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Academic Excellence in Biomedical Research at Semmelweis University Budapest, Hungary

Academic Excellence in Biomedical Research at Semmelweis University Budapest, Hungary

Academic Excellence in Biomedical Research at **Semmelweis University** Budapest, Hungary

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Contents

Distinguished Reader!

The mission of this booklet is to provide an overview on the research laboratories of highest merit at Semmelweis University and to offer an opportunity for establishing new scientific co-operation on the field of various disciplines. This review can enhance the efficiency of joint efforts between research groups on an international level, thus offering multiply strength of fruitful scientific collaboration and grant application.

Semmelweis University is widely recognized as one of Europe's leading centers of medicine and health sciences. With its 238-year-old tradition of academic excellence our University ranks among the most prestigious Hungarian research institutions where 1172 staff members in approximately 80 departments are involved in R & D activities. Research projects in the preclinical and clinical departments are supported by both Hungarian and international programs. Contract research sponsored by pharmaceutical companies is also an important part of scientific activity. Selected research groups are supported jointly by the University and the Hungarian Academy of Sciences.

Our University is one of the recognized members of a vast network of biomedical science; it is the site where academy and industry come together, where the meaning of the term multidiscipline really exists. The Szentágothai János Knowledge Center (SJKC) is a center of excellence initiated by Semmelweis University and supported by the National Office for Research and Technology. The consortium also includes Richter Gedeon Ltd., a leading Hungarian pharmaceutical company, the Faculty of Information Technologies of Pázmány Péter Catholic University and the Institute of Experimental Medicine (Hungarian Academy of Sciences).
Semmelweis University is also among the leading universities in Hungary regarding the number of research papers published in high quality international journals.

I sincerely hope that this review is a reliable indicator of the high standard research activity at Semmelweis University and it will succeed in its aim at promoting development of inter-disciplinary teamwork.

Budapest, 2008

Tivadar Tulassay
Rector of Semmelweis University

Oncohaematology Laboratory

András Matolcsy, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

B-cell lymphoma
chronic lymphocytic leukemia
Richter's transformation
follicular lymphoma
genetic instability

Molecular basis of B-cell lymphoma development and progression

The research activities of the group are centered around the molecular mechanisms underlying the development and progression of B-cell non-Hodgkin lymphomas, especially folicular lymphoma and chronic lymphocytic leukemia (CLL). Using extensive mutation profiling of different genes, including IgVH, BCL-6, BCL-2 we have characterized the clonal evolution and transformation of these lymphoma entities. Based on these studies we have confirmed that transformation of CLL to diffuse large B-cell lymphoma (Richter's transformation) occur only in the subgroup of CLL where the IgH gene is unmutated. Our group have revealed several mechanisms including abnormal methylation of hMLH1 and hMSH2 mismatch repair genes, aberrant somatic hypermutation (ASHM) targeting the c-MYC, PAX-5, RhoH and PIM-1 proto-oncogenes and elevated expression of activation-induced cytidine deaminase (AID) associated with lymphoma transformation and progression. These findings suggest that genetic instability may have a central role in the transformation process of indolent B-cell lymphomas.
Through mutational analysis of IgVH gene, we have shown that in follicular lymphoma, the early descendants of the original tumor clone and derivatives of diversified tumor clones may both invade the bone marrow, providing a direct evidence of clonal evolution.
Our current interests are aimed at finding the progenitor of the transformed tumor cell population in CLL, and we are also trying to reveal alternative molecular mechanisms responsible for the development of BCL-2 negative follicular lymphomas.

Recent publications:

Balogh, Zs., Reiniger, L., Deák, L., Bödör, Cs., Csomor, J., Szepesi, Á., Gagyi, E., Kopper, L. & Matolcsy A. (2007)
IgVH gene mutation status and genomic imbalances in chronic lymphocytic leukaemia with increased prolymphocytes (CLL/PL).
Hematol. Oncol. 25(2): 90–95.

Reiniger, L., Bödör, Cs., Bognár, A., Balogh, Zs., Csomor, J., Szepesi, Á., Kopper, L. & Matolcsy, A. (2006)
Richter's and prolymphocytic transformation of chronic lymphocytic leukemia are associated with high mRNA expression of activation-induced cytidine deaminase and aberrant somatic hypermutation.
Leukemia 20(6): 1089–1095.

Bognár, A., Csernus, B., Bödör, Cs., Reiniger, L., Szepesi, Á., Tóth, E., Kopper, L. & Matolcsy, A. (2005)
Clonal selection in the bone marrow involvement of follicular lymphoma.
Leukemia 19(9): 1656–1662.

Bödör, Cs., Bognár, A., Reiniger, L., Szepesi, Á., Tóth, E., Kopper, L. & Matolcsy, A. (2005)
Aberrant somatic hypermutation and expression of activation-induced cytidine deaminase mRNA in mediastinal large B-cell lymphoma.
Br. J. Haematol. 129(3): 373–376.

Timár, B., Fülöp, Z., Csernus, B., Angster, C., Bognár, A., Szepesi, Á., Kopper, L. & Matolcsy, A. (2004)
Relationship between the mutational status of VH genes and pathogenesis of diffuse large B-cell lymphoma in Richter's syndrome.
Leukemia 18(2): 326–330.

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Laboratory of Experimental Liver Pathology

Péter Nagy, M.D., Ph.D., D.Sc.
Professor

Key words:

liver
stem cell
regeneration
carcinogenesis

There are two alternative mechanisms of liver regeneration: (1) the hepatocytes are able to return to the cell cycle and replace the lost tissue by compensatory hyperplasia; (2) if the hepatocytes are compromised the facultative liver stem cell compartment is activated and regenerates the liver. The first option is studied by the observation of the regeneration following surgical partial hepatectomy in experimental animals. We pay special attention to the structural changes during the regenerative process. Alterations of the liver architecture is analyzed by laser scanning confocal and electron microscopy. A transgenic mouse line is maintained in our department, which overexpresses active TGF-β in the liver. These animals provide excellent opportunity to understand the role of this cytokine in the growth regulation of various liver processes including regeneration.

The stem cell driven regeneration is also studied in experimental animals and human specimens. The combination of partial hepatectomy with 2-acetaminofluorene treatment results in the synchronized, intense activation of the hepatic stem cell compartment. We study the anatomical location, phenotype and growth regulation of the stem cells in this experimental model. The so called ductular proliferation of the human liver may correspond a stem cell fed histological reaction. We try to understand the role of hepatic stem cells in different pathological liver processes by the analysis of ductular reactions with various origin.

Recent publications:

Dezső, K., Jelnes, P., László, V., Baghy, K., Bödör, Cs., Paku, S., Tygstrup, N., Bisgaard, H.C. & Nagy, P. (2007)
Thy-1 is expressed in hepatic myiofibroblasts and not oval cells in stem cell-medated liver regeneration.
Am. J. Pathol. 171: 1529–1537.

Szabó, E., Lódi, Cs., Korpos, É., Batmunkh, E., Rottenberger, Zs., Deák, F., Kiss, I., Tőkés, A., Lotz, G., László, V., Kiss, A., Schaff, Zs. & Nagy, P. (2007)
Expression of matrilin-2 in oval cells during rat liver regeneration.
Matrix Biol. 26: 554–560.

Paku, S., Kopper, L. & Nagy, P. (2005)
Development of the vasculature in “pushing-type” liver metastases of an experimental colorectal cancer.
Int. J. Cancer 115: 893–902.

Paku, S., Dezső, K., Kopper, L. & Nagy, P. (2005)
Immunohistochemical analysis of cytokeratin 7 expression in resting and proliferating biliary structures of rat liver.
Hepatology 42: 863–870.

Paku, S., Nagy, P., Kopper, L. & Thorgeirsson, S.S. (2004)
AAF-dose dependent differentiation of oval cells into hepatocytes: confocal and electron microscopic studies.
Hepatology 39: 1353–1361.

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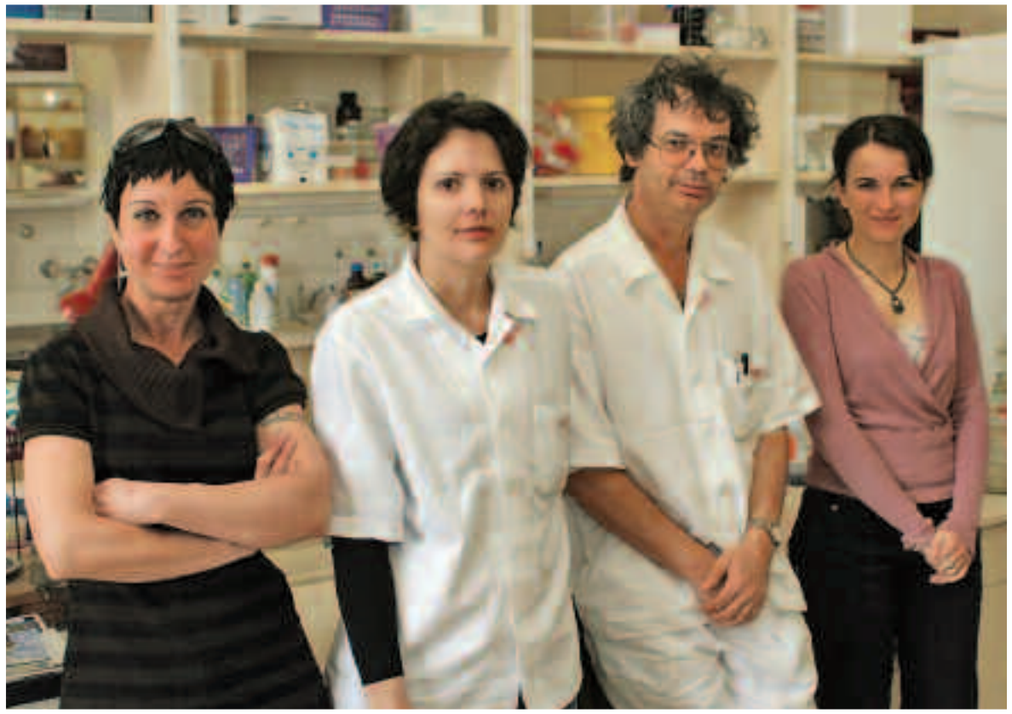
Nikolett Hegyesi



Developmental Biology Laboratory

Imre Oláh, M.D., Ph.D., D.Sc.
Professor

Key words:

embryo
avian
lymphoid tissue
dendritic cells
embryo manipulation

The Developmental Biology Laboratory was set up in 1995. Before this date the major research interest of the lab was immune morphology of the avian primary lymphoid organs, such as bursa of Fabricius and thymus, which are responsible for the B and T cell development, respectively. While the immunologists interested in the phenotypic and functional maturation of T and B cells, the morphologists turned to the early development of these organs. More than ten years ago it was an intellectual challenge to study the developmental biology of these organs which was enlarged by the development of the spleen and gut-associated lymphoid tissue (GALT). During the last decade, in the short history of the Developmental Biology Laboratory young scientists, student research associates, graduate students and postdocs create a living, active research group with international reputation. Complex research work includes morphological methods (light and electron microscopy, confocal microscopy, immunocytochemistry), cell and organ culturing, monclonal antibody production, embryo microsurgery (transplantation, ablation, recombination of organ rudiments), chimera and parabiosis (chick and quail).
The main research interest of the lab is the development of the lymphoid organs, the epithelio-mesenchymal interactions and neural crest cell differentiation.

Topics:
Development of the bursa of Fabricius, spleen and thymus; organogenesis of the mucosa-associated lymphoid tissue (MALT); differentiaton of the dendritic cells, in normal and pathological conditions; production of avian specific antibodies; hemopoietic stem cell colonization of primary and secondary lymphoid organs; development of the enteric nervous system; bone marrow-derived hemopoietic cells in the non-lymphoid organs; structure, phenotype, function.

Recent publications:

Igyártó, B.Z., Nagy, N., Magyar, A. & Oláh, I. (2008)
Identification of the avian B-cell-specific bu-1 alloantigen by a novel monoclonal antibody.
Poult. Sci. 87(2): 351–355.

Igyártó, B.Z., Magyar, A. & Oláh, I. (2007)
Origin of follicular dendritic cell in the chicken spleen.
Cell Tissue Res. 327(1): 83–92.

Nagy, N., Bíró, E., Takács, A., Pólos, M., Magyar, A. & Oláh, I. (2005)
Peripheral blood fibrocytes contribute to the formation of the avian spleen.
Dev. Dyn. 232(1): 55–66.

Nagy, N., Magyar, A., Tóth, M. & Oláh, I. (2004)
Origin of the bursal secretory dendritic cell.
Anat. Embryol. (Berl). 208(2): 97–107.

Gumati, M.K., Magyar, A., Nagy, N., Kurucz, E., Felföldi, B. & Oláh, I. (2003)
Extracellular matrix of different composition supports the various splenic compartments of guinea fowl (Numida meleagris).
Cell Tissue Res. 312(3): 333–343.

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Zsuzsa Vidra, Jutka Fügedi, Edit Orbán

Liver Pathology Research Unit

Zsuzsa Schaff, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

liver
liver cancer
hepatocarcinogenesis
tight junction
claudin

For decades the work team has been involved in studies on human and experimental liver pathology, virus-cell interactions and in particular, on chemical and viral hepatocarcinogenesis. In foreign collaborations, they have participated in the identification of hepatitis C virus (HCV) components. They proved in vivo and in vitro the association of the HCV core with endoplasmic reticulum membranes and lipid droplets. The group has also been involved in studies related to the effect of HCV on lipid metabolism. In clinical collaboration, it has been demonstrated that HCV type 1b causes liver steatosis too, as in the case of HCV type 3a. The studies on liver fibrosis have resulted in the work team being among the first to observe and describe components characteristic to the early stages of fibrogenesis in human liver diseases, their latest detection has been that of matrilin 2 in both human and experimental liver tissues. The role and significance of different growth factors, as transforming growth factor α and β have been proved in several liver diseases, especially in chronic hepatitis and hepatocellular carcinoma (HCC). The mutation of p53 was detected in 50% of HCCs of different etiology, excluding aflatoxin intoxication. Among the cell junction proteins, the work team has directed their focus on claudins, with a number of reports on the role of claudins in several tumors, including liver tumors. Based on their results, some of the studied claudins may even serve as potential therapeutic targets. From the hepatitis C virus receptors, the recently described Claudin 1 has become the work team's object of investigation.

Recent publications:

Szabó, E., Lódi, Cs., Korpos, E., Batmunkh, E., Rottenberger, Z., Deák, F., Kiss, I., Tőkés, A.M., Lotz, G., László, V., Kiss, A., Schaff, Zs. & Nagy, P. (2007)
Expression of matrilin-2 in oval cells during rat liver regeneration.
Matrix Biology 26: 554–560.

Batmunkh, E., Tátrai, P., Szabó, E., Lódi, Cs., Holczbauer, Á., Páska, Cs., Kupcsulik, P., Kiss, A., Schaff, Zs. & Kovalszky, I. (2007)
Comparison of the expression of agrin, a basement membrane heparan sulfate proteoglycan, in cholangiocarcinoma and hepatocellular carcinoma.
Human Pathology 38: 1508–1515.

Tátrai, P., Dudás, J., Batmunkh, E., Máthé, M., Zalatnai, A., Schaff, Zs., Ramadori, G. & Kovalszky, I. (2006)
Agrin, a novel basement membrane component in human and rat liver, accumulates in cirrhosis and hepatocellular carcinoma.
Laboratory Investigations 86: 1149–1160.

Lódi, Cs., Szabó, E., Holczbauer, Á., Batmunkh, E., Szijártó, A., Kupcsulik, P., Kovalszky, I., Paku, S., Illyés, Gy., Kiss, A. & Schaff, Zs. (2006)
Claudin-4 differentiates biliary tract cancers from hepatocellular carcinomas.
Modern Pathology 19: 460–469.

Tőkés, A.M., Kulka, J., Paku, S., Szik, Á., Páska, Cs., Kaposi Novák, P., Szilák, L., Kiss, A., Bögi, K. & Schaff, Zs. (2005)
Claudin-1, -3 and -4 proteins and mRNA expression in benign and malignant breast lesions: a research study.
Breast Cancer Research 7: R296–R305.

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Attila Patonai, Áron Somorácz,
Erzsébet Szabó
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Cerebrovascular Signaling Research Group of the Institute of Human Physiology and Clinical Experimental Research

Zoltán Benyó, M.D., Ph.D., D.Sc.
Senior Associate Professor

Key words:

cerebral circulation
vascular smooth muscle
endothelium
signal transduction
cerebral ischemia

Vascular diseases are the most prevalent life-threatening diseases in industrialized countries, and are rapidly increasing in importance in the developing world. In the recent Oxford Vascular Study cerebrovascular events were found to be the most frequent acute manifestation of vascular diseases (Rothwell et al. Lancet 366: 1773–1783, 2005).
Although cerebrovascular disorders have been studied extensively, several important questions could not be clarified with experimental approaches based only on classical pharmacological tools. The advent of new gene targeting techniques opened the door for better understanding of complex physiological functions of the cerebral vasculature and their disturbances in diseases. Using transgenic animal models we are currently studying the following questions:
How do nitric oxide synthase, cyclooxygenase and heme oxygenase pathways interact in the regulation of the cerebral circulation under physiological conditions and during hypoxia and hypercapnia?
Which receptor(s) and potential secondary vasoactive agents mediate the cerebrovascular effects of nicotinic acid? Are these mechanisms involved in the mediation of cerebral hyperemia and edema formation in pathological states such as acute liver failure and endotoxemia?
Which intracellular signaling mechanisms mediate the contractile effect of thromboxane-receptor activation in the cerebrovascular smooth muscle? Which of these pathways are important in the development of cerebrovascular dysfunction and vasospasm after subarachnoid hemorrhage and traumatic brain injury (TBI)?
Which GPCRs and downstream signaling pathways mediate the increased release of endothelin-1 and disruption of the blood brain barrier after TBI?

Recent publications:

Wirth, A., Benyó, Z., Lukasova, M., Leutgeb, B., Wettschureck, N., Gorbey, S., Örsy, P., Horváth, B., Maser-Gluth, C., Greiner, E., Lemmer, B., Schütz, G., Gutkind, J.S. & Offermanns, S. (2008)
G12-G13-LARG-mediated signaling in vascular smooth muscle is required for salt-induced hypertension.
Nature Medicine 14: 64–68.

Hortobágyi, L., Kis, B., Hrabák, A., Horváth, B., Huszty, G., Schweer, H., Benyó, B., Sándor, P., Busija, D.W. & Benyó, Z. (2007)
Adaptation of the hypothalamic blood flow to chronic nitric oxide deficiency is independent of vasodilator prostanoids.
Brain Research 1131: 129–137.

Benyó, Z., Gille, A., Kero, J., Csiky, M., Suchánková, M.C., Nüsing, R.M., Moers, A., Pfeffer, K. & Offermanns, S. (2005)
GPR109A (PUMA-G/HM74A) mediates nicotinic acid-induced flushing.
Journal of Clinical Investigation 115: 3634–3640.

Horváth, B., Hrabák, A., Káldi, K., Sándor, P. & Benyó, Z. (2003)
Contribution of the heme oxygenase pathway to the maintenance of the hypothalamic blood flow during diminished NO synthesis.
Journal of Cerebral Blood Flow and Metabolism 23: 653–657.

Lacza, Z., Hermán, P., Görlach, C., Hortobágyi, T., Sándor, P., Wahl, M. & Benyó, Z. (2001)
NO synthase blockade induces chaotic cerebral vasomotion via activation of thromboxane receptors.
Stroke 32: 2609– 2614.

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Professor

Potassium channels play a pivotal role in the homeostasis of every cell type. They have a major impact on the resting membrane potential and on the membrane potential changes of excitable cells. Potassium channels can be

Key words:

potassium channel
TASK
TRESK
regulation
calcineurin

divided into three major subfamilies; the inward rectifiers, the voltage sensitive-, and the two pore domain (2P) background potassium channels. The major interest of our group is the function and regulation of the 2P type channels. We have previously shown that 2P type TASK channels are present and provide highly negative membrane potential in adrenal glomerulosa cells. Upon stimulation with angiotensin II the TASK channels are inhibited what leads to depolarization and consequently to stimulation of aldosterone production. We have also demonstrated that the angiotensin-induced inhibition is not mediated by conventional second messengers; instead, it is the direct consequence of the breakdown of the polyphosphoinositides in the plasma membrane.
Different TASK channels are expressed also in neurons in the peripheral and central nervous system. We have shown that TASK1 and TASK3, if coexpressed, can form heterodimer channels, which has different characteristic from the homomers, formed by the parent subunits.
We have cloned TRESK, the last known member of the 2P family, and elucidated several details of its regulation. The channel is activated by the calcium signal. The effect is indirect and mediated by the calcium sensitive phosphatase, calcineurin. In the presence of calcium, the activated phosphatase binds to the intracellular loop of the cannel, this interaction is necessary for the activation/dephosphorylation. We have also shown that other intracellular scaffold protein/s also bind to TRESK, accordingly the regulation of its activity is even more complex.
As 2P channels are also targets of several drugs e.g. local or volatile anesthetics. The regulation or pharmacological modulation of their function may also have important clinical relevance.

Recent publications:

Czirják, G., Tóth, Z.E. & Enyedi, P. (2007)
Characterization of the heteromeric potassium channel formed by Kv2.1 and the retinal subunit Kv8.2 in Xenopus oocytes.
J. Neurophysiol. 98(3): 1213–1222.

Czirják, G. & Enyedi, P. (2006)
Zinc and mercuric ions distinguish TRESK from the other two-pore-domain K+ channels.
Mol. Pharmacol. 69(3): 1024–1032.

Czirják, G. & Enyedi, P. (2006)
Targeting of calcineurin to an NFAT-like docking site is required for the calcium-dependent activation of the background K+ channel, TRESK.
J. Biol. Chem. 281(21):14677–14682.

Lopes, C.M., Rohács, T., Czirják, G., Balla, T., Enyedi, P. & Logothetis, D.E. (2005)
PIP2 hydrolysis underlies agonist-induced inhibition and regulates voltage gating of two-pore domain K+ channels.
J. Physiol. 564(1): 117–129.

Czirják, G., Tóth, Z.E. & Enyedi, P. (2004)
The two-pore-domain K+ channel, TRESK, is activated by the cytoplasmic calcium signal through calcineurin.
J. Biol. Chem. 279(18): 18550–18558.

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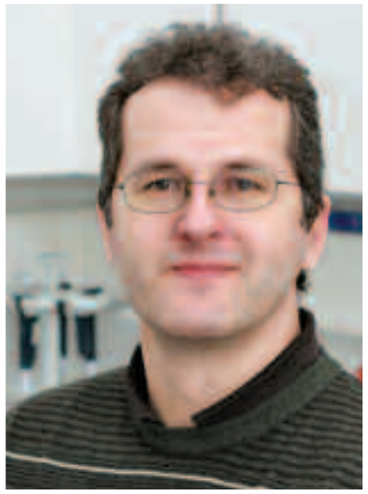

Miklós Geiszt, M.D., Ph.D.
Associate Professor

Key words:

NADPH oxidase
superoxide
hydrogen peroxide
reactive oxygen species
peroxidase

Our group studies the physiology of reactive oxygen species (ROS). Reactive oxygen species (ROS) play an important role in many physiological processes including host defense, hormone biosynthesis, fertilization and cellular signalling. Altered production of ROS have been implicated in the development of immunodeficiency, hypothyroidism and cardiovascular pathologies. In the last few years, several enzymes were identified at the molecular level, which are now thought to be responsible for ROS production observed in diverse tissues. These enzymes show a high degree of homology to the phagocytic NADPH oxidase and are now designated the Nox family of NADPH oxidases. Our group studies the function and regulation of several Nox/Duox isoforms, including Nox4, Duox1, Duox2 and Nox1. In our experiments we use different animal models, including C. elegans and mice, where the function of Nox enzymes is disrupted by different molecular biological techniques.

Recent publications:

Ueyama, T., Geiszt, M. & Leto, T.L. (2006)
Involvement of Rac1 in activation of multi-component Nox1- and Nox3-based NADPH oxidases.
Mol. Cell Biol. 26: 2160–2174.

Sirokmány, G., Szidonya, L., Káldi, K., Gáborik, Z., Ligeti, E. & Geiszt, M. (2006)
Sec14 homology domain targets p50RhoGAP to endosomes and provides a link between Rab and Rho GTPases.
J. Biol. Chem. 281: 6096–6105.

Geiszt M. (2006)
NADPH oxidases: new kids on the block.
Cardiovasc. Res. 71: 289–299.

Donkó, A., Péterfi, Z., Sum A., Leto, T. & Geiszt, M. (2005)
Dual oxidases.
Philos. Trans. R. Soc. Lond. Biol. Sci. 360: 2293–2300.

Geiszt, M. & Leto, T.L. (2004)
The Nox family of NAD(P)H oxidases: host defense and beyond.
J. Biol. Chem. 279: 51715–51718.

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Immunology of Renal and Vascular Diseases Group

Péter Hamar, M.D., Ph.D.
Associate Professor

Key words:

kidney transplantation
lupus nephritis
RNA interference
immunosuppression
atherosclerosis
NADPH oxidase

We are interested in immunologic pathomechanism of renal disease and atherosclerosis in animal models.

In renal transplantation we currently investigate the role of lymphangioneogenesis in chronic graft rejection utilizing adenoviral gene-therapy. This work is in collaboration with D. Kerjaschki (Vienna) and is supported by a bilateral grant.

In renal ischemia-reperfusion we investigate apoptosis and oxidative stress, utilizing RNA interference in vitro and in vivo, in collaboration with J. Liebermann (Boston), supported by Fogarthy International (FIRCA) and 2 OTKA grants.

In atherosclerosis we study the role of TGF-beta in double-gene-modified mice in collaboration with E. Ritz (Heidelberg), supported by a bilateral and an Else-Kröne Stiftung grant.

In diabetes we develop novel diagnostic and therapeutic tools to measure glomerular filtration and renal autoimmune activity, and to treat diabetic foot, in collaboration with L. Korányi, DRC Drug Research Center (Balatonfüred). We investigate novel protein expression in diabetic nephropathy in collaboration with H. Holthoefer (Helsinki, Dublin) and a novel antibiotic with M. Waara (Helsinki) with EU7 support.

Recent publications:

Zenclussen, A.C., Kökény, G., Thimm, O., Sollwedel, A., Godó, M., Casalis, P.A., Zenclussen, M.L., Volk, H.D. & Hamar, P (in press)
Flare of renal lupus during murine pregnancy is due to increased IgG and C3 glomerular deposition but is independent of Treg function.
Reproductive Bio. Medicine (RBM Online).

Kökény, G., Godó, M., Nagy, E., Kardos, M., Kotsch, K., Casalis, P., Bodor, C., Rosivall, L., Volk, H.D., Zenclussen, A.C. & Hamar, P (2007)
Skin disease is prevented but nephritis is accelerated by multiple pregnancies in autoimmune MRL/lpr mice.
Lupus 16(7): 465–477.

Rácz, Zs. & Hamar, P. (2006)
Can siRNA technology provide the tools for gene therapy of the future?
Curr. Med. Chem. (CMC) 13(19): 2299–2307.

Hamar, P., Song, E., Kökény, G., Chen, A., Ouyang, N. & Lieberman, J. (2004)
Short interfering RNA targeting Fas protects mice against renal ischemia-reperfusion injury.
Proc. Natl. Acad. Sci. USA 101(41): 14883–14888.

Hamar, P., Liu, S., Viklicky, O., Szabó, A., Müller, V. & Heemann, U. (2000)
Cyclosporine A and Azathioprine are equipotent in chronic kidney allograft rejection.
Transplantation 69: 1290–1295.

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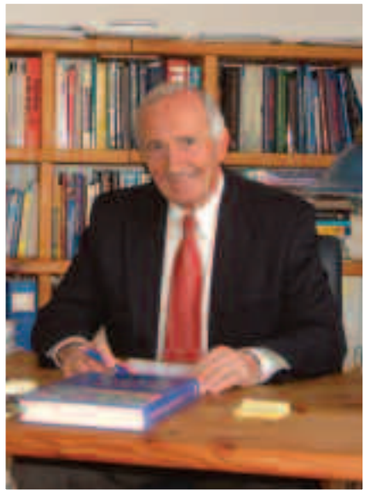

Márk Kollai, M.D., Ph.D., D.Sc.
Professor and Chair

Effect of arterial stiffness on cardiac baroreflex function

Background: The cardiac baroreflex represents a basic mechanism for short term blood pressure control, when changes in cardiac

Key words:

carotid stiffness
baroreflex
exercise
hypertension

function are affected through modulation of autonomic nervous activity. Baroreflex function influences vago–symphatetic balance and cardiac arrhythmic activity. Baroreflex sensitivity has been established as an independent cardiovascular risk factor. Sensitivity of the baroreflex is determined partly by neural mechanisms and partly by the distensibility of the vessel wall in which baroreceptors are embedded. Our recent research has focused on the contribution of carotid artery elasticity to baroreflex sensitivity (BRS).
Physiology: In young healthy volunteers BRS is directly related to carotid artery distensibility, a measure of vessel wall elasticity. Neural autonomic mechanisms mature in children, attaining peak level at adolescence, in spite of gradual carotid stiffening. During and after aerobic exercise the pressure–diameter transduction is closely related to changes in BRS, indicating importance of mechanical factors in baroreflex control during adaptive responses. Vitamin E supplementation of diet can significantly increase carotid compliance and BRS.
Pathopysiology: In young, trained subjects with a family history of hypertension, aerobic exercise training is associated with higher levels of BRS as compared to the sedentary lifestyle. BRS is reduced during pregnancy which is partly explained by increased carotid artery stiffness. Baroreflex function is markedly decreased in young adults on hemodialysis, which is partly due to loss of carotid artery elasticity; renal transplantation may prevent the impairment in baroreflex function. In patients with congenital heart disease carotid elastic variables indicate significant carotid artery stiffening which is not associated with reduced BRS. Congenital carotid stiffening might be compensated by central autonomic adaptation.

Recent publications:

Studinger, P., Lénárd, Zs., Mersich, B., Reusz, Gy. & Kollai, M. (2006)
Determinants of baroreflex function in juvenile end-stage renal disease.
Kidney International 69(12): 2236–2242.

Mersich, B., Studinger, P., Lénárd, Zs., Kádár, K. & Kollai, M. (2006)
Transposition of great arteries is associated with increased artery stiffness.
Hypertension 47: 1–6.

Lénárd, Zs., Studinger, P., Mersich, B., Pavlik, G. & Kollai, M. (2005)
Cardiovagal autonomic function in sedentary and trained offspring of hypertensive parents.
Journal of Physiology 565(3): 1031–1038.

Lénárd, Zs., Studinger, P., Mersich, B., Kocsis, L. & Kollai, M. (2004)
Maturation of cardio-vagal autonomic function from childhood to young adult age.
Circulation 110(16): 2307–2312.

Studinger, P., Lénárd, Zs., Kováts, Zs., Kocsis, L., & Kollai, M. (2003)
Static and dynamic changes in carotid artery diameter during and after strenuous exercise.
Journal of Physiology 550(2): 575–583.

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Laboratory of Tissue Engineering

Zsombor Lacza, M.D., Ph.D.

Key words:

stem cell
mitochondria
tissue engineering
cell fusion
ischemia-reperfusion

The focus of our laboratory, stem cell transplantation and tissue engineering offers novel approaches for the treatment of several diseases such as myocardial infarction or traumatic conditions with significant loss of tissue, which are difficult to treat in traditional ways. However, there are several known and suspected drawbacks which render the routine clinical applications not yet feasible. It is difficult to find an abundant source of pluripotent cells and it is problematic to make sure that the implanted stem cells will not turn into a malignant tumor. Therefore, better understanding of the behaviour of the stem cells is required before the therapeutic benefits of cell replacement therapies can be utilized. In our experiments using confocal microscopy and flow cytometry we have shown that addition of healthy cells to severely injured post-ischemic cardiomyocytes can rescue the majority of cells form death. Healthy mitochondria play a crucial role in this process either by restoring energy levels in the dying cells or by inhibiting cell death signals of damaged mitochondria. Currently we aim to: (1) identify and characterize amniotic stem cells, a novel source of human stem cells, (2) investigate mitochondrial transfer and partial cell fusion as an alternative route in the cellular mechanisms of stem cell therapy, (3) create novel 3-dimensional tissue engineering constructs for the replacement of bone tissue. We expect that optimization of the harvest and culture conditions of human amniotic stem cells will result in significant improvements in the use of these cells and new data will highlight the role nanotubes and mitochondrial transfer in stem cell therapy during oxidative stress and ischemia. Conclusions drawn from these experiments may markedly alter the current views of the therapeutic effect of stem cells since it provides a new alternative mechanism for host-graft interaction besides transdifferentiation and cellular fusion.

Recent publications:

Horváth, E.M., Lacza, Z., Csordás, A., Szabó, C., Kollai, M. & Busija, D.W. (2006) Graft derived cells with double nuclei in the penumbral region of experimental brain trauma. Neuroscience Letters 396(3): 182–186.

Busija, D.W., Lacza, Z., Rajapakse, N., Shimizu, K., Kis, B., Bari, F., Domoki, F. & Horiguchi, T. (2005) Targeting mitochondrial ATP-sensitive potassium channels – a novel approach to neuroprotection. Brain Research Reviews 46: 282–294.

Lacza, Z., Horn, T.F.W., Snipes, J.A., Zhang, J., Roychowdhury, S., Horváth, E.M., Figueroa, J.P., Kollai, M., Szabó, C. & Busija, D.W. (2004) Lack of mitochondrial nitric oxide production in the mouse brain. Journal of Neurochemistry 90: 942–951.

Lacza, Z., Snipes, J.A., Zhang, J., Horváth, E.M., Figueroa, J.P., Szabó, C. & D.W. Busija (2003) Mitochondrial nitric oxide synthase is not eNOS, nNOS or iNOS. Free Radical Biology and Medicine 35(10): 1217– 1228.

Lacza, Z., Snipes, J.A., Miller, A.W., Szabó, C., Grover, G. & Busija, D.W. (2003) Heart mitochondria contain functional ATP dependent K+ channels. Journal of Molecular and Cellular Cardiology 35(11): 1339–1347.

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Phagocyte Research Group

Erzsébet Ligeti, M.D., Ph.D.
Professor,
Member of the Hungarian Academy of Sciences

The aim of the research program is to investigate the regulation of NADPH oxidase, the enzyme responsible for superoxide (O_2^-) production, and its role in killing of bacteria by neutrophilic granulocytes (PMN).

Key words:

phagocytes
neutrophilic granulocytes
NADPH oxidase (NOX2)
small GTPases
GTPase activating proteins (GAPs)

We have demonstrated that the active, GTP-bound state of the small GTPase Rac is indispensable for continuous activity of NADPH oxidase. Hydrolysis of GTP to GDP reduces O_2^- production instantanously. In vivo this is achieved by GTPase activating proteins (GAPs). In PMN we have identified four different RacGAPs and demonstrated their role in constant down-regulation of NADPH oxidase activity. We discovered the regulation of the substrate specificity of p190GAP: acidic phospholipids inhibit the RhoGAP but accelerate the RacGAP activity of the protein. Phosphorylation by protein kinase C reverses the effect of phospholipids. In case of p50GAP we demonstrated that the protein is in an autoinhibited state that can be released by the prenyl tail of the small GTPase. We showed that in HeLa cells p50GAP localizes to the late endocytic vesicle population and participates in the regulation of receptor endocytosis.

O_2^- production is an electrogenic process that results in strong depolarization of activated phagocytes. We showed that plasma membrane depolarization is responsible for inhibition of Ca^{2+} entry into activated PMN and that cells deficient in any of the oxidase subunits (CGD) suffer serious alterations of Ca^{2+} metabolism. On the basis of careful quantitative analysis we revealed the correlation between O_2^- production, membrane depolarization, K^+ release and bacterial killing. We demonstrated that BK type K^+ channels are absent in PMN and do not play any role in the killing process. We propose that NADPH oxidase plays dual role in the antimicrobial defense: both the chemical effect of its product (O_2^- and its metabolites) and the ionic movement initiated by the electrogenic electron transfer contribute to successful elimination of microorganisms.

Recent publications:

Moskwa, P., Paclet, M-H., Dagher, M.-C. & Ligeti, E. (2005)
Autoinhibition of p50 Rho GTPase-activating protein (GAP) is released by prenylated small GTPases.
J. Biol. Chem. 280: 6716–6720.

Rada, B. K., Geiszt, M., Hably, C. & Ligeti, E. (2005)
Consequences of the electrogenic function of the phagocytic NADPH oxidase.
Phil. Trans. B 360: 2293–2300.

DeCoursey, T. & Ligeti, E. (2005)
Regulation and termination of NADPH oxidase activity.
Cellular and Molecular Life Sciences 62: 2173–2193.

Ligeti, E., Dagher, M.-C., Hernandez, S., Koleske, A.J. & Settleman, J. (2004)
Phospholipids can switch the GTPase substrate preference of a GTPase activating protein.
J. Biol. Chem. 279: 5055–5058.

Rada, B.K., Geiszt, M., Káldi, K., Timár, C. & Ligeti, E. (2004)
Dual role of phagocytic NADPH oxidase in bacterial killing.
Blood 104: 2947–2953.

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Inflammation Research Unit

Attila Mócsai, M.D., Ph.D.
Associate Professor

Key words:

inflammation
phagocytes
signaling
receptors

Our group analyzes the molecular mechanisms of phagocyte function and its role in various disease states such as autoimmune inflammation or osteoporosis. Ongoing projects in the lab include:
1) Signal transduction mechanisms in neutrophils. Using a gene-targeting approach, we are currently testing the role of various kinases (Src-family kinases, Syk, etc.) and other intracellular signaling molecules (e.g., PLCγ2, p190RhoGAP) in integrin- and Fc-receptor-mediated neutrophil functions. These studies will reveal novel receptor-proximal signal transduction processes likely involved in neutrophil-mediated inflammation.
2) Molecular mechanisms of osteoclast differentiation and function. In these studies, the development and bone-resorbing function of osteoclasts is being studied in the absence of various intracellular signaling molecules (Syk, PLCγ2, etc). We also attempt to associate these signaling molecules with specific cell surface receptors such as RANK, c-fms or β_3-integrins. These studies will reveal novel aspects of osteoclast-mediated bone resorption, likely involved in pathological bone loss during osteoporosis or autoimmune arthritis.
3) Molecular players of in vivo autoimmune inflammation. During this series of experiments, we test the contribution of the above signal transduction molecules (Src-family kinases, Syk, PLCγ2, etc.) to the development of autoimmune inflammatory diseases in vivo. We currently focus on autoantibody-induced arthritis but will extend these studies to other arthritis and glomerulonephritis models.
Our research activity will likely provide significant novel information on the molecular mechanisms of phagocyte-mediated inflammatory and bone diseases and will likely point to novel targets of pharmacological therapy.

Recent publications:

Jakus, Z., Németh, T., Verbeek, J.S. & Mócsai, A. (2008)
Critical but overlapping role of FcγRIII and FcγRIV in activation of murine neutrophils by immobilized immune complexes.
J. Immunol. 180: 618–629.

Jakus, Z., Fodor, S., Abram, C.L., Lowell, C.A. & Mócsai, A. (2007)
Immunoreceptor-like signaling by β_2 and β_3 integrins.
Trends Cell Biol. 17: 493–501.

