Institute of Molecular Genetics

Academy of Sciences of the Czech Republic

2008

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Contents

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Introduction

In 2008, the organizational changes of our Institute were finalized. The former Biotechnology Section became independent as a new Institute of Biotechnology AS CR, v. v. i., in the neighbouring building. However, we continue our close ties and multiple collaborations. We have finished construction of the last part of our research complex – the conference building and adjacent dining hall. The new lecture hall for almost 300 people will serve the entire Prague-Krč biomedical research campus. We shall soon start construction of a kindergarten and gym, adjacent to our main building; we are looking forward to opening it in the course of 2009.

Several core facilities started mostly in the previous year, e.g. information technologies, microscopy and cytofluorometry, functional genomics and bioinformatics, media preparation, cryopreservation and monoclonal antibodies have been working on routine basis. A transgenic facility became functional, but so far was mostly absorbed with servicing the embryo transfers into the new animal facility. In 2008 we started operation of an expensive electron microscope and a new-generation sequencer.

We recruited a new head of the animal facility and a new future head of our administrative and accounting office.

It is gratifying that our researchers repeatedly obtain rich and prestigious local and international grants to support their experiments aimed at discovering the still so many secrets of cells and tissues that decide about our health or disease.

We are pleased by the results of interim evaluation of the Institute for the period 2005-2007 by the "Commission for Evaluation of Research Activities of AS CR Institutes" – we were ranked into the highest category „A".

At present, 23 research groups of the Institute are dealing with the topics covering molecular and cellular immunology, molecular and cellular oncology, cell biology of the nucleus, cytoskeleton, functional genomics and bioinformatics, study of oncogenes, molecular biology of development, structural biology and mechanisms of receptor signalling. An essential part of our Institute is represented by 78 doctoral students and 47 undergraduate students. A number of our scientists also act as university teachers (e.g., five as professors and six as associate professors).

Although we consider basic research as the highest priority, we are happy that some „by-products" of our basic research have practical importance. We are collaborating with several well-prospering biotech spin-off companies that have been born at the Institute in recent years.

In 2008, the Institute scientists were again authors or co-authors of publications in a number of prestigious international journals (e.g. Science, Nature Cell Biology, Nature Structural and Molecular Biology, Genome Research, Journal of Cell Biology, Molecular and Cellular Proteomics, Molecular Biology of the Cell, Journal of Biological Chemistry, Journal of Immunology, Journal of Virology, Proceedings of the National Academy of Sciences of the USA).

The high standing of the Institute researchers is testified by awards and prizes; in 2008 Dr. Lubica Dráberová was awarded the Arnold Beckman Publication Prize of Immunotech, a. s. and Czech Society for Biochemistry and Molecular Biology for the best publication in cell biology and imunology and Milan Pospíšil Award of the Czech Immunological Society for the best scientific report in the field of innate and tumour immunology, Dr. Petr Heneberg received the Award of the Czechoslovak Microscopy Society for the best PhD thesis and J. V. Koštíř Prize of Biotech, a. s. and of the Czech Society for Biochemistry and Molecular Biology for collection of papers on new aspects of cell submembrane signalling, Dr. Daniel Smrž obtained the Award of the Czech Immunological Society for the best scientific report presented by a young immunologist. Professor Václav Hořejší was honoured with the Award of the Czech Immunological Society for his life-long merits in the progress of immunology, and Professor Václav Pačes was awarded the state Medal of Merit by the President of the Czech Republic.

It is gratifying to see that the Institute is successfully making use of the now much better conditions in the new buildings. I hope for further major improvements in our scientific productivity, and especially for really major exciting discoveries.

Václav Hořejší
Director

IMG and Its Surroundings

The Institute of Molecular Genetics, Academy of Sciences of the Czech Republic (IMG), is located at the southern outskirts of Prague, capital of the Czech Republic.

The history of the Institute dates from 1953, when the Department of Experimental Biology and Genetics of the Institute of Biology of the Czechoslovak Academy of Sciences, headed since 1953 by Milan Hašek, co-discoverer of immunological tolerance, was established. In 1962, the Department became Institute of Experimental Biology and Genetics (IEBG) with Milan Hašek as its Director until 1970. The sixties of the last century were the "golden age" of the Institute, represented besides Hašek e.g. by Pavol and Juraj Iványi, Jan Klein, Jan Svoboda, etc. The end of the „Prague Spring" after August 1968 marked the end to this famous era – many promising young scientists had emigrated (and were very successful at their new institutions abroad). In 1977, IEBG was re-organized and renamed Institute of Molecular Genetics of the Czechoslovak Academy of Sciences (IMG); Josef Říman became its Director. Among the achievements of the otherwise difficult seventies and eighties were co-discovery of reverse transcriptase (J. Říman), discovery of virogeny (J. Svoboda) or sequencing of one of the first viral genomes (V. Pačes). After 1989, the Institute was headed by Jan Svoboda (1991-1999), Václav Pačes (1999-2005) and Václav Hořejší (2005-present). In 1964-2006, the Institute was divided between two distant locations. At present, more than 350 employees and students work at the Institute.

The Prague-Krč campus of biomedical Academy Institutes

IMG is located on the Krč campus also hosting the Institute of Microbiology, Institute of Physiology, Institute of Experimental Medicine and part of the Institute of Animal Physiology and Genetics, in total over 1200 researchers and students. In close proximity to the site is also located the Institute of Clinical and Experimental Medicine (ICEM) and Thomayer Hospital. The campus is close to a major natural park (Krč forrest), easily reachable by car or public transportation.

Prague – a city of history, culture and science

Situated on the Vltava (Moldau) river, Prague has been the political, cultural, and economic centre of the Czech state for over 1000 years. The city is home to nearly 1.2 million people. Prague is widely considered to be one of the most beautiful cities in Europe and belongs to the most visited cities on the continent. Since 1992, the historic centre of Prague has been included in the UNESCO list of World Heritage Sites. Prague also has a long-standing tradition in science. Founded in 1348, the Charles University is the oldest University in Central Europe. At present, Prague is the seat of four Universities, the student population being more than 100,000. There are also 38 institutes of the Academy of Sciences and a number of other research institutions.

