 15. Postoperative complications were observed in 3 patients, requiring re-operation in 2. After a median

(range) follow-up of 32.95 (10.3-55.6) months, 2 patients are alive and remain well on immunosuppression.

**Conclusion** Severe liver trauma is an independent predictor for severe hemorrhage with a substantial increase risk of sepsis, MOF and trauma-related death. While conservative treatment of patients with liver trauma but no hemorrhage is effective, patients with hemodynamic instability seem to form a subgroup where contemporary treatment modalities are not yet sufficient. Therefore, liver transplantation in patients with otherwise surgically uncontrollable acute liver injury can be indicated as a life saving procedure and can be performed successfully in highly selected cases.

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- Radünz S, Hertel S, Schmid KW, Heuer M, Stommel P, Frühauf NR, Saner FH, Paul A, Kaiser GM: *Attitude of health care professionals to organ donation: two surveys among the staff of a german university hospital.* *Transplant Proc* 2010; 42:126-129.
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## GEORGIOS SOTIROPOULOS (2011)

### **Liver transplantation for hepatocellular carcinoma in cirrhosis: expanding the recipient pool**

*Supervisor: László Kóbori*

**Background:** LT is the best treatment option for cirrhotic patients with HCC within the Milan criteria. Aim of this study was to explore the existing possibilities to offer the transplant modality to more HCC patients.

**Methods:** A corresponding database was built and most data were prospectively collected. Accuracy of the radiological findings, efficacy of bridging treatments, LT using partial and ECD grafts, LT for special indications and LT for extended indications were evaluated. Additionally, systematic reviews and meta-analyses for related issues were contacted.

**Results:** LT represents the best therapy option for patients with HCC in the absence of extrahepatic disease/macrovascular invasion as monotherapy, even for patients exceeding the Milan criteria. Current imaging techniques have a low accuracy when evaluating HCC in cirrhosis, especially tumors <2cm. TACE provides acceptable local tumor control before LT. Achievement of complete tumor necrosis by means of bridging treatments is characterized by a very low recurrence rate. LT with split, living donor and ECD grafts represent a reliable option to extend the donor pool and to select over the standard tumor criteria; recipient age, MELD score, and AFP levels could further improve current guidelines. LT can be extended for HCC patients "beyond Milan-within UCSF" or with initial undetected/very low AFP value, irrespective of the Milan criteria. Portal vein thrombosis or pulmonary granulomas are not accurately evaluated preoperatively and reserve further consideration. Poor tumor differentiation represents an additional prognostic factor for HCC recurrence. Neither the Milan nor the UCSF criteria were associated with survival or tumor recurrence, as it stipulated by the meta-analysis of the available multivariable studies.

**Conclusion:** There is still plenty of space to improve current listing criteria and expand the recipient pool of patients with HCC in cirrhosis. A novel prognostic score for the better evaluation of transplant candidates with HCC in cirrhosis is needed.

- Sotiropoulos GC, Drühe N, Sgourakis G, Molmenti EP, Beckebaum S, Baba HA, Antoch G, Hilgard P, Radtke A, Saner FH, Nadalin S, Paul A, Malagó M, Broelsch CE, Lang H: Liver transplantation, liver resection, and transarterial chemoembolization for hepatocellular carcinoma in cirrhosis: which is the best oncological approach? *Dig Dis Sci* 2009; 54: 2264-2273.
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## PROGRAM 8/6.