Mócsai, A., Abram, C.L., Jakus, Z., Hu, Y., Lanier, L.L. & Lowell, C.A. (2006)
Integrin signaling in neutrophils and macrophages uses adaptors containing immunoreceptor tyrosine-based activation motifs.
Nat. Immunol. 7: 1326–1333.

Jakus, Z., Berton, G., Ligeti, E., Lowell, C.A. & Mócsai, A. (2004)
Responses of neutrophils to anti-integrin antibodies depends on costimulation through low-affinity FcγRs: full activation requires both integrin and nonintegrin signals.
J. Immunol. 173: 2068–2077.

Mócsai, A., Humphrey, M.B., Van Ziffle, J.A.G., Hu, Y., Burghardt, A., Spusta, S. C., Majumdar, S., Lanier, L. L., Lowell, C.A. & Nakamura, M.C. (2004)
The immunomodulatory adapter proteins DAP12 and Fc-receptor γ-chain (FcRγ) regulate development of functional osteoclasts through the Syk tyrosine kinase.
Proc. Natl. Acad. Sci. USA 101: 6158–6163.

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Emil Monos, M.D., Ph.D., D.Sc.
Professor Emeritus

Key words:

gravitational hypertension
vascular adaptation
vascular innervation
venous endothelium
venous myogenic response

Mechanism of adaptation to long-term orthostatic and anti-orthostatic gravitational loading in extremity veins and in the systemic circulation

Recently, a number of evidence has been provided to show that all three layers – the tunica intima, media, and adventitia – of rat hind limb veins respond to chronic orthostatic and in certain cases also to anti-orthostatic body position (a ground-base model of microgravity) with adaptive microvesicular, myogenic, and neural mechanisms, respectively. Vascular network properties adapt too. A part of these experimental results – e.g., microvesicular system of the venous endothelium, or enhanced myogenic response – has been verified also in human studies. In addition, using a new non-invasive method, developed by us for in vivo human investigations, fundamental information has been collected to characterize the distensibility of different healthy and diseased (e.g., postthrombotic) large veins in respect of the body position, intraluminal pressure, body region, and age.
Taking into consideration that the systemic arterial blood pressure responses to gravitation stress are decisive in ability of the whole organism to adapt, we developed combined techniques and protocols using telemetry, special tilt-cages, and appropriate conscious rat models for studying the nature and mechanism of short- and long-term cardiovascular reactions to orthostatic and anti-orthostatic effects. Interestingly, both of these body positions resulted in a hypertensive response which proved to be dependent on intact sympathetic innervation, and it was connected specifically with the gravitational effects. Non-specific stress could be excluded. Most probably, vestibulo-sympathetic reflex activation plays a role in this blood pressure response which calms down both during the head-up and the head-down tilting in a couple of days. (Number of original papers published in international journals during the last 5 years: 24.)

Recent publications:

Raffai, G., Csekő, Cs., Kocsis, L., Dézsi, L. & Monos, E. (2008)
Does long-term experimental antiorthostasis lead to cardiovascular deconditioning in the rat?
Physiol. Res. PMID: 18198992.

Monos, E., Raffai, G., Dörnyei, G., Nádasy, G. & Fehér, E. (2007)
Structural and functional responses of extremity veins to long-term gravitational loading or unloading – lessons from animal systems.
Acta Astronautica 60: 406–414.

Bérczi, V., Molnár, A.A., Apor, A., Kovács, V., Ruzics, C., Várallyai, C., Hüttl, K., Monos, E. & Nádasy, G.L. (2005)
Non-invasive assessment of human large vein diameter, capacity, distensibility and ellipticity in situ: dependence on anatomical location, age, body position and pressure.
Eur. J. Appl. Physiol. 95: 283–289.

Raffai, G., Fehér, E., Nádasy, G., Paku, S., Pogány, G., Tímár, F., Szende, B. & Monos, E. (2005)
Selective suppression of an endothelin and platelet-derived growth factor containing vesicular system in endothelium of rat saphenous vein by long-term orthostasis.
J. Vasc. Res. 42: 157–164.

Monos, E., Lóránt, M., Dörnyei, G., Bérczi, V. & Nádasy, G. (2003)
Long-term adaptation mechanisms in extremity veins supporting orthostatic tolerance.
News Physiol. Sci. 18: 210–214.

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Nephrology Research and Training Center

László Rosivall, M.D., Ph.D., D.Sc.
Professor

Key words:

renal function
microcirculation
signal transmission
juxtaglomerular apparatus
nanomedicine

Our research activities focus on the regulation of renal function and microcirculation under normal and pathological conditions, with the approach "from molecules to bedside". We have identified new morphological and functional phenomena of the juxtaglomerular apparatus and proven that the afferent arteriole is not a uniform vessel. Fenestrated endothelium and filtration were described and visualized in vivo in the distal, renin-granulated area for the first time. The short-loop feedback mechanism was demonstrated in the regulation of glomerular filtration. The development of nano-channels and regulation of permeability depend on angiotensin II and VEGF. To study kidney fibrosis we established an in vitro model of transforming growth factor-beta (TGF-beta) induced epithelial-mesenchymal transformation (EMT) in proximal tubular cells. In the presence of intact cell contacts, cells resist the transforming effect of TGF-beta. This led us to the "two-hit model": namely both epithelial cell injury and the presence of TGF-beta are necessary for the induction of EMT. In the regulation of EMT, we described a network of signaling molecules involving Rho G-proteins, the MAPK cascade, the SMAD pathway and the beta-catenin/TCF pathway. In SLE MRL/lpr mice, renal damage could not be prevented, unlike skin injuries, in response to intravenous immunoglobulin. Here pregnancy decreases the eruption of skin symptoms, augmenting lupus nephritis. We developed an in vitro complement activation model and noted that the supernatant of stimulated human lymphocytes contained a potent and natural complement inhibitor.
The results of these experiments open new scientific frontiers and may help better understand the regulation of glomerular dynamics, the renin-angiotensin system and the development of renal fibrosis. They can serve as the basis for new therapeutic approaches against progressive renal fibrosis and hypertension.

Recent publications:

Sebe, A., Leivonen, S.K., Fintha, A., Masszi, A., Rosivall, L., Kähäri, V.M., & Mucsi, I. (2008)
Transforming growth factor-β induced alpha-smooth muscle cell actin expression in renal proximal tubular cells in regulated by p38β mitogen activated protein kinase, extracellular signal regulated protein kinase 1,2 and the Smad signaling during epithelial-myofibroblast transdifferentiation.
Nephrol. Dial. Transplant. 23(5): 1537–1545.

Szebeni, J., Alving, C.R., Rosivall, L., Bünger, R., Baranyi, L., Bedöcs, P., Tóth, M. & Barenholz, Y. (2007)
Animal models of complement-mediated hypersensitivity reactions to liposomes and other lipid-based nanoparticles.
J. Liposome Res. 17(2): 107–117.

Rosivall, L., MirzaHosseini, S., Toma, I., Sípos, A. & Peti-Peterdi J. (2006)
Fluid flow in the juxtaglomerular interstitium visualized in vivo.
AJP: Renal Physiology 291: F1241–F1247.

Kispélyi, B., Lohinai, Z., Iványi, I., MirzaHosseini, S., Nyárasdy, I. & Rosivall, L. (2005)
The effect of local nitric oxide synthase inhibition on the diameter of pulpal arteriole in dental bond material-induced vasodilation in rat.
Life Sciences 77: 1367–1374.

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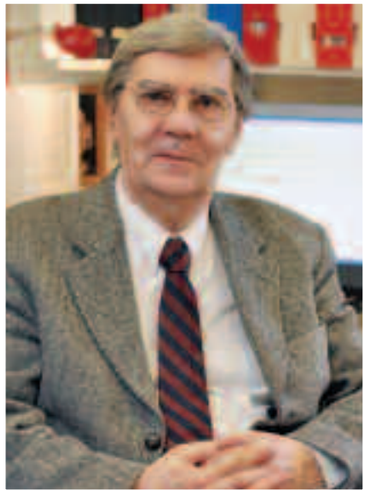
Laboratory of Cerebrovascular Research



Péter Sándor, M.D., Ph.D., D.Sc.
Professor

Key words:

cerebral blood flow
cerebral blood volume
CO_2-sensitivity
autoregulation
blood-brain barrier

Cerebrovascular diseases belong to the leading causes of death in Hungary. Rational therapy of these pathophysiologic disturbances can not be carried out without a detailed map about the main elements and mechanisms participating in the physiological regulation of the cerebral blood supply. Investigation of the role of perivascular nerves, NO, PARP enzyme and non-perikaryal elements of the brain (axons, oligodendrocytes, endothelial cells, blood-brain barrier) in the regulation of cerebral blood flow (CBF) is incomplete, especially in connection with diseases leading to brain ischemia: blood loss, circulatory shock, diabetes and stroke. Investigation of this regulatory role of the non-perikaryal elements was in the focus of our studies. The main findings, obtained in anesthetized animals, in cerebrocortical microvessels, or in endothelial cell cultures are as follows: (1) Vasodilatory action of the CO_2 in the cerebrovascular bed is mediated by nitric oxide [NO] (2) In brain ischemia, caused by severe arterial hypotension, the classic vasodilatory effect of CO_2 is reversed: increased $PaCO_2$ results in decreased CBF. (3) In the decompensated phase of the hemorrhagic shock the blood-brain barrier function is lost, mainly because the expression of occludin and cadherin is dramatically reduced. (4) Painful somatic afferent stimulation results in a significant increase of the regional cerebral blood flow (thalamus, somatosensory cortex) while total cerebral blood volume remains unchanged at the same time (5) Endothelium-dependent cerebral vasodilation is significantly reduced in insulin-resistant animals: this is a consequence of disturbed cyclooxigenase mediated processes, without simultaneous change in the NO-mediated vasodilatory processes. (6) The PARP enzyme plays an important role in the development of ischemic brain damage: selective blockade of PARP results in a significant decrease of the infarct area of the brain, both in the gray and in the white matter.

Recent publications:

Mersich, T., Szelke, E., Erdős, B., Lacza, Z., Komjáti, K. & Sándor, P. (2007)
Somatosensory pain does not affect total cerebral blood volume.
Neuroreport 18(7): 649–652.

Lenzser, G., Kis, B., Snipes, J.A., Gáspár, T., Sándor, P., Komjáti, K., Szabó, C. & Busija, D.W. (2007)
Contribution of poly(ADP-ribose) polymerase to postischemic blood-brain barrier damage in rats.
J. Cereb. Blood Flow Metab. 27(7): 1318–1326.

Erdős, B., Lacza, Z., Tóth, I.E., Szelke, E., Mersich, T., Komjáti, K., Palkovits, M. & Sándor, P. (2003)
Mechanism of pain-induced local cerebral blood flow changes in the rat sensory cortex and thalamus.
Brain Res. 960: 219–227.

Sándor, P., Reivich, M. & Komjáti, K. (2003)
Significance of endogenous opioids in the maintenance of cerebral and spinal vascular CO_2-sensitivity in deep hemorrhagic hypotension.
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Contribution of the heme oxygenase pathway to the maintenance of the hypothalamic blood flow during diminished NO synthesis.
J. Cereb. Blood Flow Metab. 23(6): 653–657.

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Member of the Hungarian Academy of Sciences

Key words:

calcium
signalling
mitochondria
aldosterone
glomerulosa

We have been studying the formation and effects of cytosolic Ca^{2+} signal for 25 years. After examining phosphoinositide metabolism, the formation of inositol trisphosphate (IP_3) in glomerulosa cells and the description of its receptor (1986), our attention shifted to the participation of mitochondria in the process of Ca^{2+} signalling. We were the first to describe the effect of cytosolic Ca^{2+} signal on the Ca^{2+}-dependent activation of mitochondrial dehydrogenases in intact cells (1992). In later studies we focused on the control of mitochondrial Ca^{2+} uptake. Although some of our data was compatible with the general view that high-Ca^{2+} microdomains are formed between the IP_3 receptor-channel in the endoplasmic reticulum and apposing mitochondria and these microdomains facilitate Ca^{2+} accumulation by mitochondria, we have also provided evidence that the low submicromolar Ca^{2+} signals can also induce net Ca^{2+} uptake by mitochondria in adrenal glomerulosa. Later we extended this observation to ovarian luteal and insulin producing tumour cells. Moreover, we observed that angiotensin II, a Ca^{2+} mobilising hormone, in addition to inducing mitochondrial Ca^{2+} signal via primarily inducing cytosolic Ca^{2+} signal, also exerts an inhibitory action on mitochondrial Ca^{2+} uptake. This inhibition is brought about by the simultaneous activation of p38 MAPK and a novel-type protein kinase C. The significance of this negative feed-back mechanism is presumably the protection of mitochondria from calcium overload that could otherwise result in apoptosis of the cell. Presently we are analysing the details of this inhibition.
Besides providing driving force for Ca^{2+} uptake mitochondrial oxidases are also sources of free radicals. To better understand the biophysical properties of such electron transfer systems, we use the phagocyte NADPH oxidase in electrophysiological measurements, focusing on the direct demonstration of reversed electron flow across oxidases.

Recent publications:

Szanda, G., Koncz, P., Rajki, A. & Spät, A. (2008)
Participation of p38 MAPK and a novel-type protein kinase C in the control of mitochondrial Ca^{2+} uptake.
Cell Calcium 43: 250–259.

Spät, A., Szanda, G., Csordás, Gy. & Hajnóczky, Gy. (2008)
High and low calcium-dependent mechanisms of mitochondrial calcium signalling.
Cell Calcium (published on-line: February 19, 2008, doi:10.1016/j.ceca.2007.11.015)

Szanda, G., Koncz, P., Várnai, P. & Spät, A. (2006)
Mitochondrial Ca^{2+} uptake with and without the formation of high-Ca^{2+} microdomains.
Cell Calcium 40: 527–537.

Pitter, J.G., Szanda, G., Duchen, M.R. & Spät, A. (2005)
Prostaglandin F2alpha potentiates the calcium dependent activation of mitochondrial metabolism in luteal cells.
Cell Calcium 37(1): 35–44.

Spät, A. & Hunyady, L. (2004)
Control of aldosterone secretion: a model for convergence in cellular signaling pathways.
Physiol. Rev. 84: 489–539.

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Cardiovascular and Volume Homeostasis Research Group of the Department of Health Sciences and Sportmedicine, Szentágothai János Knowledge Center

Miklós Tóth, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

cardiac hypertrophy
diabetes mellitus
physical training

Since 1985 our main scientific interest was on cardiovascular and volume homeostasis. Particular emphasis was put on natriuretic peptide research, and we succeeded in describing the intracellular mechanism of atrial natriuretic peptide (ANP) secretion. We have also proved that the negative feedback phenomenon is true for ANP release as well. Using direct cardiac gene transfer we located the stretch responsive elements in the promoter region of B-type natriuretic peptide (BNP) for the first time in vivo. Later our research involved other peptides as well, such as endothelin (ET), adrenomedullin (AM) and apelin (AP). We characterized the direct arrythmogenic effect of intracoronary and intrapericardial ET infusions, and showed for the first time that the human pericardial fluid can contain a 100-fold more ET as compared to human plasma. Members of our research group described the positive inotropic effect of AM and AP in isolated heart system and later we partially characterized the mechanisms of these effects, comparable to the catecholamine effect in magnitude. Extensive work was done on angiotensin II (AII) induced cardiac hypertrophy in healthy and diebetic rats. We described the antiproliferative effect of AII receptor type 2 in vivo in cardiac tissue. Lately we characterized the role NF-kappa-B and several kinases in the AII induced cardiac hypertrophy. Our current interest lies at the crossroads of physiological and pathological hypertrophy. We are about to set up a standard model of physical training in rats, which we shall combine with various disease models such as diabetes, myocardial infarction and cardiac hypertrophy.

Recent publications:

Sármán, B., Skoumal, R., Leskinen, H., Rysa, J., Ilves, M., Soini, Y., Tuukkanen, J., Pikkarainen, S., Lakó-Futó, Z., Sármán, B., Papp, L., deChatel, R., Tóth, M., Ruskoaho, H., & Szokodi, I. (2007)
Nuclear factor kappa B signaling contributes to severe, but not moderate angiotensin II-induced left ventricular remodeling.
J. Hypertension 25(9): 1927–1239.

Lengyel, C., Virág, L., Bíró, T., Jost, N., Magyar, J., Biliczki, P., Kocsis, E., Skoumal, R., Nánási, P., Tóth, M., Kecskeméti, V., Papp, J.G. & Varró, A. (2007)
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Cardiovasc. Res. 73(3): 512–520.

Ala-Kopsala, M., Ruskoaho, H., Leppaluoto, J., Seres, L., Skoumal, R., Tóth, M., Horkay, F. & Vuoilteenaho, O. (2005)
Single assay for amino-terminal fragments of cardiac A- and B-type natriuretic peptides.
Clin. Chem. 51(4): 708–718.

Lakó-Futó, Z., Szokodi, I., Sármán, B., Földes, G., Tokola, H., Ilves, M., Leskinen, H., Vuolteenaho, O., Skoumal, R., deChatel, R., Ruskoaho, H. & Tóth, M. (2003)
Evidence for a functional role of angiotensin II type 2 receptor int he cardiac hypertrophic process in vivo in the rat heart.
Circulation 108(19): 2414–2422.

Földes, G., Horkay, F., Szokodi, I., Vuolteenaho, O., Ilves, M., Lindstedt, K.A., Mayranpaa, M., Sármán, B., Seres, L., Skoumal, R., Lakó-Futó, Z., deChatel, R., Ruskoaho, H. & Tóth, M. (2003)
Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure.
BBRC 308(3): 480–485.

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Endoplasmic Reticulum Research Group

Gábor Bánhegyi, M.D., Ph.D., D.Sc.
Professor

The endoplasmic reticulum (ER) is a continuous membrane network in the cytosol. Its closed internal compartment, the ER lumen, can comprise about 10% of the total cell volume. Several metabolic pathways related to carbohydrate metabolism, biotransformation, steroid metabolism and protein processing are compartmentalized in the ER. The involved enzymes usually receive their substrates and cofactors from, or release their products to, the cytosol. Therefore, passage of those compounds across the ER membrane is indispensable. Moreover, these reactions often require a special microenvironment provided by the ER lumen. Since the lumen is regarded as a more oxidizing compartment than the cytosol, the regulation of its redox homeostasis is crucial. Our group has been interested in the study of intraluminal enzymatic processes, the corresponding transporters and luminal redox. In particular, the more important recent research topics are as follows:

Participation of small redox-active compounds in the electron transfer of the oxidative protein folding. Transport of pro- and antioxidants in the ER. Luminal redox homeostasis and ER stress.

The functioning of the glucose-6-phosphate transporter – hexose-6-phosphate dehydrogenase – 11β-hydroxysteroid dehydrogenase type 1 axis in the ER. Its role in preadipocyte differentiation and in the pathogenesis of the metabolic syndrome. Extra-hepatic manifestations of the system. Redox state and anti-apoptotic properties of the luminal pyridine nucleotide pool. Cross-talk between the pyridine nucleotide and thiol/disulfide redox systems.

Role of ER channels (e. g., translocon) in the non-specific low-affinity low-capacity transport of small molecules and ions. Contribution to the substrate supply of luminal enzymes.

Effect of phytopharmacons on the ER. Green tea flavanols as inhibitors of prereceptorial steroid hormone activation.

In vivo animal models of the redox-based ER stress and ER-dependent cell death. ER stress in anti-oxidant deficiency and in prooxidant dominancy.

Key words:

endoplasmic reticulum
redox homeostasis
transport
oxidative protein folding
11β-hydroxysteroid dehydrogenase type 1

Recent publications:

Csala, M., Marcolongo, P., Lizák, B., Senesi, S., Margittai, É., Fulceri, R., Magyar, É.J., Benedetti, A. & Bánhegyi, G. (2007)
Transport and transporters in the endoplasmic reticulum (review).
Biochim. Biophys. Acta – Biomembr. 1768: 1325–1341.

Bánhegyi, G., Benedetti, A., Csala, M. & Mandl, J. (2007) Stress on redox.
FEBS Lett. 581: 3634–3640.

Piccirella, S., Czegle, I., Lizák, B., Margittai, É., Senesi, S., Papp, E., Csala, M., Fulceri, R., Csermely, P., Mandl, J., Benedetti, A. & Bánhegyi, G. (2006)
Uncoupled redox systems in the lumen of the endoplasmic reticulum: pyridine nucleotides stay reduced in an oxidative environment.
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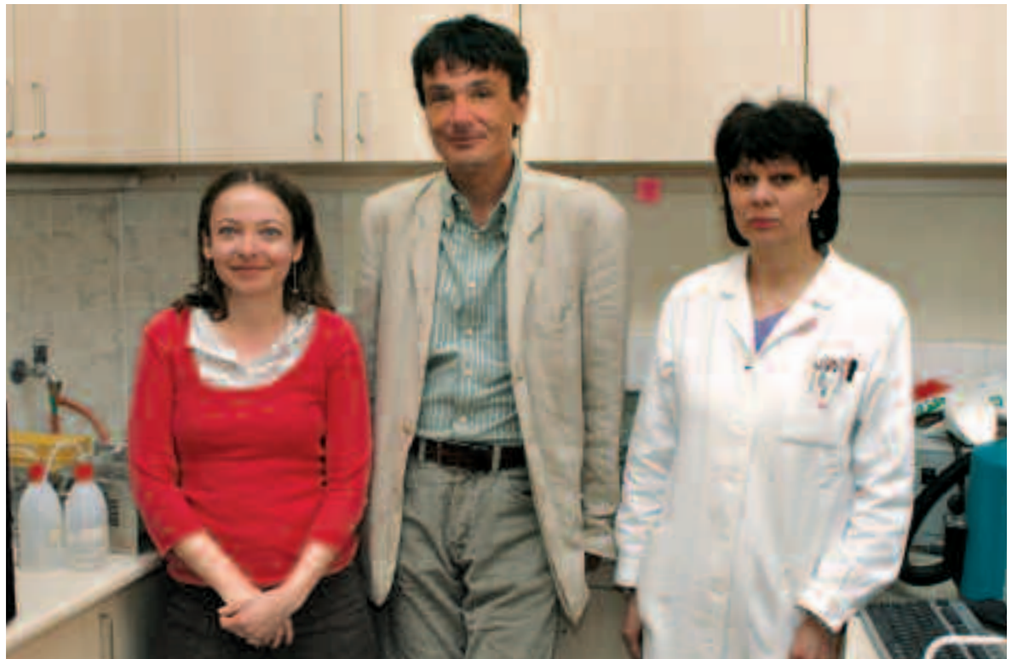
Csala, M., Bánhegyi, G. & Benedetti, A. (2006)
Endoplasmic reticulum: a metabolic compartment. (review)
FEBS Lett. 580: 2160–2165.

Lizák, B., Czegle, I., Csala, M., Benedetti, A., Mandl, J. & Bánhegyi, G. (2006)
Translocon pores in the endoplasmic reticulum are permeable to small anions.
Am. J. Physiol. – Cell Physiol. 291: C511–517.



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Signal Transduction Laboratory

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Key words:

tyrosine kinase
protein interaction
cortactin
scaffold protein
caskin

The Signal Transduction Laboratory focuses on tyrosine kinase signaling pathways, with particular interest on protein-protein interactions. Cortactin is a ubiquitous actin-binding protein that was originally identified as a substrate for the protein tyrosine kinase Src. It is accumulated in peripheral, actin-enriched structures of cells, including lamellipodia and membrane ruffles, suggesting that cortactin facilitates actin network formation. In addition, recent data suggest that it regulates various aspects of cell dynamics, including integrin signaling, vesicular transport, axon guidance, and cell migration. A large body of evidence indicates that cortactin is also implicated in the pathogenesis of human neoplasia. Using dominant negative constructs and siRNA techniques, our laboratory wishes to reveal the mechanism by which cortactin regulates integrin signaling and cell movement.

Caskin proteins belong to the family of large scaffold proteins participating in the formation of large multi-protein complexes at the post-synaptic density. Caskin1 has been identified through its interaction with Cask, an adaptor protein of the plasma membrane. The structure of Caskins suggests that they may interact with several other proteins, therefore, we searched for binding partners. Using a yeast two-hybrid technique several novel binding partners of Caskin-1 were identified. Currently, we validate and analyze those interactions. Finally, our laboratory will produce Caskin1, Caskin2, and double conditionally knock-out mice to study the physiological roles of this scaffold protein family in the brain.

Recent publications:

Buday, L. & Downward, J. (2007)
Roles of cortactin in tumor pathogenesis.
Biochim. Biophys. Acta
Reviews on Cancer 1775: 263–273.

Illés, A., Enyedi, B., Tamás, P., Balázs, A., Bögel, G. & Buday, L. (2006)
Inducible phosphorylation of cortactin is not necessary for cortactin-mediated actin polymerisation.
Cellular Signalling 18: 830–840.

Tompa, P., Szász, C. & Buday, L. (2005)
Structural disorder throws new light on moonlighting. TIBS 30(9): 484–489.

Várnai, P., Bondeva, T., Tamás, P., Tóth, B., Buday, L., Hunyady, L. & Balla, T. (2005)
Selective cellular effects of overexpressed pleckstrin-homology domains that recognize PtdIns(3,4,5)P_3 suggest their interaction with protein binding partners.
J. Cell Science 118: 4879–4888.

Tamás, P., Solti, Z., Bauer, P., Illés, A., Sipeki, S., Bauer, A., Faragó, A., Downward, J. & Buday, L. (2003)
Mechanism of EGF regulation of Vav2, a guanine nucleotide exchange factor for Rac.
J. Biol. Chem. 278: 5163–5171.

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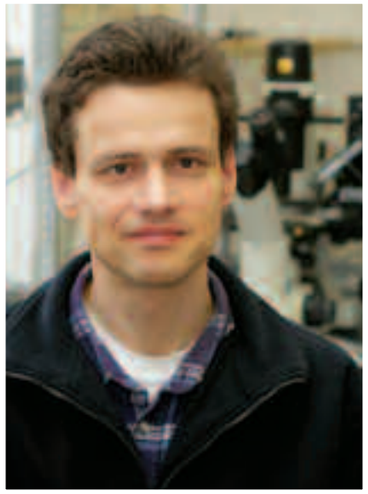
Laboratory of Ion Channel Research



László Csanády, M.D., Ph.D.
Assistant Professor

Gating of the CFTR chloride channel

CFTR is a chloride ion channel expressed at the apical surfaces of epithelia, where it regulates transepithelial salt and water movement. Defects in CFTR function, due to mutations, underlie the lethal inherited disease cystic fibrosis. CFTR belongs to the superfamily of ABC proteins, which couple hydrolytic cycles at conserved nucleotide-binding domains (NBDs) to diverse cellular functions. The 48 human ABC proteins are involved in insulin secretion, antigen presentation, cholesterol- and bile-salt transport, drug detoxification, and multidrug resistance. CFTR is unique among ABC proteins in that its transmembrane domains comprise an ion channel. This provides an opportunity to study individual conformational transitions of a native ABC protein by recording the ionic current which flows through its pore. Opening and closing of CFTR's ion-permeation pathway is controlled by dynamic dimerization-dissociation of its NBDs, driven by a cycle of ATP binding and hydrolysis. We study the various steps of this enzymatic cycle, and the conformational coupling between the catalytic site and the channel gate.

Key words:

patch-clamp
ion channel
gating
CFTR
TrpM2

Gating of the TrpM2 cation channel

TrpM2 ion channels are found in the plasma membrane and play a central role in the development of cell death following ischaemic brain injury. These Ca^{2+}-permeable nonselective cation channels are activated by ADP-ribose released from mitochondria, and modulated by other NAD metabolites, Ca^{2+}, and H_2O_2. The molecular mechanisms of these effects are unknown. The C-terminal domain of TrpM2 is an active ADP-ribose pyrophosphatase, but the role of this enzymatic activity is unclear. Our aim is to reveal the molecular mechanism by which binding of ligands and the enzymatic activity of the C-terminal domain regulate gating of the channel pore.

Our experimental approaches include recording and analysis of single-channel and macroscopic patch-clamp currents, site-directed mutagenesis, and protein biochemistry.

Recent publications:

Chan, K.W., Wheeler, A. & Csanády, L. (2008)
Sulfonylurea receptors type 1 and 2A randomly assemble to form heteromeric K_{ATP} channels of mixed subunit composition.
J. Gen. Physiol. 131: 43–58.

Csanády, L. (2006)
Statistical evaluation of ion-channel gating models based on distributions of LogLikelihood Ratios.
Biophys. J. 90: 3523–3545.

Gadsby, D.C., Vergani, P. & Csanády, L. (2006)
The ABC protein turned chloride channel whose failure causes cystic fibrosis.
Nature 440: 477–483.

Csanády, L., Nairn, A.C. & Gadsby, D.C. (2006)
Thermodynamics of CFTR channel gating: a spreading conformational change initiates an irreversible gating cycle.
J. Gen. Physiol. 128: 523–533.

Csanády, L., Chan, K.W., Nairn, A.C. & Gadsby, D.C. (2005)
Functional roles of nonconserved structural segments in CFTR's NH_2-terminal Nucleotide Binding Domain.
J. Gen. Physiol. 125: 43–55.

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Chaperone and Network Group

Péter Csermely, Ph.D., D.Sc.
Professor

Key words:

aging
chaperones
heat shock proteins
networks
stress

The research team has a long-standing expertise in stress protein (molecular chaperone) research. The group has discovered the ATP-binding properties and two ATP-binding sites of the 90 kDa heat shock protein (Hsp90) and contributed a lot to our understanding of the functions of this wide-spread chaperone of key importance in a growing number of anticancer therapies. We proposed and partially proved the concept of "chaperone-overload", i.e. the functional shortage of active, "damaged protein-free" molecular chaperones in stress and aged organisms. Péter Csermely is a leading figure of the chaperone field, who was involved in the delineation of the mechanism of action of the emerging class of novel drug-candidates, chaperone co-inducers. Csaba Sőti is a recognized expert in aging-research, who made significant advances in the recognition of the role of molecular chaperones in aging organisms and cells. The present research of the group is performed in two major areas: (1) role of stress proteins in ageing; and (2) analysis of the topology, dynamics and evolution of biological networks. In aging-related research we use cellular models and C. elegans to study the interdependence of the sirtuin-related and heat shock factor-dependent pathways. In network-related studies we proposed the 'weak-link concept', listing a large number of examples showing that weak links stabilize all networks from molecules to societies. We recently discovered the novel, integrative ModuLand method family to determine overlapping modules of complex systems. We use the modular analysis to determine the hot-spots of drug-target proteins, to discover novel drug targets in cellular networks including protein-protein interaction networks, metabolic networks and signal transduction networks. We also assess network dynamics by comparing the changes of hierarchical modules of various cellular networks in stress, aging and diseases.

Recent publications:

Putics, Á, Végh, E.M., Csermely, P. & Sőti, C. (2008)
Resveratrol induces the heat shock response and protects human cells from severe heat stress.
Antiox. Redox Signaling 10: 65–76.

Csermely, P. (2006)
Weak links: stabilizers of complex systems from proteins to social networks.
Springer Verlag, 392 pp.

Pál, C., Papp, B., Lercher, M.J., Csermely, P., Oliver, S.G. & Hurst, L.D. (2006)
Chance and necessity in the evolution of minimal metabolic networks.
Nature 440: 667–670.

Papp, E., Száraz, P., Korcsmáros, T. & Csermely, P. (2006)
Changes of endoplasmic reticulum chaperone complexes, redox state and impaired protein disulfide reductase activity in misfolding alpha-1-antitrypsin transgenic mice.
FASEB J. 20: 1018–1020,

Csermely, P., Ágoston, V. & Pongor, S. (2005)
The efficiency of multi-target drugs: the network approach might help drug design.
Trends Pharmacol. Sci. 26: 178–182.

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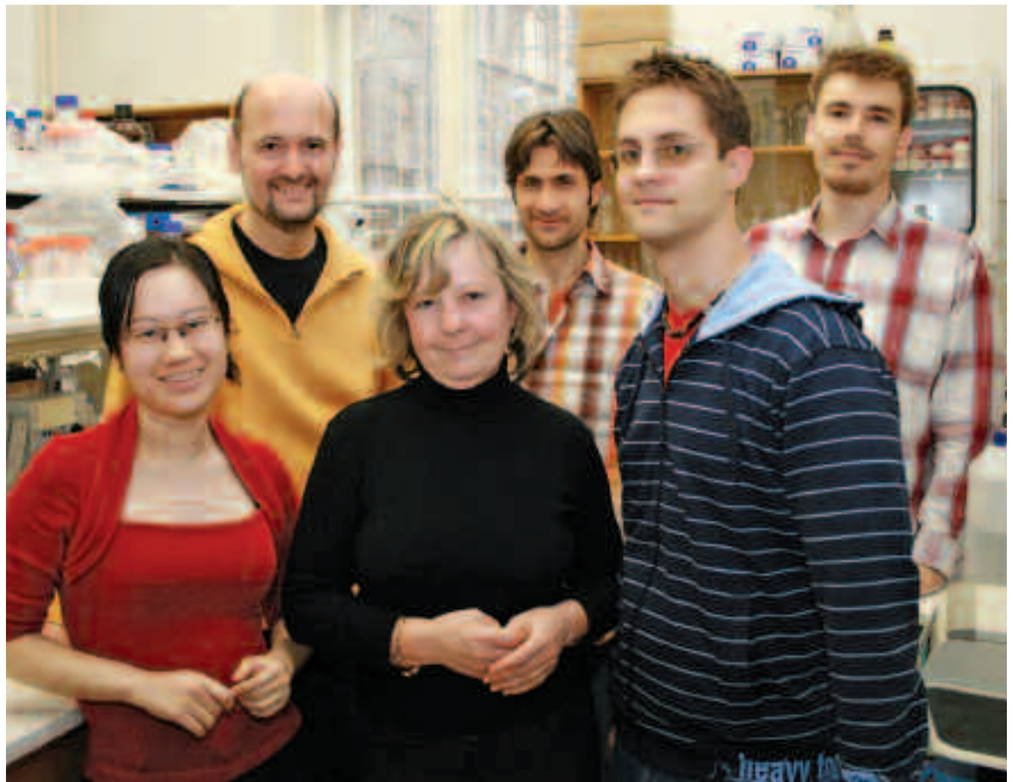

Drug – Target Interactions Unit

Gabriella Csík, Ph.D.
Associate Professor

In recent years, we have two main research topics: (1) Photodinamic inactivation of microbial systems; (2) targeting of antimicrobial drugs to M. tuberculosis.

Key words:

porphyrins
virus inactivation
drug targeting

ad1. For the better understanding of the mechanism of photodynamic inactivation it is necessary to have a deeper knowledge about the interaction of sensitizers with macromolecules of biological importance. Two main targets of photodynamic inactivation are the cellular membranes and nucleic acids. With the aim to study the effect of molecular structure on dye – DNA binding, a series of free base and metal complexed cationic porphyrins bearing 1–4 positive charges have been selected. T7 phage nucleoprotein (NP) serves as a model on which the structural and functional consequences of dark binding of drugs and consequent photoinduced reactions can be studied simultaneously. The structural studies can be extended also to isolated T7 DNA and nucleosomes so that the role of various DNA packaging conditions can be followed. The effect of the symmetry and polarity of the porphyrin molecules on their membrane localization and interaction with membrane lipids were investigated by fluorescent labeling of liposomes.
ad2. Tuberculosis is a devastating disease against which present countermeasures are clearly not enough. Isoniazid (INH) is a first-line drug for the inactivation of M. tuberculosis. Recently new INH derivatives were synthesized. Membrane-separated compartments are the main targets of these drugs and therefore their interactions constitute a particular focus. Our aim is the characterization of the molecular forces that govern complexation of candidate compounds with cellular membranes and target proteins.
Experimental techniques include: CD, absorption and emission spectroscopy, Dynamic Light Scattering, Differential Scanning Calorimetry, Isothermal Titration Calorimetry, PCR, microbiological titration; preparation of T7 bacteriophage with optical grade purity; preparation of liposomes with various techniques.

Recent publications:

Zupan, K., Egyeki, M., Tóth, K., Fekete, A., Herényi, L., Módos, K. & Csík, G. (2008)
Comparison of the efficiency and the specificity of DNA-bound and free cationic porphyrin in photodynamic virus inactivation.
J. Photochem. Photobiol. B (Biol.) 90: 105–112.

Egyeki, M., Tóth, K., Waldeck, W., Schmezer, P., Langowski, J. & Csík, G. (2006)
DNA damaging capability of hematoporphyrin derivative towards DNAs of various accessibilities.
J. Photochem. Photobiol. B. (Biol.) 84: 119–127.

Voszka, I., Szabó, Zs., Csík, G., Maillard, Ph. & Gróf, P. (2005)
Interaction of tetraphenyl-porphyrin derivatives with DPPC-liposomes: an EPR study.
J. Photochem. Photobiol. B. (Biol.) 79: 83–88.

Hudecz F., Bánóci Z. & Csík G. (2005)
Medium-sized peptides as built in carriers for biologically active compounds.
Med. Res. Rev. 25: 679–736.

Zupan, K., Herényi, L., Tóth, K., Majer, Z. & Csík, G. (2004)
Binding of cationic porphyrin to isolated and encapsidated viral DNA analyzed by comprehensive spectroscopic methods.
Biochemistry 43(28): 9151–9159.

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Technicians:
Mónika Drabant, Edit Völgyi

Functional Protein Dynamics Laboratory

Judit Fidy, Ph.D., D.Sc., Habil. Med.
Professor and Chair

Key words:

protein conformational dynamics

The vital role of protein conformational dynamics in their functioning has been recognized now more than 30 years ago. The hierarchy of the interactions between the atoms and atomic groups that build up the structure of macromolecules allows for a broad scale of conformational fluctuations both on a time scale and in their amplitudes. These internal motions of the conformation allow for ligands, substrates and antagonists to penetrate the volume of large proteins and diffuse to the active center, and equally, are needed for macromolecules to be able to interact with each other.

The research group applies both experimental and computational approaches to unravel the role of conformational dynamics in protein function, and the dynamic consequences of modifications.

Experimental techniques include: Fourier Transform Infrared and UV-VIS Absorption and Emission (fluorescence and phosphorescence) Spectroscopy – both time resolved and steady state methods, thermodynamic stability measurements, Dynamic Light Scattering, Isothermal Titration Calorimetry. Computational approaches rely on the 8-modul cluster SGI Altix 350, 2-processor PC-s, and an SGI workstation. The group performs molecular dynamics simulations using the CHARMM software package, and elaborates computational methods to describe the large scale, collective motions of proteins.

In recent years, the following proteins and problems have been studied: (1) Interpretation of the effect of various allosteric effectors of human hemoglobin on the cooperative oxygen binding; (2) Domain-domain interactions in phosphoglycerate kinase. Dynamic coupling of the domains in the folding and misfolding phenomena, dynamic conditions of substrate binding, optimization of conditions for designing L-nucleotide analog drug molecules that are efficiently phosphorylated by PGK; (3) Understanding the functional conformational changes of dUTPase.

Recent publications:

Balog, E., Laberge, M. & Fidy, J. (2007)
The influence of interdomain interactions on the intradomain motions in yeast phosphoglycerate kinase. A molecular dynamics study.
Biophys. J. 92: 1–8.

Schay, G., Smeller, L., Tsuneshige, A., Yonetani, T. & Fidy, J. (2006)
Allosteric effectors influence the tetrameric stability of both R and T states of hemoglobin A.
J. Biol. Chem. 281: 25972–25983.

Laberge, M., Kövesi, I., Yonetani, T. & Fidy J. (2005)
R-state hemoglobin bound to heterotropic effectors: models of the DPG, IHP and RSR13 binding sites.
FEBS Letters 579: 627–632.