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Laboratory of Cell Signalling and Apoptosis

Death receptors, apoptosis, Daxx

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Research topics

The major focus of our group is aimed at the molecular and functional characterization and regulation of signalling pathways unlashed by the activated death receptors from the TNFR superfamily, namely by pro-apoptotic TRAIL receptors (DR4 and DR5), by the Death Receptor 6 (DR6), or affected by apoptosis- and transcription-regulatory adapter protein Daxx.

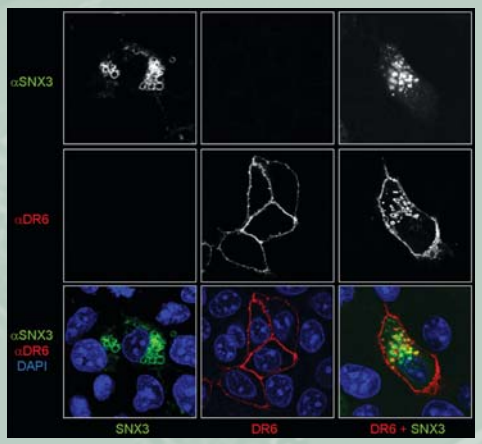
TRAIL is considered a novel anti-tumour agent, and thus in-depth knowledge of the regulation of TRAIL-induced signalling is undoubtedly important. Our recently published studies document involvement of DR4-interacting adapter protein ARAP1 in the efficacy of DR4 presentation at the cytoplasmic membrane and Wnt1-expressing Rat2 fibroblast-mediated suppression of TRAIL-induced apoptosis of pre-B leukaemia cells. The current major project deals with the elucidation of the role of activated oncogenes in sensitizing colorectal cancer cells to TRAIL-induced apoptosis. We also evaluate TRAIL-induced signalling in tumour-initiating cells and examine the role of endocytosis in TRAIL receptor signalling and trafficking. DR6 can participate in the regulation of T- and B-cell activation. We have discovered that posttranslational modifications regulate the cellular localization of this highly glycosylated and palmitoylated receptor and we currently characterize potential functions of proteins interacting with its intracellular part. Daxx is an essential adapter protein that is involved in stress- and Fas/CD95-triggered apoptosis and also participates in the regulation of transcription. Using Y2H screening we uncovered several new Daxx-interacting proteins such as Brg1 or SAP30 and we currently characterize functional consequences of their interaction with Daxx.

Current grant support

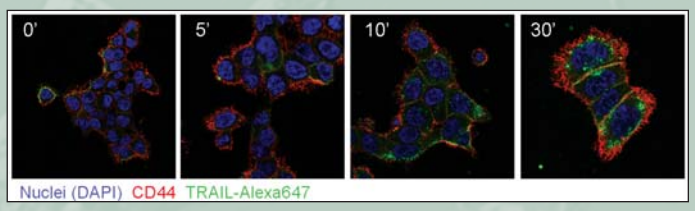
Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology, 1M0506); EC FP6 STREP project (Oncodeath, LSHG-CT-2006-037278); GA AS CR (Nanomed, KAN200520703)

Selected recent papers

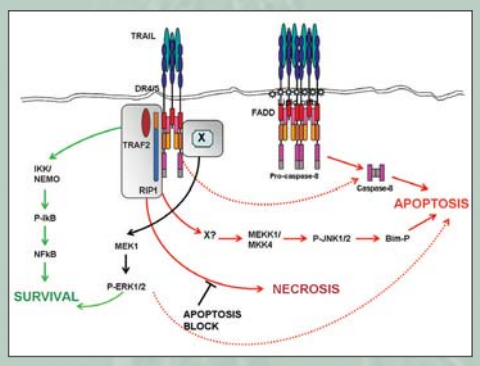
1. Psahoulia FH, Drosopoulos KG, Doubravska L, Andera L, Pintzas A. Quercetin enhances TRAIL-mediated apoptosis in colon cancer cells by inducing the accumulation of death receptors in lipid rafts. **Mol Cancer Ther.** 2007;6:2591-2599.
2. Oikonomou E, Kothonidis K, Zografos G, Nasioulas G, Andera L, Pintzas A. Newly established tumourigenic primary human colon cancer cell lines are sensitive to TRAIL-induced apoptosis in vitro and in vivo. **Br J Cancer.** 2007;97:73-84.
3. Doubravska L, Simova S, Cermak L, Valenta T, Korinek V, Andera L. Wnt-expressing rat embryonic fibroblasts suppress Apo2L/TRAIL-induced apoptosis of human leukemia cells. **Apoptosis.** 2008;13:573-587.
4. Simova S, Klima M, Cermak L, Sourkova V, Andera L. Arf and Rho GAP adapter protein ARAP1 participates in the mobilization of TRAIL-R1/DR4 to the plasma membrane. **Apoptosis.** 2008;13:423-436.



Transfected DR6(ICP)-interacting protein SNX3 pulls DR6 from the cytoplasmic membrane into vesicle-like structures.



Kinetics of Alexa 647-labelled TRAIL endocytosis in HCT116 colon carcinoma cells



TRAIL-induced signalling pathways

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Laboratory of Genome Integrity

DNA damage response, cell cycle, oncogenic transformation, ageing

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Markéta Černohorská / Diploma Student
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Research topics

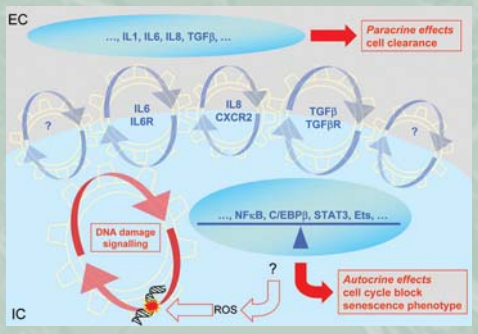
The research focus of the group established in January 2008 is centered on the mechanisms of maintenance of genomic integrity, which is a fundamental biological mechanism that care-takes against genetic diseases including cancer. Cellular senescence is one of the barriers guarding the organism against uncontrolled proliferation of cells with damaged genome. We focus on the mechanisms of oncogene- and chemically-induced senescence. We found that human cancer cells forced to chemically-induced senescence produce a large spectrum of cytokines including interferons, IL-1β, IL-6, IL-8, IL-10 and members of TNF and TGF families as a part of their secretory phenotype. Two of these cytokines, IL-6 and IL-8, play a pivotal role in promotion and maintenance of oncogene-induced senescent phenotype via autocrine regulatory loops. To understand the molecular mechanisms of persistent operation of these loops in senescent cells, we are investigating the role of DNA damage signalling in the regulatory pathways involved in cytokine gene expression, the role of post-translational modifications such as sumoylation in establishment and stabilization of cytokine loops, the role of cytokines in maintenance of the cell cycle arrest characteristic for senescent cells and the paracrine effects of secreted cytokines on surrounding cells - for example, in adaptation of neighbouring cells to DNA damage.