### HEALTH SCIENCES

#### **Coordinator:**

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**Program overview:** To provide research facilities of high standard for students in a wide range of topics in the field of health sciences. Health sciences became an internationally acknowledged branch of science in the last quarter of the 20<sup>th</sup> century. This is partly due to the rapid technical development, considerable differentiation and increased costs of biomedicine, and partly to the “pathogenetic” role of socio-economic processes and the development of prevention on the level of society (international and national prevention programs). Health sciences, as part of medicine (Government edict nr. 169/2000 IX. 29.), study principles and development facilities of human health maintenance in a system-based interdisciplinary approach. The main aim of health sciences is to study the biological and social factors of the population’s state of health and quality of life. Health maintenance strategies include providing facilities for the choice of a healthy lifestyle, supporting health maintenance attitudes and avoiding a health-damaging lifestyle. Research in health sciences is characterized by an interdisciplinary approach and the application of methods of genetics, epidemiology, biostatistics, dietetics, behavioural sciences and health economics. However, research methods of health sciences differ from research methods of biomedicine in that besides methods of natural sciences they also apply methods of social sciences to a great extent.

#### **Titles of research projects**

Role of mission in health occupations

Prevention of pediatric obesity

The relationship of childhood obesity to adulthood

cardiovascular diseases with special respects to comorbidity

#### **Supervisors**

Péter Balázs

Mária Barna

Antal Czinner

Development of an intelligent telediabetology system	Tibor Deutsch
The examination of the long-term life quality and rehabilitation possibilities of patients with systematic autoimmune diseases (SLE, PSS, RA., etc.)	Gyula Domján
The examination of the long-term life quality and rehabilitation possibilities of thrombophilic patients with thrombotic disorders	Gyula Domján
The examination of the long-term life quality and rehabilitation possibilities of hematological patients with Myeloma multiplex	Klára Gadó
The examination and preservation of nutritive value of greenery and fruits through modern storing and production processes	Mária Pankotai
Gillingerné	
The significance of monitoring in acute treatment	Tibor Gondos
Identity of profession and counselling in nursing	Kornélia Helembai
Development of teaching in higher education of health - Paradigms in nursing and teaching at XXI century	Sándor Hollós
The effect of selenium replacement on subclinical hypothyroidism	Gábor László Kovács
Analysis of effects in health education and nursing	Judit Mészáros
The significance and treatment methods of food allergies and intolerances	Kristóf Nékám
Psychosocial characteristics of addictive disorders	József Rác
Interaction of iodine and selenium supply in elderly ages	István Szabolcs
Quality of life in subclinical hypothyreosis	István Szabolcs
Food production by fermentation for patients with food allergy and intolerance	Zsuzsa Varga
The sociocultural context of the health-status, health-culture, and the health care system	István Vingender
Deviant behaviour and sociopathology	István Vingender
Characteristics of morbidity and basic needs of homeless people as compared to the general population	Ágnes Simek
Investigate the risk for HIV and HCV infections among Hungarian injecting drug users	Anna Gyarmathy

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Annamária Karamánné Pakai	pt

***Supervisors***

István Szabolcs
Péter Balázs

a, absolutorium; pt, part-time; ft, full-time; na, not affiliated

***Abstracts of Ph.D. theses successfully defended in 2011*****MÁRTA VERESNÉ BÁLINT (2011)****Analysis of nutritional status, dietary routines, nutrient intake values and food consumption frequency in the hungarian elderly**

*Supervisor: István Szabolcs*

In my study I investigated voluntary elderly people over the age of 55. It is positive that data were obtained by dietetics students, and anthropometric data were calculated based on measured values. In my study both malnutrition ( $BMI < 20 \text{ kg/m}^2$ ) and obesity ( $BMI > 30 \text{ kg/m}^2$ ) are frequent. Average energy intake is below recommended value, nevertheless, a third of the participants are obese (31,19%). Comparing BMI, MNA and waist/hip ratio more detailed anthropometric data were available for me. As a new finding I found that