Osváth, S., Köhler, G., Závodszky, P. & Fidy, J. (2005)
Asymmetric effect of domain interactions on the kinetics of folding in yeast phosphoglycerate kinase.
Protein Science 14: 1609–1616.

Laberge, M., Szigeti, K. & Fidy, J. (2004)
The charge transfer band in horseradish peroxidase correlates with heme in-plane distortions induced by calcium removal.
Biopolymers (Biospectroscopy) 74: 41–45.

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Laboratory of Molecular Endocrinology

László Hunyady, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

angiotensin II
cannabinoid receptors
G-protein-coupled receptors
receptor endocytosis
signal transduction

The type 1 (AT_1) angiotensin II receptor (AT_1R) has important roles in cardiovascular regulation and salt-water homeostasis, and drugs targeting the renin-angiotensin system are widely used in medicine. The aim of this laboratory is to reveal the relationship between the structure and function of AT_1Rs. Molecular biological and biophysical methods are employed to investigate these questions, including studies in expression systems using confocal microscopy, biochemical analysis of signal transduction and intracellular trafficking pathways, and resonance energy transfer methods. The results of the laboratory have provided evidence that AT_1R internalization is β-arrestin and dynamin dependent, and have identified and characterized the compartments involved in intracellular trafficking of the receptors after internalization. The research also focuses on the mechanisms of the signal transduction of angiotensin receptors, including studies on G-protein dependent and independent pathways, and receptor dimerization. The findings of this group have provided evidence that stimulation of AT_1R can cause diacylglycerol lipase-mediated activation of cannabinoid CB1 receptors, and current studies are aimed to elucidate the mechanism of this response. The laboratory participates in international collaborations, collaborative studies with clinical scientists to identify genetical abnormalities in endocrine or metabolic disorders and in a project aimed to develop compounds that modify the signal transduction for the treatment of cardiovascular diseases.

Recent publications:

Turu, G., Simon, A., Gyombolai, P., Szidonya, L., Bagdy, G., Lenkei, Z. & Hunyady, L. (2007)
The role of diacylgycerol lipase in constitutive and angiotensin AT1 receptor-stimulated cannabinoid CB1 receptor activity.
J. Biol. Chem. 282: 7753–7757.

Szidonya, L., Süpeki, K., Karip, E., Turu, G., Várnai, P., Clark, A.J.L. & Hunyady, L. (2007)
AT1 receptor blocker-insensitive mutant AT1A angiotensin receptors reveal the presence of G protein-independent signaling in C9 cells.
Biochem. Pharmacol. 73: 1582–1592.

Hunyady, L. & Catt, K.J. (2006)
Pleiotropic AT1 receptor signaling pathways mediating physiological and pathogenic actions of angiotensin II.
Mol. Endocrinol. 20: 953–70.

Gáborik, Zs. & Hunyady, L. (2004)
Intracellular trafficking of hormone receptors. Trends Endocrinol. Metab. 15:286-93, (2004).

Gáborik, Zs., Jagadeesh, G., Zhang, M., Spät, A., Catt, K.J. & Hunyady, L. (2003)
The role of a conserved region of the second intracellular loop in AT1 angiotensin receptor activation.
Endocrinology 144: 2220–2228.

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Hemostasis Group

Raymund Machovich, M.D., Ph.D., D.Sc.
Professor

Key words:

thrombolysis
fibrinolysis
platelet
endothelium
polymorphonuclear cell

The theme of the research activity is thrombolysis (dissolution of thrombi under physiological and pathological conditions). The main aim is to learn the fibrinolytic processes under in vivo condition. Fibrinolysis by the plasmin(ogen) system is rather well known in vitro, but how it is changed in compartments (between solid and fluid phase, where there are extreme alterations in reactions rates) is poorly understood. In a thrombus, besides fibrin and platelet there are other molecular and cellular components, which may modify fibrinolysis (plasminogen activation, fibrin degradation, plasmin inactivation) and their influences are also poorly described.
Therefore, the components, present in a human arterial thrombus removed by surgery, are studied with immuno-morphological methods, and their effect on fibrinolysis is determined in vitro by enzymology. According to our hypothesis and our preliminary experimentations, the role of endothelial cells, platelets (and their components), polymorphonuclear cells, immunoglobulins and the protease inhibitors of blood plasma seem to be reasonable for study.

Recent publications:

Rábai, Gy., Váradi, B., Longstaff, C., Sótonyi, P., Kristof, V., Timár, F., Machovich, R. & Kolev, K. (2007)
Fibrinolysis in a lipid environment: modulation through release of free fatty acids.
J. Thromb. Haemost. 5: 1265–1273.

Galántai, R., Módos, K., Fidy, J., Kolev, K. & Machovich, R. (2006)
Structural basis of the cofactor function of denatured albumin in plasminogen activation by tissue-type plasminogen activator.
Biochem. Biophys. Res. Commun. 341: 736–741.

Váradi, B., Kolev, K., Tenekedjiev, K., Mészáros, Gy., Kovalszky, I., Longstaff, C. & Machovich, R. (2004)
Phospholipid-barrier to fibrinolysis: role for the anionic polar head charge and the gelphase crystalline structure.
J. Biol. Chem. 279: 39863–39871.

Kolev, K., Tenekedjiev, K., Ajtai, K., Kovalszky, I., Gombás, J., Váradi, B. & Machovich, R. (2003)
Myosin: a non-covalent stabilizer of fibrin in the process of clot dissolution.
Blood 101: 4380–4386.

Kolev, K. & Machovich, R. (2003)
Molecular and cellular modulation of fibrinolysis.
Thromb. Haemost. 89: 610–621.

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Technicians:
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Pathobiochemistry Research Group of the Department of Medical Chemistry, Molecular Biology and Pathobiochemistry and the Hungarian Academy of Sciences, Szentágothai János Knowledge Center

József Mandl, M.D., Ph.D.
Professor and Chair,
Member of the Hungarian Academy of Sciences

György Kéri, Professor

Key words:

protein kinase
signal transduction therapy
angiogenesis
endoplasmic reticulum
neuroprotection

The research group has developed an original tumor-selective somatostatin analogue, TT-232, which successfully passed clinical phase II/a trial. The group has designed novel follow up compounds identifying the most important domains essential for biological activity. Some of the new compounds inhibit cell proliferation and neurogenic and non-neurogenic inflammation even more efficiently than TT232. Patent application has been filed. Utilization of the invention would result in a new non-steroid type anti-inflammatory drug.

More than 80 diseases are connected to insufficient angiogenesis. The research group successfully designed and developed two small molecular weight compounds of different type which are able to induce angiogenesis both in vitro and in vivo. The lead compound caused a 10-times enhancement in the generation of veins compared to the control. International patent application has been filed.

The group has participated in the development of novel peptidomimetic kinase inhibitors for various pathologically relevant targets.

The research group has an intensive cooperation with N-Gene Kft. in the field of development of hepato- and dermatoprotective agents. Our scientific approach is based on the recently revealed central role of endoplasmic reticulum stress in a wide variety of diseases. N-Gene developed an antidiabetic agent, which successfully passed clinical phase II trial. Our group investigated and proved the hepatoprotective effect of these compounds, which work was supported by an NKTH grant.

The endoplasmic reticulum related effects of the tea-flavanols was studied by the research group. The results show that epigallocatechin gallate efficiently inhibits a key enzyme in the processing and quality control of glycoproteins in the endoplasmic reticulum. The observed effect can lead to the accumulation of misfolded proteins in the lumen and to a consequent endoplasmic reticulum stress, which may contribute to the antitumor effect of the molecule.

Recent publications:

Bánhegyi, G., Benedetti, A., Csala, M. & Mandl, J. (2007)
Minireview Stress on redox.
FEBS Lett. 581: 3634–3640.

Nagy, G., Kardon, T., Wunderlich, L., Szarka, A., Kiss, A., Schaff, Zs., Bánhegyi, G. & Mandl, J. (2007)
Acetaminophen induces ER dependent signaling in mouse liver.
Arch. Biochem. Biophys. 459: 273–279.

Horváth, A., Kéri, Gy., Tóvári, J., Seprődi, J., Vántus, T., Tanai, H. et al. (2007)
Peptides for activation of angiogenesis, pharmaceutical compounds containing same and use of these compounds.
PCT announcement.
(International application No.: PCT/HU07/000095).

Helyes, Zs., Szabó, Á., Németh, J., Jakab, B., Pintér, E., Bánvölgyi, Á., Kereskai, L., Kéri, Gy. & Szolcsányi, J. (2004)
Antiinflammatory and analgesic effects of somatostatin released from capsaicin-sensitive sensory nerve terminals in Freund's adjuvant-induced chronic arthritis model of the rat.
Arthritis Rheum. 50: 1677–1685.

Szende, B., Horváth, A., Bökönyi, Gy. & Kéri, Gy. (2003)
Effect of a novel somatostatin analogue combined with cytotoxic drugs on human tumour xenografts and metastasis of B16 melanoma.
Br. J. Cancer 88: 132–136.

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Laboratory of Cell Biology, Section of Vascular Neurology

Zoltán Nagy, M.D., Ph.D., D.Sc.
Professor

Key words:

blood-brain barrier
neuroprotection
apoptosis
neuronal plasticity
early restenosis

Our research interests focus on two main fields: neuroprotection in the ischemic brain and investigation of the brain microvessel endothelium as a blood-brain barrier (BBB) model. We are experienced in the culture of different cell types, neuronal cells (PC12), fibroblasts, vascular smooth muscle cells, cells from early restenosis, and endothelial cells especially from human brain microvessel (HBEC). Furthermore transient and permanent brain ischemia models are used to study apoptosis and repair mechanisms of neurons in the ischemic penumbra. Different anti-apoptosis strategies, stem cell implantation, anti-apoptotic bcl genes transfer using adenovirus constructs and propargyl-amine molecules are tested after ischemia or hypoxia. Repair strategies are measured with behavioral tests. Different signal molecules are monitored with immunocyto(histo)chemical methods by confocal microscope. The protein expressions are detected with Western blot and ELISA. Genetic methods are completed our techniques. In the laboratory, a new double labeling method was developed to simultaneous measure of ROS and mitochondrial permeability pore opening. We described a reverse regulation of HBEC and myointimal hyperplasia cell proliferation by a heat-shock protein co-inducer after hypoxia.
Our previous endothelial studies demonstrate that the HBEC culture appears to be a relevant system to study the interaction between endothelial cells and the pathological factors (hypoxia, elevated level of inflammatory cytokines, hemostatic factors and lipids). Presently we are characterizing the expression of efflux transporters of the ATP binding-cassette superfamily on HBEC. We are modulating their expression and efflux activity in physiological and pathological circumstances. We are investigating the expression of different genes according to whether are constitutively or inducibly expressed in HBEC culture.

Recent publications:

Dénes, L., Bori, Z., Csonka, E., Entz, L. & Nagy, Z. (2008)
Reverse regulation of endothelial cells and myointimal hyperplasia on cell proliferation by a heatshock protein-coinducer after hypoxia.
Stroke 39(3): 1022–1024.

Óváry, Cs., Szegedi, N., May, Z., Gubucz, I. & Nagy, Z. (2007)
Comparison of stroke ward care versus mobile stroke teams in the Hungarian stroke database project.
Eur. J. Neurol. 14(7): 757–761.

Bali, B., Nagy, Z. & Kovács, K.J. (2007)
Oxygen-glucose deprivation-induced changes in organotypic cultures of the rat hippocampus.
Ideggyógy. Sz. 60(3/4): 140–143.

Pongrácz, E., Andrikovics, H., Csornai, M., Bernát, I.S. & Nagy, Z. (2006)
Contribution of the –455G/A polymorphism at beta-fibrinogen gene and of the Leiden mutation to hemorheological parameters in ischemic stroke patients.
Clin. Hemorheol. Microcirc. 35(1/2): 75–82.

Ágoston, V.A., Zádori, A., Demeter, K., Nagy, Z. & Madarász, E. (2005)
Studies on the use of NE-4C embryonic neuroectodermal stem cells for targeting brain tumour.
Neurosci. Res. 53(3): 331–342.

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Technicians:
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Inflammation Immunology Group

Edit Buzás, M.D., D.Sc.
Associate Professor

Research projects

I. The role of posttranslational modifications in autoimmunity:

Glycosylation. We are characterizing glycosidase expression pattern of the joints in rheumatoid arthritis and osteoarthritis. We are currently carrying out analysis of SNPs of glycosylation-related genes in search for association with rheumatoid arthritis. We perform database analysis combined with artificial neural network-based prediction of glycosylation in order to compare the glycosylation of normal human and bacterial proteins, known human autoantigens and human T cell epitopes. We are investigating the role of NO in regulation of the expression of galectins as well as other glycosylation-related genes.

Citrullination. Experiments are on their way to clarify the role of citrullination of the "shared epitope"-containing autologous cartilage aggrecan T cell epitopes in rheumatoid arthritis.

II. The immunoregulatory role of cell-derived microvesicles: microvesicles (exosomes, ectosomes and apoptotic bodies) are generated by cells upon activation and apoptosis-inducing signals, and are recognized as novel mediators of the intercellular communication. We are currently carrying out (1) basic structural studies on microvesicles, (2) studies that focus on basic functional aspects of the microvesicle-mediated intercellular communication and (3) on the in vivo function of cell-derived microvesicles.

III. The immunological roles of mast cells: Cross-linking the high affinity IgE receptors by IgE and antigen results in the activation of mast cells. As activated mast cells play a crucial role not only in allergy and asthma, but also in tumorigenesis, intestinal helminth infections, autoimmune diseases, such as rheumatoid arthritis. Our research group focuses on the identification of genes and stimulatory mechanisms that are novel in mast cells. To accomplish this aim, expression micro-array technology and a wide variety of molecular biological and immunological methods are applied.

Key words:

autoimmunity
arthritis
microvesicle
glycobiology
mast cell

Recent publications:

Koncz, A., Pásztói, M., Mazan, M., Fazakas, F., Buzás, E., Falus, A. & Nagy, G. (2007)
Nitric oxide mediates T cell cytokine production and signal transduction in histidine decarboxylase knockout mice.
J. Immunol. 179(10): 6613–6619.

Gilicze, A., Kőhalmi, B., Pocza, P., Keszei, M., Jaeger, J., Görbe, E., Papp, Z., Tóth, S., Falus, A. & Wiener, Z. (2007)
HtrA1 is a novel mast cell serine protease of mice and men.
Mol. Immunol. 44(11): 2961–2968.

Buzás, E., Hanyecz, A., Murad, Y., Hudecz, F., Rajnavölgyi, E., Mikecz, K. & Glant, T.T. (2003)
Differential recognition of altered peptide ligands distinguishes two functionally discordant (arthritogenic and nonarthritogenic) autoreactive T cell hybridoma clones.
J. Immunol. 171(6): 3025–3033.

Ortutay, Z., Polgár, A., Gömör, B., Géher, P., Lakatos, T., Glant, T.T., Gay, R.E., Gay, S., Pállinger, É., Farkas, C., Farkas, E., Tóthfalusi, L., Kocsis, K., Falus, A. & Buzás, E.I. (2003)
Synovial fluid exoglycosidases are predictors of rheumatoid arthritis and are effective in cartilage glycosaminoglycan depletion.
Arthritis Rheum. 48(8): 2163–2172.

Fitzpatrick, L.A., Buzás, E., Gagne, T.J., Nagy, A., Horváth, C., Ferencz, V., Mester, A., Kari, B., Ruan, M., Falus, A. & Bársony, J. (2003)
Targeted deletion of histidine decarboxylase gene in mice increases bone formation and protects against ovariectomy-induced bone loss.
Proc. Natl. Acad. Sci. USA 100(10): 6027–6032.

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National Angioedema Center

Henriette Farkas, M.D., Ph.D., D.Sc.
Associate Professor

The main focus of the Hungarian Angioedema Research Group is to study the pathophysiological mechanisms, genetic background, diagnosis, provoking factors and treatment of differential types of angioedema especially in the C1-inhibitor deficiency.

Key words:

angioedema
C1-inhibitor
complement
hereditary
deficiency

The most important findings:
Presentation of the first evident of Helicobacter pylori infection as a triggering factor of attacks in patients with hereditary angioedema (HAE). This result was confirmed by a multicenter study within the EU Concerted Action PREHAEAT Project.
Sex hormones play an important role in HAE. Predictive value of SHBG and progesterone levels in frequency of attacks were shown.
Creating a novel interactive, locus-specific mutation database of the C1-inhibitor gene (www.hae.biomembrane.hu). Mutation screening of the C1-inhibitor gene among Hungarian patients was performed.
Relationship exsists between the copy number of genes (C4A, C4B) encoding the fourth component of complement and the clinical course of HAE. We proved the efficacy and safety of human C1-inhibitor concentrate with retrospective analyis.
Strong correlation was found between the with C1-inhibitor (C1-INH) autoantibodies and the severity of disease in C1-INH concentrate naive patients.
The proatherogenic lipid profiles of danazol prophylaxis was demonstrated.
Our group participated in creating of international consensus algorithm for the diagnosis, therapy and management of HAE.
We established the European HAE Working Group in 1998 and launched a conference series. International C1-INH Deficiency Workshops have been organized since 1999 every second year. The 5th Workshop took place in 2007.
We initiated the HAENETWORK project which aims education, introduction of modern diagnostic methods and appropriate treatment modalities in different neighbouring countries. Up to now, assistance to establishing regional HAE Centers has been provided for Ukraine, Bulgaria, Macedonia, and Romania.

Recent publications:

Varga, L., Széplaki, G., Visy, B., Füst, G., Harmat, G., Miklós, K., Németh, J., Cervenák, L., Karádi, I. & Farkas, H. (2007)
C1-inhibitor (C1-INH) autoantibodies in hereditary angioedema. Strong correlation with the severity of disease in C1-INH concentrate naive patients.
Mol. Immunol. 44(6): 1454–1560.

Visy, B., Füst, G., Bygum, A., Bork, K., Longhurst, H., Bucher, C., Bouillet, L., Cicardi, M. & Farkas, H. (2007)
Helicobacter pylori infection as a triggering factor of attacks in patients with hereditary angioedema.
Helicobacter 12(3): 251–257.

Farkas, H., Jakab, L., Temesszentandrási, G., Visy, B., Harmat, G., Füst, G., Széplaki, G., Fekete, B., Karádi, I. & Varga L. (2007)
Hereditary angioedema: a decade of human C1-inhibitor concentrate therapy.
J. Allergy Clin. Immunol. 120(4): 941–947.

Farkas, H., Varga, L., Széplaki, G., Visy, B., Harmat, G. & Bowen, T. (2007)
Management of hereditary angioedema in pediatric patients.
Pediatrics 120(3): e713–e722.

Széplaki, G., Varga, L., Valantin, Sz., Kleiber, M., Karádi, I., Romics, L., Füst, Gy. & Farkas, H. (2005)
Adverse effects of danazol prophylaxis on the lipid profiles of hereditary angioedema.
J. Allergy Clin. Immunol. 115: 864–869.

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Immunogenomics and Immunomics of the Department of Genetics, Cell- and Immunobiology and the Hungarian Academy of Sciences, Szentagothai Janos Knowledge Center

András Falus, Ph.D.
Professor and Chair,
Member of the Hungarian Academy of Sciences

Key words:

immunogenomics
micro RNA
gene expression
cancer
immunoinformatics

The Imunogenomics Research Group primarily is involved in oncogenomic studies. The central question in the last years is the role of histamine in generation, maintenance and metastases of tumors. For these experiments, in vivo and in vitro models are used, including histidine decarboxylase (HDC) gene targeted mice and transfected cell lines. For gene transfection to murine melanoma cell lines HDC sense and antisense constructs are used. The influence of overexpressed HDC resulting in high histamine content is studied by microarray experiments studying the global expression of human genome. Our data show, that histamine reveals procarcinogenic effect on the tumors (melanoma, colorectal cancer). Based on gene pathway analysis new gene regulatory circuits pathways were identified, suggesting that histamine targets anti-cancer mechanisms at multiple points, through downregulating both insulin-like growth factor receptor expression, inhibitory TGF β production and anti-angiogenic fibulin-5, simultaneously. Several peptides cleaved by surface proteases from extracellular matrix were also proved to be involved in colorectal cancer spreading. Using surgical material from colon cancer, microarray experiments and gene pathway analysis identified that downregulation of insulin-like growth factor receptor expression on tumor tissue, leads to decrease of MDR1, an ABC transporter molecule. A definite shift of histamine receptor expression (suppression of H1 and H4 histamine receptor expression) was also found adenocarcinoma cells from colon tumor. The inhibition requires MAP kinase pathway. The in vivo genomic data were also confirmed by experiments carried out on human colon cancer cell lines. Moreover in adrenal cancer micro RNA (miRNA) pattern is examined, as well. Informatic analysis is performed in order to predict of the targets of elevated miRNA. The role of mast cells in cancer microenvironment is studied; too, several new genes (mostly serine proteases) were annotated affecting the growth of tumor.

Recent publications:

Pos, Z., Wiener, Z., Pocza, P., Rácz, M., Tóth, S., Darvas, Z., Molnár, V., Hegyesi, H. & Falus, A. (2008)
Histamine suppresses fibulin-5 and insulin-like growth factor-II receptor expression in melanoma.
Cancer Res. 68(6): 1997–2005.

Gilicze, A., Kőhalmi, B., Pocza, P., Keszei, M., Jaeger, J., Görbe, E., Papp, Z., Tóth, S., Falus, A. & Wiener, Z. (2007)
HtrA1 is a novel mast cell serine protease of mice and men.
Mol. Immunol. 44(11): 2961–2968.

Koncz, A., Pásztói, M., Mazan, M., Fazakas, F., Buzás, E., Falus, A. & Nagy, G. (2007)
Nitric oxide mediates T cell cytokine production and signal transduction in histidine decarboxylase knockout mice.
J. Immunol. 179(10): 6613–6619.

Pos, Z., Sáfrány, G., Müller, K., Tóth, S., Falus, A. & Hegyesi, H. (2005)
Phenotypic profiling of engineered mouse melanomas with manipulated histamine production identifies histamine H2 receptor and rho-C as histamine-regulated melanoma progression markers.
Cancer Res. 65: 4458–4466.

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Targeted deletion of histidine decarboxylase gene in mice increases bone formation and protects against ovariectomy-induced bone loss.
Proc. Natl. Acad. Sci. USA 100: 6027–6032.

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Research Group of Immunogenetic and Complement Investigations, 3rd Department of Internal Medicine, Szentágothai János Knowledge Center

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Key words:

stroke
myocardial infarction
complement
MHC
C4B

Main activities of the research group was concentrated in two topics: (1) association between some alleles and extended haplotypes in the central (class III) region of main histocompatibility complex (MHC) with some diseases with high morbidity and mortality; (2) role of the complement system in stroke and other cerebrovascular diseases.
Main findings of these studies:
Topic 1: (a) Serum C4 (fourth component of complement) protein concentrations correlate with C4 gene size and polygenic variations, and body mass index; (b) regular smoking is strongly associated with the 8.1 extended haplotype (AH8.1) mainly in women; (c) in patients with cystic fibrosis carriers of AH8.1 had a significantly delayed pulmonary colonization; (d) a novel method based on real-time PCR was worked out which allows counting of the copy numbers of the two genes (C4A and C4B) of the C4 protein; (e) a strong association was detected in the Icelandic and Hungarian populations between carrier state of low C4B gene copy number, and the susceptibility to coronary artery disease and myocardial infarction, this association, however, was restricted only those subjects who were smokers at the time of the investigation; (f) the short term (1 year) mortality of the patients with myocardial infarction was markedly and significantly higher among smoking carriers of low C4B copy number; (g) susceptibility of the AH8.1 carriers for colorectal cancer was significantly higher as compared to the non-carriers.
Topic 2: (a) Strong association was found between high serum concentration of the third component of complement (C3) with pre-existing severe coronary artery disease and new vascular events in women; (b) ischemia-reperfusion led to systemic complement activation after carotis endarterectomy operation; (c) early complement activation that occurs already during admission in patients with ischemic stroke was demonstrated, the intensity of complement activation is correlated with the unfavorable outcome of the stroke.

Recent publications:

Tóth, É. K., Kocsis, J., Madaras, B., Bíró, A., Pocsai, Zs., Füst, G., Blaskó, B., Karádi, I., Ádány, R. & Laki, J. (2007)
The 8.1 ancestral MHC haplotype is strongly associated with colorectal cancer risk.
Int. J. Cancer 121: 1744–1748.

Szilágyi, A., Blaskó, B., Szilassy, D., Füst, G., Sasvári-Székely, M. & Rónai, Z. (2006)
Real-time PCR quantification of human complement C4A and C4B genes.
BMC Genet. 7: 1.

Füst, G., Arason, G.J., Kramer, J., Szalai, C., Duba, J., Yang, Y., Chung, E.K., Zhou, B.,Blanchong, C.A., Lokki, M.L., Bodvarsson, S., Prohászka, Z., Karádi, I., Vatay, A., Kovács, M., Romics, L., Thorgeirsson, G. & Yu, C.Y. (2004)
Genetic basis of tobacco smoking: strong association of a specific major histocompatibility complex haplotype on chromosome 6 with smoking behavior.
Int. Immunol. 16(10): 1507–1514.

Széplaki, G., Prohászka, Z., Duba, J., Rugonfalvi-Kiss, S., Karádi, I., Kókai, M., Kramer, J., Füst, G., Kleiber, M., Romics, L. & Varga L. (2004)
Association of high serum concentration of the third component of complement (C3) with pre-existing severe coronary artery disease and new vascular events in women.
Atherosclerosis 177(2): 383–389.

Yang, Y., Chung, E.K., Zhou, B., Blanchong, C.A., Yu, C. Y., Füst, G., Kovács, M., Vatay, A., Szalai, C., Karádi, I. & Varga, L. (2003)
Diversity in intrinsic strengths of the human complement system: serum c4 protein concentrations correlate with c4 gene size and polygenic variations, hemolytic activities, and body mass index.
J. Immunol. 171(5): 2734–2745.

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Acute Phase Reaction Research Group

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Professor and Chair

Key words:

human fetuin A/alpha2HS glycoprotein
acute phase reactants
liver disease

The clinical significance of the negative acute phase reactant human fetuinA/alpha2HS glycoprotein

The acute phase reaction plays a crucial role in the organization and execution of the response to various injuries. Human fetuinA/alpha2HS glycoprotein (AHSG) a negative acute phase reactant: its serum concentration decreases during the acute phase reaction. AHSG is a multifunctional molecule. It accumulates in calcified tissues, inhibits extraosseal calcification, is in involved in embryonic tissue differentiation, facilitates phagocytosis and inhibits lymphocyte mitogenic response. In adults AHSG is produced by the liver parenchyma cells.

We found decreased serum AHSG concentration in chronic liver diseases (cirrhosis, fatty liver and tumors) but not in acute viral hepatitides. Low AHSG level was associated with high mortality rate in patients with alcoholic liver cirrhosis. Its 1-year predictive value was equal to that of the Child-Pugh and was better than the MELD scores. In chronic C virus hepatitis we observed a paradoxical alteration of acute phase reactants that returned to normal on successful therapy. This reflects that the virus modifies the acute phase response.

The rat analogue protein pp63 was shown to be a natural inhibitor of the insulin receptor tyrosine kinase (IRTK). We demonstrated that human recombinant AHSG inhibited the IRTK activity suggesting that AHSG may increase tissue insulin resistance. We found that serum AHSG was significantly higher in gestation diabetes (GDM) compared to non-diabetic pregnant women. We observed significant negative correlations between serum AHSG and anthropologic parameters of the newborn in GDM. With tumor necrosis factor alpha and leptin AHSG contributes to the insulin resistance of pregnancy and may negatively regulate embryonic development.

Now we focus on phosphorylated AHSG in obesity, metabolic syndrome and type 2 diabetes mellitus as tissue insulin resistance is probably associated with this form of the molecule.

Recent publications:

Kalabay, L., Gráf, L., Vörös, K., Jakab, L., Benkő, Zs., Telegdy, L., Fekete, B., Prohászka, Z. & Füst, G. (2007)
Human serum fetuin A/α2HS-glycoprotein level is associated with long-term survival in patients with alcoholic liver cirrhosis. Comparison with the Child-Pugh and MELD scores.
BMC Gastroenterology 7: 15.

Molvarecz, A, Prohászka, Z., Nagy, B., Kalabay, L., Szalay, J., Füst, G., Karádi, I. & Rigó, J. Jr. (2007)
Association of increased serum heat shock protein 70 and C- reactive protein concentrations and decreased serum alpha2-HS glycoprotein concentration with the syndrome of hemolysis, elevated liver enzymes and low platelet count.
J. Reprod. Immunol. 73: 172–179.

Kalabay, L., Prohászka, Z., Füst, G., Benkő, Zs., Telegdy, L., Szalay, F., Tóth, K., Gráf, L., Jakab, L., Pozsonyi, T., Arnaud, P., Fekete, B. & Karádi, I. (2005)
Human fetuin/α2HS-glycoprotein levels in sera of patients with liver disease.
Pp. 63–75 in: **Chen, T.M.** (ed.), Liver Cirrhosis: New Research. Nova Science Publ. Inc., Hauppauge, New York, USA.

Kalabay, L., Nemesánszky, E., Csepregi, A. Pusztay, M., Dávid, K., Horváth, G., Ibrányi, E., Telegdy, L., Pár, A., Bíró, A., Fekete, B., Gervain, J., Horányi, M., Ribiczey, P., Csöndes, M., Kleiber, M., Walentin, Sz., Prohászka, Z. & Füst, G. (2004)
Paradoxic alteration of acute phase protein levels in patients with chronic hepatitis C treated with interferon-α-2b.
Int. Immunol. 16: 51–54.

Kalabay, L., Cseh, K., Pajor, A., Baranyi, É., Csákány, Gy.M., Melczer, Zs., Speer, G., Kovács, M., Siller, Gy., Karádi, I. & Winkler, G. (2002)
Correlation of maternal serum fetuin/α2-HS-glycoprotein concentration with maternal insulin resistance and anthropometric parameters of neonates in normal pregnancy and gestational diabetes.
Eur. J. Endocrinol. 147: 243–248.

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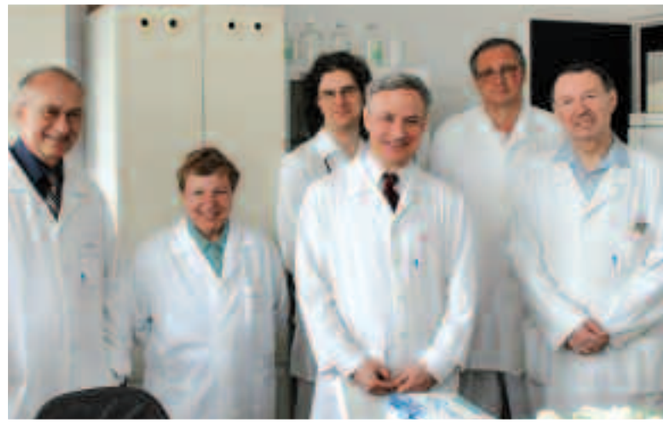

Immunology Laboratory of Pulmonary Diseases

György Losonczy, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

asthma
autoimmune lung disease
rejection
immunosuppression
T cells

During recent years we have successfully demonstrated new cellular immunological interactions between mechanisms maintaining bronchial asthma and those activated be pregnancy. T lymphocytes of pregnant asthmatics are able to release larger amounts of cytokines like interferon-gamma and interleukin-4. These observations may lead to better understand the mechanism along which pregnancy impairs asthma. Our later similar studies indicated, that the number of activated CD4 and CD8 T cells, NK T cells, NK as well as B cells remain unchanged in asthmatic pregnant versus healthy pregnant women. This contrast with the non-pregnant state, when asthma induces doubling of activated pool of these lymphocyte subsets. We were the first to demonstrate these pregnancy-specific modifications of the pathogenesis of asthma (about 7% of pregnant women suffer from asthma). In an experimental asthma model in mice we have created a new, steroid resistant form of allergic asthma by timed treatment of allergic asthmatic mice by bacterial endotoxin. In this study we have also shown that specific inhibition of iNOS is a strong inhibitor of airway hyperresponsiveness. The other line of our immunological research is transplantation immunology. Recently we have published on neuronal NOS, sex differences and single nucleotide polymorphisms in tracheal and kidney transplant rejection. Currently our cell immunological investigations have been extended to pulmonary sepsis and lung cancer.

Recent publications:

Müller, V., Molnár, Z. & Szabó, A. (2007)
Single nucleotide polymorphism: is it only genetic palmistry?
Transplantation 84: 1.

Komlósi, Zs.I., Pozsonyi, E., Tabi, T., Szökő, E., Nagy, A., Bartos, B., Kozma, G.T., Tamási, L., Orosz, M., Magyar, P. & Losonczy, Gy. (2006)
Lipopolysaccharide exposure makes allergic airway inflammation and hyperresponsiveness less responsive to dexamethasone and inhibition of iNOS.
Clin. Exp. Allerg. 36: 951–959.

Losonczy, Gy., Bohács, A., Komlósi, Zs., Tamási, L., Rigó, J., Müller, V. Magyar, P. (2006)
Allergia és immunstimuláció terhességben.
Medicina Thoracalis 40: 37–47.

Tamási, L., Bohács, A., Pállinger, É., Falus, A., Rigó, J., Müller, V., Komlósi, Zs.I., Magyar, P. & Losonczy, Gy. (2005)
Increased interferon-gamma and interleukin-4 synthesizing subsets of circulating T lymphocytes in pregnant asthmatics.
Clin. Exp. Allerg. 35: 1197–1203.

Losonczy, Gy., Kriston, T., Szabó, A., Müller, V., Harvey, J., Hamar, P., Heemann, U. & Baylis, C. (2000)
Male gender predisposes to development of endotoxic shock in the rat.
Cardiovasc. Res. 47: 183–191.

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Sarolta Kárpáti, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

autoimmune skin specific disorders
genodermatoses
pharmacogenomics
pathogen-drug interactions
genomics of skin tumors

In 2007 the research group created a software for its pharmacogenomic biobank and database in active collaboration with the Pázmány Péter Catholic University Faculty of Information Technology, the Hungarian Academy of Sciences Research Group for Veterinary Medicine and with the Laboratory of Toxicology of the Semmelweis University Department of Forensic Medicine. In collaboration with the Rt. Europe Ltd. and the Roche Diagnostics Division we are developing a laboratory unit of pharmacogenomics with both diagnostic and research capabilities.

Within this multicentric facility we aim to carry out pharmacogenomic genotyping and phenotyping to determine metabolic factors in individuals before chronic or "dangerous" medication is administered (medication by drugs that are known to provoke certain severe adverse reactions) or even before a strategy for therapy is devised. This unit will serve as a medical service unique in the Central Hungarian region. The growing knowledge on genetically determined metabolic factors will facilitate decreasing the possibility of life threatening drug side effects.

Diagnostics include complete genotyping and phenotyping of the CYP2D6, CYP2C8/9 and CYP2C18/19 gene systems, and determination of certain polymorphisms of the NAT1/NAT2 genes with phenotyping of acethylation-metabolization speed via HPLC. Further research will complete the diagnostic palette with the enzyme system CYP3A4/5, and also the full genotyping analysis of NAT1 and NAT2. This research work is based on our clinical experiences dealing with many patients with drug induced diseases, majority of them manifest in skin symptoms.

Recent publications:

Blazsek, A., Silló, P., Ishii, N., Gergely, P. Jr., Poor, Gy., Preisz, K., Hashimoto, T., Medvecz, M. & S. Kárpáti (in press)
Searching for foreign antigens as possible triggering factors of autoimmunity: Torque Teno virus DNA prevalence is elevated in sera of patients with bullous pemphigoid
Exp. Dermatol.

Wunderlich, L., Paragh, G., Wikonkál, N. M., Bánhegyi, G., Kárpáti, S. & Mandl, J. (2008)
UVB induces a biphasic response of HIF-1alpha in cultured human keratinocytes.
Exp. Dermatol. 17(4): 335–342.

Sárdy, M., Csikós, M., Geisen, C., Preisz, K., Kornseé, Z., Tomsits, E., Töx, U., Hunzelmann, N., Wieslander, J., Kárpáti, S., Paulsson, M. & Smyth, N. (2007)
Tissue transglutaminase ELISA positivity in autoimmune disease independent of gluten-sensitive disease.
Clin. Chim. Acta 376(1/2): 126–135.

Marschalkó, M., Csomor, J., Erős, N., Szigeti, A., Hársing, J., Szakonyi, J., Désaknai, M., Matolcsy, A., Demeter, J. & Kárpáti, S. (2007)
Coexistence of primary cutaneous anaplastic large cell lymphoma and mycosis fungoides in a patient with B-cell chronic lymphocytic leukaemia.
Br. J. Dermatol. 157(6): 1291–1293.

Rácz, E., Kornseé, Z., Csikós, M., Dobos, M., Salacz, P. & Kárpáti, S. (2006)
Darier's disease associated with cutis verticis gyrata, hyperprolactinaemia and depressive disorder.
Acta Derm. Venereol. 86(1): 59–60.

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Zoltán Prohászka, M.D., D.Sc.
Associate Professor

The hypothesis that multiple risk factors and interactions between genetic and environmental factors are involved in the predisposition to multifactorial diseases is well supported by our understanding of their pathomechanisms. The development of statistical methods to analyze thousands of genetic and biochemical markers in clinical studies, however, have not kept pace with the progress of high-throughput technologies. Furthermore, biostatistical strategies are underdeveloped to analyze complex interactions in clinical studies.

The aim of our group is to introduce a data-mining tool, described in operations-research for non-medical applications, into medical research, allowing the analysis of complex interactions. This goal will be achieved by the organization of a model clinical study and determination of large number of genetic and biochemical markers. Chronic heart failure is investigated to build up a large database containing pathway-based genomic data together with detailed clinical characteristics, phenotypes and outcomes. Analysis of this database will be done by logical analysis of data (LAD). LAD is able to describe patterns of interacting variables with high power to predict phenotypes/outcomes. The components (molecular-, or other types of interactions) of predictive patterns obtained in LAD models will be checked and biologically validated in new studies including functional genetic, endothelial cell-based-, and immunochemical assays to delineate the molecular interactions within the models. As a result, interaction based risk-stratification models, together with mechanism of action, will be obtained for characterization of clinical phenotypes; for prediction of outcomes. Furthermore, the improved LAD software may fuel follow-up research in a wide spectrum of applications where identification of interacting variables is the cardinal question. We are looking forward to get contact with interested groups to apply LAD on their databases.

Key words:

data mining
clinical studies
genetics
bioinformatics
endothelial cells

Recent publications:

Gombos, T., Förhécz, Zs., Pozsonyi, Z., Jánoskuti, L. & Prohászka, Z. (in press)
Interaction of serum 70-kDa heat shock protein levels 5 and HspA1B (+1267) gene polymorphism with disease 6 severity in patients with chronic heart failure.
Cell. Stress Chap.

Szabó, A., Laki, J., Madsen, H.O., Dósa, E., Prohászka, Z., Rugonfalvi-Kiss, S., Kókai, M., Acsádi, G., Karádi, I., Entz, L., Selmeci, L., Romics, L., Füst, G., Garred, P. & Cervenak, L. (2007)
Early rise in serum VEGF and PDGF levels predisposes patients with a normal MBL2 genotype to restenosis after eversion endarterectomy.
Stroke 38(8): 2247–2253.