Current grant support

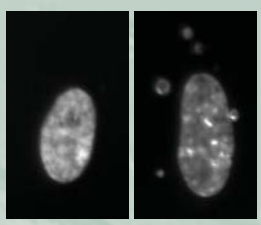
GA AS CR (IAA50039050); GA CR (GA204/081418, GA301/08/0353); FP7-HEALTH-2007-B (223575)

Selected recent papers

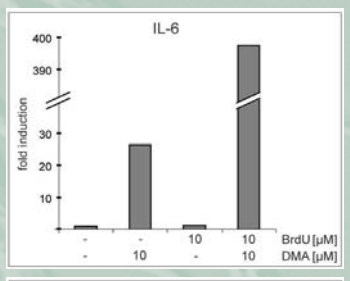
1. Bartek J, Hodny Z, Lukas J. Cytokine loops driving senescence. **Nat Cell Biol.** 2008;10:887-889.
2. Novakova Z, Hubackova S, Janderova-Rossmeislova L, Dobrovolna J, Vasicova P, Horejsi Z, Hozak P, Bartek J, Hodny Z. Cytokine expression and signaling in chemically induced cellular senescence. (submitted)

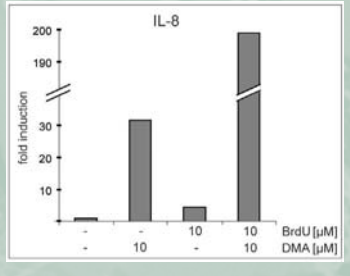


Model of cellular senescence promoted and maintained by concerted action of cytokine autocrine loops and the DNA damage response (DDR). DDR activates specific transcription factors (for example, NF-κB, C/EBPβ), which induce expression of several cytokine genes (for example, IL-1, IL-6, IL-8). Secreted cytokines trigger their respective signalling pathways by autocrine stimulation of plasma membrane receptors. Thus, the combined and interlocked activity of DNA damage and cytokine signalling pathways results in balanced cocktail of activated transcription factors, which induce a specific set of genes responsible for cell cycle block, promotion and maintenance of senescent phenotype, the induction of cytokine transactivator genes themselves and production of reactive oxygen species, which enclose the vicious cycle. EC, IC, extra/intracellular space.

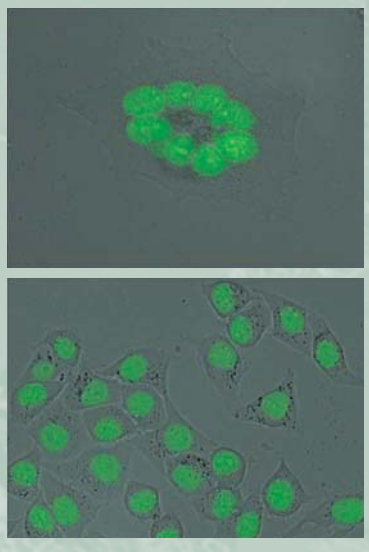


Bacterial toxin-induced cellular senescence accompanied by chromosomal aberrations detected as micronuclei. Nucleus of control (left) and intoxicated cell (right).





Interleukins IL-6 and IL-8 elevated in cultivating media of chemically senescent tumour cells



Polynucleation in aphidicolin-induced HeLa senescent cells. Histone-GFP labelled nuclei of normal (top) and senescent cell (bottom)

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Laboratory of Cell Differentiation

Haematopoietic and neural cell differentiation

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Research topics

In the body the brain is the most cholesterol-rich organ. Despite this, remarkably little is known about the mechanisms in the brain that regulate cholesterol homeostasis. Due to the blood-brain barrier, plasma lipoproteins are unable to traverse and instead cholesterol must be synthesized *de novo* from within the CNS. Thyroid hormone receptors, activated in response to thyroid hormone (T3), are known to modulate the level of serum cholesterol via complex regulatory pathways. By screening for T3-regulated genes we have identified Disp3, a sterol-sensing domain-containing protein that is related to the Dispatched family of proteins. Analysis by RT-PCR and immunohistochemistry demonstrated that DISP3 is predominantly expressed in specific cell types of the brain, retina and testis. DISP3 localizes within the endoplasmic reticulum and was further found to co-localize with cholesterol (Fig. 1). Ectopic expression of DISP3 in fibroblasts resulted in elevated cholesterol levels combined with an altered cholesterol distribution. We propose that DISP3 represents a new molecular link between thyroid hormone and cholesterol metabolism in the brain.

We have also identified, cloned and characterized the first non-mammalian Tpo, chicken thrombopoietin, and its receptor c-Mpl (2). Discovery of chicken Tpo and c-Mpl will greatly facilitate future studies regarding thrombocytic differentiation (Fig. 2) and haematopoietic stem cell development. Moreover, we have introduced an experimental model of chicken bi-potent thrombo/erythropoietic progenitors that can be used to identify key regulators of cell fate determination (2).