there is a discrepancy between the three methods. I maintain that MNA validated for the elderly is more informative and more successful method than BMI. According to their waist/hap ratio a very high percent (73,39%) of the elderly belong to visceral fat mass, high risk group (man > 0,95; woman > 0,8), which emphasises that even those with normal BMI can be concerned. I found significant correlation between the nutrient intake values and life style factors (gender, residence, family background, qualification, age group). The fat E % is lower among elderly people with higher qualifications. Vitamin B12 and C intake are better for people living in their homes. On the other hand, their sugar and vitamin D intakes are lower than for those living in institutions. During the analysis of nutrient content, the low level of E% of added sugar, low cholesterol intake and sufficient protein intake are favourable. High fat E%, low dietary fibre intake, carbohydrate E% and insufficient liquid consumption are all unfavourable. Excessive sodium intake is also unwanted, which is accompanied by insufficient potassium intake, thus sodium-potassium rate is multiple of the recommended value. It is also unfavourable that calcium intake is insufficient in both genders, excessive phosphorus as well as calcium and intake rates are both far from ideal. It is novelty, that the dietician students was in possession of the menu of the given day during 24 hour recall so they did not rely only on the memory of the interviewee and the documentation of the consumed food was made easier. My study proved that elderly people stick to their well-known tastes since white bread of poor-nutrient content, traditional pasta, potato or hulled rice were all popular. Only 10-14% consumes several servings of vegetables and fruit on a daily basis, fish is eaten monthly or even rarer and they do not prefer light margarine or butter. However, they accept low- fat milk and liked lean meat. It is a good result that 'consumer products' consumption is at a tolerable level. It is also favourable that the elderly have their meals at regular times, at least three times a day, and rarely have snacks. Significant differences can be found in the national guidelines for the elderly and nutrient intake reference values in different countries, which renders comparative studies of data difficult. Thus I conclude that it is necessary to standardise the methodology of nutrition and nutrient intake analysis.

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- Veresné Bálint M, Lichthammer A, Pálfi E, Szabolcs I: *Malnutrition and nutrient intake values in the Hungarian elderly. New Medicine 2010; 4:133-137.*
- Veresné Bálint M, Prikkné Nagy Á: *Idősek tápláltsági állapotának, és étel- és ital-fogyasztási szokásainak felmérése. 2010; Új Diéta 2:12-13.*

## ANNAMÁRIA KARAMÁNNÉ PAKAI (2011)

### Study of women's motivation for non-utilization of cervix cancer screening

Supervisor: Péter Balázs

The occurrence of cervix cancer is outstandingly high in Zala County situated in the Western Transdanubian region of Hungary. Cervix cancer screening based on personal invitation was launched within the framework of the National Programme in Hungary in 2003. The aim of our study was to reveal why women do not take the opportunity offered by the state and what reasons there are for the non-attendance of screenings. Using a cross-sectional approach, we accomplished our study on women between the ages of 18 and 60 without any medical qualifications, and among nurses of the Hungarian Zala County Hospital, in the Australian Queensland North Arm City Hospital and in the German "Stralsund Nursing Service" coupled with the Frankfurt Diakonia Clinic and the Bethania Hospital.

The results of our study revealed that 13.8% of women participating in our research program have never been to a gynaecological cancer screening. Concerning this fact, the following groups deserve greater attention: 15-19 year-olds, those only with basic school qualifications, the unmarried and the unemployed. The women, who think they did not appear on the screening because they had not received a specific appointment, have almost a four times greater chance to stay away from the cervix cancer screenings. Those women, who stated to be ashamed of such a screening, have a 2.21 times greater chance never to have attended a gynaecological screening before. Those not willing to sacrifice their free time have a 2.5 times greater chance not to have attended a gynaecological screening at all before. 89.4% of the nurses have already been to a cytological screening at least once in their lives. A significant difference can be experienced among the nursing groups related to the frequency of screening attended. The majority of Hungarian and German nurses are utilizing annually the screening, whereas 50% of the Australian sample do it every second year, nevertheless it fits exactly to the recommendation of the Australian National Programme. In order to improve our national mortality indexes it is necessary to continue the cancer screenings in a well motivated target population. Achieving this in cervix cancer screening, there are available conception and infrastructure alike provided by the health administration. The weakness of the system is the low participation rate of the population. Although, it cannot be forgotten that the major share of those participated in the screening programs feel responsible for their own state of health.

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