Széplaki, G., Varga, L., Laki, J., Dósa, E., Rugonfalvi-Kiss, S., Madsen, H.O., Prohászka, Z., Kocsis, A., Gál, P., Szabó, A., Acsády, G., Karádi, I., Selmeci, L., Garred, P., Füst, G. & Entz, L. (2007)
Low c1-inhibitor levels predict early restenosis after eversion carotid endarterectomy.
Arterioscler. Thromb. Vasc. Biol. 27(12): 2756–2762.

Jánoskuti, L., Förhécz, Z., Hosszúfalusi, N., Kleiber, M., Walentin, S., Bálint, O., Duba, J., Rugonfalvi-Kiss, S., Romics, L., Karádi, I., Füst, G. & Prohászka, Z. (2005)
High levels of C-reactive protein with low total cholesterol concentrations additively predict all-cause mortality in patients with coronary artery disease.
Eur. J. Clin. Invest., 35(2): 104–111.

Oroszlán, M., Herczenik, E., Rugonfalvi-Kiss, S., Roos, A., Nauta, A.J., Daha, M.R., Gombos, I., Karádi. I., Romics, L., Prohászka, Z., Füst, G. & Cervenak, L. (2006)
Proinflammatory changes in human umbilical cord vein endothelial cells can be induced neither by native nor by modified CRP.
Int. Immunol. 18(6): 871–878.

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Szigeti Antalné

Experimental Renal Research Group

Attila J. Szabó, M.D., Ph.D.
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Our research focuses on the pathophysiology and treatment possibilities of ischemia/reperfusion (I/R) induced renal failure and kidney transplantation. We also study the molecular genetics and functional aspects of gender differences.

Key words:

kidney
ischemia/reperfusion
transplantation
gender
erythropoietin

We presented first that female gender and estradiol improves survival and attenuates renal tissue damage following renal I/R injury. We demonstrated that females are more protected from the functional disorders of Na^+,K^+ ATPase enzyme caused by loss of tubular polarity. Our data suggest that heat shock protein (HSP) 72 plays a major part in the reintegration of Na^+,K^+ ATPase.

We are working in several areas: (1) importance of erythropoietin treatment related to renal I/R injury and kidney transplantation; (2) role of sex hormones and gender in control and progression of renal failure; (3) mechanisms of HIF-HSP pathway, with particular interest in erythropoietin susceptibility as part of long-term graft survival; (4) role of nitric oxide in control of kidney function and renal ischemic susceptibility; interactions with other systems, such as PI3-kinase/SGK1 pathway.

We use a variety of techniques. Animal studies involve rat models of: (1) I/R injury; (2) kidney transplantation; (3) experimental ureter obstruction. Blood sampling and urine collection allows to look at electrolyte-water homeostasis and responses to several agents following animals longitudinally through evolving kidney disease. In vitro techniques are: cell culture, cloning strategies, siRNA. mRNA expression by real-time PCR and protein levels by Western-blot are used to quantify of molecular changes. We use histochemical staining and confocal laser scanning microscopy. In collaboration with laboratories we evaluate biochemical assays on enzyme activity and have access to FACS analysis.

Our research may help to improve the ability of the kidney to tolerate I/R damage. Furthermore possible gender differences might change our existing therapeutic protocols in everyday clinical therapy.

Recent publications:

Müller, V., Szabó, A.J., Erdély, A., Tain, Y. L. & Baylis, C. (in press)
Sex differences in response to cyclosporine immunosuppression in experimental kidney transplantation.
Clin. Exp. Pharmacol. Physiol.

Fekete, A., Vannay, A., Vér, A., Rusai, K., Müller, V., Reusz, G., Tulassay, T. & Szabó, A.J. (2006)
Sex differences in heat shock protein 72 expression and localization in rats following renal ischaemia-reperfusion injury.
Am. J. Physiol. Renal Physiol. 291(4): F806–F811.

Fekete, A., Vannay, A., Vér, A., Vásárhelyi, B., Müller, V., Ouyang, N., Reusz, G., Tulassay, T. & Szabó, A.J. (2004)
Sex differences in the alterations of Na^+/K^+-ATPase following ischemia/reperfusion injury in the rat kidney.
J. Physiol. (London) 555(2): 471–480.

Szabó, A. J., Wagner, L., Erdély, A., Lau, K. & Baylis, C. (2003)
Renal neuronal nitric oxide synthase protein expression as a marker of renal injury.
Kidney Int. 64(5): 1765–1771.

Müller, V., Losonczy, G., Heemann, U., Vannay, A., Fekete, A., Reusz, G., Tulassay, T. & Szabó, A.J. (2002)
Sexual dimorphism in renal ischemia-reperfusion injury in rats: possible role of endothelin.
Kidney Int. 62(4): 1364–1371.

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Clinical Genomics Unit

Csaba Szalai, Ph.D., D.Sc.

Our research group began to work in the field of the investigation of the genetic background and pathomechanism of asthma and allergy in 1999. First we started with the collection of blood, DNA and clinical data from children with allergy, asthma and from healthy children.

Key words:

genomics
SNP
asthma
allergy
oncology

Presently we have genomic DNA and clinical data from 425 children with asthma, 150 allergic, but without asthma and 300 healthy controls. First, we investigated selected polymorphisms in candidate genes for association with asthma or allergy. Later we studied several genetic polymorphisms, whether they influence the susceptibility to asthma in individuals infected with Chlamydia pneumoniae or Mycoplasma pneumoniae. We have also developed a mouse model of allergic airway inflammation, with similar symptoms as the human asthma. We have used histidine decarboxylase gene-targeted (HDC KO) mice, lacking histamine, to investigate the effect of histamine deficiency on the development of asthma. Presently we carry out partial genome screenings in asthma and allergy in chromosome regions of 11q13, 14q22 and 17q12–21 with a high-throughput genotyping method. These are regions earlier found to be associated with asthma, but the exact causative variations are still unknown.

Our other research focus is the genetic, genomic and pharmacogenomic study of acute lymphoblastic leukemia, testicular cancer and osteosarcoma. We have collected DNA samples and clinical data from more than 700 patients. We investigate several polymorphisms and haplotypes in candidate genes, whether they influence the susceptibility to the disease or the effect or side effects of the applied therapy. Presently, we study, whether 48 SNPs in 11 genes, involved in the metabolism of Vincristin, influence the effect of the chemotherapy. We are also planning to screen the genes involved in the metabolism of methotrexate for SNPs with our high-throughput genotyping system, and analyze their effect on the chemotherapy.

Recent publications:

Erdélyi, D.J., Kámory, E., Csókay, B., Andrikovics, H., Tordai, A., Kiss, C., Félné-Semsei, Á., Janszky, I., Zalka, A., Fekete, G., Falus, A., Kovács, G. T. & Szalai, Cs. (in press)
Synergistic interaction of ABCB1 and ABCG2 polymorphisms predicts the prevalence of toxic encephalopathy during anticancer chemotherapy.
Pharmacogenomics J.

F. Semsei, Á., Erdélyi, D.J., Ungvári, I., Kámory, E., Csókay, B., Andrikovics, H., Tordai, A., Cságoly, E., Falus, A., Kovács, G.T. & Szalai, Cs. (in press)
Association of some rare haplotypes and genotype combinations in the MDR1 gene with childhood acute lymphoblastic leukaemia.
Leukemia Res.

Ungvári, I., Tölgyesi, G., F. Semsei, Á., Nagy, A., Radosits, K., Keszei, M., Kozma, G. T., Falus, A. & Szalai, Cs. (2007)
CCR5Δ32 mutation, Mycoplasma pneumoniae infection and asthma.
J. Allergy. Clin. Immunol. 119(6): 1545–1547.

Tölgyesi, G., Keszei, M., Ungvári, I., Nagy, A., Falus, A. & Szalai, Cs. (2006)
Involvement of TNFα-308A promoter polymorphism in the development of asthma in children infected with Chlamydophila pneumoniae.
Pediatr. Res. 60(5): 543–548.

Kozma, G. T., Losonczy, Gy., Keszei, M., Komlósi, Z., Buzás, E., Pállinger, É., Appel, J., Szabó, T., Magyar, P., Falus, A. & Szalai, Cs. (2003)
Histamine deficiency in gene-targeted mice strongly reduces antigen-induced airway hyperresponsiveness, eosinophilia and allergen specific IgE.
Int. Immunol. 15(8): 963–973.

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Genetics Unit

Zoltán Papp, M.D., Ph.D., D.Sc.
Professor

Key words:

prenatal diagnosis
genetic disease
free DNA

Our research group has intensive studies on the following fields: (1) isolation and detection of free DNA; (2) isolation of fetal cells in maternal blood; (3) searching genes, gene polymorphisms in complex diseases (preeclampsia); (4) detection of genetic diseases using modern methods and technologies. We obtained very interesting results on introduction of non-invasive prenatal detection of genetic disease. We were able to isolate free fetal DNA from maternal blood and to isolate fetal nucleated cells from maternal blood. Two publications from our research group appeared in the respected Clinical Chemistry. We continue our studies on this field to avoid the invasive amniocentesis and chorionic villus sampling, and to have a simple method to predict genetic disease in the fetus.

We received significant results on study of complex diseases like preeclampsia and HELLP syndrome. We studied several mutations (Leiden mutation, prothrombin) and gene polymorphisms (VEGF, MTHFR) on high number of preeclamptic and HELLP syndrome patients. Several publications appeared from our group in different high quality journals.

Significant improvements have occured in the molecular diagnostic technics since the development of polymerase chain reaction (PCR). Quantitative real-time PCR method became available in the last couple of years. This method combines amplification of the target DNA with detection of the amplicons in the same capillary tube. The risk of carry over or contamination is significantly reduced in this closed system. Multiplexing can be assesed in the same sample.

We have the experience to optimize the PCR reactions for all kind of applications with SYBRGreen I or FRET probe systems using different type of tissues.

Recent publications:

Nagy, B., Berkes, E., Rigó, B., Bán, Z., Papp, Z. & Hupuczi, P. (2008)
Under-expression of CD24 in pre-eclamptic placental tissues determined by quantitative real-time RT-PCR.
Fetal Diagn. Ther. 23: 263–266.

Nagy, B., Hupuczi, P. & Papp, Z. (2007)
High frequency of C677T methylenetetrahydrofolate reductase mutation in Hungarian HELLP syndrome patients determined by quantitative real-time PCR.
J. Hum. Hypertension 21: 154–158.

Sziller, I., Babula, O., Hupuczi, P., Nagy, B., Rigó, B., Szabó, G., Papp, Z., Linhares, I.M. & Witkin, S.S. (2007)
Mannose-binding lectin (MBL) codon 54 gene polymorphism protects against development of preeclampsia, HELLP syndrome and preeclampsia-associated intrauterine growth restriction.
Hum. Mol. Reproduction. 13: 281–285.

Lázár, L., Nagy, B., Bán, Z., Nagy, G.R. & Papp, Z. (2006)
Presence of Cell-Free Fetal DNA in plasma of women with ectopic pregnancies.
Clinical Chemistry 52: 1599–1601.

Nagy, G.R., Györffy, B., Galamb, O., Molnár, B., Nagy, B. & Papp, Z. (2006)
Use of routinely collected amniotic fluid for whole-genome expression analysis of polygenic disorders.
Clinical Chemistry 52: 2013–2020.

Nagy, B., Bán, Z., Beke, A., Nagy, G.R., Lázár, L., Papp, C., Tóth-Pál, E. & Papp Z. (2006)
Detection of Toxoplasma gondii from amniotic fluid, a comparison of four different molecular biological methods.
Clinica Chimica Acta 368: 131–137.

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Laboratory of Molecular Genetics

Mária Sasvári-Székely, Ph.D., D.Sc.
Professor

Key words:

molecular genetics
psychogenetics
complex diseases
polymorphism
expression analysis

The main research activity of the laboratory is the study of the nature of genetic polymorphisms in the human population. Our specific interest is related to genetic background of human behavior and psychiatric disorders. Numerous polymorphisms of the dopamine and serotonin neurotransmitter system have been studied in the laboratory in respect to their association to various human traits and psychiatric disorders. Molecular biology of the determined promoter polymorphisms have been assessed by reporter gene constructs and by cotransfection of transcription factors in neuronal and astroglial cell lines.

Recently we started to work on the transcriptional effects of hypoxia and its relation to various genes of the dopamine and serotonin system. Moreover, we just started to investigate the expression changes in rat nervous system as the consequence of diabetes.

The laboratory has numerous ongoing funds for the research, including an EU and an NIH-FIRCA fund, as well as national grants of OTKA and ETT. Our research group also participates in K+F activity.

As our research has a strongly interdisciplinal nature, we have numerous national and international collaborations, including EU member and non-member states, as well as the US.

Recent publications:

Kereszturi, E., Király, O., Csapó, Z., Tárnok, Z., Gádoros, J., Sasvári-Székely, M. & Nemoda, Z. (2007)
Association between the 120-bp duplication of the dopamine D4 receptor gene and attention deficit hyperactivity disorder: genetic and molecular analyses.
Am. J. Med. Genet. B (Neuropsychiatric Genetics) 144(2): 231–236.

Kereszturi, E., Király, O., Barta, C., Molnár, N., Sasvári-Székely, M. & Csapó, Z. (2006)
No direct effect of the -521 C/T polymorphism in the human dopamine D4 receptor gene promoter on transcriptional activity.
BMC Mol. Biol. 7: 18.

Keszler, G., Spasokoukotskaja, T., Csapó, Z., Talianidis, I., Eriksson, S., Staub, M. & Sasvári-Székely, M. (2004)
Activation of deoxycytidine kinase in lymphocytes is calcium dependent and involves a conformational change detectable by native immunostaining.
Biochem. Pharmacol. 67(5): 947–955.

Lakatos, K., Nemoda, Z., Tóth, I., Rónai, Z., Ney, K., Sasvári-Székely, M. & Gervai, J. (2002)
Further evidence for the role of the dopamine D4 receptor (DRD4) gene in attachment disorganization: interaction of the exon III 48-bp repeat and the -521 C/T promoter polymorphisms.
Mol. Psychiatry. 7(1): 27–31.

Lakatos, K., Tóth, I., Nemoda, Z., Ney, K., Sasvári-Székely, M. & Gervai, J. (2000)
Dopamine D4 receptor (DRD4) gene polymorphism is associated with attachment disorganization in infants.
Mol. Psychiatry. 5(6): 633–637.

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Antibiotic Resistance Research Unit

Dóra Szabó, M.D., Ph.D.
Assistant Professor

Key words:

antibiotic resistance
Gram-negative
beta-lactamase
fluoroquinolone

Our research group has been working on antibiotic resistance mechanisms in Gram-negative bacteria to determinate the molecular basis of beta-lactamase mediated resistance in Gram-negative bacteria. Our group has published the first extended-spectrum – beta-lactamase (ESBL) producing Klebsiella pneumoniae outbreak in Hungary. We investigated the risk factors for colonization and infection of ESBL and non-ESBL-producing K. pneumoniae and K. oxytoca strains. We have also done animal experiments with ESBL-producing K. pneumoniae strain to compare the therapeutic effect of different antibiotics – beta-lactams, aminglycosides, carbapenems and to investigate the in vitro and in vivo inoculum effect. In collaboration with Dr. David Paterson's laboratory at the University of Pittsburgh, PA, US we have conjointly isolated and identified 5 novel beta-lactamases. We were working on the ESBL-detection in Enterobacter cloacae too. We developed a real-time PCR method for detection of multiple SHV beta-lactamases in a single isolate. We determinate the antibiotic resistance profile of multidrug-resistance (MDR) Gram-negative bacteria – specially Enterobacteriaceae, Pseudomonas aeruginosa – isolated from clinical samples. We investigate the phenotypic and genotypic backgrounds of the antibiotic resistance special regard to beta-lactams, aminoglycosides and quinolones. We determinate the minimal inhibitory concentrations (MICs) of the tested drugs, the isoelectric points, the kinetic parameters, the presence of the outer membrane proteins and their role in the resistance. We study the genetic background of the resistance mechanisms by detecting with PCR the genes of different beta-lactamases, topoisomerases and other quinolone resistant determinants, the genes of multi-drug efflux pumps. We determinate the sequences of that genes. We study the molecular epidemiological relation among the resistant strains using different molecular techniques.

Recent publications:

Máthé, A., Szabó, D., Anderlik, P., Rozgonyi, F. & Nagy, K. (2007)
The effect of amikacin and imipenem alone and in combination against an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae strain.
Diagn. Microbiol. Infect. Dis. 58(1): 105–110.

Kristóf, K., Szabó, D., Marsh, J.W., Cser, V., Janik, L., Rozgonyi, F., Nobilis, A., Nagy, K. & Paterson, D.L. (2007)
Extended-spectrum beta-lactamase-producing Klebsiella spp. in a neonatal intensive care unit: risk factors for the infection and the dynamics of the molecular epidemiology.
Eur. J. Clin. Microbiol. Infect. Dis. 26(8): 563–570.

Szabó, D., Silveira, F., Hujer, A.M., Bonomo, R.A., Hujer, K.M., Marsh, J.W. Bethel, C.R., Doi, Y., Deeley, K. & Paterson, D.L. (2006)
Outer membrane protein changes and efflux pump expression together may confer resistance to ertapenem in Enterobacter cloacae.
Antimicrob. Agents Chemother. 50(8): 2833–2835.

Bonomo, R.A. & Szabó, D. (2006)
Mechanisms of multidrug resistance in Acinetobacter species and Pseudomonas aeruginosa.
Clin. Infect Dis. 43 (Suppl. 2): S49–S56.

Szabó, D., Bonomo, R.A., Silveira, F., Pasculle, W.A., Baxter, C., Linden, P., Hujer, A.M., Hujer, K.M., Deeley, K. & Paterson, DL. (2005)
SHV-type extended-spectrum beta-lactamase production is associated with reduced cefepime susceptibility in Enterobacter cloacae.
J. Clin. Microbiol. 43(10): 5058–5064.

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Vera Ádám-Vizi, M.D., Ph.D.
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Key words:

brain
oxidative stress
excitotoxicity
mitochondria
neurodegeneration

Mitochondrial dysfunction and reactive oxygen species (ROS) are involved in the pathogenesis of acute and chronic brain diseases. Mitochondria are susceptible to ROS-mediated functional injury, but also responsible for the generation of ROS. One of the aims of our team is to reveal mitochondrial mechanisms and molecules responsible for the ROS production. Special emphasis is put on the regulation of ROS production by in situ mitochondria present in their normal intracellular environment.

Permeability transition could also be part of the pathological scenario leading to neuronal cell death. Understanding the molecular details of mitochondrial permeability transition pore (mPTP) is important to elaborate effective cytoprotective strategies. Using tissue culture of genetically modified mice (lacking components of PTP), changes in mitochondrial functions and morphology are studied with microfluorimetric methods developed in our laboratory.

We have recently developed an online kinetic assay for the adenine nucleotide translocase (ANT) activity. Based on this assay, a computer model was developed to predict ANT activity as a function of mitochondrial membrane potential, as well as 22 other mitochondrial parameters to investigate the conditions mimicking tissue ischemia in which mitochondria become ATP consumers. Using the ANT assay and the computer model, we are establishing a diagnostic test for mitochondrial dysfunction-related myopathies.

Recent publications:

Tretter, L. & Ádám-Vizi, V. (2007)
Uncoupling is without an effect on the production of reactive oxygen species by in situ synaptic mitochondria.
J. Neurochem. 103: 1864–1871.

Ádám-Vizi, V. & Chinopoulos, C. (2006)
Bioenergetics and the formation of mitochondrial reactive oxygen species.
Trends Pharmacol. Sci. 27: 639–645.

Gerencsér, A.A. & Ádám-Vizi, V. (2005)
Mitochondrial Ca^{2+} dynamics reveals limited intramitochondrial Ca^{2+} diffusion.
Biophys. J. 88: 698–714.

Tretter, L. & Ádám-Vizi, V. (2004)
Generation of reactive oxygen species in the reaction catalyzed by alpha-ketoglutarate dehydrogenase.
J. Neurosci. 24: 7771–7778.

Sipos, I., Tretter, L. & Ádám-Vizi, V. (2003)
Quantitative relationship between inhibition of respiratory complexes and formation of reactive oxygen species in isolated nerve terminals.
J. Neurochem. 84: 112–118.

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Reproductive Neuroendocrinology Laboratory of the Department of Human Morphology and Developmental Biology and the Hungarian Academy of Sciences

Ida Gerendai, M.D., Ph.D., D.Sc.
Professor

Key words:

supraspinal innervation
reproductive organs
viral transneuronal tracing
ovary
adrenal gland

Our main interest is the supraspinal innervation of the reproductive organs and of the adrenal gland using the viral transneuronal tracing technique. Inoculation of an organ with the neurotropic virus (Bartha's strain of pseudorabies virus) results in infection of all spinal and cerebral neuronal structures trans-synaptically connected with the organ studied. The number of labeled neurons in an infected structure depends on the density of innervation of the inoculated area. We demonstrated neural connections between the brain and the organs of reproduction. The findings provided the neuromorphological evidence for the existence of the "brain-reproductive organs-brain" neuronal circuit that presumably is involved in the fine-tuning control of the reproductive system. Further studies have indicated that the intensity of supraspinal labeling varies. In rats with pharmacologically induced polycystic ovary syndrome viral infection of cerebral structures was considerably diminished. Trans-synaptic labeling from the uterus also showed variations. Recently we have demonstrated in individual rats, by means of dual transneuronal tracing using isogenic recombinant strains of pseudorabies virus expressing a red fluorescent protein or a green fluorescent protein gene, the predominance in the innervation of both the left ovary and the left adrenal gland. Data also revealed that each ovary and each adrenal gland is innervated both by side-specific neurons and neurons which project to both the left- and right-sided organ.

Recent publications:

Gerendai, I., Banczerowski, P., Csernus, V. & Halász, B. (2007)
Innervation and serotoninergic receptors of the testis interact with local action of interleukin-1beta on steroidogenesis.
Auton. Neurosci. Basic and Clin. 131: 21–27.

Tóth, I.E., Wiesel, O., Boldogkői, Zs., Bálint, K., Tapaszti, Zs. & Gerendai, I. (2007)
Predominance of supraspinal innervation of the left ovary.
Microsc. Res. Tech. 70: 710–718.

Gerendai, I., Wiesel, O., Tóth, I.E., Boldogkői, Zs., Hornyák, Á. & Halász, B. (2005)
Occasional transsynaptic viral labeling in the central nervous system from the polycystic ovary induced by estradiol valerate.
Microsc. Res. Tech. 66: 186–192.

Wiesel, O., Tóth, I.E., Boldogkői, Zs., Hornyák, Á., Bokor, V., Halász, B. & Gerendai, I. (2004)
Comparison of transsynaptic viral labeling of central nervous system structures from the uterine horn in virgin, pregnant, and lactating rats.
Microsc. Res. Tech. 63: 244–252.

Banczerowski, P., Csaba, Zs., Csernus, V. & Gerendai, I. (2003)
Lesion of the amygdala on the right and left side suppresses testosterone secretion but only left-sided intervention decreases serum luteinizing hormone level.
J. Endocrinol. Invest. 26: 429–434.

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Key words:

hypothalamus
glutamatergic
vesicular glutamate transporters
anterior pituitary
synaptic connections

The research unit, supported by the Hungarian Academy of Sciences and the Department of Human Morphology and Developmental Biology of the Semmelweis University, studies since decades the central nervous system – anterior pituitary – target endocrine gland system. Presently we are primarily interested in the structural and functional aspects of the glutamatergic innervation of prominent hypothalamic cell groups. We use vesicular glutamate transporters as markers of glutamatergic elements and inject glutamate receptor antagonists into various hypothalamic structures to examine the functional significance of the glutamatergic innervation. As techniques autoradiography, single and double label immunocytochemistry at the light and electron microscopy level are applied, by means of minipumps drugs are injected into hypothalamic cell groups via implanted cannula, we determine hormones by radioimmunoassay.

In the last five years we have reported that in the hypothalamus glutamatergic fibers terminate on gonadotropin-releasing hormone-containing neurons, on growth hormone-releasing hormone-containing nerve cells and on somatostatin immunoreactive neurons. Further we have demonstrated that glutamate receptor antagonist injected into the hypothalamus blocks the suckling stimulus-induced release of prolactin, and inhibits the prolactin response to formalin stress. By means of radiolabeled aspartate autoradiography, we mapped the location of glutamatergic neurons projecting to hypothalamic cell groups.

Currently we study the glutamatergic innervation of the suprachiasmatic nucleus, key-structure of the control of circadian rhythms, and investigate the effect of sex steroids on the glutamatergic neurons in various structures of the brain.

Recent publications:

Kiss, J., Halász, B., Csáki, Á., Liposits, Zs. & Hrabovszky, E. (2007)
Vesicular glutamate transporter 2 protein and mRNA containing neurons in the hypothalamic suprachiasmatic nucleus of the rat.
Brain Res. Bull. 74: 397–405.

Kiss, J., Csaba, Zs., Csáki, Á. & Halász, B. (2006)
Glutamatergic innervation of growth hormone-releasing hormone-containing neurons in the hypothalamic arcuate nucleus and somatostatin-containing neurons in the anterior periventricular nucleus of the rat.
Brain Res. Bull. 70: 278–288.

Bodnár, I., Bánky, Zs., Nagy, M.G. & Halász, B. (2005)
Non-NMDA glutamate receptor antagonist injected into the hypothalamic paraventricular nucleus blocks the suckling stimulus induced release of prolactin.
Brain Res. Bull. 65: 163–168.

Kocsis, K., Kiss, J., Csáki, Á. & Halász, B. (2003)
Location of putative glutamatergic neurons projecting to the medial preoptic area of the rat hypothalamus.
Brain Res. Bull. 61: 459–468.

Kiss, J., Kocsis, K., Csáki, Á. & Halász, B. (2003)
Evidence for vesicular glutamate transporter synapses onto gonadotropin-releasing hormone and other neurons in the rat medial preoptic area.
Eur. J. Neurosci. 18: 3267-3278.

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Research Group for Stroke and Dementia

Dániel Bereczki, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

dementia
stroke
pathology
epidemiology

The activity of the research group focuses on clinical, epidemiological and pathological features of cerebrovascular disorders and dementias. A single-center large database including data of over 8000 patients with acute stroke has been established. The effects of risk factors on stroke severity and outcome are compared among different populations. Early features of atherosclerosis are evaluated in the carotid arteries by non-invasive methods. The pathomechanism, clinical and imaging characteristics of stroke subtypes are analyzed in international co-operations. Imaging features of cerebral small vessel diseases are related to subtypes of cerebral infarcts. The effects of small subcortical lesions on cognitive functions are evaluated by psychometric tests. Systematic reviews of health care interventions are prepared to evaluate the scientific evidence in the background of therapeutic practice. Pathological features of stroke and dementia are also studied in relation to the clinical findings. The distribution of the hallmark lesions and their relation to other (especially vascular) pathologies in Alzheimer's disease and in degenerative Parkinsonian-syndromes (mainly in multiple system atrophy) are investigated using stereological and morphometric methods. Autopsy tissue is available from the Károly Schaffer Neuropathology Laboratory and from international co-operations. The pathological features of transneuronal degeneration in stroke are analyzed in the corticospinal system and in the spinal cord. Patients with familiar and rare forms of dementias are followed with clinical, genetic and neuropathological methods. Imaging and clinical studies in Alzheimer's disease are carried out.

Recent publications:

Bereczki, D., Liu, M., do Prado, G.F. & Fekete, I. (2008)
Mannitol for acute stroke.
Stroke 39: 512–513.

Bereczki, D. & Fekete, I. (2008)
Vinpocetine for acute ischaemic stroke.
Cochrane Database of Systematic Reviews
2008, Issue 1, Art. No.: CD000480.

Bereczki, D. (2007)
The seven wonders of China in stroke
therapy: fact or illusion?
Stroke 38: e142.

Papp, M.I., Komoly, S., Szirmai, I.G. & Kovács, T. (2006)
Similarities between CSF-brain extracellular
transfer and neurofibrillary tangle invasion
in Alzheimer's disease.
Neurobiol. Aging 27: 402–412.

Kovács, T., Beck, J.A., Papp, M.I., Lantos, P.L.,
Arányi, Z., Szirmai, I.G., Farsang, M., Stuke, A.,
Csillik, A. & Collinge, J. (2007)
Familial prion disease in a Hungarian family
with a novel 144-base pair insertion in the
prion protein gene.
J. Neurol. Neurosurg. Psychiatry 78: 321–323.

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Sleep Research and Psychophysiology Group

Róbert Bódizs, Ph.D.

Our scientific interests are mainly, but not exclusively related to sleep research, more specifically to the relationship between sleep, behavior and psychological phenomena. Sleep is an ancient component of the mammalian behavioral repertoire which has been being preserved in its original form during the course of evolution. According to our opinion sleep provides a perfect insight so as to understand human behavior. One of the defining characteristics of sleep is the widespread synchronization of individual neurons and networks, which leads to the appearance of specific low frequency EEG patterns. As synchronization needs connectivity, the neuroanatomical condition of efficient synchronization lies in intracortical and corticothalamic synaptic infrastructure. Stable individual differences in sleep-EEG are called individual fingerprints and are supposed to reflect functional neuroanatomy of underlying brain tissue. Based on this idea we focus our research on sleep-EEG correlates of aging, general and specific cognitive abilities, personality and of trait-like affective styles in normal and pathological conditions such as autism spectrum disorders and borderline personality disorder. The hitherto hidden aspects of the latter traits and conditions are being unraveled by newly developed quantitative EEG methods and the parallel use of volumetric MRI assessed brain morphology. We consider that sleep-EEG combined with brain morphology and complex psychological examination offers the appropriate multidisciplinary approach towards a more exhaustive understanding of the neurobiology of normal and pathological mental conditions. Besides significantly enriching our factual knowledge of the composite relationship between brain function, structure and behavior, this approach also hides expectedly multiple possibilities for developing new diagnostic tools in different psychiatric disease.

Key words:

sleep
EEG
cognition
individual differences

Recent publications:

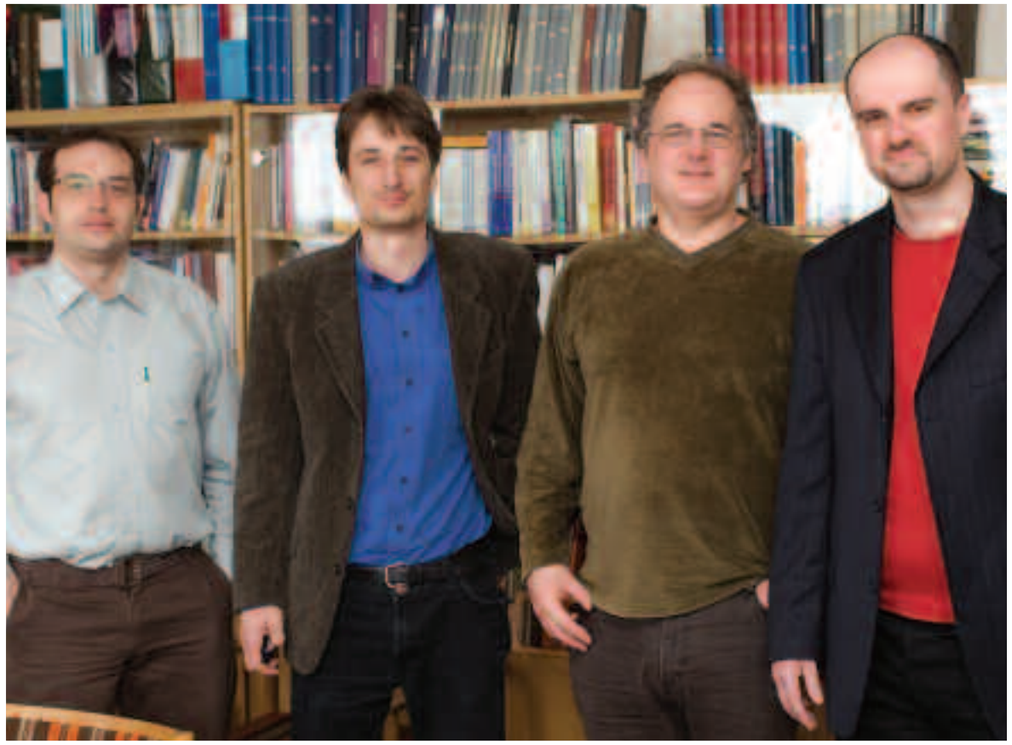
Bódizs, R., Sverteczki, M. & Mészáros, E. (2008)
Wakefulness-sleep transition: emerging electroencephalographic similarities with the rapid eye movement phase.
Brain. Res. Bull. doi:10.1016/j.brainresbull.2007.11.013

Harmat, L., Takács, J. & Bódizs, R. (2008)
Music improves sleep quality in students.
J. Adv. Nurs., doi: 10.1111/j.1365-2648.2008.04602.x

Bódizs, R., Sverteczki, M., Lázár, A.S. & Halász, P. (2005)
Human parahippocampal activity: non-REM and REM elements in wake-sleep transition.
Brain Res. Bull. 65: 169–176.

Bódizs, R., Kis, T., Lázár A.S., Havrán L., Rigó, P., Clemens, Z. & Halász, P. (2005)
Prediction of general mental ability based on neural oscillation measures of sleep.
J. Sleep Res. 14: 285–292.

Halász, P., Terzano, M., Parrino, L. & Bódizs, R. (2004)
The nature of arousal in sleep.
J. Sleep Res. 13: 1–23.



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Laboratory of Comparative Neurocytology and Neuroethology

András Csillag, M.D., Ph.D., D.Sc.
Professor and Chair

The main objectives of the research unit comprise investigation of the neural correlates of learning, motivation and addiction, employing the avian model system based on young domestic chicks. These birds are precocial and provide a suitable model due to the reproducibility of their behavior. Furthermore, they serve as an evolutionary alternative to mammalian systems, revealing key elements of neural mechanisms underlying behavior. Current research is focused on neural connectivity, neurogenesis, and the role of neurotransmitter systems in synaptic plasticity, using modern methods of descriptive and chemical neuroanatomy.

Key words:

avian brain
striatum
learning
synaptic plasticity
dopamine

The methods employed by the laboratory include light and electron microscopic immunohistochemistry and cytochemistry, confocal laser scanning microscopy, pathway tracing, cerebral lesion studies and in vivo microdialysis of freely behaving chicks. Most of these methods are coupled with functional analysis of behavior, using contexts of motivation and stress, and visual discrimination tests for innate and acquired preferences.

Recent results from the laboratory have revealed numerous anatomical circuits underlying learning, memory and motivation in avian subpallial systems including the septum, thalamus, striatum, nucleus accumbens and amygdala, as well as in the prefrontal cortical equivalent regions of pallium. Chemical neuroanatomical data obtained by combined light and electron microscopic immunocytochemistry and pathway tracing have demonstrated dopaminergic and cannabinoid-related circuits underlying reward related behavior of domestic chicks. They also suggested the selective distribution and potential signaling role of L-aspartate in amygdalo-striatal pathways and striatal synapses in parallel with, or in addition to the better known role of L-glutamate. Part of the new results have been achieved in collaboration with the Japanese avian research group led by Prof. Toshiya Matsushima (Hokkaido University, Sapporo).

Recent publications:

Csillag, A., Bálint, E., Ádám, Á.S. & Zachar, G. (in press)
The organization of the basal ganglia in the domestic chick (Gallus domesticus): anatomical localisation of DARPP-32 in relation to glutamate.
Brain Res. Bull.

Bálint, E. & Csillag, A. (2007)
Nucleus accumbens subregions: hodological and immunohistochemical study in the domestic chick (Gallus domesticus).
Cell Tiss. Res. 327: 221–230.

Ádám, Á.S. & Csillag, A. (2006)
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. 498: 266–276.

Jarvis, E. D., Güntürkün, O., Bruce, L., Csillag, A., Karten, H., Kuenzel, W., Medina, L., Paxinos, G., Perkel, D.J., Shimizu, T., Striedter, G., Wild, J.M., Ball, G.F., Dugas-Ford, J., Durand, S., Hough, G., Husband, S., Kubikova, L., Lee, D.W., Mello, C.V., Powers, A., Siang, C., Smulders, T.V., Wada, K., White, S.A., Yamamoto, K., Yu, J., Reiner, A. & Butler, A.B. (2005)
Avian brains and a new understanding of vertebrate brain evolution.
Nature Reviews: Neuroscience 6: 151–159.

Montagnese, C. M., Székely, A. D., Ádám, Á. & Csillag, A. (2004)
Efferent connections of septal nuclei of the domestic chick (Gallus domesticus): an anterograde pathway tracing study with a bearing on functional circuits.
J. Comp. Neurol. 469: 437–456.

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Immunohistological Laboratory

Katalin Köves, M.D., Ph.D., D.Sc.
Professor

We have been studying the distribution and the role of Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) and the secretin in the central nervous system.
We have described that PACAP has a wide distribution in the central and peripheral nervous system and in endocrine glands as well.

Key words:

hypothalamo-hypophysial-gonad axis
immunohistochemistry
tracing techniques
in situ hybridization
rat

PACAP has a multifunctional role. We have studied its role in the gonadotropic hormone secretion. PACAP was mainly inhibitory at hypothalamic and pituitary levels as well. 1) It was shown that PACAP administered intracerebroventricularly before the critical period of the proestrous stage could prevent the ovulation. 2) In the pituitary gland the expression and release of PACAP were highest at the end of the preovulatory LH surge implying its role to ceasing the LH surge.
We have described that there is a direct connection between several limbic structures and retina. A part of neurons, which send their axons to the retina, contains PACAP. We have also found neurons in the hypothalamus which axons project to the retina. These pathways were named limboretinal- and hypothalamoretinal ones. The fibers of these pathways seem to be terminated on the retinal amacrin cells and it was supposed that through these cells the limbic and hypothalamic structures may modulate the response of ganglion cells to light impulses.
About ten years ago it was supposed that secretin could improve the autistic phenomenon in children with gastrointestinal syndrome. This observation led us to map the occurrence of secretin in the central nervous system. It was found that secretin is present in the cerebellar Purkinje cells, in some neurons of the cerebellar nuclei, in the hippocampus, in the large pyramidal cells of the motor cortex and in sensory ganglia. In autism one of the most consequent disturbances in the central nervous system is the Purkinje cell loss. Among other disturbances the level of secretin may be lower than in healthy persons which may explain its beneficial effect in a part of autistic persons.