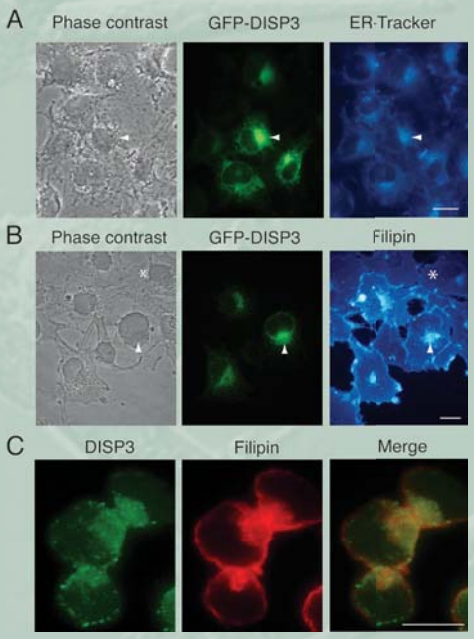

Fig. 1. DISP3 localizes to the ER and co-localizes with cholesterol. COS7 cells transiently transfected with GFP-DISP3 were labelled with (A) an ER-Tracker dye to show the sub-cellular localization of DISP3 and (B) filipin to visualize cellular cholesterol. Arrowheads highlight selected DISP3-GFP-transfected cells; asterisks mark non-transfected cells. (C) Y79 cells were stained with Disp3 antibody (green) and filipin (red-pseudocoloured). Yellow staining represents areas of co-localization.

Current grant support

EC FP6 (Integrated project CRESCENDO); GA AS CR (IAA500520705); GA CR (GA310/08/0878)

Selected recent papers

1. Karafiat V, Dvorakova M, Krejci E, Kralova J, Pajer P, Snajdr P, Mandikova S, Bartunek P, Grim M, Dvorak M. Transcription factor c-Myb is involved in the regulation of the epithelial--mesenchymal transition in the avian neural crest. **Cell Mol Life Sci.** 2005;62:2516-2525.
2. Bartunek P, Karafiat V, Bartunkova J, Pajer P, Dvorakova M, Kralova J, Zenke M., Dvorak M. Impact of chicken thrombopoietin and its receptor on hematopoietic cell development. **Exp Hematol.** 2008; 36:495-505.

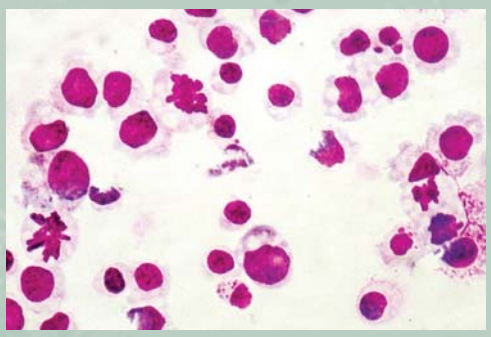

Fig. 2. Thrombocytic progenitors sorted from chicken bone marrow and cultivated in the presence of recombinant chicken Tpo. Several thrombocytic cells and various stages of development including the dividing cells are shown.

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Laboratory of Molecular Pharmacology

G-protein coupled receptors, neurotransmitters, cannabinoid receptor

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Kateřina Sedláčková / Secretary

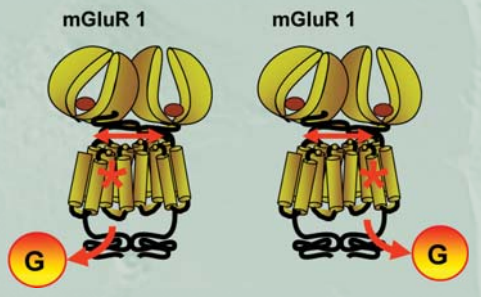
Research topics

We aim to describe principles of activation of G-protein-coupled receptors (GPCRs) for major neurotransmitters. The research is focused on the structure-function relationships of these receptors and molecular machinery that regulates their signalling properties. The metabotropic glutamate (mGlu) receptors that belong to family 3 GPCRs are composed of two identical subunits. The relevance of dimerization of these receptors in respect to activation of the transmembrane heptahelical domain (HD) of each subunit is of our particular interest. Using the mutagenesis approach combined with a functional expression system we showed that within the homodimeric structure only one HD reaches active state. Interestingly, this situation is very similar to that observed in GABAb receptor. Within the GABAb receptor that is composed of two different proteins, only one of them activates G-proteins. The activation process of these family 3 GPCRs is thus asymmetrical. Currently, we take use of this observation to reveal the mechanism of action of allosteric modulators on these receptors. To this aim we analyse energy transfer deviations upon activation and/or modulation of the receptors tagged with different fluorochromes at distinct portions of the receptors.

Regulation of the receptor activity on the cell surface is examined by search for associated proteins that interact mainly with the intracellular C-termini. This project is focused on signalling of cannabinoid receptor 1. It is approached by molecular biology means combined with biochemical tools including yeast two-hybrid technology, *in vivo* introduction of tagged "bites" into living animal brains followed up by the pull-down method for isolation of the interactors and their successive identification.

Class C GPCR activation process is assymetrical

In heterodimeric GABAb receptor (gamma-aminobutyric acid receptor-type b) only the GB2 subunit is capable of G-protein activation, while the ligand-binding site is located within the extracellular domain of GB1 subunit.



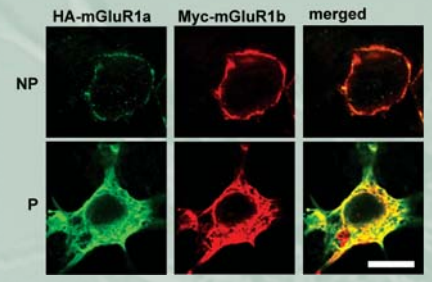
In our studies we showed that in metabotropic glutamate receptors, upon competitive agonist binding within both extracellular „venus-fly trap-like" domains only one of two identical subunit's transmembrane heptahelical domains reaches activated state.

Current grant support

Ministry of Education, Youth and Sports (LC06063 „FLUMBIOL"); GA CR (GA204/05/0920); GA AS CR (IAA400400621, IAA500390701)

Selected recent papers

1. Bertaso F, Lill Y, Airas JM, Espeut J, Blahos J, Bockaert J, Fagni L, Betz H, El-Far O. MacMARCKS interacts with the metabotropic glutamate receptor type 7 and modulates G protein-mediated constitutive inhibition of calcium channels. **J Neurochem.** 2006;99:288-298.
2. Kumpost J, Syrova Z, Kulihova L, Frankova D, Bologna JC, Hlavackova V, Prezeau L, Kralikova M, Hruskova B, Pin JP, Blahos J. Surface expression of metabotropic glutamate receptor variants mGluR1a and mGluR1b in transfected HEK293 cells. **Neuropharmacology.** 2008;55:409-418.