Recent publications:

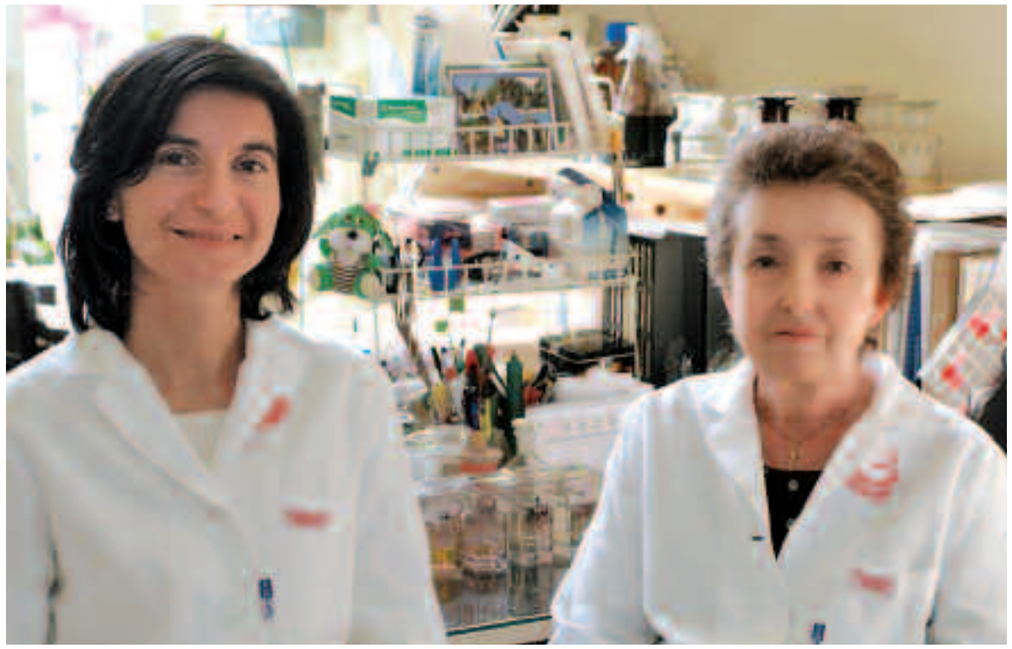
Heinzlmann, A., Kirilly, E., Meltzer, K., Szabó, E., Baba, A., Hashimoto, H. & Köves, K. (2008)
PACAP is transiently expressed in anterior pituitary gland of rats. In situ hybridization and cell immunoblot assay studies.
Peptides 29: 571–577.

Köves, K. & Heinzlmann, A. (2008)
Neurotransmitters and neuropeptides in autism.
Pp. 1–67 in: **Mesmere, B.** (ed.).
New autism research developments.
Nova Science Publishers, Inc., New York.

Vereczki, V., Köves, K., Csáki, Á., Grósz, K., Hoffman, G. & Fiskum, G. (2006)
Distribution of hypothalamic, hippocampal and other limbic peptidergic neuronal cell bodies giving rise to retinopetal fibers: anterograde and retrograde tracing and neuropeptide immunohistochemical studies.
Neuroscience 140: 1089–1100.

Köves, K., Kausz, M., Reser, D., Illyés, Gy., Takács, J., Heinzlmann, A., Gyenge, E. & Horváth, K. (2004)
Secretin and autism: a basic morphological study about the distribution of secretin in the nervous system.
Regul. Pep. 123: 209–216.

Köves, K., Kántor, O., Molnár, J., Heinzlmann, A., Szabó, E., Szabó, F., Nemeskéri, Á., Horváth, J. & Akira, A. (2003)
The role of PACAP in gonadotropic hormone secretion at hypothalamic and pituitary levels.
J. Mol. Neurosci. 20: 141–152.



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Neurochemical Research Unit

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Member of the Hungarian Academy of Sciences

Two families of aminoxidases; namely monoamine oxidase (MAO) and semicarbazide-sensitive amine oxidase (SSAO) are investigated in our group, in respect of neuro- and vasoprotection.

Key words:

deprenyl
neuroprotection
pharmacokinetics
monoaminoxidase
semicarbazide-sensitive aminoxidase

(-)-Deprenyl (selegiline) is a selective inhibitor of MAO-B, which is widely used in the treatment of neurodegenerative diseases. The principal objective of our present studies is to improve the therapeutic spectrum of the inhibitor.
Selegiline has an intensive “first pass” metabolism after oral application. Less than 25% of the parent compound reaches the systemic circulation. Our aim is to develop parenteral drug formulas (transdermal, liposomal preparations, etc.), which increase the bioavailability of the compound. In these cases the significant inhibition of MAO-A, without influencing enzyme activity in the liver and the gastrointestinal tract, leads to a new spectrum of activity (antidepressive).
The metabolites of selegiline with propargylamine group possess neuroprotective activity, which was demonstrated at much lower concentrations, than it is needed for MAO inhibition. Deprenyl-N-oxide (DNO) displays remarkable neuroprotective properties. DNO, in contrast to selegiline, even at high concentrations does not possess pro-apoptotic properties. Changing the pharmacokinetic profile of selegiline its therapeutic indication can be widened (effective in depression, AD/HD, withdrawal syndrome, etc.). It is rational, that selegiline and its congeners might be effective to treat co–morbidities.
SSAO exists in soluble and solid form. Its functional role still is not discovered. Our aim is to develop new inhibitors, better than semicarbazide to elucidate the consequences of SSAO inhibition in therapy. Inhibitors are synthesized in collaboration and screened in our laboratory.
The topic of neuro- and vasoprotection belongs to the leading line of pharmacological research, possessing social impact and practical benefit.

Recent publications:

Magyar, K., Szatmáry, I., Szebeni, G. & Lengyel, J. (2007)
Pharmacokinetic studies of (-)-deprenyl and some of its metabolites in mouse.
J. Neural Transm. (Suppl.) 72: 165–173.

Magyar, K., Pálfi, M., Jenei, V. & Szökő, É. (2006)
Deprenyl: from chemical synthesis to neuroprotection.
J. Neural. Transm. (Suppl.) 71: 143–156.

Magyar, K., Pálfi, M., Tábi, T., Kalász, H., Szende, B. & Szökő, É. (2004)
Pharmacological aspects of (-)-deprenyl.
Curr. Med. Chem. 11: 2017–2031.

Magyar, K. & Szende, B. (2004)
(-)-Deprenyl, a selective MAO-B inhibitor, with apoptotic and anti-apoptotic properties.
Neurotoxicol. 25 (1/2): 233–242.

Magyar, K. & Mészáros, Zs. (2003)
Semicarbazide-sensitive amine oxidase (SSAO): present and future.
Inflammopharm. 11(2): 165–173.

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Molecular and Cellular Neuroendocrine Research Laboratory

György M. Nagy, M.D., Ph.D., D.Sc.
Professor

Key words:

pituitary
hypothalamus
dopamine
neuropeptides
receptor signaling

Nowadays, it is clear that the biological actions of prolactin are not limited solely to reproduction, rather it controls variety of behaviors and more importantly, it plays an indispensable role in control of the homeostasis. Bidirectional communications likely exist between major players of the hypothalamic centers controlling internal milieu, like osmoregulation, metabolism, reproduction and/or the most important hypophysiotrophic (like neuroendocrine dopaminergic) neurons of the endocrine homeostasis. Based on this consideration, it is not surprising that neuropeptides can directly (at the pituitary level) and/or indirectly (through the hypothalamus) influence prolactin release from the pituitary gland. At the same time, prolactin can play a role in the mediation of the influences of the above mentioned systems on target organs, like fluid and electrolite transport trough mammary epithelial cells and/or through its action as an adipokine on fat cells. Moreover, prolactin can feed back hypothalamic neuroendocrine neurons that have a relationship with other homeostatic regulatory centers. According to our working hypothesis all of these communications are required for the adequate control of the internal milieu, therefore, several aspects of them are targets of our research projects. It is also obvious, that the most precise knowledge about signal transduction mechanisms of pituitary D2-type dopamine receptors is required to understand not only the physiological significance of the desensitization/sensitization processes but the dominant and tonic inhibition of mammotropes exercised by the hypothalamic dopaminerg neurons. Learning more about dopamine signaling mechanisms regulating cell survival (including the inhibition of the apoptotic cascade) in the anterior lobe of the pituitary gland, as an integral part of the tonic inhibition of prolactin secretion, hopefully give us a new and effective way for treatment of prolactinomas as well as other pituitary tumors.

Recent publications:

Mravec, B., Bodnár, I., Tillinger, A., Uhereczky, G., Kvetnansky, R., Palkovits, M. & Nagy, Gy.M. (2007)
Prolactin response to formalin is related to the acute nociceptive response and it is attenuated by combined application of different stressors.
Neuroendocrinology 86(2): 69–76.

Székács, D., Bodnár, I., Vizi, E.Sz., Nagy, Gy. M. & Fekete, M.I. (2007)
The role of catecholamines in the prolactin release induced by salsolinol.
Neurochem. Int. 51(5): 319–322.

Iván, G., Szigeti-Csúcs, N., Oláh, M., Nagy, Gy.M.& Góth, M.I. (2005)
Treatment of pituitary tumors: dopamine agonists.
Review Endocrine 28(2): 101–110.

Bodnár, I., Mravec, B., Kubovcakova, L., Tóth, E.B., Fülöp, F., Fekete, M.I.K., Kvetnansky, R. & Nagy, Gy.M. (2004)
Stress-, as well as suckling-induced prolactin (PRL) response is blocked by a structural analogue of the putative hypophyseotrofic PRL releasing factor, salsolinol (SAL).
Journal of Neuroendocrinology 16(3): 208–213.

Naoi, M., Maruyama, W. & Nagy, Gy. M. (2004)
Dopamine-derivatives as endogenous monoamine oxidase inhibitors: occurrence, metabolism and function in human brains.
Neurotoxicology 25(1/2): 193–204.

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Miklós Palkovits, M.D., Ph.D.
Professor,
Member of the Hungarian Academy of Sciences

The research studies are aimed to reveal the identity, the topography and the chemical characters of new pathways which constitute functional neuronal circuits in and between the hypothalamus and the central autonomic system. The research activity includes neuromorphological investigations of central regulatory mechanisms, like food intake, pain, stress and neurohumoral effects on the sympathetic outflow. Information obtained from this study may help to introduce a new attitude in neuroscience, the "system neuromorphology". Major deliverables: (1) localization of dorsolateral hypothalamic projections to medullary parasympathetic and spinal sympathetic preganglionic neurons; (2) neuroanatomical and neurochemical studies on the neuronal connections between the ventromedial and other, food intake-related neurons in mice; (3) topographical localization and neurochemical characterization of the ulcus-related cortico-amygdaloid-vagal neuronal pathways in rats; (4) topographical localization, neurotransmitters and neuropeptides in the trigemino-hypothalamic pathway; (5) topographical distribution of the stomach- and duodenum-innervating sympathetic and parasympathetic premotor neurons in the hypothalamus, limbic system and the lower brainstem; (6) selective brainstem and spinal cord projections from peptidergic neurons of the arcuate nucleus; (7) the Human Brain Tissue Bank (HBTB) has been established and kept in operation by the Neuromorphological Research Group. The HBTB is unique for two important reasons: (a) microdissection of over 100 different brain nuclei is performed on frozen brains and the samples are kept on –70 °C. These samples have been improved to be excellent for neuroendocrine, molecular genetic, proteomic and various types of neurochemical microassay and microarray studies; (b) very short post mortem delay: brains were removed from the skull and frozen within 2–6 hours after death. The collection of the HBTB consists over 32000 samples.

Key words:

food intake
stress
pain
neuroanatomy
neurochemistry

Recent publications:

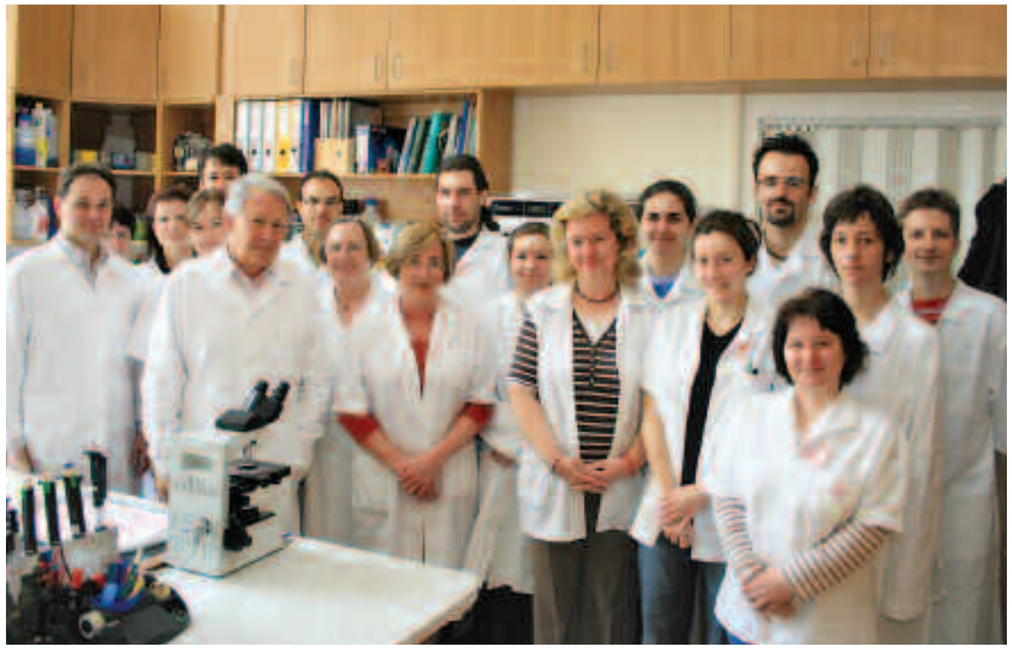
Dobolyi, Á. & Palkovits, M. (2008)
Expression of latent transforming growth factor beta binding proteins in the rat brain.
J. Comp. Neurol. 507: 1393–1408.

Tóth, Z.E., Zelena, D., Mergl, Z., Kirilly, E., Várnai, P., Mezey, É., Makara, G.B. & Palkovits, M. (2008)
Chronic repeated restraint stress increases prolactin-releasing peptide/tyrosine hydroxylase ratio with gender-related differences in the rat brain.
J. Neurochem. 104: 653–666.

Palkovits, M., Deli, M.A., Gallatz, K., Tóth, Z.E., Buzás, E. & Falus, A. (2007)
Highly activated c-fos expression in specific brain regions (ependyma, circumventricular organs, choroid plexus) of histidine decarboxylase deficient mice in response to formalin-induced acute pain.
Neuropharmacology 53: 101–112.

Shahar, T. & Palkovits, M. (2007)
Cross over of forebrain and brainstem neuronal projections to spinal cord sympathetic preganglionic neurons in the rat.
Stress 10: 145–152.

Hansen, A., Chen, Y., Imman, J.M., Phan, Q.N., Qi, Z.-Q., Xiang, C.C., Palkovits, M., Cherman, N., Kuznetsov, S.A., Robey, P.G., Mezey, E. & Brownstein, M.J. (2007)
Sensitive and specific method for detecting G protein-coupled receptor mRNAs.
Nature Methods 4: 35–37.



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Laboratory of Cell and Molecular Biology

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Key words:

photoreceptor
visual pigment
color cone
immunocytochemistry
development

Novel monoclonal antibodies recognizing color-specific cones of the retina have been produced in our Department. The monoclonals can be used on simple histological preparations to map the distribution of various cone types. Comparative analysis of mammals, incl. primates and humans revealed that the majority (90%) of the mammalian cones are sensitive to green (and red) colors (M/L), whereas 10% fall in the blue-sensitive category (S). In addition, we have observed a striking asymmetry in their distribution. In a number of species M/L cones dominate only in the dorsal part of the retina. The S cones, in contrast, are more numerous in the ventral retina. Considering the inverse image produced by the lens, the logical interpretation is that light beams arriving form the sky are projected onto the ventral retina, whereas the image of the green vegetation of the earth is reflected on the upper retina. Another discovery was the detection of dual cones expressing both S and M/L pigments at the same time. These cones are located in the transition zone binding the upper and lower fields. Their presence indicates that it is the two visual pigments that change their ratio from above downwards in a spatially organized pattern, rather than having two different cone types that gradually replace one another. Dual cones have also been identified in the early postnatal weeks all over the retina. It has been shown that the first cones appearing after birth express exclusively S pigment. A few days later the majority of these cones start to express M/L pigment as well, however the expression of the original S pigment is downregulated soon, thereby producing the definitive green cone contingent. Cones that never express M/L pigment and retain the ancestral blue pigment make the definitive S cone population. Morphological and molecular biological methods are used to search for factors that regulate the identity and topography of the developing cones.

Recent publications:

Berta, I.Á., Kiss, A.L., Kemény-Beke, Á., Lukáts, Á., Szabó, A. & Szél, Á. (2007)
Different caveolin isoforms in the retina of melanoma malignum affected human eye.
Mol. Vis. 13: 881–886.

Berta, Á., Kiss, A. L., Lukáts, Á., Szabó, A. & Szél, Á. (2007)
Distribution of caveolin isoforms in the lemur retina.
J. Vet. Sci. 8: 295–297.

Lukáts, Á., Szabó, A., Röhlich, P., Vígh, B. & Szél, Á. (2005)
Photopigment coexpression in mammals: comparative and developmental aspects.
Histol. Histopathol. 19: 607–628.

Vígh, B., Manzano, E., Silva, M.J., Frank, C.L., Dávid, C., Czirok, S. J., Vincze, C., Rácz, G., Lukáts, Á. & Szél, Á. (2004)
The circumventricular organs of the brain: do they represent a cerebrospinal fluid-dependent regulatory system?
Med. Hypotheses Res. 1: 77–100.

Van der Spuy, J., Kim, J.H., Yu, Y.S., Szél, Á., Luthert, P.J., Clark, B.J. & Cheetham, M.E. (2003)
The expression of the Leber congenital amaurosis protein AIPL1 coincides with rod and cone photoreceptor development.
Invest. Ophthalmol. Vis. Sci. 44: 5396–5403.

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Clinical Neurophysiology Laboratory

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Key words:

motor and cognitive event related EEG
electronystagmography
tremor
Parkinson's disease

Our Clinical Neurophysiology Laboratory carries out both diagnostic and research activity. During the last 15 years methods were elaborated for the investigation of movement disorders. The complex pathomechanism of Parkinson's disease was approached by the analysis of event related EEG activity especially post movement beta synchronization. The results served the understanding of the asymmetry of clinical signs and the cortical involvement of Parkinson's disease. With the help of sophisticated mathematical analysis we were able to differentiate the basic types of tremors; furthermore evidences were gathered that the generators of Parkinsonian- and essential-type tremors are different. During cognitive effort EEG, blood flow velocity in the middle cerebral artery and autographic method. Close correlation was found between laterality of blood flow and EEG power. Mental stress elicits significant change of blood pressure, heart rate and respiration. Decrease of end tidal pCO_2 exerts strong influence on the intracerebral vascular resistance, which modifies the regional blood flow within the activated regions of the hemispheres. Results suggested that the increase of localized theta activity may not be a unique indicator of working memory, but the physiological consequence of hyperventilation caused by cognitive stress.
The cortical mechanisms of gaze and nystagmus are intensively investigated fields of neuroscience. We constructed a complex system for the parallel investigation of optokinetic nystagmus and EEG in healthy volunteers and patients. Characteristic and reproducible change of EEG power was found during optokinetic saccads. We clarified the role of attentive components with the help of time locked EEG synchronization. The clinical usefulness of nystagmography in localization of structural damage has increased in the last years since minimal dysfunction of the neuronal system of gaze can be identified using this method.

Recent publications:

Gulyás, S., Pálvölgyi, L., Kamondi, A. & Szirmai, I. (2007)
EEG correlates of subcortical optokinetic Nystagmus.
Clin. Neurophysiol. 118: 551–557.

Farkas, Zs., Szirmai, I. & Kamondi, A. (2006)
Impaired rhythm generation in essential tremor.
Mov. Disord. 21: 1196–1199.

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Asymmetry of tremor intensity and frequency in Parkinson's disease and essential tremor.
Park. Rel. Disord. 12: 49–55.

Szirmai, I., Amrein, I., Pálvölgyi, L., Debreczeni, R. & Kamondi, A. (2005)
Correlation between blood flow velocity in the middle cerebral artery and EEG during cognitive effort.
Cogn. Brain Res. 24: 33–40.

Tamás, G., Szirmai, I., Pálvölgyi, L., Takáts, A. & Kamondi, A. (2003)
Impairment of post-movement beta synchronisation in Parkinson's disease is related to laterality of tremor.
Clin. Neurophysiol. 114: 614–623.

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Opioid Research Group

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Key words:

opioids
peripheral antinociception
blood brain barrier

Since the serious side effects (e.g., respiratory depression, dependence) of morphine (MO) and derivatives, strongly limit their clinical use, there is a continuous search for safer analgesic drugs. Opioid analgesics with limited access to the central nervous system (CNS) represent a new approach to the treatment of severe pain. Strategies to restrict the access of opioids to the CNS e.g. quaternization resulted in reduced analgesic potency. 14-O-methyloxymorphone was developed by our group and reported to be about 400-and 40-fold more potent than MO and oxymorphone (OXM), respectively, in mice. We studied the peripheral and central components of the antinociceptive actions of 6-amino acid conjugates (glycine, alanine, and phenylalanine) of 14-O-methylOXM. Their antinociceptive activities were compared to those of the centrally penetrating μ-opioid agonist MO in the tail-flick test in rats. The 6-amino acid conjugates were 45-to 1170-fold more potent than MO after i. c. v. and 19-to 209-fold after s. c. administration. Systemic administration of the peripherally selective opioid antagonist quaternary naloxone antagonized the effects after s. c. but not after i. c. v. S. c. 6-amino acid derivatives also elicited antihyperalgesic effects in the formalin test in rats, reversed by systemically administered quaternary naloxone. The potent antinociceptive actions of classical opioids such as MO are traditionally considered to be mediated centrally through an action at the supraspinal or spinal level. However, according to our data, the investigated new opioids interact primarily with peripheral opioid receptors after s. c. administration. These data support the hypothesis that the 6-amino acid conjugates of 14-O-methylOXM have limited access to the CNS and can mediate antinociception at peripheral sites. Therefore, these compounds might find clinical application when the central actions of opioids are unwanted (this work was supported by a grant from the European Community).

Recent publications:

Al-Khrasani, M., Spetea, M., Friedmann, T., Riba, P., Király, K., Schmidhammer, H. & Fürst, S. (2007)
DAMGO and 6-β glycine substituted 14-O-methyl-oxymorphone but not morphine show peripheral, preemptive antinociception after systemic administration in a mouse visceral pain model and high intrinsic efficacy in the isolated rat vas-deferens.
Brain Res. Bull. 74: 369–375.

Tömböly, Cs., Ballet, S., Feytens, D., Kövér, K.E., Borics, A., Lovas, S., Al-Khrasani, M., Fürst, S., Tóth, G., Benyhe, S. & Tourwe, D. (2007)
Endomorphin-2 with a β-turn backbone constraint retains the potent opioid receptor agonist properties.
J. Med. Cem. 51: 173–177.

Király, K.P., Riba, P., Addario, C.D., Di Benedetto, M., Landuzzi, S., Candeletti, S., Romualdi, P. & Fürst, S. (2006)
Alterations in prodynorphin gene expression and dynorphin levels in different brain regions after chronic administration of 14-methoxymethopon and oxycodone-6-oxime.
Brain Res. Bull. 70: 233–239.

Fürst, S., Riba, P., Friedmann, T., Timár, J., Al-Khrasani, M., Obara, I., Makuch, W., Spetea, M., Schütz, J., Przewlocki, R., Przewlocka, B. & Schmidhammer, H. (2005)
Peripheral versus central antinociceptive actions of 6-amino acid-substituted derivatives of 14-O-methyloxy-morphone in acute and inflammatory pain in the rat.
J. Pharm. Exp. Ther. 312: 609–618.

Spetea, M., Friedmann, T., Riba, P., Schütz, J., Wunder, G., Langer, T., Schmidhammer, H. & Fürst, S. (2004)
In vitro opioid activity profiles of 6-amino acid substituted derivatives of 14-O-methyloxymorphone.
Eur. J. Pharm. 483: 301–308.

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Gastroenterological Research Laboratory

Klára Gyires, M.D., Ph.D., D.Sc.
Professor and Chair

Key words:

gastric mucosal defense
brain-gut axis

Integrity of gastric mucosa depends on the balance of aggressive and protective factors. While numerous therapeutic agents are available for the treatment of gastric damage due to the dominancy of aggressive factors (e.g., anti-secretory drugs), practically no therapeutic possibility exists, when the development of the gastric mucosal lesions is the consequence of the reduced gastric mucosal defensive processes. Our laboratory aims to study how gastric mucosal defense can be increased pharmacologically acting either in the periphery or in the central nervous system. Our interest mainly focuses on the role and function of endogenous mediators and modulators in the maintenance of gastric mucosal integrity. For the experiments we use different ulcer models (acute, chronic, acid dependent and acid independent) in the rat, the compounds are given either peripherally (intravenously, subcutaneously, orally) or centrally to the lateral ventricles, to cisterna magna, or by the means of stereotaxic apparatus to different, selected brain areas. Besides the determination of gastric mucosal lesions, also mucosal microcirculation is measured by laser Doppler technique. The pharmacological analysis of gastric mucosal protection has been completed with examination of gastric acid secretion, as well as gastric motor activity in vivo/in vitro and intestinal transit. Another line of our research interest is the development of analgesic and anti-inflammatory agents which devoid of gastric mucosal damage. For this purpose we introduced several methods which are appropriate for the examination of acute and chronic inflammatory processes as well as inflammatory and non-inflammatory pain reactions. In cooperation with organic chemists synthesis and development of new molecules with the desired pharmacological profile may be expected.

Recent publications:

Szabó, Gy., Fisher, J., Kis-Varga, Á. & Gyires, K. (2008)
New celecoxib derivatives as anti-inflammatory agents.
J. Med. Chem. 51(1): 142–147.

Gyires, K., Zádori, Z.S., Shujaa, N., Minorics, R., Falkay, Gy. & Mátyus, P. (2007)
Analysis of the role of central and peripheral α2-adrenoceptor subtypes in gastric mucosal defense in the rat.
Neurochem. International. 51: 289–296.

Zádori, Z.S., Shujaa, N., Fülöp, K., Dunkel, P. & Gyires, K. (2007)
Pre- and postsynaptic mechanisms in the clonidine- and oxymetazoline-induced inhibition of gastric motility in the rat.
Neurochem. Int. 51: 297–305.

Gyires, K. (2005)
Gastric mucosal protection: from prostaglandins to gene therapy.
Current Med. Chem. 12(2): 203–215.

Fülöp, K., Zádori, Z., Rónai, A.Z. & Gyires, K. (2005)
Characterisation of α2-adrenoceptor subtypes involved in gastric emptying, gastric motility and gastric mucosal defence.
Eur. J. Pharmacol. 528: 150–157.

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Application of Bioanalytical Methods in Pharmaceutical Research

Imre Klebovich, Ph.D., D.Sc.
Professor

Key words:

drug-food interaction
in-vitro simulation
pharmacokinetics
metabolism
bioanalytics

The identification of Active Pharmaceutical Ingredients (API) is an important and growing field in drug discovery. The concentration of the API and its metabolites have to be determined in very low levels in complex biological matrices, in both in-vitro and in-vivo models. To achieve this, modern hyphenated bioanalytical techniques have to be used.

One of the main aspects of medicine safety are the reactions that might occur in-vivo between the consumed food and medicine. This phenomena can dramatically influence the bioavailability of drugs taken, thus having a direct effect on patient safety.

Our research group in the Department of Pharmaceutics of the Semmelweis University is involved in the application of different high sensitivity analytical techniques (e.g., GC; GC/MS; HPLC; HPLC/MS; CE etc.), in the investigation of drug-food interactions, in metabolite research, in the application and analysis of antibiotics in artificial bones and in the formulation of liposomes as drug carrier systems.

Our main focus is: (a) the investigation of the effect of different food components on the in-vitro dissolution of drug molecules (in-vitro, in-vivo drug-food interactions, IVIVC); (b) quantitative and qualitative evaluation of metabolites from body fluids; (c) stability and bioavailability of antibiotics applied in artificial bone substitutives used in surgery; (d) the application of liposomes as stabilizing agents of light sensitive materials, for example in ophthalmic formulations; (e) pharmacokinetics in different species; (f) bioanalytical method development in pharmacokinetic and metabolite kinetic studies.

Our work is usually done in co-operation with other research groups as well as pharmaceutical companies. Our aim is the publication of the results for the benefit of patients resulting in safer, more effective and higher quality drug formulations.

Recent publications:

Budai, L., Hajdú, M., Budai, M., Gróf, P., Béni, Sz., Noszál, B., Klebovich, I. & Antal, I. (2007)
Gels and liposomes in optimized ocular drug delivery: studies on ciprofloxacin formulations.
Int. J. Pharm. 343: 34–40.

Kalász, H., Petroianu, G., Tekes, K., Klebovich, I., Ludányi, K. & Gulyás, Z. (2007)
Metabolism of moexipril to moexiprilat: determination of in vitro metabolism using HPLC-ES-MS.
Med. Chem. 3: 101–106.

Pápai, K., Ludányi, K., Budai, M., Antal, I. & Klebovich I. (2007)
In vitro studies on ciprofloxacin-milk interaction using LC-MS method.
Acta Pharm. Hung. 77: 33–38.

Monostory, K., Kőhalmy, K., Ludányi, K., Czira, G., Holly, S., Vereczkey, L., Ürmös, I., Klebovich, I. & Kóbori, L. (2005)
Biotransformation of deramciclane in primary hepatocytes of rat, mouse, rabbit, dog, and human.
Drug Metab. Dispos. 33: 1708–1716.

Horváth, V., Tolokán, A., Egresi, A., Pap, T., Horvai, Gy., Balogh-Nemes, K. & Klebovich I. (2005)
High performance liquid chromatography-tandem mass spectrometric method for the determination of clemastine in human plasma.
J. Chromatogr. B, 816: 153–159.

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Research Laboratory for Organic and Medicinal Chemistry of the Department of Organic Chemistry and Szentágothai János Knowledge Center

Péter Mátyus, Ph.D., D.Sc.
Professor and Chair

Key words:

organic synthesis
medicinal chemistry
heterocyclic chemistry
cardiovascular system
central nervous system

The main research fields of the Department are related to synthetic and medicinal chemistry of heterocyclic compounds, which include
i) synthesis;
ii) chemical, physico-chemical and theoretical aspects of potentially bioactive nitrogen-containing heterocyclic compounds;
iii) development of new synthetic strategies for polyfused heterocyclic systems, by application of carbon-carbon bond formation reactions;
iv) structure-activity study and lead optimization using structure-based design and 3D QSAR methods to develop new drug candidates for cardiovascular and central nervous systems (e.g., antiarrhythmic agents, compounds effecting on NMDA-receptor system, respectively), for G-protein coupled cationic neurotransmitter receptors, semicarbazide-sensitive amine oxidase (SSAO) and monoamine oxidase (MAO) enzymes as well as for treatment of malaria.
Classical and modern preparative, analytical and spectroscopic methods are all available at the Department.
As references, a number of domestic and international collaborations with academic institutions and pharmaceutical industry may be mentioned.

Recent publications:

Balogh, B., Jójárt, B., Wágner, Zs., Kovács, P., Gyires, K., Zádori, Z., Falkay, Gy., Márki, Á., Viskolcz, B. & Mátyus, P. (2007)
3D QSAR models for α_{2a}-adrenoceptor agonists.
Neurochemistry International 51: 268–276.

Maes, B.U.W., Tapolcsányi, P., Meyers, C. & Mátyus, P. (2006)
Palladium-catalyzed reactions on 1,2-diazines.
Curr. Org. Chem. 10: 377–417.

Hársing, L.G., Jurányi, Z., Gacsályi, I., Tapolcsányi, P., Czompa, A. & Mátyus, P. (2006)
Glycine transporter type-1 and its inhibitors.
Curr. Med. Chem. 13: 1017–1044.

Mátyus, P., Dajka-Halász, B., Földi, Á., Haider, N., Barlocco, D. & Magyar, K. (2004)
Semicarbazide-sensitive amine oxidase: current status and perspectives.
Curr. Med. Chem. 11: 1285–1298.

Mátyus, P., Maes, B.U.W., Riedl, Zs., Hajós, Gy., Lemiére G.L.F., Tapolcsányi P., Monsieurs, K., Éliás, O., Dommisse, R.A. & Krajsovszky, G. (2004)
New pathways towards pyridazino-fused ring systems.
Synlett 7: 1123–1139.

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Research Group for Drug Profiling and Analysis

Béla Noszál, Ph.D., D.Sc.
Professor and Chair

Objectives and recent achievements of the Research Group for Drug Profiling and Analysis include:
Micro- and submicro speciation of bio- and drug molecules. This novel, interdisciplinary field provides the currently most profound characterization of protonation, a ubiquitous process in drug absorption, receptor binding and metabolism.
Introduction and determination of new microscopic physico-chemical parameters such as rotamer-specific partition coefficient, microscopic rate constant of ester hydrolysis and electrophoretic migration. Preparation and characterization of drug delivery systems by nanotechnology methods.
Structure-activity relationship (SAR and QSAR) studies on drugs and drug families. Determination and quantum-chemical calculation of physico-chemical parameters (logP, lipophilicity, logk, site-specific basicity) that influence the biological effects of dugs. Prediction of pharmacokinetic properties at early stage of drug research.
Synthesis of natural alkaloids, their derivatives and polycyclic condensed-ring heterocycles of potential biological activity either as new chemical entities in exploratory research or as minor species model compounds in microspeciation. Preparation of combinatorial libraries by techniques of multiple synthesis and combinatorial chemistry.
Separation of enantiomers and other structurally related active principles by hyphenated separation techniques such as high performance liquid, gas and layer chromatography (including LC-NMR, LC-CD/UV) and capillary electrophoresis.
Method development and comparison of assays in the European and Hungarian Pharmacopoeias. Research and development for drug quality control and registration.
Metabolic ex vivo characterization of urine, amniotic fluid and other biological liquids without separation by direct NMR and combined NMR-MS methods, using also chemometric analysis.
Conformation analysis of polypeptides and small proteins by 2D and 3D NMR techniques. Ligand-protein binding studies.

Key words:

microspeciation
drug analysis
lipophilicity
NMR
protein conformation

Recent publications:

Szakács, Z., Béni, S. & Noszál, B. (2008)
Resolution of carboxylate protonation microequilibria of NTA, EDTE and related complexones
Talanta 74: 666–674.

Boros, M., Kökösi, J., Vámos, J., Kövesdi, I. & Noszál, B. (2007)
Methods for syntheses of N-methyl-DL-aspartic acid derivatives.
Amino Acids 2007 00: 1–9.

Noszál, B., Visky, D. & Kraszni, M. (2006)
Characterisation of ester hydrolysis in terms of microscopic rate constants.
J. Phys. Chem. B 110: 14507–14514.

Szakács Z., Béni Sz, Varga Z., Őrfi L., Kéri Gy. & Noszál B. (2005)
Acid-base profiling of imatinib (Gleevec) and its fragments.
J. Med. Chem. 48: 249–255.

Kraszni, M., Szakács, Z. & Noszál, B. (2004)
Determination of rotamer populations and related parameters from NMR coupling constants: a critical review.
Anal. Bioanal. Chem. 378: 1449–1463.

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Medicinal Chemistry Research Group, Rational Drug Design Laboratory

László Őrfi, Ph.D.

Key words:

medicinal chemistry
synthesis
drugdesign
QSAR

Development of new kinase inhibitor molecules, targeting cancer, inflammation and infectious diseases

In the past 15 years our research team have established a kinase inhibitory compound library containing thousands of molecules in cooperation with several Hungarian and international research groups. The core of this compound library had been constituted of clinically and preclinically relevant lead molecules published in the scientific literature. We have synthesized analogues of these lead molecules and prepared small focused libraries around these compounds. We have utilized all of the traditional and recently developed, high yield reactions of medicinal chemistry in the synthesis of the compounds. We have developed standardized parallel synthetic paths for the preparation of focused libraries ("combinatorial chemistry"). These reaction paths were built up from elementary organic reaction steps (active methylene reactions, diazo-couplings, halogenations, acylations, alkylations, oxidation, reduction, condensations, cyclisations, Suzuki- and other Pd coupling reactions etc.) which make easier the preparation of the focused libraries and give the opportunity of automation.

We have developed QSPR (water solubility, lipophilicity) and QSAR (EGFR, Akt, VEGF, PKNG kinase) models from the calculated and measured properties of the compounds. These models are capable for the reliable prediction of physical-chemical properties and biological activity of planned compounds therefore research costs can be significantly decreased. Recently we have designed and synthesized new inhibitors of EGFR, PDGFR, Her2 and Flk1. Some of these compounds showed antitumor activity in in vivo animal models. In our present research we apply rational drug design methods for the development of kinase inhibitor compounds against therapeutically validated kinase targets. These inhibitors are potential drug candidates for the treatment of tumors, inflammation and some infectious diseases.

Recent publications:

Szántai-Kis, C., Kövesdi, I., Erős, D., Bánhegyi, P., Ullrich, A., Kéri, Gy. & Őrfi, L. (2006)
Prediction oriented QSAR modelling of EGFR inhibition.
Current Medicinal Chemistry 13(3): 277–287.

Szakács Z., Béni Sz, Varga Z., Őrfi L., Kéri Gy. & Noszál B. (2005)
Acid-base profiling of imatinib (Gleevec) and its fragments.
J. Med. Chem. 48: 249–255.

Kéri, Gy., Székelyhidi, Z., Bánhegyi, P., Varga, Z., Hegymegi-Barakonyi, B., Szántai-Kis, C., Hafenbradl, D., Klebl, B., Müller, G., Ullrich, A., Erős, D., Horváth, Z., Greff, Z., Marosfalvi, J., Pató, J., Szabadkai, I., Szilágyi, I., Szegedi, Z., Varga, I., Wáczek, F. & Őrfi, L. (2005)
Drug discovery in the kinase inhibitory field using the Nested Chemical Library™ technology.
Assay and Drug Development Technologies 3(5): 543–551.

Godl, K., Gruss, O.J., Eickhoff, J., Wissing, J., Blencke, S., Weber, M., Degen, H., Brehmer, D., Őrfi, L., Horváth, Z., Kéri, G., Muller, S., Cotten, M., Ullrich, A. & Daub, H. (2005)
Proteomic characterization of the angiogenesis inhibitor SU6668 reveals multiple impacts on cellular kinase signaling.
Cancer Research 65(15): 6919–6926.

Őrfi, L., Wáczek, F., Pató, J., Varga, I., Hegymegi-Barakonyi, B., Houghten, R.A. & Kéri, G. (2004)
Improved, high yield synthesis of 3H-quinazolin-4-ones, the key intermediates of recently developed drugs.
Current Medicinal Chemistry 11(19): 2549–2553.

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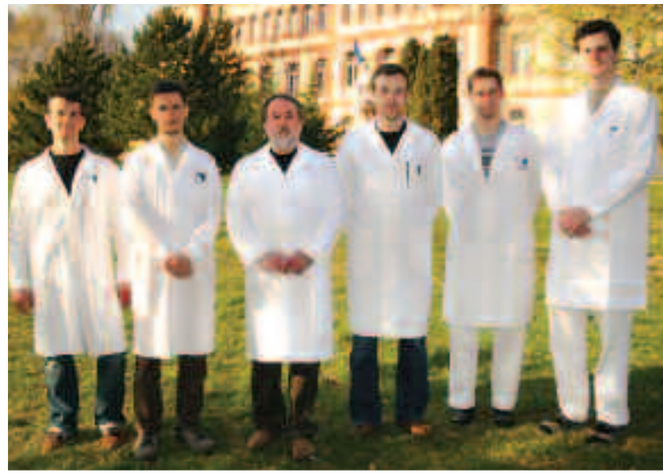

Research Group of Phytochemistry and Pharmaceutical Biotechnology

Éva Szőke, Ph.D., D.Sc.
Professor and Chair

Scientific activity of the research group covers all aspects of modern Pharmacognosy and pharmaceutical biotechnology. Specific aims are focus attention on potential for the development of new drugs from medicinal plants.