Distribution of mGluR1a and mGluR1b splice variants in transfected HEK293 cells
Cells were transfected with the mGluR1a or mGluR1b coding plasmids. Paraformaldehyde-fixed cells transfected with the indicated plasmids were permeabilized (P) or not (NP) and stained with rabbit anti-HA (for HA-mGluR1a) or mouse anti-c-Myc (for Myc-mGluR1b) antibodies and visualized with corresponding secondary antibodies labelled with FITC or Cy3, respectively. Staining was analysed by confocal microscopy with co-localized fluorescence being shown in yellow. Bar equals 10 μm in vivo. This together with other results suggests that splicing within intracellular C-terminus of mGlu1 receptor does not encode targeting signals into distinct cell compartments.

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Laboratory of Biology of Cytoskeleton

Modulation of microtubule organization, microtubule proteins

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Vladimíra Marková, MSc / Research Assistant
Věra Richterová, MSc / Research Assistant
Ladislav Cupák / Technician
Irena Mlchová / Technician
Barbora Hořejší, MSc / PhD Student
Stanislav Vinopal, MSc / PhD Student
Zuzana Hájková / Diploma Student
Karel Beránek / Diploma Student
Tetyana Sulimenko / Maternity Leave

Research topics

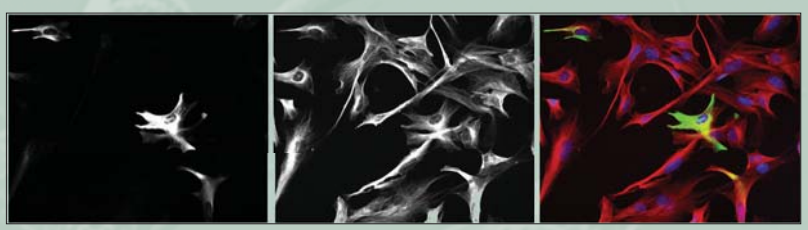
The long-term research programme of the laboratory has been focused on studying the structure-function relationships of microtubule (MT) proteins and their interactions with other cytoskeletal elements in cells under normal and pathological conditions. The organization of MT networks is controlled by microtubule organizing centres (MTOCs). One of the key components of MTOCs is γ-tubulin, which is necessary for nucleation of MT. There are cumulative data indicating that γ-tubulin could also have other functions. Current work focuses on the understanding of the function of γ-tubulin forms, modulation of MT properties by signal transduction molecules, and molecular and functional characterization of MTOC components. To address these questions, techniques of molecular biology, biochemistry and immunology are being used, as well as a variety of microscopic techniques, including live cell imaging. Our results demonstrate that non-receptor protein tyrosine kinase Fyn of the Src family and phosphoinositide 3-kinase play an important role in MT nucleation from membranes. We have also shown that ectopic cellular expression of γ-tubulin in gliomas may serve as a novel marker of anaplastic changes. Finally, we have identified class III β-tubulin, which is regarded as a neuronal marker, in primary cultures of astrocytes expressing GFAP and nestin.

Current grant support

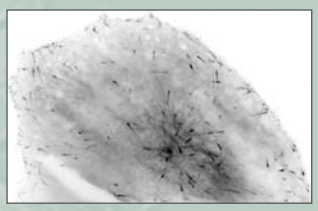
Ministry of Education, Youth and Sports (Center of Cell Functional Organization, LC545); GA CR (GD204/05/H023), GA AS CR (KAN200520701)

Selected recent papers

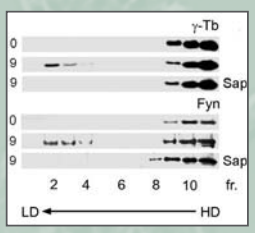
1. Sulimenko V, Dráberová E, Sulimenko T, Macůrek L, Richterová V, Dráber Pe, Dráber P. Regulation of microtubule formation in activated mast cells by complexes of γ-tubulin with Fyn and Syk kinases. **J Immunol**. 2006;176:7243-7253.
2. Katsetos CD, Reddy G, Dráberová E, Šmejkalová B, Del Valle L, Ashraf Q, Tadevosyan A, Yelin K, Maraziotis T, Mishra OP, Mörk S, Legido A, Nissanov J, Baas PW, de Chadarévian JP, Dráber P. Altered cellular distribution and subcellular sorting of γ-tubulin in diffuse astrocytic gliomas and human glioblastoma cell lines suggest centrosome protein amplification. **J Neuropathol Exp Neurol.** 2006;65:465-477.
3. Dráberová E, Del Valle L, Gordon J. Marková V, Šmejkalová B, Bertrand L, de Chadarévian JP, Agamanolis DP, Legido A, Khalili K. Dráber P, Katsetos CD. Class III β-tubulin is constitutively co-expressed with GFAP and nestin in midgestational human fetal astrocytes in primary culture: comparative observations in the fetal brain and implications in phenotypic identity. **J Neuropathol Exp Neurol.** 2008;67:341-354.
4. Macůrek L, Dráberová E, Richterová V, Sulimenko V, Sulimenko T, Dráberová L., Marková V, Dráber P. Regulation of microtubule nucleation in differentiating embryonal carcinoma cells by complexes of membrane-bound γ-tubulin with Fyn kinase and phosphoinositide 3-kinase. **Biochem J.** 2008;416:421-430.