Key words:

pharmacognosy
phytochemistry
supercritical fluid extraction
natural antioxidants
pharmaceutical biotechnology

Phytochemical re-evaluation of traditionally used medicinal plant has resulted in isolation and identification of active compounds. New, selective spectroscopic (LC-MS) methods were developed for the determination of alkaloids, phenoloids and lupane-type triterpens; GC-MS methods were used for the analyses of volatile oils and phytosterols. Essential oil research includes valuation and studying the influence of technological and biological factors on their composition. The use of chiral gas chromatography provided possibility to investigate the stereospecifity of essential oils.

As supercritical fluids have been shown to exhibit several advantages in the extraction of natural products from plant matrices our effort was to evaluate whether it can replace organic solvent extraction methods. It was concluded that the yields of some bioactive constituents were 10–20 times higher in supercritical then in the corresponding traditional extracts. Supercritical fluid extracts proved to be true alternatives to the conventional procedures.

Plant polyphenols widely diffused in medicinal plants are successfully applied as antioxidants in the prevention and treatment of various degenerative diseases. Structure-activity relations were established by bioassay-directed characterization of natural antioxidants by using complex examination system. The application of biotechnological methods to the study of medicinal plants: production of bioactive compounds in cell- (fermentation) and in genetically transformed hairy root cultures was investigated. Various factors have been observed playing important part in determining the biosynthetic potential in *in vitro* cultures. Metabolite production improved (10–15 times) by using precursors, hormones and various elicitors. Induced production was noticed by bioregulation or genetic transformation.

Recent publications:

Szőke, É., Máday, E., Tyihák, E., Kuzovkina, I.N. & Lemberkovics, É. (2004)
New terpenoids in cultivated and wild chamomile (in vivo and in vitro).
Journal of Chromatography B 800: 231–238.

Szőke, É., Máday, E., Kiss, A.S. & Lemberkovics, É. (2004)
Effect of magnesium on essential oil formation of genetically transformed and non-transformed chamomile culture.
Journal of the American College of Nutrition 23(6): 763–767.

Kursinszki, L., Hank, H., László, I. & Szőke, É. (2005)
Simultaneous analysis of hyoscyamine, scopolamine, 6,-hydroxyhyoscyamine and apoatropine in Solanaceous hairy roots by reversed-phase high-performance liquid chromatography.
Journal of Chromatography A 1091: 32–39.

Kéry, Á., Balázs, A., Kursinszki, L., Apáti, P., Szőke, É., Blázovics, A., Hagymási, K. & Nagy, É. (2003)
Radical scavenger and antioxidant activities of selected medicinal plants.
Acta Horticulturae 597: 177–184.

Lemberkovics, É., Czinner, E., Szentmihályi, K., Balázs, A. & Szőke, É. (2002)
Comparative evaluation of Helichrysi flos herbal extracts as dietary sources of plant polyphenols, and macro- and microelements.
Food Chemistry 78: 119–127.

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Key words:

nociceptinerg system
biogenic amines
acetycholinesterase reactivators

Nociceptinerg system is the recently recognized member of the opioids with widespread pharmacological activity both in the central nervous system and the periphery. The interrelation of nociceptinerg and the classical biogenic amine-neurotransmission (noradrenergic, dopaminergic, serotonergic, histaminergic) as well as cholinergic is poorly understood, however its better understanding would be needed for design of drugs with new mode of action. The main focus of our in vitro and in vivo studies is the better understanding of the functional role of nociceptin and nocistatin (the two neuropeptides derived from preproorphaninFQ) in the central nervous system, and in such clinical items as primary headaches (migraine,cluster headache) chronic hepatic disorders, cardiovascular disorders.

Recent publications:

Lorke, D.E.,Kalász, H., Petroianu, G.A. & Tekes, K. (2008)
Entry of oximes into the brain: a review.
Curr. Med. Chem. 15(8): 743–753.

Gyenge, M., Kalász, H., Petroianu, G.A., Laufer, R., Kuca, K. & Tekes, K. (2007)
Measurement of K-27, an oxime-type cholinesterase reactivator by high-performance liquid chromatography with electrochemical detection from different biological samples.
J. Chromatogr. A. 1161(1/2): 146–151.

Tekes, K., Gyenge, M., Hantos, M. & Csaba, G. (2007)
Effect of beta-endorphin imprinting during late pregnancy on the brain serotonin and plasma nocistatin levels of adult male rats.
Horm. Metab. Res. 39(7): 479–481.

Tekes, K., Hantos, M., Gyenge, M. & Csaba, G. (2007)
Perinatal alcohol exposure enhances nocistatin levels in adulthood.
Addict. Biol. 12(2): 173–175.

Tekes, K., Hantos, M., Gyenge, M., Karabélyos, C. & Csaba, G. (2006)
Prolonged effect of stress at weaning on the brain serotonin metabolism and sexuality of female rats.
Horm. Metab. Res. 38(12): 799–802.

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Stability Research Group

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Associate Professor and Chair

Key words:

physical ageing
amorphous state
polymer
free volume
positron annihilation lifetime spectroscopy
(PALS)

Different polymers are widely used in pharmaceutical technology for a diversity of purposes. They can be applied as fillers, binders, matrix-forming and film-forming excipients in solid dosage forms, and most of the gelling agents of semisolid preparations and solutions are polymers, as well. Furthermore, a wide variety of packaging materials is based on macromolecules. Although the chemical structure of the above mentioned polymers is rather heterogeneous, their physical state is usually similar, as most of them are amorphous or partly amorphous. A well-known property of such materials is that they undergo physical ageing, which is accompanied by volume and enthalpy relaxation and thus might result in severe structural changes in the polymer. The enhanced molecular mobility, caused by the plasticization effect of absorbed water, has been proposed to be the major underlying factor in chemical and physical instability of amorphous pharmaceutical materials. This so called physical ageing can be initiated by several factors (e.g., humidity) and is manifested in macrostructural (enthalpy and volume) and microstructural (free volume distribution) alterations. These changes also occur during the processing and storage of pharmaceutical dosage forms containing such polymers, thus influencing their stability and bioavailability. Tracking the possible ageing process of polymeric excipients is possible using an array of techniques. Macrostructural changes can be followed by dilatometry and calorimetry, while microstructural alterations can be monitored by means of positron annihilation lifetime spectroscopy, electron spin resonance spectroscopy, fluorescence spectroscopy, small angle X-ray scattering and scanning electron microscopy. Such investigations are of high importance because of the consequences considering the stability of the excipients themselves and dosage forms prepared using these materials.

Recent publications:

Patai, K., Kiss, D., Dévényi, L. & Zelkó, R. (2007)
In utero incrustation of intrauterine systems – consequent complications and monitoring.
Fertil. Steril. 87: 1210–1211.

Zelkó, R., Orbán, Á. & Süvegh, K. (2006)
Tracking of the physical ageing of amorphous pharmaceutical polymeric excipients by positron annihilation spectroscopy.
J. Pharm. Biomed. Anal. 40: 249–254.

Kiss, D., Süvegh, K., Marek, T., Dévényi, L., Novák, Cs. & Zelkó, R. (2006)
Tracking the physical aging of poly(ethylene oxide) – a technical note.
AAPS Pharm. Sci. Tech. 7(4), Article 95.
doi: 10.1208/pt070495.

Zelkó, R. & Süvegh, K. (2005)
Correlation between the release characteristics of theophylline and the free volume of polyvinylpirrolidone.
Eur. J. Pharm. Sci. 24: 351–354.

Zelkó, R. & Süvegh, K. (2004)
Comparison of the enthalpy recovery and free volume of polyvinylpyrrolidone during anomalous glassy to rubbery transition.
Eur. J. Pharm. Sci. 21: 519–523.

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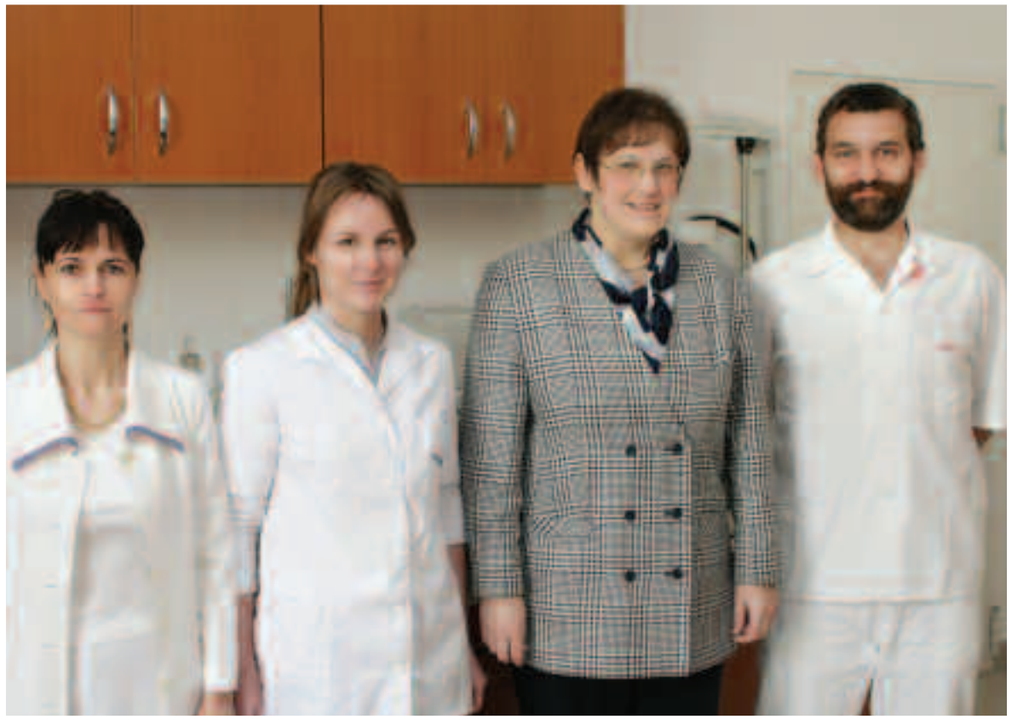

Molecular Oral Biology Research Group

Gábor Varga, Ph.D., D.Sc.
Professor and Chair

The main focus of the group is on topics related to the interface between modern biology and clinical dentistry.

Key words:

oral biology
cell biology
molecular biology
stem cell
gene polymorphism

Postnatal stem cells of dental origin. We isolate cells from human dental pulp and periodontal ligament, to develop in vitro model systems and processes, for identification of stem cells, which have the potential for full or partial regeneration of dental tissues. Cultures containing pluripotent postnatal stem cells from the dental pulp (DPSC), from deciduous pulp (SHED) and periodontal ligament (PDLSC) are prepared. We determine their proliferative capacity and clonogenity, and study the effect of BMPs and extracellular matrix components on proliferation and (trans)differentiation of these cultures.

Human salivary gland model for exploring the molecular mechanisms of epithelial secretion and for developing gene delivery techniques. Primary cultures are prepared of human submandibular gland to provide optimal conditions for the formation of either ductal- or acinar-like polarized epithelia. We use cell lines as reference systems. The HSG cells are capable of ductal-acinar transdifferentiation but it does not form a tight epithelial monolayer. Par-C10, Capan-1, Panc-1 and HPAF can form high-resistance epithelia capable of transepithelial electrolyte and water transport. The work helps to establish the basis for future gene therapeutic interventions by pinpointing possible target genes to correct salivary gland dysfunction.

Polymorphism studies of genes potentially involved in periodontitis and hypodontia. The purpose is to map single nucleotide polymorphisms (SNP) related to these disorders in the Hungarian population. Besides polymorphism of genes that are already implicated as factors involved in periodontitis and hypodontia, new SNPs are identified that have not been considered previously as hazards for oral health. These observations may lead to the development of new diagnostic strategies and provide novel tools for early detection and primary control.

Recent publications:

Rakonczay, Z. Jr., Hegyi, P., Hasegawa, M., Inoue, M., You, J., Iida, A., Ignath, I., Alton, E.W., Griesenbach, U., Óvári, G., Vág, J., Da Paula, A.C., Crawford, R.M., Varga, G., Amaral, M.D., Mehta, A., Lonovics, J., Argent, B.E. & Gray M.A. (2008)
CFTR gene transfer to human cystic fibrosis pancreatic duct cells using a Sendai virus vector.
J. Cell. Physiol. 214: 442–455.

Szlávik, V., Vág, J., Markó, K., Demeter, K., Madarász, E., Oláh, I., Zelles, T., O'Connell, B.C. & Varga, G. (2008)
Matrigel-induced acinar differentiation is followed by apoptosis in HSG cells.
J. Cell. Biochem. 103: 284–295.

Baggaley, E., McLarnon, S., Demeter, I., Varga, G. & Bruce, J.I. (2007)
Differential regulation of the apical plasma membrane Ca^{2+}-ATPase by protein kinase A in parotid acinar cells.
J. Biol. Chem. 282: 37678–37693.

Vág, J., Byrne, E.M., Hughes, D.H., Hoffman, M., Ambudkar, I., Maguire, P. & O'Connell, B.C. (2007)
Morphological and functional differentiation of HSG cells: role of extracellular matrix and trpc1.
J. Cell. Physiol. 212: 416–423.

Rácz, G.Z., Szűcs, Á., Szlávik, V., Vág, J., Burghardt, B., Elliott, A.C. & Varga, G. (2006)
Possible role of duration of PKC-induced ERK activation in the effects of agonists and phorbol esters on DNA synthesis in Panc-1 cells.
J. Cell. Biochem. 98: 1667–1680.

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Salivary Research Laboratory

Tivadar Zelles, Ph.D., D.Sc.
Professor

Key words:

oral biology
cell biology
salivary research

The researchers of the Department of Oral Biology and the Group of Oral Morphology at the Faculty of Dentistry are involved in the saliva and salivary gland studies. The standard body of the working group consisted of three professors. In addition there is a number of faculty members and Ph.D. students involved in the conducted projects. The laboratory is well known for its activities on experimental and human salivary research. Research is conducted in conjunction with other departments of the Dental Faculty. The research focuses on the characterization in functional and structural terms of the salivary gland function and morphology in normal and pathological conditions. The working hypothesis of the unit is that saliva is a key determinant of the oral and general health. Numerous research instruments and equipments are available for research personnel interested in both basic and clinical studies. Investigations and programs are supported by Hungarian National Scientific Research Fund (OTKA) and Health Research Council (ETT) grants.

Recent publications:

Márton, K., Boros, I., Varga, G., Zelles,T., Fejérdy, P., Zeher, M. & Nagy, G. (2006)
Evaluation of palatal saliva flow rate and oral manifestations in patients with Sjögren's syndrome.
Oral Dis. 12: 480–486.

Fehér, E., Batbayar, B., Vér, A. & Zelles, T. (2006)
Changes of the different neuropeptide-containing nerve fibers and immunocells in the diabetic rat's alimentary tract.
Ann. N.Y. Acad. Sci. 1084: 280–295.

Barta, A., Tarján, I., Kittel, Á., Horváth, K., Pósa, A., László, F., Kovács, A., Varga, G. & Zelles, T. (2005)
Endotoxin can decrease isolated rat parotid acinar cell amylase secretion in a nitric oxide-independent manner.
Eur. J. Pharmacol. 524: 169–173.

Barbayar, B., Nagy, G., Kövesi, G., Zelles, T. & Fehér, E. (2004)
Morphological basis of sensory neuropathy and neuroimmunomodulation in minor salivary glands of patients with Sjögren's syndrome.
Arch. Oral Biol. 49: 529–538.

Márton, K., Boros, I., Fejérdy, P. & Madléna, M. (2004)
Evaluation of unstimulated flow rates of whole and palatal saliva in healthy patients wearing comlpete dentures and in patients with Sjögren's sydrome.
J. Prosthet. Dent. 91: 577–581.

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Division of Haematology, 1st Department of Medicine

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Professor

Key words:

lymphomagenesis
myeloproliferative disorders
hairy cell leukemia
metabolic bone disease

The clinical research activity of our group focuses mainly on oncohaematological and haematological-osteological topics. 1. Lymphoma research: In 1989 our group presented the first evidence of the relationship between clinical stage and natural killer cell activity. The national hairy cell leukemia register is functioning in our clinic since a decade. 2. In oncohaematology the role of infection and immunity in lymphomagenesis is of primary interest. We and others have found that ocular adnexal lymphoma is capable to regress after Chlamydia psittaci eradicating therapy. Our collaboration with the dermatological clinic regarding cutaneous lymphomas is very intense. 3. A thorough medical history focusing on haematological abnormalities in the first, second and third degree relatives helps to identify familial occurrence of chronic myeloproliferative disorders. We have identified an unique family with polycythaemia vera (father and son), where JAK2V617F mutation was found in three generations of the family. Further research is necessary to identify which mechanisms are responsible for the development of this myeloproliferative neoplasm as the JAK2 V617F mutation seems to be only a secondary genetic event. Medical history helped us also to identify familial occurrence of congenital thrombocytopenia, where the pathogenesis of the disease was studied with international collaboration. 4. In multiple myeloma bone involement is one of the major causes of morbidity and mortality, but bone involvement should be looked for also in nodal lymphomas as well as in hairy cell leukemia. Earlier work from our group focused on bone remodelling in hairy cell leukemia. With the advent of potentially curative treatment in HCL, our main interest is the effect of new therapeutic possibilities (bisphosphonates, bortezomib) on bone events in multiple myeloma including osteonecrosis of the jaw.

Recent publications:

Marschalkó, M., Csomor, J., Erős, N, Szigeti, A,, Hársing, J., Szakonyi, J., Désaknai, M., Matolcsy, A., Demeter, J. & Kárpáti, S. (2007)
Coexistence of primary cutaneous anaplastic large cell lymphoma and mycosis fungoides in a patient with B-cell chronic lymphocytic leukaemia.
Br. J. Dermatol. 157: 1291–1293.

Demeter, J. (2007)
A krónikus myeloid leukémia modern diagnosztikája és kezelése.
[Modern diagnostics and treatment of chronic myeloid leukemia.]
Pp. 101–105 in: **Demeter, J.** (ed.)
Klinikai hematológia kötelező szinten tartó tanfolyam szakorvosok számára.
J. Hematológia és Transzfuziológia, Suppl. 1/2007.

Nagy, Zs. (2007)
Hematológiai betegségek és a csontrendszer.
[Haematological diseases and bone].
Pp. 49–57 in: **Demeter, J.** (ed.)
Klinikai hematológia kötelező szinten tartó tanfolyam szakorvosok számára.
J. Hematológia és Transzfuziológia, Suppl. 1/2007.

Dong, F., Li, S., Pujol-Moix, N., Luban, N.L., Shin, S.W., Seo, J. H., Ruiz-Saez, A., Demeter, J., Langdon, S. & Kelley MJ. (2005)
Genotype-phenotype correlation in MYH9-related thrombocytopenia.
Br. J. Haematol. 130: 620–627.

Ferreri, A.J., Ponzoni, M., Guidoboni, M., De Conciliis, C., Resti, A. G., Mazzi, B., Lettini, A.A., Demeter, J., Dell'oro, S., Doglioni, C., Villa, E., Boiocchi, M. & Dolcetti, R. (2005)
Regression of ocular adnexal lymphoma after Chlamydia psittaci-eradicating antibiotic therapy.
J. Clin. Oncol. 23: 5067–5073.

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Molecular Genetic Unit, 2nd Department of Pediatrics

György Fekete, M.D., Ph.D., D.Sc., F.R.C.P.
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Congenital adrenal hyperplasia (CAH) is a common inborn endocrine disorder. The aim of our study was to analyze the genotype–phenotype correlation in CAH patients. We identified mutations in 94–99% of the diseased alleles. The role

Key words:

gene polymorphisms
hereditary pediatric diseases

of the sensitizing N363S polymorphism of glucocorticoid receptor (GR) was also examined in CAH patients. We found that the association of sensitizing the GR variant with impaired cortisol production in CAH might be compensatory in mild NC-CAH and may prevent severe intrauterine virilization in classical form.

Primary ciliary dyskinesia (PCD) is a genetically heterogeneous disorder characterized by chronic infections of the airways. Our goal was to identify the DNAL1 gene and establish a novel genetically determined diagnosis of PCD. We were the first to show the interaction of human DNAH5 and DNAL1 with co-immunoprecipitation method. Immunofluorescence staining with anti-DNAH5 and anti-DNALI1 antibodies provides a novel diagnostic tool of PCD.

Nonketotic hyperglycinemia (NKH) is an inborn error of metabolism characterized by accumulation of glycine in body fluids and various neurological symptoms. Our goal was to determine the mutational spectrum of genes, which are part of the glycine cleavage multi-enzyme system. We provided the genetic background of NKH (mutation analysis of GLDC, AMT and GCSH genes), as first result in Hungary.

Polymorphisms of the ABCB1 and ABCG2 genes were analyzed in acute leukemia patients. The primary goal was to find individual treatment options. Connection between the ABCB1 3435T>C, 2677G>T/A, 1236C>T and ABCG2 421C>A, 34G>A genes polymorphisms and the encephalopathy (during the treatments with chemotherapies) and the neutropenic episodes were proved.

Pediatric glioblastoma (pGBM) is a rare, but devastating brain tumor. Our aim was to gain insight into the molecular pathways of pGBM. Our work is the first study of gene expression profiles in pGBM, resulted in active pathways (Ras and Akt) and targets.

Recent publications:

Erdélyi, D.J., Kámory, E., Csókay, B., Andrikovics, H., Tordai, A., Kiss, C., Félné-Semsei, A., Janszky, I., Zalka, A., Fekete, Gy., Falus, A., Kovács, G.T. & Szalai, Cs. (in press)
Synergistic interaction of ABCB1 and ABCG2 polymorphisms predicts the prevalence of toxic encephalopathy during anticancer chemotherapy.
Pharmacogenomics Journal.

Kure, S., Kato, K., Dinopoulos, A., Gail, C., DeGrauw, T.J., Christodoulou, J., Bzduch, V., Kálmánchey, R., Fekete, Gy., Trojovsky, A., Plecko, B., Breningstall, G., Tohyama, J., Aoki, Y. & Matsubara, Y. (2006)
Comprehensive mutation analysis of GLDC, AMT, and GCSH in nonketotic hyperglycinemia.
Human Mutation 27(4): 343–352.

Luczay, A., Török, D., Ferenczi, A., Majnik, J., Sólyom, J. & Fekete, Gy. (2006)
Potential advantage of N363S glucocorticoid receptor polymorphism in 21-hydroxylase deficiency.
European Journal of Endocrinology 154(6): 859–864.

Dolzan, V., Sólyom, J., Fekete, Gy., Kovács, J., Rakosnikova, V., Votava, F., Lebl, J., Pribilincova, Z., Baumgartner-Parzer, S.M., Riedl, S., Waldhause Trojovsky, A., Plecko, B., Breningstall, G., Tohyama, J., Aoki, Y. & Matsubara, Y. (2005)
Mutational spectrum of steroid 21-hydroxylase and the genotype-phenotype association in Middle European patients with congenital adrenal hyperplasia.
European Journal of Endocrinology 153(1): 99–106.

Horváth, J., Fliegauf, M., Olbrich, H., Kispert, A., King, S.M., Mitchison, H., Zariwala, M.A., Knowles, M.R., Sudbrak, R., Fekete, Gy., Neesen, J., Reinhardt, R. & Omran, H. (2005)
Identification and analysis of axonemal dynein light chain 1 in primary ciliary dyskinesia patients.
American Journal of Respiratory Cell and Molecular Biology 33(1): 41–47.

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Krisztina Staub

Research Group of Metabolism and Clinical Genetics

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Key words:

lipoprotein
thrombophilia
endothelin
cholesteryl-ester transfer protein
apolipoprotein E

The main topic of our research activity is focused on the investigation of the pathophysiology of lipoproteins, proinflammatoric and prothrombotic factors play important role in the pathogenesis of atherosclerosis. Polymorphism of genes participating in lipoprotein metabolism, diabetes and thrombogenesis may enhance the cardiovascular risk and influence the course of atherosclerosis.

There are only a few evidences available concerning the influence of genetic thrombophilias on atherogenesis. In the majority of thromboembolic disorders Leiden mutation, a genetic variation of Factor V can be detected. We measured the frequency of Leiden mutation in patients suffering from severe femoropopliteal stenotic atherosclerosis and reoperated due to restenosis occurring after the first reconstructing surgery. The frequency of Leiden mutation was significantly increased in the atherosclerotic patients compared to healthy blood donors and employers. In the same group of patients the occurrence of apolipoprotein ε4 of the apolipoprotein E gene was determined, as well. The number of apolipoprotein E genotypes containing ε4 allele (ε3/4, ε2/4 and ε4/4) was significantly higher in the atherosclerotic patients with peripheral vascular disease and reoperated after the first surgical intervention. In conclusion, Leiden factor and apolipoprotein ε4 allele contribute to the progression of atherosclerosis and may enhance the chance of restenosis in peripheral vascular disease.

Cholesteryl-ester transfer protein (CETP) is a central enzyme of reverse cholesterol transport directed from the peripheral tissues to the liver and to low (LDL) and very low density lipoproteins (VLDL). The activity of CETP shows an inverse correlation with the serum concentration of high density lipoprotein (HDL). According to our observations the I405V polymorphism of CETP gene may influence the cardiovascular risk in patients suffering from severe peripheral atherosclerotic vascular disease.

Recent publications:

Laki, J., Kiszel, P., Vatay, A., Blaskó, B., Kovács, M., Korner, A., Madacsy, L., Blatniczky, L., Almássy, Z., Szalai, C., Rajczy, K., Pozsonyi, E., Karádi, I., Fazakas, A., Hosszúfalusi, N., Pánczél, P., Arason, G.J., Wu, Y.L., Zhou, B., Yang, Y., Yu, C.Y. & Füst, G. (2007)
The HLA 8.1 ancestral haplotype is strangly linked to the C allele of –429T>C promoter polymorphism of receptor of the advanced glycation endproduct (RAGE) gene. Haplotype-independent assotiation of the –429C allele with high hemoglobin (A1C) levels in diabetic patients.
Mol. Immunol. 44(4): 648–655.

Molvarec, A., Nagy, B., Kovács, M., Walentin, S., Imreh, E., Rigó, J. Jr., Szalay, J.. Füst, G., Prohászka, Z. & Karádi, I. (2007)
Lipid, haemostatic and inflammatory variables in relation to the estrogen receptor alpha (ESR1) Pvull and Xbal gene polymorphisms.
Clin. Chim. Acta 380(1/2): 157–164.

Vallus, G., Dlustus, B., Acsády, G., Papp, Z., Skopál, J., Nagy, Z., Prohászka, Z., Romics, L., Karádi, I. & Nagy, B. (2007)
Factor V Leiden and apolipoprotein E genotypes in severe femoropopliteal atherosclerosis with restenosis.
Clin. Chim. Acta 377(1/2): 256–260.

Bíró, A., Dósa, E., Horváth, A., Prohászka, Z., Rugonfalvi Kiss, S., Szabó, A., Karádi, I., Acsády, G., Selmeczi, L., Entz, L., Füst, G. & Romics, L. (2005)
Dramatic changes in the serum levels of anti-cholesterol antibodies after eversion endarterectomy in patients with severe carotid atherosclerosis.
Immunmol. Lett. 99: 51–56.

Zsáry, A., Szűcs, S., Keltai, K., Schneider, T., Rosta, A., Sarman, P., Fenyvesi, T. & Karádi, I. (2004)
Endothelins: a possible mechanism of cytostatics-induced cardiomyopathy.
Leukemia Lymphoma 45: 351–355.

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Key words:

diabetic neuropathy
hepatic neuropathy
somatic neuropathy
sensory neuropathy
autonomic neuropathy

The Neuropathy Research Group at the Semmelweis University has been established in 1982. We assessed the frequency, risk factors and clinical characteristics of neuropathy in patients with diabetes mellitus and chronic liver diseases. Patients with newly diagnosed and long standing Type-1 and Type-2 diabetes mellitus, gestational diabetes mellitus, just as those with fatty liver, alcohol-related cirrhosis, HbsAg-positive and anti-HCV positive chronic liver diseases were studied. Comprehensive assessment of autonomic function and different quantitative sensory tests were applied. As the most reliable method, the Neurometer CPT (Neurotron Incorp., MD, USA) has been used to quantify hypaesthesia and hyperaesthesia evaluating large and small myelinated and small unmyelinated sensory nerve fiber function. We have firstly described autonomic neuropathy in patients with chronic liver diseases. A correlation between the severity of autonomic neuropathy and prolongation of the corrected QT interval has been documented. A rational diagnostic model has been developed for the assessment of the autonomic neuropathy. Our data indicate that para-sympathetic neuropathy contributes to the development of the hypertension in patients with diabetes. We have shown that classical cardiovascular risk factors contribute to the development of neuropathy even in patients with newly diagnosed Type-1 diabetes. Several international scientific cooperations were developed including the EURODIAB IDDM Complications Study. Central manifestations of diabetic neuropathy just as gastrointestinal complications of autonomic neuropathy were studied as part of a long term cooperation with the 1st Department of Medicine, University of Szeged (Tamás Várkonyi, Csaba Lengyel). Based on our scientific achievements a nationwide neuropathy screening and teaching center has been developed, where about 2000 patients with neuropathy are examined yearly and regular small group postgraduate courses are organized.

Recent publications:

Istenes, I., Keresztes, K., Tündik, A., Hermányi, Zs., Putz, Zs., Vargha, P., Kertész, T., Emery, C., Gandhi, R., Tesfaye, S. & Kempler, P. (2007)
Blood pressure response to standing in the diagnosis of autonomic neuropathy: are initial (supine) values of importance?
Diabet. Med. 24: 325–326.

Várkonyi, T., Börcsök, É., Tót, F., Fülöp, Zs., Takács, R., Rovó, L., Lengyel, Cs., Kiss, J.G., Janáky, M., Hermányi, Zs., Kempler, P. & Lonovics, J. (2006)
Severity of autonomic and sensory neuropathy and the impairment of visual- and auditory-evoked potentials in Type 1 diabetes.
Diabetes Care 29: 2325–2326.

Witte, D.R., Tesfaye, S., Chaturvedi, N., Eaton, S.E.M., Kempler, P., Fuller, J.H. & the EURODIAB Prospective Complications Study Group (2005)
Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus.
Diabetologia 48: 164–171.

Tesfaye, S. & Kempler, P. (2005)
Painful diabetic neuropathy.
Diabetologia 48: 805–807.

Keresztes, K., Istenes, I., Hermányi, Zs., Vargha, P., Barna, I. & Kempler, P. (2003)
Risk factors of autonomic and sensory nerve dysfunction in patients with newly diagnosed type 1 diabetes.
Diabetes Care 26: 2213–2214.

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Technicians:
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Clinical Research Laboratory, 1st Department of Medicine

Péter Lakatos, M.D., Ph.D., D.Sc.
Professor

Key words:

molecular biology
bone metabolism
metabolic bone diseases
thyroid

The investigation of bone metabolism has been in the focus of our group for more than 50 years. By now, we cover a number of different research areas including clinical sciences as well as basic research. We have performed extensive studies on bone cell and organ cultures looking for signal transduction pathways, cytokine actions and systemic hormonal effects. We also participate in pivotal clinical trials that included a number of thyroid works. During the past 12 years, we concentrated on molecular biology of the bone tissue and the relation of calcium metabolism to cardiovascular diseases and cancer development. The starting point in this work was the red deer model that was established together with Prof. László Orosz from ELTE University. Antlers of a red deer stag are large branched bony structures that shed each year then re-grow. The process of calcification of the developing antlers of the stag is so rapid that grazing in June does not cover its calcium requirements. The missing part is deposited from the skeletal bones, leading to calcium depletion and bone loss, i.e. osteoporosis. This osteoporosis reverses and re-calcification is completed in 3–4 weeks (in July) when the stag feeds on the lush calcium-rich vegetation and rests only. Thus, the red deer constitutes an extremely plausible model for osteoporosis including the potential of studying the mechanism of complete restoration of lost bone tissue. We could identify gene expression patterns in the skeletal bones of the red deer stag that are involved in this bone loss and its reversal. We have verified the role of these genes in human bone tissues of different metabolic bone diseases, opening up a brand new way of anabolic treatment of osteoporosis. We also study calcium metabolism-related genes in cardiovascular diseases and cancers.

Recent publications:

Lazáry, Á., Balla, B., Kósa, J.P., Bácsi, K., Nagy, Z., Takács, I., Varga, P.P., Speer, G. & Lakatos, P. (2007)
Effect of gypsum on proliferation and differentiation of MCT3T3-E1 mouse osteoblastic cells.
Biomaterials 28: 393–399.

Bácsi, K., Kósa, J.P., Borgolya, G., Balla, B., Lazáry, Á., Nagy, Z., Horváth, C., Speer, G. & Lakatos, P. (2007)
CYP3A7*1C polymorphism, serum dehydroepiandrosterone sulfate level, and bone mineral density in postmenopausal women.
Calcif. Tissue Int. 80: 154–159.

Gyurján, I., Molnár, A., Borsy, A., Stéger, V., Hacklet, L., Zomborszky, Z., Papp, P., Duda, E., Dea, F., Lakatos, P., Puskás, G.L. & Orosz, L. (2007)
Gene expression dynamics in deer antler: mesenchymal differentiation toward chondrogenesis.
Mol. Genet. Genomics 277: 221–235.

Donáth, J., Speer, G., Poór, G., Gergely, P. Jr., Tabak, A. & Lakatos, P. (2004)
Vitamin D receptor, oestrogen receptor-alpha and calcium-sensing receptor genotypes, bone mineral density and biochemical markers in Paget's disease of bone.
Rheumatology (Oxford) 43: 692–695.

Speer, G., Szenthe, P., Kósa, J.P., Tabak, A., Folhoffer, A., Fuszek, P., Cseh, K. & Lakatos, P (2006)
Myocardial infarction is associated with Sp1 binding site polymorphism of collagen type 1A1 gene.
Acta Cardiol. 61: 321–325.

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Clinical Nephrology Research Group

István Mucsi, M.D., Ph.D.
Associate Professor

Our research interest covers diverse areas, such as: 1) Molecular mechanisms of the progression of renal fibrosis; 2) renal and post-transplant anemia; 3) disorders of the calcium and phosphate metabolism in CKD patients; 4) cardiovascular morbidity in CKD patients; 5) malnutrition-inflammation complex syndrome (MICS).

Key words:

molecular mechanisms of renal fibrosis
renal anemia
chronic inflammation
cardiovascular disease
disorders of calcium and phosphate metabolism

In collaborations with laboratories in Europe and Canada we have identified salient intracellular signaling mechanisms contributing to the fibrogenic effects of angiotensin II and transforming growth factor-beta. We have also studied the regulation of epithelial-mesenchymal transition in renal tubular epithelial cells.

We have studied the prevalence and clinical significance of vitamin D deficiency in dialysis patients and assessed the effect of native vitamin D supplementation in these patients. We have collected data on the significance of reduced bone density in dialysis patients.

Currently we study the association between calcium and phosphate metabolism, renal bone disease and reduced bone mass versus cardiovascular calcification, endothelial dysfunction and morbidity and mortality.

Finally, we have assessed the correlates of anemia both in dialysis and kidney transplanted patients in cross sectional studies. In a large prospective cohort study we have demonstrated that anemia predicts mortality in kidney transplanted patients. Now we assess the association of the malnutrition-inflammation complex syndrome with bone disease, anemia and morbidity and mortality in kidney transplanted patients.

Dr. Mucsi is an internationally recognized nephrologist with a strong interest in interdisciplinary research, intracellular signaling and clinical epidemiology. He has published 64 papers, 15 book chapters. Internationally he has active collaborations both in Europe (The United Kingdom, Finland, Germany) and in North America (Canada, Ann Arbor Collaborative for Health, US). His cumulative impact factor is 122, Hirsch index 14 with 603 independent citations.

Recent publications:

Sebe, A., Leivonen, S.-K., Fintha, A., Masszi, A., Rosivall, L., Kähäri, V.-M. & Mucsi, I. (2008)
Transforming growth factor-, induced alpha-smooth muscle cell actin expression in renal proximal tubular cells is regulated by p38, mitogen activated protein kinase, extracellular signal regulated protein kinase1,2 and the SMAD signaling during epithelial-myofibroblast transdifferentiation.
Nephrol. Dial. Transplant. 23(5): 1537–1545.

Molnár, M. Zs., Czira, M., Ambrus, Cs., Szeifert, L., Szentkirályi, A., Bekő, G., Rosivall, L., Remport, A., Novák, M. & Mucsi, I. (2007)
Anemia is associated with mortality in kidney transplanted patients – a prospective cohort study.
Am. J. Transplant. 7(4): 818–824.

Othmane Tel, H., Bakonyi, G., Egresits, J., Fekete, B.C., Fodor, E., Járai, Z., Jekkel, C., Nemcsik, J., Szabó, A., Szabó, T., Kiss, I. & Tisler, A. (2007)
Effect of sevelamer on aortic pulse wave velocity in patients on hemodialysis: a prospective observational study.
Hemodial. Int. 11(Suppl. 3): S13–S21.

Molnár, M. Zs., Novák, M., Ambrus, Cs., Kovács, A., Pap, J., Remport, A., Szeifert, L. & Mucsi, I. (2005)
Anemia in kidney transplanted patients.
Clin. Transplant. 19(6): 825–833.

Mucsi, I., Almási, Cs., Deák, Gy., Marton, A., Ambrus, Cs., Berta, K., Lakatos, P., Szabó, A. & Horváth, Cs. (2005)
Serum 25(OH)-vitamin D levels and bone metabolism in patients on maintenance hemodialysis.
Clin. Nephrol. 64(4): 288–294.

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Endocrinological Research Group

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Professor

Key words:

metabolic disorders
cortisol metabolism
11-beta-hydroxysteroid dehydrogenase
glucocorticoid receptor gene polymorphisms

Cortisol regulates a wide range of physiological functions, including metabolic and homeostatic processes. The action of cortisol on target organs is partly determined at the prereceptor level by the 11β-hydroxysteroid dehydrogenase type 1 and type 2 isoenzymes (11β-HSD1 and 11β-HSD2), which catalyse the interconversion of hormonally active cortisol and inactive cortisone. Alterations in glucocorticoid receptor (GR) sensitivity may also modify cortisol-induced biological responses. The principal aim of the research is to identify and characterize naturally-occurring variants of the HSD11B1, HSD11B2 and GR genes which may be linked to alterations in biological action and metabolism of cortisol reportedly present in various human disorders including hypertension, diabetes mellitus, metabolic syndrome, polycystic ovary syndrome, acromegaly and renal diseases. The studies include an extensive search for nucleotide sequence variants of the coding region of the HSD11B1, HSD11B2 and GR genes using an in silico approach. The natural occurrence of these polymorphisms are verified by population-based studies, then the results are correlated with parameters of cortisol metabolism and glucocorticoid sensitivity. The functional significance of gene variants is directly tested in in vitro expression systems using COS1 cells. Finally, haplotype analysis is also performed to evaluate the impact of coexistence of different functionally important polymorphisms of these genes on clinical phenotype. It is presumed, that the studies may reveal new data which lead to a better understanding of genetic components of altered cortisol action and metabolism. It seems possible that analysis of haplotype patterns may provide clinically useful data on the risk of disorders characterized by altered cortisol action and metabolism, or it may help to predict the risk of adverse effects associated with glucocorticoid treatment.

Recent publications:

Gergics, P., Patócs, A., Majnik, J., Balogh, K., Szappanos, A., Tóth, M. & Rácz, K. (2006)
Detection of the Bcl I polymorphism of the glucocorticoid receptor gene by single-tube allele-specific polymerase chain reaction.
J. Steroid Biochem. Mol. Biol. 100: 161–166.

Majnik, J., Patócs, A., Balogh, K., Tóth, M., Gergics, P., Szappanos, A., Mondok, A., Borgulya, G., Pánczél, P., Prohászka, Z. & Rácz, K. (2006)
Overrepresentation of the N363S variant of the glucocorticoid receptor gene in patients with bilateral adrenal incidentalomas.
J. Clin. Endocrinol. Metab. 91: 2796–2799.

Likó, I., Igaz, P., Patócs, A., Tóth, S., Pázmány, T., Tóth, M. & Rácz, K. (2005)
Sequence variants of the ligand-binding domain of the glucocorticoid receptor gene and their functional consequences on the three dimensional protein structure.
Curr. Med. Chem. 11: 3229–3237.

Patócs, A., Likó, I., Varga, I., Gergics, P., Boros, A., Futó, L., Kun, I., Bertalan, R., Tóth, S., Pázmány, T., Tóth, M., Szűcs, N., Horányi, J., Gláz, E. & Rácz, K. (2005)
Novel mutation of the CYP17 gene in two unrelated patients with combined 17alpha-hydroxylase/17,20-lyase deficiency: demonstration of absent enzyme activity by expressing the mutant CYP17 gene and by three-dimensional modeling.
J. Steroid Biochem. Mol. Biol. 97: 257–265.

Majnik, J., Patócs, A., Balogh, K., Tóth, M. & Rácz, K. (2004)
A rapid and simple method for detection of Asn363Ser polymorphism of the human glucocorticoid receptor gene.
J. Steroid Biochem. Mol. Biol. 92: 465–468.

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Dr. Henrietta Butz, Dr. Péter Reismann
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Mária K. Vaczula

Pediatric Nephrology Research Group

György Reusz, M.D., D.Sc.
Professor

Our research is based on two pillars: first, the description of the genetic background of kidney injury in children with urinary tract infections (UTI), the most common cause of kidney damage in children and a specific model involving genes of innate immunity following renal transplantation (Tx).

Key words:

uremia
transplantation
cardiovascular risk
pulse wave velocity
calcium metabolism

Second, non-invasive monitoring used to assess cardiovascular damage of CRF.
1. Gene polymorphisms. We studied the role of the heat shock proteins (HSP) and the toll like receptors (TLR) on recurrent UTI and on long-term graft survival following Tx. The presence of the alleles HSPA1B 1267G and TLR4 896G increase the risk of recurrent UTI independently of other factors, which requires the reconsideration of the actual therapeutic strategies (chemoprophylaxis).
TLR4 299G was coupled with long term graft survival indicating a decreased proinflammatory response and protection against acute rejection. The presence of HSP72 1267G is cytoprotective and increases graft survival.
2. CV damage is the leading cause of morbidity and mortality among patients with chronic renal failure. Studies in adults suggest that transplantation may reduce the overall cardiovascular risk caused by CRF by slowing down and/or even reversing the involved pathological processes. Autonomic nervous dysfunction (AND) and arterial stiffness (AS) are independent CV risk factors CRF.
Heart rate variability (HRV) is used to characterize AND, whereas pulse wave velocity (PWV) serves as a measure of arterial stiffness. According to our results AND is already present in children with CRF, it is due to sympathetic overactivity and is reversible following Tx. We established pediatric normal values for PWV. PWV is increased in Tx compared to healthy controls and decreased compared to CRF. Disturbed Ca-P metabolism and the calcitriol treatment before transplantation may have a major role in determining arterial stiffness after transplantation. Renal transplantation may have a beneficial effect on PWV.

Recent publications:

Kis, E., Cseprekál, O., Horváth, Zs., Katona, G., Fekete, B.C., Hrapka, E., Szabó, A., Szabó A.J., Fekete, A. & Reusz, Gy.S. (2008)
Pulse wave velocity in end-stage renal disease: influence of age and body dimensions.
Pediatr. Res. 63: 95–98.

Károly, É., Fekete, A., Bánki, N.F., Szebeni, B., Vannay, Á., Szabó, A.J., Tulassay, T. & Reusz, Gy. S. (2007)
Heat shock protein 72 (HSPA1B) gene polymorphism and toll-like receptor (TLR) 4 mutation are associated with increased risk of urinary tract infection in children.
Pediatr. Res. 61: 371–374.

Studinger, P., Lénárd, Z., Mersich, B., Reusz, Gy.S. & Kollai, M. (2006)
Determinants of baroreflex function in juvenile end-stage renal disease.
Kidney Int. 69: 2236–2242.

Tory, K., Horváth, E., Süveges, Zs.. Fekete, A., Sallay, P., Berta, K., Szabó, T., Szabó, A., Tulassay, T. & Reusz, Gy.S. (2004)
Effect of propranolol on heart rate variability in patients with end-stage renal disease: a double-blind, placebo-controlled, randomized crossover pilot trial.
Clin. Nephrol. 61: 316–323.

Amann, K., Törnig., J, Kugel, B., Gross, M.L., Tyralla, K., El-Shakmak, A., Szabó, A. & Ritz, E. (2003)
Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia.
Kidney Int. 63: 1296–1301.

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Marina Varga, M.D.
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Lipid and Atherosclerosis Research Group

László Romics, M.D., Ph.D.
Professor Emeritus,
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Key words:

lipid homeostasis
apolipoprotein A
HDL
inflammation
chronic heart failure

The cholesterol paradox in chronic heart failure

Chronic heart failure (CHF) is one of the biggest public health problems in the developed societies. CHF is considered a complex syndrome having an affect on most of the organs, causing changes in the immunological and nutritional status, haemopoesis, liver function, respiration, and activation of the neurohormones. According to recent findings low serum cholesterol levels are related to impaired prognosis in patients with CHF.

The aim of our studies is to investigate the correlation between low serum lipid levels and the severity of the disease, to determine the prognostic activity of low cholesterol, and try to define the reason/relationship of low lipid levels with other markers of CHF. The ongoing inflammation and worsening heart failure are both decreasing total cholesterol levels.

We are intending to perform a complex, prospective clinical research, with the participation of 200 patients suffering of chronic heart failure. Total cholesterol, triglycerides, HDL, LDL, VLDL, lipoprotein A, ApoA1, ApoB-100 levels will be measured. Determination of polymorphisms, with potential influence on lipid metabolism, including ApoE, CEPT, HL, LPL, ApoA5, will be determined. The patients will be followed by and cardiovascular events/mortality will be recorded. At the end of the study a complex data base containing basic clinical data, mode of therapy, diet and quality of life, biomarker levels and genetic factors will be built. Based on the results of or study we expect to better understand the causes, pathways and intervention points of cardiac cachexia, malnutrition, anemia and worse prognosis in CHF. As a conclusion, our data may provide a basis for changes in therapeutic lipid target levels in defined patient populations, and show the exact place of nutritional and medical interventions in chronic heart failure. These new therapeutical standards may apply for other chronic devastating diseases, such as chronic renal failure, as well.

Recent publications:

Szabó, A., Laki, J., Madsen, H.O., Dósa, E., Prohászka, Z., Rugonfalvi-Kiss, S., Kókai, M., Acsádi, G., Karádi, I., Entz, L., Selmeci, L., Romics, L., Füst, G., Garred, P. & Cervenak, L. (2007)
Early rise in serum VEGF and PDGF levels predisposes patients with a normal MBL2 genotype to restenosis after eversion endarterectomy.
Stroke 38(8): 2247–2253.

Vallus, G., Dlustus, B., Acsády, G., Papp, Z., Skopál, J., Nagy, Z., Prohászka, Z., Romics, L., Karádi, I. & Nagy, B. (2007)
Factor V Leiden and apolipoprotein E genotypes in severe femoropopliteal atherosclerosis with restenosis.
Clin. Chim. Acta 377(1/2): 256–260.

Rugonfalvi-Kiss, S., Dósa, E., Madsen, H.O., Endrész, V., Prohászka, Z., Laki, J., Karádi, I., Gönczöl, E., Selmeci, L., Romics, L., Füst, G., Entz, L. & Garred, P. (2005)
High rate of early restenosis after carotid eversion endarterectomy in homozygous carriers of the normal mannose-binding lectin genotype.
Stroke 36(5): 944–948.

Dósa, E., Rugonfalvi-Kiss, S., Prohászka, Z., Szabó, A., Karádi, I., Selmeci, L., Romics, L., Füst, G., Acsády, G. & Entz, L. (2004)
Marked decrease in the levels of two inflammatory markers, hs-C-reactive protein and fibrinogen in patients with severe carotid atherosclerosis after eversion carotid endarterectomy.
Inflamm. Res. 53(11): 631–635.

Jánoskuti, L., Förhécz, Z., Hosszúfalusi, N., Kleiber, M., Walentin, S., Bálint, O., Duba, J., Rugonfalvi-Kiss, S., Romics, L., Karádi, I., Füst, G. & Prohászka, Z. (2005)
High levels of C-reactive protein with low total cholesterol concentrations additively predict all-cause mortality in patients with coronary artery disease.
Eur. J. Clin. Invest. 35(2): 104–111.

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Diabetes and Metabolism Study Group

Anikó Somogyi, M.D., Ph.D., D.Sc.
Associate Professor

Diabetes and Genetics:
Although the most common form of diabetes has a complex genetic background involving numerous genetic and environmental risk factors, only a few components are well documented. Our study group is designated to search for novel risk-factors of T2DM, and particularly concentrates on the interaction of environmental and genetic risk factors. Our final goal is a better understanding of the complex environmental and genetic background of T2DM.

Key words:

diabetes
arteriosclerosis
oxidative stress
depression
genetics

Diabetes and Depression:
Clinical evidence suggests that the prevalence of depression is twice as high in diabetic patients compared to the general population. The presence of depression has a negative effect on the compliance of diabetic patients, increasing the frequency of diabetes complications. Our study group sets out to investigate the possible causes, effects, and genetic background of this co-morbidity (i. e., gene environment interactions).
Methods: DNA sampling, self reported depression and anxiety questioners.

Diabetes and the Incretin System:
Dysfunction of entero-insular axis and the failure of islet beta-cell adaptation might contribute to the development of T2DM in addition to and independently from other well known factors, such as insulin resistance. In our study we are investigating if there is any alteration in the entero-insular axis (serum DPP-4 activity and Incretin hormone levels – fasting and prandial) in patients with T2DM compared to healthy controls.
Methods: Elisa.

Diabetes and its Complications:
The pathogenesis of the late complications of diabetes mellitus is still unclear from many aspects. In diabetes as a result of hyperglycaemia increased oxidative stress causes endothelial dysfunction. Endothelial dysfunction is one of the first signs of late diabetic complications and it is a result of a complex malfunction of many endothelium derived relaxation and contracting factors. Our study group conducts in vivo and in vitro human and animal studies. Our recent investigations discuss changes of oxidative stress, antioxidants, (vitamin A and E), vasoactive peptides (such as Endothelin 1 and Adrenomedullin) and the NO/cGMP pathway during fasting and in postprandial states.
Methods: Radioimmunoassay, Elisa, Electron Spin Resonance Spectroscopy, HPLC.

Recent publications:

Somogyi, A., Rosta, K., Pusztai, P., Tulassay, Zs. & Nagy, G. (2007)
Antioxidant measurements.
Physiol. Meas. 28: R41–R55.

Somfai, G. M., Knippel, B., Ruzicska, E., Stadler, K., Tóth, M., Salacz, G., Magyar, K. & Somogyi, A. (2006)
Increased oxidative stress and inflammation in streptozotocin-induced diabetic rats and their relationship with soluble SSAO activity.
Neurochem. Int. 48: 746–752.

Farkas, K., Jermendy, ?, Herold, M., Ruzicska, É., Sasvári, M. & Somogyi, A. (2004)
Impairment of the NO/GMP pathway in the fasting and postprandial state in type 1 diabetes mellitus.
Exp. Clin. Endocr. Diab. 112: 258–263.

Ruzicska, E., Földes, G., Lakó-Futó, Z., Szénási, G., Tulassay, Zs., Ruskoaho, H., Tóth, M. & Somogyi A. (2004)
The cardiac gene expression of natriuretic substances altered in streptozotocin-induced diabetes during pressure overload.
J. Hypertension 22: 1191–1200.

Stadler, K., Jenei, V., Bölcsházi, V.G., Somogyi, A. & Jakus, J. (2003)
Increased nitric oxide levels as an early sign of premature aging in diabetes.
Free Rad. Biol. Med. 35: 1240–1251.

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Hepatology Unit

Ferenc Szalay, M.D., Ph.D., D.Sc.
Professor

The main field of our scientific activity is clinical research on liver diseases. We study the hepatic and extrahepatic complications of chronic liver diseases as metabolic bone disease and autonomic neuropathy. We investigate epidemiological, clinical and genetic aspects of Wilson's disease using advanced molecular biological methods. Different aspects of chronic intrahepatic cholestatic liver diseases as primary biliary cirrhosis are also investigated. Serum osteoprotegerin, leptin, soluble leptin receptor, alfa2HS glycoprotein, dipeptidyl-peptidase (DPP IV), sensory and autonomic neuropathy, the endothelial function is investigated in primary biliary cirrhosis, chronic C hepatitis and other liver diseases. The biliary and hepatic complications of inflammatory bowel diseases were also studied.

We perform investigations in experimentally induced liver cirrhosis and hepatocellular carcinoma model in rat as well. Bone abnormalities and nociceptin (endogenous opioid like receptor agonist) alterations were detected.

Our work is performed in frame of national and international cooperation. We participate in the work of EuroWilson study group presenting epidemiological and clinical data to the European database. We described new mutations of ATP7B gene in Wilson's disease patients from Hungary.

We contribute to the liver transplantation program in Hungary. More that 300 liver transplantation have been performed. The pre and post transplantation care, the research on osteopathy, autonomic function is a subject of our ongoing work.

We participate in a number of international multicenter clinic pharmacological trials on the treatment of chronic hepatitis C, primary biliary cirrhosis, autoimmune hepatitis and complications of liver cirrhosis as portosystemic encephalopathy and ascites.

Our results may contribute to the better understanding of the pathomechanism of liver diseases and their complications, and also to the earlier diagnosis and appropriate treatment.

Key words:

hepatic osteopathy
Wilson's disease
autonomic neuropathy
viral hepatitis
primary biliary cirrhosis

Recent publications:

Folhoffer, A., Ferenci, P., Csák, T., Horváth, A., Hegedűs, D., Firneisz, G., Osztovits, J., Kósa J.P., Willheim-Polli, C., Szőnyi, L., Abonyi, M., Lakatos, P.L. & Szalay, F. (2007)
Novel mutations of the ATP7B gene among 109 Hungarian patients with Wilson's disease.
Eur. J. Gastroenterol. Hepatol. 19: 105–111.

Ferenci, P., Czlonkowska, A., Merle, U., Szalay, F., Gromadzka, G., Yuradin, C., Vogel, W., Bruha, R., Hartmut, T., Schmidt, W. & Stremmel, ? (2007)
Late-onset Wilson's disease.
Gastroenterology 132: 1294–1298.

Szalay, F., Folhoffer, A., Horváth, A., Csák, T., Speer, G., Nagy, Zs., Lakatos, P., Horváth, C., Habior, A., Tornai, I. & Lakatos, P. L. (2005)
Serum leptin, soluble leptin receptor, free leptin index and bone mineral density in patients with primary biliary cirrhosis.
Eur. J. Gastroenterol. Hepatol. 17: 923–928.

Lakatos ,P. L,. Bajnok, E., Tornai, I., Folhoffer, A., Horváth, A., Lakatos, P., Habior, A. & Szalay F. (2004)
Insulin-like growth factor I gene microsatellite repeat, collagen type Ialfa1 gne Sp1 polymorphism, and bone disease in primary biliary cirrhosis.
Eur. J. Gastroenterol. Hepatol. 16: 753–759.

Szalay, F., Dalma, H., Lakatos, P.L., Tornai, I., Bajnok, E., Dunkel, K. & Lakatos, P. (2003)
High serum osteoprotegerin and low RANKL in primary biliary cirrhosis.
J. Hepatol. 38: 395–400.

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Research Laboratory of Pediatrics and Nephrology 1st Department of Pediatrics and the Hungarian Academy of Sciences, Szentágothai János Knowledge Center

Tivadar Tulassay, M.D., Ph.D.
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Member of the Hungarian Academy of Sciences

The main research interest of the group is dedicated to the altered balance of proliferative and antiproliferative processes which may occur in diseases beginning in the childhood and manifest throughout the entire life.

Key words:

molecular biology
immunology
neonatology
diabetes
gastroenterology

Imprinting of civilization diseases in low birth weight (LBW) infants

In our earlier investigations an increased susceptibility to chronic vascular and endothel-related disorders was detected in young adulthood born with LBW. Altered endocrine milieu along with genetic polymorphisms may contribute to this phenomenon. Currently we investigate the role of altered immunity in this process. We are also developing flow cytometry methods in order to describe kinetic alterations of intracellular processes.

Gastroenterological studies

We have verified an altered expression of toll-like receptors (TLR) in the mucous membrane of patients with immune mediated gastroenterological disorders. In order to investigate the impact of TLR2, TLR4 and TLR9 expression on disease progression we analyze the association of TLRs expression with peroxisome proliferator activated receptor gamma. Our hypothesis is that the impaired expression of this transcriptional factor may be a contributor to the development of inflammatory bowel and celiac disease.

Diabetes-related projects

Based on a biobank (500 blood samples and clinical data of type 1 diabetic patients) we examine the immuno-genomics of T1DM and association between the risk of diabetes and carrier state of several genetic polymorphisms.

Molecular biological techniques

In recent years we investigated the link between renal ischaemia/reperfusion injury and vascular endothelial factor (VEGF). We described the biology of VEGF and the prevalence of genetic polymorphisms in clinical disorders. We have successfully constructed the VEGF165-protein with the aid of recombinant gene technique, and established a breakthrough diagnostic system to detect different VEGF isoforms.

Recent publications:

Treszl, A., Kaposi, A., Hajdú, J., Szabó, M., Tulassay, T. & Vásárhelyi, B. (2007)
The extent that genotype information may add to the prediction of disturbed perinatal adaptation: none, minor or major?
Pediatric Res. 62: 610–614.

Kaposi, A.S., Veress, G., Vásárhelyi, B., Macardle, P., Bailey, S., Tulassay, T. & Treszl, A. (2007)
Cytometry-acquired calcium-flux data analysis in activated lymphocytes.
Cytometry A: Dec. 28, 2007.

Szebeni, B., Veress, G., Dezsőfi, A., Rusai, K., Vannay, Á., Bokodi, G., Vásárhelyi, B., Korponay-Szabó, I.R., Tulassay, T. & Arató, A. (2007)
Increased mucosal expression of Toll-like receptor (TLR)2 and TLR4 in coeliac disease.
J. Pediatr. Gastroenterol. Nutr. 45(2): 187–193.

Hermann, C., Krikovszky, D., Füst, G., Kovács, M., Körner, A., Szabó, A., Vannay, Á. & Madácsy, L. (2005)
Association between IL-6 polymorphism and the age at the onset of type 1 diabetes. Epistatic influences of the TNFα and IL-1β polymorphisms.
Eur. Cytokine Netw. 16: 277–228.

Vannay, Á., Fekete, A., Adori, C., Tóth, T., Losonczy, G., László, L., Vásárhelyi, B., Tulassay, T. & Szabó, A. (2004)
Divergence of renal vascular endothelial growth factor mRNA expression and protein level in post-ischaemic rat kidneys.
Exp. Physiol. 89: 435–444.

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Key words:

microarray
colorectal tumors
Helicobacter pylori
bioinformatics
gene expression

The new DNS and RNA microarray methods provide outstanding advantages over conventional molecular biologic methods for the research of gastrointestinal disorders. An Affimetrix 3000 Gene Scanner (U133 plus 2.0) installed at the 2nd Department of Medicine, Semmelweis University is suitable for processing whole genom microarrays. Using the high-throughput microarray technology, the research dealing with gastrointestinal disorders includes the following main topics: characterization of molecular alterations of gastric mucosa obtained from peptic lesions with and without Helicobacter infection; elucidation of the mechanisms leading to alterations in cell functions in NSAID-induced gastric mucosal lesions; examination of mRNA expression of the intestinal mucosa in inflammatory bowel disorders; comparison of gene expression profiles of peripheral blood samples obtained from patients with various gastrointestinal disorders, and identification of alterations in mRNA expression in colorectal cancer using a comparative genomic approach. The data obtained from mRNA expression microarrays are confirmed with quantitative real-time multiple RT-PCR and with immunohistochemistry. The tissue microblock approach used for immunohistochemistry is able to analyze 144 samples collected from gastrointestinal biopsies. Target genes are sequenced with an automated DNA sequencer. The results of mRNA expression are analysed and compared together with those obtained from DNA sequencing. For the cellular localization of possible alterations found in these studies, different types of cells are dissected from tissue slices with the use of a microdissector and their DNA and are evaluated and compared. It is expected that the use of bioinformatics for the evaluation of disease-specific genetic data and their association with clinical and pathologic findings may reveal novel pathogenetic pathways and may provide new knowledge on molecular mechanisms of gastrointestinal disorders.

Recent publications:

Ficsor, L., Varga, V.S., Tagscherer, A., Tulassay, Zs. & Molnár, B. (2008)
Automated classification of inflammation in colon histological sections based on digital microscopy and advanced image analysis.
Cytometry Part A, 73: 230–237.

Galamb, O., Győrffy, B., Sipos, F., Spisák, S., Németh, A.M., Miheller, P., Tulassay, Zs., Dinya, E. & Molnár, B. (2007)
Inflammation, adenoma and cancer: objective classification of colon biopsy specimens with gene expression signature.
Cancer Biomarkers 3: 1–13.

Galamb, O., Sipos, F., Molnár, B., Szőke, D., Spisák, S. & Tulassay, Zs. (2007)
Evaluation of malignant and benign gastric biopsy specimens by mRNA expression profile and multivariate statistical methods.
Cytometry Part B, 72B: 299–309.

Ficsor, L., Varga, V., Bérczi, L., Miheller, P., Tagscherer, A., Wu, M.L., Tulassay, Zs. & Molnár, B. (2006)
Automated virtual microscopy of gastric biopsies.
Cytometry Part B, 70B: 423–431.

Hritz, I., Herszényi, L., Molnár, B., Tulassay, Zs. & Prónai, L. (2005)
Proton pump inhibitor co-therapy normalizes the increased cell turnover of the gastric mucosa both in NSAID and selective COX-2 users.
Int. J. Immunopathol. Pharmacol. 18: 75–84.

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Unit of Pelvic Floor Dysfunction

Imre Romics, M.D., Ph.D., D.Sc.
Professor and Chair

The pelvic floor dysfunction, especially urinary incontinence and voiding dysfunctions are common complications in patients underwent radical prostatectomy, or radical cysto-prostatectomy with orthotopic bladder replacement.

Key words:

prostate cancer
bladder cancer
urinary incontinence
urodynamics
pelvic floor

Urinary incontinence influences the quality of life of these patients significantly. The cost of urinary incontinence can be reduced with preoperative patient selection according to their pelvic floor status.
Our aim are to investigate the prae- and peri-operative risk factors associated with urinary incontinence, to develop a non invasive method for examination of preoperative pelvic floor muscle function and to improve the rehabilitation of incontinent patients. During a prospective study we analyzed the effects of radical retropubic prostatectomy (RRP) on bladder and sphincter function by comparing preoperative and postoperative urodynamic data.
Our results showed that the sphincter incompetence is the primary reason of urinary incontinence after radical prostatectomy. Non published data demonstrated that the urinary incontinence after radical cysto-prostatectomy with neobladder replacement can be explained through urinary sphincter incompetence and decreased neobladder capacity. Multivariate analyses proved that the postoperatively measured shorter posterior urethral length (sphincter length and proximal urethra stump length) is the only independent risk factor for urinary incontinence after radical prostatectomy. We suggest the anal sphincterometry, as a non invasive method, is able to screen the preoperative pelvic floor weakness. In a prospective study we could demonstrate, that patients who had already decreased pelvic floor muscle function before surgery, have a chance to be serious urinary incontinent after the operation.
On the basis of preoperative urodinamical and other functional examinations there is a probability for preoperative patient-selection according to pelvic floor function. The postoperative incontinence management can be also changed according to the results of functional examinations.

Recent publications:

Majoros, A., Bach, D., Keszthelyi, A., Hamvas, A., Mayer, P., Riesz, P., Seidl, E. & Romics, I. (2007)
Analysis of risk factors for urinary incontinence after radical prostatectomy.
Urol. Int. 78(3): 202–207.

Romics, I., Pánovics, J., Majoros, A. & Riesz, P. (2006)
Our results with radical retropubic prostatectomy in the first hundred patients.
Orv. Hetil. 147(24): 1107–1112.

Majoros, A., Bach, D., Keszthelyi, A., Hamvas, A. & Romics, I. (2006)
Urinary incontinence and voiding dysfunction after radical retropubic prostatectomy (prospective urodynamic study).
Neurourol. Urodyn. 25(1): 2–7.

Romics, I., Hamvas, A. & Majoros, A. (2004)
Complications related to neurogenic bladder dysfunction, II: Reflux and renal insufficiency.
Pp. 683–692 in: **Corcos, J. & Schick, E.** (eds.)
Textbook of the neurogenic bladder.
Adults and children.
Martin Dunitz Ltd., London.

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Laboratory of Tumor Biology, 1st Department of Pathology and Experimental Cancer Research, Szentágothai János Knowledge Center

László Kopper, M.D., Ph.D., D.Sc.
Professor

Key words:

cancer
targeted therapy
molecular diagnostics
signaling pathways
apoptosis

In the past several years the lab activity was focused on those molecular targets which may play essential role both in the development, growth and progression as well as in the clinical management of cancer. One of the important regulatory factors is transforming growth factor beta (TGFb) with a capacity to block the proliferation of lymphoid cells. However, many lymphoid malignancies lost the responsiveness to TGFb. It has been shown that besides the traditional signaling (Smad) pathway an alternate route involving MAPK has equal importance. The missed capability of cancer cells to die is the consequence of the overproduction of survival factors. The EGFR-pathway can be activated at several levels. Our aim is to clarify the role of mTOR especially in combinations with other factors (mainly rapalogs). The survival can be supported or modified by the expression of those molecules which influence stem cell activity, e.g. the Notch-pathway. Different in vitro and in vivo techniques are used including gene transfer, PCR technology, sequencing, human tumor xenografts etc. Tissue microarray is a useful tool to search relavant biomarkers for cancer therapy as well as to understand the driving force in progression. One study was designed to identify differently expressed gene products in lung cancer with and without brain metastases. A set of 5 proteins were described. Similar technique is used in DBCL and Hodgkin lymphoma and the preliminary results suggest the unique expression of mTOR targets. More studies are under way on different solid tumors (e.g. colorectal cc, bone tumors) in order to select molecules for explaining pathogenesis and also to refine diagnostic targets.

Recent publications:

Sebestyén, A., Hajdú, M., Kiss, L., Barna, G. & Kopper, L. (2007)
Smad4-independent, PP2A-dependent apoptotic effect of exogenous transforming growth factor beta 1 in lymphoma cells.
Exp. Cell. Res. 313(15): 3167–3174.

Pápay, J., Krenács, T., Moldvay, J., Stelkovics, E., Furák, J., Molnár, B. & Kopper, L. (2007)
Immunophenotypic profiling of non small cell lung cancer progression using the tissue microarray approach.
Appl. Immunohistochem. Mol. Morphol. 15(1): 19–30.

Hajdú, M., Sebestyén, A., Barna, G., Reiniger, L., Jánosi, J., Sréter, L., Várkonyi, J., Demeter, J. & Kopper, L. (2007)
Activity of the notch-signalling pathway in circulating human chronic lymphocytic leukaemia cells.
Scand. J. Immunol. 65(3): 271–275.

Peták, I., Houghton, J.A. & Kopper, L. (2006)
Molecular targeting of cell death signal transduction pathways in cancer.
Current Signal Transduction Therapy 1: 113–131.

Kopper, L. & Tímár, J. (2005)
Genomics of lung cancer may change diagnosis, prognosis and therapy.
Pathol. Oncol. Res. 11: 5–10.

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Technician:
Gézáné Csorba

Proteoglycan Research Group

Ilona Kovalszky, M.D., Ph.D., D.Sc.
Professor

Key words:

tumor stroma
proteoglycan
liver fibrosis and cancer
cell signaling

Proteoglycans in the development and progression of liver diseases

The role of extracellular matrix as reservoir for regulatory molecules implicated in cell proliferation, differentiation and movement has been recently established. The molecular basis for storage of regulatory factors is provided by proteoglycans, glycanated proteins of the extracellular matrix and the pericellular area. Especially heparan sulfates, as consequence of their negative charge as well as specific structure, are capable to interact with growth factors, cytokines, hormones, etc.

We demonstrated the enhancement of glycosaminoglycan content in several tumors. Since then our goal is to determine which PGs contribute to the measured changes and how can the abnormal PG composition interfere with the behavior of cells.

We described the proteoglycan pattern of cirrhotic and tumorous liver, showing that syndecan-1 which is the major PG of hepatocytes, but also expressed on Kuppfer cells, increases in liver cirrhosis, and decreases in liver cancer. Agrin, as a basement membrane HSPG, differentiates between cirrhotic and tumorous nodules in the liver serving as a marker of liver cancer. Heparan sulfates from liver cancer differ from that of normal liver in its potential to influence nuclear proteins as topoisomerases and transcription factors. This indicates that heparan sulfates are active not only in the extracellular matrix but also in the cell nuclear functions.

Expression of Syndecan-1 changes in other malignant tumors, as well. In oral and cervical cancer the loss of syndecan-1 from the parenchymal cells is accompanied by the gain of syndecan positivity by the stromal cells. In oral cancer this phenomenon is an independent poor prognostic factor.

Recently, using transgenic animals we proved, that decorin, a small ECM dermatan sulfate proteoglycan is capable to inhibit the fibrogenesis in liver by inhibiting the effect of TGF-beta1 and turning down the collagen production of hepatic stellate cells.

Recent publications:

Batmunkh, E., Tátrai, P., Szabó, E., Lódi, Cs., Holzbauer, A., Páska, Cs., Kupcsulik, P., Kiss, A., Schaff, Zs. & Kovalszky, I. (2007)
Comparison of the expression of agrin, a basement membrane heparan sulfate proteoglycan, in cholangiocarcinoma and hepatocellular carcinoma.
Human Pathology 38: 1508–1515.

Máthé, M., Suba, Z., Németh, Z., Tátrai, P., Füle, T., Borgulya, G., Barabás, J. & Kovalszky, I. (2006)
Stromal syndecan-1 expression is an adverse prognostic factor in oral carcinomas.
Oral Oncol. 42(5): 493–500.

Tátrai, P., Dudás, J., Batmunkh, E., Máthé, M., Zalatnai, A., Schaff, Zs., Ramadori, G. & Kovalszky, I. (2006)
Agrin, a novel basement membrane component in human and rat liver, accumulates in cirrhosis and hepatocellular carcinoma.
Lab. Invest. 86: 1149–1160.

Resch, M.D., Nagy, Z.Z., Szentmáry, N., Máthé, M., Kovalszky, I. & Süveges, I. (2005)
Spatial distribution of keratan sulfate in the rabbit cornea following photorefractive keratectomy.
J. Refract. Surg. 21(5): 485–493.

Tímár, J., Lapis, K., Dudás, J., Sebestyén, A., Kopper, L. & Kovalszky, I. (2002)
Proteoglycans and tumor progression: Janus-faced molecules with contradictory functions in cancer.
Semin. Cancer Biol. 12(3): 173–186.

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Molecular Therapy Laboratory

István Peták, M.D., Ph.D.
Senior Scientist

Key words:

tumor cell biology
molecular pharmacology
apoptosis
signal transduction therapies
predictive molecular diagnostics

Our basic research field is the molecular regulation of apoptosis and novel forms of active cell death in tumors cells. Based on this basic research we investigate the molecular pharmacology of anti-cancer therapeutics directly activating cell death like TRAIL (Tumor Necrosis Factor-related Apoptosis Inducing Ligand) or inhibiting survival pathways, in particular kinase inhibitors. The aim of these studies is to form the preclinical rational of novel drug combinations, explore the mechanisms of drug resistance and identify biomarkers which predict individual tumor response. The research group is in strong collaboration with biotechnology companies to develop new targeted signal transduction therapies, in particular tyrosin kinase inhibitors and novel molecular diagnostic technologies. This laboratory is the largest centrum of predictive diagnostics of targeted therapies of EGFR (Epidermal Growth Factor Receptor) in Hungary, which includes the routine DNA sequence analysis of EGFR and RAS genes in archived lung cancer and colon cancer samples (even small biopsies or cytology smears), EGFR fluorescence in situ hybridation and immunohystochemistry. We have recently published the largest comprehensive study in this subject in the Central-European region. In collaboration with our partners, we are developing multiple target tyrosin kinase inhibitors to overcome resistance to current EGFR inhibitors, and targeted delivery with nanotechnology. Other projects investigate the molecular mechanism of action and predictive diagnostics of proteasome inhibitors, a novel important group of anti-cancer agents. The laboratory has several international collaborations which include: St. Jude Children's Research Hospital, USA; Max Planck Institute, Germany; University of Modena and Reggio Emilia, Italy and Queen's University, UK. The research group has been involved and also coordinated several Hungarian and EU founded large R&D projects.

Recent publications:

Pintér, F., Pápay, J., Almási, A., Sápi, Z., Szabó, E., Kánya, M., Tamási, A., Jori, B., Várkondi, E., Moldvay, J., Szondy, K., Kéri, G., Dominici, M., Conte, P., Eckhardt, S., Kopper, L., Schwáb, R. & Peták, I. (in press)
Epidermal Growth Factor Receptor (EGFR) high gene copy number and activating mutations in lung adenocarcinomas are not consistently accompanied by positivity for EGFR protein by standard immunohistochemistry.
J. Mol. Diagn.

Imre, G., Dunai, Z., Peták, I. & Mihalik, R. (2007)
Cystein cathepsin and Hsp90 activities determine the balance between apoptotic and necrotic cell death pathways in caspase-compromised U937 cells.
Biochem. Biophys. Acta. 1773(10): 1546–1557.

Schwáb, R., Micsik, T., Szokolóczi, O., Schafer, E., Tihanyi, B., Tihanyi, T., Kupcsulik, P., Diófalvi, K., Mersich, T., Besznyák, I. Jr., Zaránd, A., Mihalik, R., Sarkadi, B., Kéri, G., Pap, A., Jakab, F., Kopper, L. & Peták, I. (2007)
Functional evaluation of multidrug resistance transporter activity in surgical samples of solid tumors.
Assay Drug Dev. Technol. 5(4): 541–550.

Nagy, K., Székely-Szűts, K., Izeradjene, K., Douglas, L., Tillman, M., Barti-Juhász, H., Dominici, M., Spano, C., Luca Cervo, G., Conte, P., Houghton, J.A., Mihalik, R., Kopper, L. & Peták, I. (2006)
Proteasome inhibitors sensitize colon carcinoma cells to TRAIL-induced apoptosis via enhanced release of Smac/DIABLO from the mitochondria.
Pathol. Oncol. Res. 12(3): 133–142.

Schwáb, R., Pintér, F., Moldávy, J., Pápay, J., Strausz, J., Kopper, L., Kéri, G., Pap, A., Oreskovich, K., Mangel, L. & Peták, I. (2005)
Modern treatment of lung cancer: case 1. Amplification and mutation of the epidermal growth factor receptor in metastatic lung cancer with remission from gefitinib.
J. Clin. Oncol. 23(30): 7736–7738.

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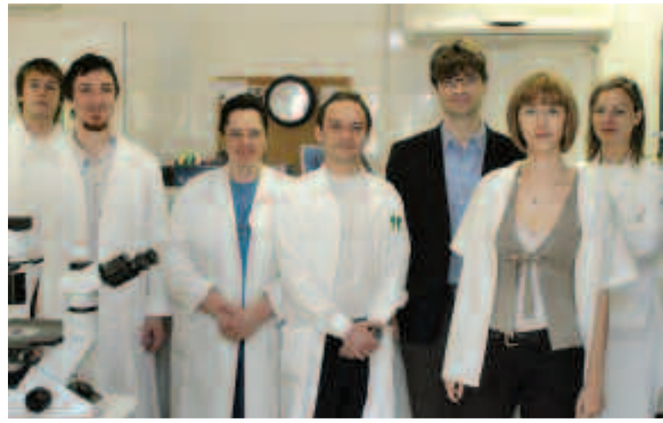

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István Bitter, M.D., D.Sc.
Professor and Chair

We have a multi-disciplinary research team that includes clinicians and research scientists with internationally recognized expertise in psychiatry, psychopharmacology, neuropsychology, psychophysiology, biostatistics, and psychiatric genetics and epidemiology. Our research team conducts a broad range of studies, covering both basic and clinical research in order to investigate the etiology, treatment, prevention, and rehabilitation of severe, and persistent mental illnesses. Principal areas of our research are the following:

Key words:

psychopharmacology
neuropsychology
emotion recognition
clinical trials
biostatistics

Studies of Adult Attention Deficit Hyperactivity Disorder (ADHD), including epidemiologic investigation of ADHD in Hungarian population, and research into genetic, neuropsychological, psychophysiological and psychopathological underpinnings of ADHD.
Molecular genetic studies in schizophrenia, including the investigation of candidate gene polymorphisms in relation to the deficit syndrome of schizophrenia.
Neuropsychological and psychophysiological studies in schizophrenia, bipolar disorder and ADHD.
Psychopharmacological research (studying clinical response in principal psychopathological and neurocognitive variables in relation to treatment with typical and atypical antipsychotics; identification of predictors of treatment response to psychotropic medications and psychotherapy).
Emotion recognition in psychiatric disorders including major mental illnesses such as schizophrenia and major depression (specific topics include: emotion recognition based on visual and auditory inputs, including facial expressions using standard computer-generated 3D pictures and sounds of speech; recognition of emotions conveyed by non-verbal communication including gestures).
Research into possible application of virtual reality therapy in psychiatry and psychotherapy.
Additional important areas of our research: studies of disorders of mood and affect, measurements of effectiveness in psychotherapy, organic psychosyndromes and gerontopsychiatry.

Recent publications:

Kéri, S. (2008)
Interactive memory systems and category learning in schizophrenia.
Neuroscience & Biobehavioral Reviews
32(2): 206–218.

Polgár, P., Farkas, M., Nagy, O., Kelemen, O., Réthelyi, J., Bitter, I., Myers, C.E., Gluck, M.A. & Kéri, S. (2008)
How to find the way out from four rooms? The learning of "chaining" associations may shed light on the neuropsychology of the deficit syndrome of schizophrenia.
Schizophrenia Research 99(1/3): 200–207.

Csukly, G., Czobor, P., Simon, L. & Takács, B. (2008)
Basic emotions and psychological distress: association between recognition of facial expressions and Symptom Checklist-90 subscales.
Comprehensive Psychiatry 49(2): 177–183.

Unoka, Zs., Tölgyes, T. & Czobor, P. (2007)
Early maladaptive schemas and body mass index in subgroups of eating disorders: a differential association.
Comprehensive Psychiatry 48(2): 199–204.

Bitter, I., Czobor, P., Dossenbach, M. & Volavka, J. (2005)
Effectiveness of clozapine, olanzapine, quetiapine, risperidone, and haloperidol monotherapy in reducing hostile and aggressive behavior in outpatients treated for schizophrenia: a prospective naturalistic study.
(IC-SOHO) European Psychiatry 20(5/6): 403–408.