Distribution of glial fibrillary acidic protein (green) and class III β-tubulin (red) in primary culture of foetal astrocytes



Growing ends of microtubules detected by EB1-GFP in U2OS cells (TIRF microscopy)



Distribution of γ-tubulin and Fyn kinase during density gradient centrifugation of lysates from resting (0) and retinoic acid-differentiated (9) P19 cells (Sap, lysates with cholesterol-depleting agent saponin)

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Laboratory of Signal Transduction

Plasma membrane signalosomes

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Monika Bambousková / Diploma Student
Martin Machyna / Diploma Student
Michal Šimíček / Diploma Student

Research topics

Recent studies in our laboratory are mainly focused on comprehension of the role of selected plasma membrane components in initial stages of mast cell activation. We have analysed the function of several proteins, including transmembrane adaptor proteins NTAL, LAT, and PAG and phospholipid scramblase I (PLSCRI). We found that in mast cells activated by aggregation of the high-affinity IgE receptor or Thy-1 glycoprotein, tyrosine phosphorylation of PLSCRI is dramatically increased. This had no effect on topography of PLSCRI or membrane symmetry as determined by externalization of phosphatidylserine (PS). During these studies we have found, unexpectedly, that inhibition of phosphatases by pervanadate induces exocytosis in the absence of PS externalization. Our data indicate that changes in topography of PLSCRI and its tyrosine phosphorylation, PS externalization, and exocytosis are independent phenomena that could be distinguished by employing specific conditions of activation. Furthermore, we have produced new monoclonal antibody specific for cell membrane molecule CD9 and found new additives enhancing the performance of polymerase chain reaction.

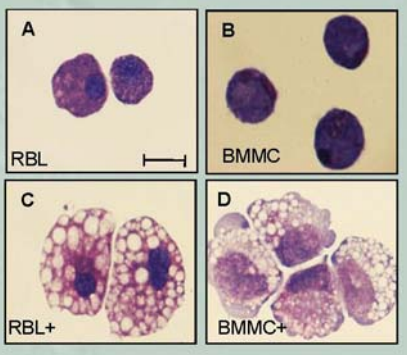
Current grant support

Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology, 1M0506); GA CR (GA301/06/0361); GA AS CR (KAN200520701)

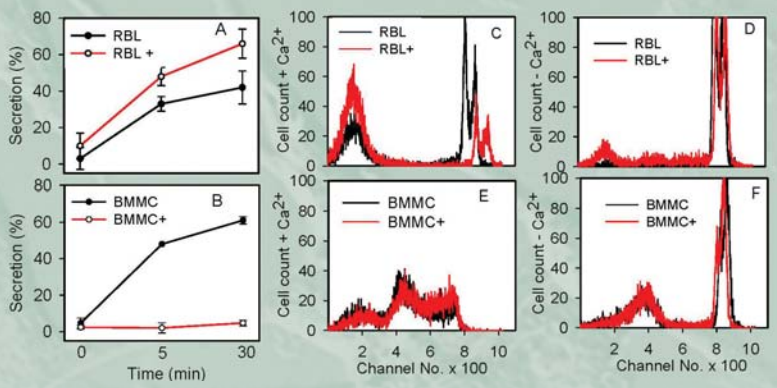
Telemetry. Implanted probes are used to measure body temperature continuously in the course of allergy reaction.

Selected recent papers

1. Dráberová L, Shaik GM, Volná P, Heneberg P, Tůmová M, Lebduška P, Korb J, Dráber P. Regulation of Ca^{2+} signaling in mast cells by tyrosine-phosphorylated and unphosphorylated non-T cell activation linker. **J Immunol.** 2007;179:5169-5180.
2. Smrž D, Dráberová L, Dráber P. Non-apoptotic phosphatidylserine externalization induced by engagement of glycosylphosphatidylinositol-anchored proteins. **J Biol Chem.** 2007;282:10487-10497.
3. Dráber P, Dráberová L, Heneberg P, Šmid F, Farghali H, Dráber P. Preformed STAT3 transducer complexes in human HepG2 cells and rat hepatocytes. **Cell Signal.** 2007;19:2400-2412.
4. Smrž D, Lebduška P, Dráberová L, Korb J, Dráber P. Engagement of phospholipid scramblase 1 in activated cells: implication for phosphatidylserine externalization and exocytosis. **J Biol Chem.** 2008;283:10904-10918.
5. Shaik GM, Dráberová L, Dráber P, Boubelik M, Dráber P. Tetraalkylammonium derivatives as real-time PCR enhancers and stabilizers of the qPCR mixtures containing SYBR Green I. **Nucleic Acids Res.** 2008;36:e93-e103.



Formation of vacuoles in vacuolin-1-treated mast cells. Rat basophilic leukaemia (RBL) cells (A,C) or bone marrow-derived mast cells (BMMCs, B,D) were treated with vehicle (A,B) or vacuolin-1 (C,D; +) and 3 h later the cells were stained with Giemsa-Romanowski stain. Bar, 10 μm. Interestingly, treatment with vacuolin-1 enhanced exocytosis and resealing of damaged membranes in RBL cells, but inhibited these processes in BMMCs (see data on the right).



Correlation between exocytosis and membrane repair in vacuolin-1-treated mast cells. Antigen-mediated exocytosis after treatment with vacuolin-1 was enhanced in RBL cells (A) but inhibited in BMMCs (B). Vacuolin-1 also had a different effect on repair of the plasma membrane damaged by streptolysin O. In the presence of Ca^{2+}, vacuolin-1 enhanced membrane repair in RBL cells (C), but inhibited it in BMMCs (E). In the absence of Ca^{2+} the repair was poor in both cell types (D, F).

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Laboratory of Molecular Virology

Carcinogenesis, cell differentiation, photodynamic therapy

Research topics

The research efforts of the group focus on genes and molecular mechanisms involved in

1) fate determination in multipotent haematopoietic and neural cells and terminal differentiation of haematopoietic, neural and myogenic cells;
2) malignant transformation of haematopoietic cells, melanocytes, nephrogenic blastema and lung cells;
3) apoptosis induced by photoactivation of specific porphyrins;
4) epithelial to mesenchymal and mesenchymal to epithelial transitions.

In studies on cell fate determination, differentiation and malignant transformation of haematopoietic and neural cells (collaboration with the Institute of Anatomy, Prague), c-*myb* and v-*myb* genes are used as tools to modulate development of avian cells and tissues. In studies on the nephrogenic blastema transformation and lung tumour formation, MAV retroviruses serve as tumour inductors in experimental chicks. Porphyrin derivatives synthesized by the cooperating group (Institute of Chemical Technology, Prague) are used for experiments with targeted drug delivery and induction of cell death in cancer cells and tissues. Finally, genes of the *egr* family serve as tools to affect epithelial and mesenchymal cell phenotypes.

Current grant support

Ministry of Education, Youth and Sports (Center of Cell Invasiveness in Embryonic Development and Tumor Metastases, LC06061; Center of Chemical Genetics, LC06077); GA CR (GA204/06/1728, GA203/06/1038); GA AS CR (IAA500520608)

Selected recent papers

1. Pajer P, Pečenka V, Králová J, Karafiát V, Průková D, Zemanová Z, Kodet R, Dvořák M. Identification of potential human oncogenes by mapping the common viral integration sites in avian nephroblastoma. **Cancer Res.** 2006;66:78-86.
2. Karafiat V, Dvorakova M, Pajer P, Cermak V, Dvorak M. The melanocyte fate in neural crest is triggered by Myb proteins through activation of c-kit. **Cell Mol Life Sci.** 2007;64:2975-2984.
3. Bartunek P, Karafiat V, Bartunkova J, Pajer P, Dvorakova M, Kralova J, Zenke M, Dvorak M. Impact of chicken thrombopoietin and its receptor c-Mpl on hematopoietic cell development. **Exp Hematol.** 2008;36:495-505.
4. Kaspar P, Dvorak M. Involvement of phosphatidylserine externalization in the down-regulation of c-myb expression in differentiating C2C12 cells. **Differentiation.** 2008;76:245-252.
5. Kralova J, Dvorak M, Koc M, Kral V. p38 MAPK plays an essential role in apoptosis induced by photoactivation of a novel ethylene glycol porphyrin derivative. **Oncogene.** 2008;27:3010-3020.
6. Kralova J, Bříza T, Moserova I, Dolensky B, Vašek P, Poučkova P, Kejik Z, Kaplanek R, Martasek P, Dvořak M, Kral V. Glycol porphyrin derivatives as potent photodynamic inducers of apoptosis in tumor cells. **J Med Chem.** 2008;51:5964-5973.
7. Bříza T, Kejík Z, Císařová, I, Králová J, Martásek P, Král V. Optical sensing of sulfate by polymethinium salt receptors: colorimetric sensor for heparin. **Chem Commun (Camb).** 2008;16:1901-1903.

Effect of photodynamic therapy on human breast carcinoma implanted to experimental NuNu mice.

Control untreated mouse

Mouse 30 days after treatment application (only the scar after tumour removal is visible)

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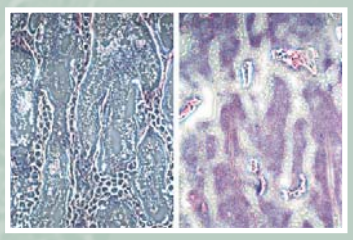
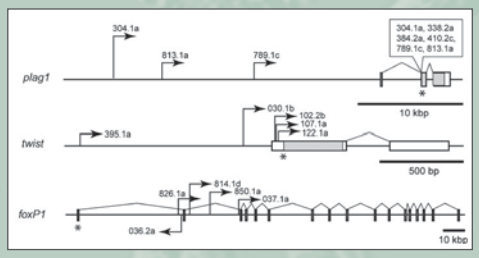


Search for factors causing disintegration of bone marrow microenvironment in experimental acute monoblastic leukaemia. *The growth plate regions of long bones (femur) in healthy (left) and leukaemic (right) experimental animals*



Identification of plag1, twist, and foxP1 genes as oncogenes in experimental nephroblastomas. *The exon-intron structure of chicken genes and sites of proviral integrations. Arrows indicating gene-activating integration sites and orientation of transcription are marked by code numbers of tumours in which they were found.*

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Laboratory of Immunobiology

Innate immune receptors and their signalling, sterile inflammation, TCR signalling

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Research topics

Our newly formed group became functional in the summer of 2007. The central theme of our research is the molecular and functional characterization of innate immune mechanisms involved in the process of sterile inflammation, developmental tissue remodelling and chronic inflammatory diseases.

Our main effort is focused on Toll-like receptors and the identification of their putative endogenous, self-derived ligands. Data accumulated so far point to spatially and temporarily regulated expression of TLRs on embryonal phagocytes, suggesting their involvement in sterile inflammation during early development. The characterization of the complete set of innate immune receptors (IIRs) expressed on embryonal phagocytes and evaluation of their signaling competence, together with elucidation of the nature of endogenous ligands for these IIRs represent our main objectives. Further, the cDNA microarray analyses performed on embryonal phagocytes revealed a cell-specific expression of several uncharacterized molecules that could play an essential role in the processes supporting embryonal homeostasis. The insight gained from genetic, biochemical and microscopic approaches (Figs. 1 and 2) will contribute to our understanding of the process of sterile inflammation and its role in embryonal development.

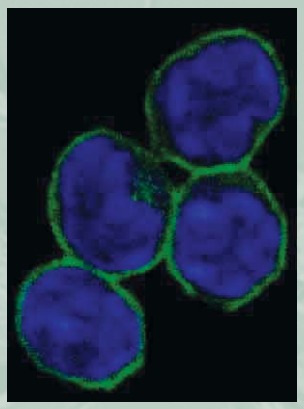

Fig. 1. Fluorescent microscopy of the primary CD4⁺ T cells stained with DAPI (blue, nuclei) and anti-Lck (green). Activation and subsequent translocation of membrane-associated Lck to lipid rafts predicates T-cell activation (see the paper and references in it).

Other researchers in our group study early events leading to activation of two Src-family tyrosine kinases (SFK) Lck and Fyn during the initiation of membrane proximal T-cell signalling. The essential event in this process is the translocation and subsequent enrichment of kinase active Lck in lipid rafts (LR) (Fig. 1). While other regulatory proteins are also recruited to LR upon T-cell activation, the mechanism of these translocations, indispensable for T-cell activation, is largely unknown. In this context, we have identified the previously uncharacterized role of the C-terminal sequence of Lck (YQPQP) in its targeting to LR (ref. 1). The main goal of this line of research is the characterization of the molecular mechanism underpinning the recruitment of Lck and other signalling molecules to LR.