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Patricia Polgár

Mental Health Research Group of Semmelweis University and the Hungarian Academy of Sciences

Mária S. Kopp, M.D., Ph.D.
Professor

Key words:

chronic stress
epidemiology
premature mortality
mental health
chronic disorders

The main goal of the research group is to work out a broad program for understanding the mental and behavioral factors implicated in health promotion and disease prevention with a special emphasis on chronic disorders with especially high incidence in our region. The group approaches this goal by the integration of basic and applied research activities going on the frontiers of social and natural sciences. It endeavors to harmonize the methods of epidemiology, health promotion, and prevention with the methods of psychophysiology and neurophysiology. The group focuses on identifying the combined mode of action and relationships of neurophysiologic, psychological, behavioral and social factors in connection with the psychosocial risk factors related to chronic disorders of great public health significance. The Hungarian society might be regarded an "unique natural experimental laboratory", it is suitable for analyzing the physiological, health-related, and quality of life related consequences of social changes, chronic stress, and insufficient coping skills. The main research topics are: the relationship of mental and somatic health; psycho-physiologic study of behavioral and mental factors of individual vulnerability; the impact of psychological, behavioral factors on the health deterioration and premature mortality in the Hungarian population, and on the epidemiology and prevention of diseases of great public health significance; introducing evidence-based health promotion methods. The research group works in the frame of extensive international and national collaborations. The group leader is the Hungarian coordinator of three European Public Health programmes.

Recent publications:

Kopp, M.S., Stauder, A., Purebl, Gy., Janszky, I. & Skrabski, Á. (in press)
Work stress and mental health in a changing society.
Eur. J. Publ. Health.

Neculai, K., Győrffy, Zs., Ádám, Sz. & Kopp, M. (in press)
Work-related stress factors and menstrual pain:
a nation-wide representative survey.
J. Psychos. Obst. Gynecol.

Kopp, M., Skrabski, Á., Székely, A., Stauder, A. & Williams, R. (2007)
Chronic stress and social changes, socioeconomic determination of chronic stress.
Ann. N.Y. Acad. Sci. 1113: 325–338.

Székely, A., Balog, P., Benkő, E., Breuer, T., Székely, J., Kertai, M.D., Horkay, F., Kopp, M. & Thayer, J.F. (2007)
Anxiety predicts mortality and morbidity after coronary artery and valve surgery. A 4-year follow-up study.
Psychos. Med. 69(7): 625–631.

Kopp, M.S., Skrabski, Á., Szántó, Zs. & Siegrist, J. (2006)
Psychosocial determinants of premature cardiovascular mortality differences within Hungary.
J. Epidem. Comm. Health 60: 782–788.

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Anna Susánszky, Gábor Szabó
Technicians:
András Székely, Csilla Raduch

Gene and Environment

Péter Sótonyi, M.D., Ph.D.
Professor,
Member of the Hungarian Academy of Sciences

Key words:

gene
environment
tetrasomy
duplication

The research group – previously demonstrating derivative chromosome 15 in four healthy members of a three-generation family – has achieved the exact mapping of the chromosome 15 fragment. It gained verification that approximately half of the small supernumerary marker chromosomes (sSMC) originate from the near centromeric region of chromosome 15 (15p-q11–13). Considering cases in which such supernumerary chromosomes contain euchromatic fractions, the sSMC carrying individuals may be symptom free, but may also be mentally retarded or affected with the Prader-Willi and Angelman syndrome. The tetrasomy of this chromosome region may cause severe disorders of both the nervous system and behaviour, as well as fertility problems (oligospermia, azoospermia). In collaboration with the Genetic Institute of the Szeged Biology Center of the Hungarian Academy of Sciences, studies with high resolution fluorescence in situ hybridization (FISH) technique have determined the breakpoint which is responsible for the development of the supernumerary pseudodicentric isochromosome (der 15). Location of the chromosome fracture leading to development of sSMC was defined with 10 kb accuracy, found in the 15q11.2 subregion in a neurofibromatous pseudogene. It was established that the tetrasomy of the 15p-q11.2b region involving the 19.4 million base pairs studied does not cause clinical symptoms, i. e. duplication of this region of chromosome 15 does not result in any phenotypic alterations. By means of detailed sequence analyses, the research group was successful in demonstrating that chromosome 15 carries extended segmental duplications in the 15q11.1–15q13.1 (18.2–27 Mb) region, which may play role in the frequent structural changes of this chromosome region.

Recent publications:

Bellovits, O., Rusz, A., Romics, I., Csonka, E., Hadlaczky, G., Sótonyi, P. & Bujdosó, G (2006)
Chromosomal aneuploidy in azoospermic men.
Int. J. Hum. Genet. 2: 171–176.

Bellovits, O., Rusz, A., Csókay, B., Fodor, F., Csonka, E., Hadlaczky, G., Romics, I., Sótonyi, P. & Bujdosó, G. (2006)
Cytogenetic and molecular characterisation of Y chromosome abnormalities coupled with infertility.
Eur. J. Hum. Genet. 14: 191–196.

Bellovits, O., Rusz, A., Romics, I., Csonka, E., Hadlaczky, G., Sótonyi, P. & Bujdosó, G. (2005)
Chromosomal disorders in patients with azoospermia.
Eur. J. Hum. Genet. 13: 95–97.

Bujdosó, G., Sótonyi, P., Bellovits, O., Csonka, E. & Hadlaczky, G. (2004)
Translocation of chromosome 13 in the course of family investigation.
Chrom. Res. 12: 121–122.

Bujdosó, G., Sótonyi, P., Bellovits, O., Csonka, E. & Hadlaczky, G. (2003)
Inheritance of a balanced translocation through three generations. Proof of paternity.
Ann. Génét., Int. J. Hum. Med. Genet. 2003(2/3): 230–231.

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Technicians:
Bíró Rezsőné, Éva Wehovszky

Division of Assisted Reproduction

János Urbancsek, M.D., Ph.D., D.Sc.
Professor

Pregnancies obtained after in vitro fertilization and embryo transfer are at increased risk for an adverse outcome compared with women who conceive naturally. Multiple gestations also occur more frequently after in vitro fertilization.

Key words:

in vitro fertilization
pregnancy outcome
human choriogonadotropin
inhibin
CA–125

Therefore, there is a need for markers that accurately detect the establishment of pregnancy and predict its outcome as early as possible, allowing for modification of monitoring and treatment if required.
Our aim was to assess the predictive value of the following potential serum markers, measured in the second week after embryo transfer in samples collected prospectively during the past ten years at the Division of Assisted Reproduction of our department: total β-hCG, inhibin A, and CA–125.
Data of patients undergoing IVF or intracytoplasmic sperm injection and embryo transfer between 1995 and 2001 were analyzed. Establishment of pregnancy was assessed by measuring total β-hCG concentrations in two serum samples collected between 8 and 16 days after ET with a difference of two days. Measurement of inhibin A and CA–125 levels was performed in the same samples. Logistic regression analyses were used to study the association of these serum markers and the number of retrieved oocytes and transferred embryos with pregnancy outcome. Receiver-operating characteristic (ROC) curves were constructed to identify optimal cutoff levels for outcomes and to assess overall predictive accuracy.
(1) Day 11 total β-hCG can be used to compare hCG levels in samples from different sampling days and to predict early pregnancy losses and multiple ongoing pregnancies with high sensitivity and specificity.
(2) Inhibin A concentrations are more accurate than day 11 hCG levels for predicting preclinical abortion after IVF but they have no advantage in forecasting ongoing or multiple ongoing pregnancies.
(3) Prognostic accuracy of CA–125 measurements for the prediction of pregnancy as well as its outcome is inferior to that achieved with inhibin A.

Recent publications:

Urbancsek, J., Hauzman, E., Klinga, K., Rabe, T., Papp, Z. & Strowitzki, T. (2005)
Use of serum inhibin B levels at the start of ovarian stimulation and at oocyte pickup in the prediction of assisted reproduction treatment outcome.
Fertil Steril 83: 341–348.

Urbancsek, J., Hauzman, E., Lagarde, A.R., Nagy, K., Osztovits, J., Jánoki, Gy., Rabe, T., Papp, Z. & Strowitzki, T. (2005)
Serum CA–125 levels in the second week after embryo transfer predict clinical pregnancy.
Fertil Steril 83: 1414–1421.

Urbancsek, J., Hauzman, E., Murber, Á., Lagarde, A.R., Rabe, T., Papp, Z. & Strowitzki, T. (2005)
Serum CA–125 and inhibin B levels in the prediction of ovarian response to gonadotrophin stimulation in IVF cycles.
Gynecol. Endocrinol. 21(1): 38–44.

Hauzman, E., Lagarde, A.R., Fancsovits, P., Murber, Á., Jánoki, Gy., Papp, Z. & Urbancsek, J. (2005)
Prognostic value of serum CA-125 measurements on stimulation day 1 and on the day of oocyte pickup in the prediction of IVF treatment outcome.
J. Ass. Reprod. Gen. 22: 265–268.

Hauzman, E., Fedorcsák, P., Klinga, K., Papp, Z., Rabe, T., Strowitzki, T. & Urbancsek, J. (2004)
Use of serum inhibin A and human chorionic gonadotropin measurements to predict the outcome of in vitro fertilization pregnancies.
Fertil Steril 81: 66–72.

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Albertné Magyaros, Istvánné Pál,
Anna Lengyel

Research Institute of Sport Science

Zsolt Radák, Ph.D., D.Sc.
Professor

Key words:

exercise
oxidative stress
aging, sirtuins
neurotrophins

Single bout of exercise has a capability to increase the generation of free radicals but regular exercise evoked adaptation decreases the accumulation of oxidative damage. We are interested in the molecular processes by which regular exercise increases mean life-span, especially on those which are related to oxidative challenge. Our data revealed that exercise induces the activity of some DNA repair enzymes especially in the nucleus. We also reported that the regulation of mitochondrial base excision repair appears to be different from nuclear ones. Since exercise has a systemic effect on the body, we are monitoring the molecular adaptation in different organs, including brain, spinal cord, liver, heart and skeletal muscle. Our earlier result showed that regular exercise is able to attenuate the deleterious effects of aging on brain, by decreasing the accumulation of oxidative damage and by the induction of housekeeping enzymes. We have also reported that age-associated increase of the DNA binding of NF-kB in the liver and the beneficial effects of exercise through redox regulation. The role of sirtuins in aging process and the possible effects of exercise on these proteins are very intriguing. Currently, we are interested in how sirtuins mediated histone deacetylation modified by exercise training and the impact on cell, organ and system aging. Our laboratory has collaboration with American, Japanese, Chinese, Greek, Indian, Holland, Canadian, South-Korean, Finn, French and British institutions which includes visits of researchers, exchange of samples and publishing joint papers.

Recent publications:

Radák, Z., Chung, H.Y. & Goto, S. (2008)
Systemic adaptation to oxidative challenge induced by regular exercise.
Free Radic. Biol. Med. 44: 153–159.

Radák, Z., Chung, H.Y., Koltai, E., Taylor, A.W., & Goto, S. (2008)
Exercise, oxidative stress and hormesis.
Aging Res. Rev. 7: 34–42.

Radák, Z., Kumagai, S., Nakamoto, H. & Goto, S. (2007)
8-oxoguanosine and uracil repair of nuclear and mitochondrial DNA in red and white skeletal muscle of exercise, trained old rats.
J. Appl. Physiol. 102: 1696–1701.

Radák, Z., Toldy, A., Szabó, Z., Siamilis, S., Nyakas, C., Silye, G., Jakus, J. & Goto, S. (2006)
The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain.
Neurochem. Int. 49: 387–392.

Radák, Z., Chung, H.Y., Naito, H., Takahashi, R., Jung, K.J., Kim, H.J. & Goto, S. (2004)
Age-associated increase in oxidative stress and nuclear factor kappaB activation are attenuated in rat liver by regular exercise.
FASEB J. 18: 749–750.

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Technicians:
Zoltán Bori, Judit Molnár

Research Laboratory of Biomechanics

József Tihanyi, Ph.D., D.Sc.
Professor and Chair

The research interests are as follows:

Study of voluntary muscle contractions

We have studied the eccentric contraction and the elastic energy reuse due to muscle stretch under different conditions. The experiments have been carried out on single muscle group or during multi-joint movements. We studied the

Key words:

muscle mechanics
neuromuscular adaptation
motor control
rehabilitation

effect of pretension level on active force enhancement. Also, we studied the effect of previous state of the muscle on elastic energy storage, on reuse of elastic energy and on mechanical efficiency. The influence of the residual passive force enhancement on the active force enhancement was also studied.

We study the reasons of bilateral deficit and facilitation on cortical, subcortical and muscular level by applying functional MR imaging. Also, we investigate the effect of whole body vibration on motor cortex activation and muscle metabolism using fMRI and MR spectroscopy.

Kinematic and kinetic analysis of handicapped people

Recently we finished studying the postural stability of single or double amputees and stroke patients using stabilometry. Also, gait analysis were performed on patients with acute and chronic stroke.

Adaptation and rehabilitation

We have studied the acute, acute residual and chronic effect of WBV on muscle strength of trained, untrained subject, and acute stroke patients. We estimated the optimum resonance frequency that makes the vibration intervention to be individualized.

We studied the daily strenuous eccentric training and its effect on delayed onset of muscle soreness. Also, we studied how gene expression alterations due to muscle stretch. Immune histological analysis was carried out on muscle biopsy samples estimating the degree of damage of slow and fast muscle fibers.

The research projects have been carried out in collaboration with several Hungarian and foreign universities and institutes, such as Semmelweis University, Magnetic Resonance Center and Genomic, Cellular and Immunbiological Institute, as well as East Caroline University, Biomechanical Laboratory.

Recent publications:

Costa, A., Dalloul, H., Hegyesi, H., Apor, P., Csende, Zs., Rácz, L., Váczi, M. & Tihanyi, J. (2007)
Impact of repeated bouts of eccentric exercise on myogenic gene expression.
Eur. J. Appl. Physiol. 101: 427–436.

Tihanyi, T., Horváth, M., Fazekas, G., Hortobágyi, T. & Tihanyi, J. (2007)
One session of whole body vibration increases voluntary muscle strength in patients with stroke.
Clin. Rehab. 9: 782–793.

Horváth, M., Fazekas, G., Tihanyi, T. & Tihanyi, J. (2005)
Standing stability of hemiparetic patients estimated in different ways.
Facta Univ. 3: 59–58.

Rácz, L., Béres, S., Hortobágyi, T. & Tihanyi, J. (2002)
Contraction history affects the in vivo quadriceps torque-velocity relationship in humans.
Eur. J. Appl. Physiol. 87: 393–402.

Bosco, C., Tsarpela, O., Foti, C., Cardinale, M., Tihanyi, J., Bonifazi, M., Viru, M. & Viru, A. (2002)
Mechanical behaviour of leg extensor muscles in male and female sprinters.
Biol. Sport 19: 189–202.

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Technician:
Zsolt Gréger

Glaucoma Clinical and Research Group

Gábor Holló, M.D., Ph.D., D.Sc.
Associate Professor

Key words:

glaucoma
imaging
neuroprotection
scanning laser polarimetry

Glaucoma is one of the most frequent causes of irreversible visual deterioration and blindness worldwide. This group of clinically heterogeneous diseases is characterized by progressive apoptosis of the retinal ganglion cells, which leads to visual field damage as well as deterioration of several other visual functions. Though the number of retinal ganglion cells cannot be directly measured in patients, certain new and still evolving non-invasive imaging technologies allow measurement of the axon layer of these cells. Our group has been active in the development and clinical application of these techniques for 15 years.

Our research group has been working both on clinical and experimental fields related to glaucoma. Of these the most important topics are early instrumental diagnosis of glaucoma, increase of accuracy of mass glaucoma screening using combined evaluation of imaging and functional tests, detection of fine disease progression with modern imaging techniques, ocular and systemic alterations of perfusion in pseudoxefoliative glaucoma, ocular absorption of topically applied ocular medications with potential neuroprotective properties in the human eye, evaluation of intraocular pressure lowering medications, glaucoma surgery and biochemical modulation of wound healing in glaucoma surgery, as well as objective measurement and improvement of patients' adherence to long-term intraocular pressure lowering medication. Our international collaboration is wide and involves several experimental and clinical projects.

Recent publications:

Tóth, M., Kóthy, P., Vargha, P. & Holló, G. (2007)
Accuracy of combined GDx-VCC and matrix FDT in a glaucoma screening trial.
J. Glaucoma 16: 462–470.

Visontai, Zs., Merisch, B., Kollai, M. & Holló, G. (2006)
Increase of carotid artery stiffness and decrease of baroreflex sensitivity in exfoliation syndrome and glaucoma.
Br. J. Ophthalmol. 90: 563–567.

Holló, G., Whitson, J.T., Faulkner, R., McCue, B., Curtis, M., Wieland, H., Chastain, J., Sanders, M., DeSantis, L., Przydryga, J. & Dahlin, D.C. (2006)
Concentrations of betaxolol in ocular tissues of human glaucoma patients and normal monkeys following one month of topical ocular administration.
Invest. Ophthalmol. Vis. Sci. 47: 235–240.

Tóth, M. & Holló, G. (2005)
Enhanced corneal compensation for scanning laser polarimetry on eyes with atypical polarization pattern.
Br. J. Ophthalmol. 89: 1139–1142.

Holló, G., Katsanos, A., Kóthy, P., Kerek, A. & Süveges, I. (2003)
Influence of LASIK on scanning laser polarimetric measurement of the retinal nerve fibre layer with fixed angle and customised corneal polarisation compensation.
Br. J. Ophthalmol. 87: 1241–1246.

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Corneal and Refractive Surgical Unit

Zoltán Z. Nagy, M.D., D.Sc., Med. Habil.

Corneal wound healing following refractive surgical and corneal procedures

Introduction

Refractive surgery gained world-wide acceptance during the last decade. Treatment and diagnostic modalities are developing continuously. It seems that corneal wound healing and genetic background might be responsible for different outcomes. The program tries to identify the factors which may provide the best results using customized techniques in refractive and corneal surgery.

Key words:

cornea
wound healing
refractive surgery

Topics under research and future research

Corneal wound healing was studied following 193 nm excimer laser treatment using light and electron microscopy, histochemical changes of the cornea were also added. The role of secondary ultraviolet-B exposure in corneal wound healing following refractive surgery was identified and studied. The possible treatment of harmful effect of secondary UV-B exposure will be researched.

Genetic research

The genetic modeling of normal and pathological corneal wound healing was examined by one member of the staff. Besides this the genetic background of intraocular pressure rise after topical steroid treatment was analyzed.

Current trends in research

What are the refractive results with different types of procedures (PRK, LASIK, LASEK, Epi-LASIK) and different types of excimer lasers. What are the limits of refractive surgery, alternative procedures (phacic IOL, phacoemulsification with PCL in high myopia/hyperopia). The newest trend in refractive surgery is the treatment modalities (conservative and surgical) of presbyopia. The quality of vision and life following refractive procedures are of paramount importance. The role of aspheric IOL-s in quality of vision is also a current research area. Pseudoaccomodative lenses in restoring presbyopia and far vision affects a large part of the population.

New diagnostic tools in refractive surgery

Aberrometry, topography, Pentacam, pachymeter, anterior segment OCT are being investigated.

Surgical techniques

Outcome of corneal transplantation using different surgical technique (lamellar, penetrating, femto-laser), results of posterior lamellar keratoplasty (endothelial transplantation) being investigated.

Recent publications:

Szabó, V., Borgulya, G., Filkorn, T., Majnik, J., Bányász, I. & Nagy, Z.Z. (2007)
The variant N363S of glucocorticoid receptor in steroid-induced ocular hypertension in Hungarian patients with photorefractive keratectomy.
Mol.Vis. 13: 659–666.

Szabó, V., Süveges, I., Rácz, K., Hunyadi, L. & Nagy, Z.Z. (2006)
The role of lumican and keratocan genes in persistent subepithelial corneal haze following laser photorefractive keratectomy.
Mol. Vis. 12: 597–605.

Nagy, Z.Z., Resch, M. & Süveges, I. (2004)
Ultrasound evaluation of flap thickness, ablation depth, and corneal edema after laser in situ keratomileusis.
J. Cataract Refract. Surg. 20: 279–281.

Nagy, Z.Z. (2003)
Laser in situ keratomileusis combined with topography supported customized ablation after repeated pentrating keratoplasty – case report.
J. Cataract. Refract. Surg. 29: 792–794.

Nagy, Z.Z., Kelemen, E. & Kovács, A. (2003)
Herpes simplex keratitis after photorefractive keratectomy.
J. Cataract. Refract. Surg. 29: 222–223.

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Ocular Surface and Cornea Laboratory

János Németh, M.D., Ph.D., D.Sc.
Professor and Chair

1. Ocular surface.
Besides investigation of the tear film dynamics, including definition of tear film build-up time, instrumental development of a new corneal suface examination method is performed.

Key words:

cornea
tear film
ocular surface
topography
amniotic membrane

Mathematical description of the corneal surface by polynomials in cooperation with the MTA SZTAKI and ELTE has been published. Changes in the frequency of blinking in different circumstances is investigated.

2. Refractive surgery.
Corneal wound healing and the role of secondary UV-B irradiation after different techniques of refractive surgery (PRK, LASIK, LASEK) were analyzed. Higher order aberrations are measured in healthy volunteers and in patients after refractive surgery.

3. Corneal histopathology.
The pathways of apoptosis of corneas with Fuchs' dystrophy, pseudophakic bullous keratopathy and keratoconus are studied. We determine by means of immunohistochemical analysis the expression of p21, p27, p63, survivin, CD95, cathepsin, bax, bcl-2 and Ki67 in the above corneal pathologies. We determine, wheather apoptosis is a pathogenic factor or the consequence of the disfuncion of the corneal cells in the above conditions. Classification of corneal amniotic membrane integration patterns was published on histopathological, immunohistochemical and electron microscopic bases.

4. Genetics of corneal wound healing.
A PCR-based mutation analysis of cornea-specific small keratan sulfate proteoglycans, lumican and keratocan genes, was carried out to investigate whether germline genetic alterations have an effect on development of severe corneal haze occurring after photorefractive keratectomy (PRK) in humans. In the same group of patients we examined the role of three functional polymorphisms of the glucocorticoid receptor gene in ocular hypertension using PCR and RFLP methods. We found a significant association between N363S heterozygosity and steroid-induced ocular hypertension occuring after administration of topical prednisolon acetate 0.5% eyedrops after PRK.

Recent publications:

Imre, L., Resch, M., Megyesi, M. & Németh, J. (2007)
In-vitro-Untersuchung der Mikrostruktur von handelsüblichen ophthalmologischen Suspensionen mittels HRT-II Rostock Cornea Modul. [In vitro microstructural analysis of commercial ophthalmic suspensions by HRT II Rostock Cornea Module.]
Ophthalmologe 104: 697–704.

Nagy, Z.Zs. (2003)
Laser in situ keratomileusis combined with topography-supported customized ablation after repeated penetrating keratoplasty.
J. Cataract. Refract. Surg. 29: 792–794.

Resch, M., Schlötzer-Schrehardt, U., Hofmann-Rummelt, C., Sauer, R., Kruse, F.E. & Seitz, B. (2006)
Adhesion structures of amniotic membranes integrated into human corneas.
Invest. Ophthalmol. Vis. Sci. 47: 1853–1861.

Szabó, V., Balogh, K., Süveges, I., Rácz, K., Hunyady, L. & Nagy, Z.Zs. (2006)
The role of lumican and keratocan genes in persistent subepithelial corneal haze following excimer laser photorefractive keratectomy.
Mol. Vis. 12: 597–605.

Szentmáry, N., Takács, L., Berta, A., Szende, B., Süveges, I. & Módis, L. (2007)
Cell proliferation and apoptosis in stromal corneal dystrophies.
Histol. Histopathol. 22: 837–845.

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Laboratory of Corneal Wound Healing

Ildikó Süveges, M.D., Ph.D., D.Sc.
Professor

Ocular surface diseases concern both the conjunctiva and the cornea. The latter is the most important refractive medium of the eye. It is transparent; and its degree of transparency does not alter during the lifetime of a healthy individual. It normally contains no blood vessels. The **wound-healing process** of the cornea is of a very special kind since, provided that the wound does not involve the perilimbal area, cells other than keratocytes play no part in the process.

Key words:

corneal dystrophies
stem cells
wound healing
keratoplasty

For the normal integrity of the cornea to be preserved, the presence of a healthy epithelium is indispensable. If the epithelium is damaged or missing, then in the absence of rapid reepithelisation corneal ulcer, inflammation, and consequent loss of transparency will usually result. Epithelial cells regenerate from the stem cells of the limbus, and if these latter cells are lacking or damaged, this will in turn lead to a deficit of corneal epithelium, with its adverse consequences. Fortunately however the limbal stem cells can be successfully cultured, under certain special conditions. Autologous or homologous transplants of these cells can allow the management of ocular surface diseases caused by a lack of limbal stem cells.

In a major part of our present study we are **culturing limbal stem cells**, working with the assistance of colleagues at the Institute of Experimental Medicine of the Hungarian Academy of Sciences. The resulting cultured cells can easily be removed from the fibrin culturing layer and implanted onto the surface of an injured eye. However, further studies are required to establish how well the cell-transplant survives in the ocular environment.

Limbal stem cells can also be replaced using homologous transplants, employing donor corneas. Exploration of the most appropriate techniques for this surgery comprises a further area of our research work. The reason for such transplants being able to heal without tissue rejection is not yet fully understood. In this case, corneo-scleral tissue is implanted; but despite the fact that scleral transplants are highly vascularised, rejection does not occur.

A further aim of our study is to attempt to elucidate **the role of toll-like receptors** in the vascularisation of the cornea. These receptors may play a part in corneal inflammation, but this mechanism has up to now not been studied for the cornea.

Recent publications:

Resch, M., Nagy, Z.Zs., Szentmáry, N., Máthé, M., Kovalszky, I. & Süveges, I. (2005)
Spatial distribution of keratan sulfate in the rabbit cornea following photorefractive keratectomy.
J. Refract. Surg. 21: 485–493.

Szentmáry, N., Resch, M., Nagy, Z.Zs., Szende, B. & Süveges, I. (2005)
Proliferation and apoptosis in the corneal stroma in long-term follow-up after photorefractive keratectomy.
Pathol. Res. Pract. 201: 399–404.

Kerényi, Á. & Süveges, I. (2003)
Corneal topographic results after excentric biconvex penetrating keratoplasty.
J. Cataract Refract. Surg. 29: 752–756.

Nagy, Z.Zs., Resch, M. & Süveges, I. (2004)
Ultrasound evaluation of flap thickness, ablation depth, and corneal oedema after laser in situ keratomileusis.
J. Refract. Surg. 20: 279–281.

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Heart Center

Béla Merkely, M.D., Ph.D., D.Sc.
Director

Key words:

cardiac electrophysiology
ischemic heart disease
cardioprotection
heart failure
neurohormonal regulation

The research activity of the Heart Center is focused on diagnosis and therapy of ischemic heart diseases and cardiac arrhythmias. Aim of the research unit is the effective use of resources – both governmental and other research grants – in order (i) to improve understanding of pathomechanisms of ischemic heart diseases, (ii) to introduce new approaches in cardiovascular revascularization therapy, (iii) to adopt the latest methods of acute cardiac care, (iv) to optimize management of heart transplantation patients, (v) to improve understanding of electrophysiological backgrounds of cardiac arrhythmias, (vi) to investigate new techniques and equipments especially in the field of non-pharmacological therapy of cardiac arrhythmias, (vii) to train researchers – postgraduate students as well as qualified clinicians – in broad areas of cardiovascular sciences. Clinical research is supported by an Experimental Research Laboratory which work is focused on the investigation of (viii) autonomic regulation of the cardiovascular system, (ix) changes in humoral and metabolic regulatory processes in different cardiovascular diseases, (x) effects and local interactions of endogenous cardioactive agents, (xi) techniques of coronary venous interventions, (xii) new approaches of intraoperative cardioprotection, (xiii) non-invasive monitoring of myocardial blood supply by intraoperative cardiothermography, (xiv) molecular processes during increased cardiac load, and (xv) myocardial dysfunction and tissue damage of transplanted heart. The Heart Center is qualified to organize, fulfill and maintain postgraduate (Ph.D.) programs.

Recent publications:

Szilágyi, S., Merkely, B., Róka, A., Zima, E., Fülöp, G., Kutyifa, V., Szűcs, G., Becker, D., Apor, A. & Gellér, L. (2007)
Stabilization of the coronary sinus electrode position with coronary stent implantation to prevent and treat dislocation.
J. Cardiovasc. Electrophysiol. 18(3): 303–307.

Szabó, G., Soós, P., Bährle, S., Radovits, T., Weigang, E., Kékesi, V., Merkely, B. & Hagl, S. (2006)
Adaptation of the right ventricle to an increased afterload in the chronically volume overloaded heart.
Ann. Thorac. Surg. 82: 989–995.

Zima, E., Gergely, M., Soós, P., Gellér, L., Nemes, A., Acsády, G. & Merkely, B. (2006)
The effect of induction method on defibrillation threshold and ventricular fibrillation cycle length.
J. Cardiovasc. Electrophysiol. 16: 377–381.

Soós, P., Merkely, B., Maurovich Horvát, P., Zima, E. & Schauerte, P. (2005)
Determinants and effects of electrical stimulation of the inferior interatrial parasympathetic plexus during atrial fibrillation.
J. Cardiovasc. Electrophysiol. 16: 1362–1367.

Kiss, O., Zima, E., Soós, P., Kékesi, V., Juhász-Nagy, A. & Merkely, B. (2004)
Intracoronary endothelin-1 infusion combined with systemic isoproterenol treatment: antagonistic arrhythmogenic effect.
Life Sci. 75: 537–548.

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Biochemical Research Group, 2nd Department of Medicine

Anna Blázovics, Ph.D., D.Sc.

Redox homeostasis can be considered as the cumulative action of free radicals and antioxidant defense, providing a suitable condition for life. Antioxidant consumption is sine qua non for a healthy way of life, but the concentration range is large and dependent on an individual genetic background. Moderate nutritional customs with natural scavengers or antioxidants can help to restore the normal function of tissues and organs, but the immoderate consumption of vitamins and other bioactive agents is contraindicated. The balance between oxidative

Key words:

redox homeostasis
free radical reactions
functional foods
bioavailability
gastrointestinal diseases

stress and antioxidant defense is turned over in diseases. Moderate oxidative stress is important in signal transduction pathways and essential for proliferation and apoptosis. Antioxidant overflow as well as oxidative stress means a serious problem. Diet related bioactive compounds are intensively examined in vitro, although their in vivo and in vitro effects are different and the modes of actions in in vivo are not yet known in detail. Several active agents are important in cancer prevention as well. Metals are also important both in free radical formation and in antioxidant defense in signal transduction.

Our research group aims to study the effects of bioactive small molecules and metal element rich drugs, fruit and vegetable concentrates or special foods on the redox parameters in gastrointestinal diseases; the roles of the metal elements and methylating process in redox homeostasis.

The levels of our scientific program are:

In vitro studies: We have developed several spectrophotometric, luminometric and fluorometric measurements to determine the scavenging property and antioxidant capacity of natural products.

In vivo experimental studies: Animal models (fatty liver, partial hepatectomy, ischaemia-reperfusion, extrahepatic cholestasis models) have been used to study the biological effectiveness of special foods and drugs. Methods for routine laboratory parameters, immune parameters, redox parameters and elements of liver, plasma and erythrocyte have been applied to study the bioavailability of bioactive agents (functional foods).

In vivo human studies: Special food supplementation of patients with liver and other gastrointestinal diseases as well as cancer patients in interval of chemotherapy and/or X-ray therapy has been studied.

Recent publications:

Blázovics, A., Kovács, Á. & Lugasi, A. (2007)
The effect of short and long term antioxidant treatments on redox homeostasis in experimental and clinical studies.
Chapter 4, pp. 1–34 in: **Watkins, S.V.** (ed.).
Nutritional research advances. Nova Science Publisher, ISBN 978–1–60021–516–2,

Blázovics, A. (2007)
Redox homeostasis, bioactive agents and transduction therapy.
Current Transduction Therapy,
Bentham Science Publisher 2: 226–239.

Váli, L., Stefanovits-Bányai, E., Szentmihályi, K., Fébel, H., Kocsis, I. & Blázovics, A. (2007)
Liver-prorecting effect of the table beet (Beta vulgaris var. rubra) during ischaemia reperfusion.
Nutrition 23: 172–178.

Székely, E., Vereckei, A., Almási, A., Rapavi, E., Tasnádi, Gy., Várnai, K., Pallai, Zs., Lugasi, A. & Blázovics, A. (2007)
Effect of vitamin E administration on the hemorrheological status and redox homeostasis of patients with porphyria cutanea tarda treated with phlebotomy.
Clin. Hemorheol. Microcirc. 36: 13–23.

Stefanovits-Bányai, É., Szentmihályi, K., Hegedűs, A., Koczka, N., Váli, L., Taba, G. & Blázovics, A. (2006)
Metal ion and antioxidant alterations in leaves between different genders of Ginkgo biloba L. (Ginkgoaceae).
Life Sci. 78: 1049–1056.

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Sleep Medicine Unit

Márta Novák, M.D., Ph.D.
Associate Professor

The group focuses its research on the following areas: 1) Epidemiology of sleep disorders both in the general population and in patients with different chronic medical conditions; 2) Psycho-social and medical consequences of sleep disorders; 3) The role of restorative sleep in memory consolidation and daytime neurocognitive functioning.

Key words:

insomnia
sleep apnea syndrome
restless legs syndrome
epidemiology
outcomes research

We have determined the prevalence and correlates of specific sleep disorders in patients with chronic kidney disease. We have demonstrated increased cardiovascular morbidity and increased health care resource utilization by individuals with sleep problems. We have also reported the association of specific outcome measures (health related quality of life and mortality) both in cross-sectional datasets and in prospective cohort studies.
We utilize data from epidemiologic surveys, and also use standard questionnaires and standard polysomnography. We employ psychological testing and complex analysis of extended EEG recordings.
Currently we study the association of obstructive sleep apnoe (OSA) with measures of cardiovascular morbidity in patients with high cardiovascular risk. We also analyze the association of OSA with new onset cardiovascular morbidity and mortality. We also analyze the association of sleep problems with chronic inflammation to reveal potential factors in the pathomechanism of those disorders.
Finally, we currently investigate complex interrelationship between objectively measured sleep parameters, phasic and tonic sleep EEG activity, levels of subjective (Epworth Sleepiness Scale) and objective (Multiple Sleep Latency Test) sleepiness and neurocognitive impairments.
Dr. Novák is an internationally recognized somnologist, psychiatrist. She has published 40 papers, 17 book chapters and edited the most comprehensive handbook on sleep medicine in Hungary. She has active collaborations both in Europe and in North America. Her cumulative impact factor is 59.42, with 63 independent citations.

Recent publications:

Dunai, A., Mucsi, I., Keszei, A., Shapiro, C.M., Kopp, M.S. & Novák, M. (2008)
Cardiovascular diseases and health care utilization amongst snorers in a large population sample.
Sleep 31(3): 411–416.

Molnár, M.Zs., Szentkirályi, A., Lindner, A., Czira, M.E., Szabó, A., Mucsi, I. & Novák, M. (2007)
High prevalence of patients with high risk for Obstructive Sleep Apnea Syndrome after kidney transplantation – association with declining renal function.
Nephrol. Dial. Transplant. 22(9): 2686–2692.

Molnár, M.Zs., Szentkirályi, A., Lindner, A., Czira, M.E., Szeifert, L., Kovács, A.Zs., Fornadi, K., Szabó, A., Rosivall, L., Mucsi, I. & Novák, M. (2007)
Restless legs syndrome is associated with mortality in kidney transplanted patients.
Am. J. Kidney Dis. 50(5): 813–820.

Novák, M., Molnár, M.Zs., Ambrus, Cs., Kovács, A., Koczy, A., Remport, A., Szeifert, L., Szentkirályi, A., Shapiro, C.M., Kopp, M. & Mucsi, I. (2006)
Chronic insomnia in kidney transplanted patients.
Am. J. Kidney Dis. 47(4): 655–665.

Molnár, M.Zs., Novák, M., Ambrus, Cs., Szeifert, L., Kovács, A., Pap, J., Remport, A. & Mucsi, I. (2005)
Restless Legs Syndrome in patients after renal transplantation.
Am. J. Kidney Dis. 45(2): 388–396.

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Photocarcinogenesis, Photodermatology Unit

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Key words:

UV
skin
carcinogenesis
apoptosis
BCC

The Department of Dermatology at Semmelweis University has a long history of patient care and research on the field of UV-related skin diseases. The department serves as regional center for skin oncology and provides various types of phototherapy services for a large patient population. It is also a Central Hungarian center for UV-induced skin diseases, photodermatoses.

Dr. Norbert M. Wikonkál, the head of photodermatology and phototherapy unit, has strong research background on the fields of photocarcinogenesis and photoimmunology. He is also a trained oncologist with nationwide and international connections to those dermatologists working in the field. He is member of the ESDR and EADV, and member of the supervisory board for the Hungarian Dermatological Society.

The primary research interest of the group is various aspects of UV-induced changes in the skin that lead to formation of non-melanoma skin cancers and provide further insight into that complex regulatory mechanism that protects the skin from harmful effects of UV. In a more practical approach, we study tumor suppressor genes that are involved in skin cancers, such as p53 and PTCH. The latter is mutated in patients with Gorlin-Goltz syndrome, a genetic disease with autosomal dominant inheritance that leads to the development of basal cell cancers at an early age. Also, sporadic basal cell cancers with unusual clinical representation are investigated in search for genetic changes.

The role of p53 is well known in skin tumors, yet all details of apoptosis regulation in the skin beyond the obvious involvement of p53 are not understood. The p53-independent apoptosis regulation through the transcription factor of E2F1 is an area where significant contributions have been published, yet additional information is still needed. Recently, the role of hypoxia and its regulation in the skin has become one of our primary research interests, where the role of Hif-1α is being studied in keratinocytes after UV-exposure.

Recent publications:

Paragh, Gy., Schling, P., Ugocsai, P., Kel, A., Liebisch, G., Heimerl, S., Moehle, C., Schiemann, Y., Wegmann, M., Farwick, M., Wikonkál, N., Mandl, J., Langmann, T. & Schmitz, G. (in press)
Novel sphingolipid derivatives promote keratinocyte differentiation.
Exp. Dermatol.

Wunderlich, L., Paragh, Gy., Wikonkál, N.M., Bánhegyi, G., Kárpáti, S. & Mandl, J. (2008)
UVB induces a biphasic response of HIF-1α in cultured human keratinocytes.
Exp. Dermatol. 17: 335–342.

Gustafsson, A.C., Asplund, A., Wikonkál, N.M., Seli, A., Leffell, D.J., Kidd, K., Lundeberg, J., Brash, D.E. & Pontén, F. (2005)
PTCH codon 1315 polymorphism and risk for non-melanoma skin cancer.
Br. J. Dermatol. 152(5): 868–873.

Remenyik, E., Wikonkál, N.M., Zhang, W. & Brash, D.E. (2003)
Antigen-specific immunity does not influence initiation, expansion, or early-phase regression of UVB-induced p53-mutant clones.
Oncogene 22(41): 6369–6376.

Wikonkál, N. M., Knezevic, D., Remenyik, E., Zhang, W., Liu, M., Zhao, H., Berton, T., Johnson, D.G. & Brash, D.E. (2003)
Inactivating E2f1 reverts the UVB-apoptosis resistance and cancer sensitivity of Trp53-deficient mice.
Nature Cell Biology 5(7): 655–660.

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