Current grant support

GA AS CR (IAA500520707); Ministry of Education, Youth and Sports (2B08066-4)

Selected recent papers

Filipp D, Moemeni B, Ferzoco A, Kathirkamathamby K, Zhang J, Ballek O, Davidson D, Veillette A, Julius M. Lck dependent Fyn activation requires C-terminus dependent targeting of kinase active Lck to lipid rafts. **J Biol Chem.** 2008;283:26409-26422.

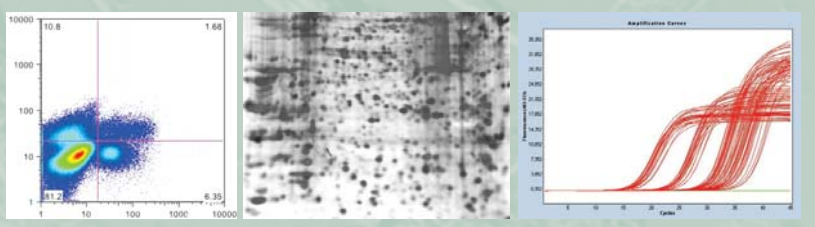

Fig. 2. FACS analysis, 2-D gel electrophoresis, 384-multiwell qRT-PCR and immunofluorescent confocal microscopy (Fig. 1) belong to a standard battery of techniques used in the laboratory to analyse the cells and molecules of immune system.

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Laboratory of Mouse Molecular Genetics

Meiotic silencing, aneuploidy, genomics, hybrid sterility genes

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David Homolka, MSc / PhD Student
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Hana Vágnerová / Secretary

Research topics

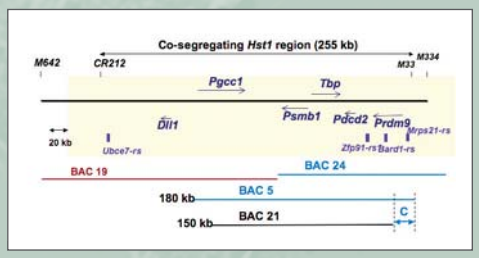
We study **meiotic X-chromosome inactivation** by genome-wide expression profiling and by monitoring X-chromosome histone modifications in meiotic and post-meiotic testicular cells of carriers of male-sterile autosomal rearrangements and in male-sterile inter-species hybrids.

Genetic architecture of hybrid male sterility is analysed on the model of PWD/Ph x C57BL/6 sterile male hybrids. The candidate genes are evaluated by transgenic rescue for the *Hst1* locus and by positional cloning and expression profiling of sorted testicular cells for the *Hstx1* locus.

We have established a **new mouse model of human aneuploidy syndromes**. The Ts43H segmental trisomy of proximal 30 MB of mouse chromosome 17 encompasses over 300 protein-coding genes. Phenome analysis of aneusomic animals is realized by collaboration with Dr. M. Hrabe de Angelis, GSF, Munich.

Chromosome substitution strains C56BL/6.PWD, recently constructed in our laboratory, are used for phenome analysis in collaboration with The Jackson Laboratory, Bar Harbor, Maine, USA (Dr. K.L. Svenson) and for the genetics of gene expression and splicing in a systems genetics project with the Max-Planck-Institute for Molecular Genetics in Berlin (Dr. H. Lehrach).

We have identified the first vertebrate hybrid sterility gene, **the mouse Hybrid sterity 1** *(Hst1)* **with *Prdm9*, encoding a meiotic histone H3 lysine-4 tri-methyltransferase**. Positional cloning was confirmed by hybrid male infertility rescue by using the intact *Prdm9* transgene in bacterial artificial chromosomes with the „fertility" *Hst1*^{f} allele. Identification of the first vertebrate hybrid sterility gene reveals a role for epigenetics in speciation, and opens a window to a hybrid sterility gene network.



Functional mapping of hybrid sterility 1 locus to Prdm9 gene encoding histone H3 lysine-4 methyltransferase. Hybrid male sterility rescue was achieved in transgenic inter-subspecific hybrids (PWD x B6) with BAC5 and BAC24, but not with BAC21. The Prdm9 gene is the only gene shared by BAC5 and BAC24 but absent in BAC21 (see Mihola et al., Science, 2008).

Current grant support

Ministry of Education, Youth and Sports (Center of Applied Genomics, 1M0520); GA CR (GA301/06/1334, GA301/07/1264, GA301/07/1383); GA AS CR (IAA5052406); 6th FP EC (037627); Praemium academiae

Selected recent papers

1. Homolka D, Ivanek R, Capkova J, Jansa P, Forejt J. Chromosomal rearrangement interferes with X-chromosome inactivation. **Genome Res.** 2007;17:1431-1437.
2. Gregorová S, Divina P, Storchova R, Trachtulec Z, Fotopulosova V, Svenson KL, Donahue LR, Paigen B, Forejt J. Mouse consomic strains: Exploiting genetic divergence between Mus m. musculus and Mus m. domesticus subspecies. **Genome Res.** 2008;18:509-515.
3. Pialek J, Vyskocilova M, Bimova B, Havelkova D, Pialkova J, Dufkova P, Bencova, V., Dureje L, Albrecht T, Hauffe HC, Macholan M, Munclinger P, Storchova R, Zajicova A, Holan V, Gregorova S, Forejt J. Development of unique house mouse resources suitable for evolutionary studies of speciation. **J Hered.** 2008;99:34-44.
4. Trachtulec Z, Vlcek C, Mihola O, Fotopulosova V, Forejt J. Fine haplotype structure of a chromosome 17 region in the laboratory and wild mouse. **Genetics.** 2008;178:1777-1784.
5. Mihola O, Trachtulec Z, Schimenti JC, Vlcek C, Forejt J. A mouse speciation gene encodes a meiotic histone H3 methyltransferase. **Science.** Published online 11 December 2008 (10.1126/science.1163601).

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Laboratory of Viral and Cellular Genetics

Receptors for retroviruses, retroviral vectors, endogenous retroviruses, silencing of retroviruses

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Anton A. Buzdin, PhD / Visiting Scientist

Research topics

The main scientific interest of our group has been traditionally focused on the interactions of retroviruses with the host cells. Retroviruses enter their natural host cells via specific receptors, integrate into the host genome, and use the cell transcription machinery to express their structural or enzymatically active proteins. Specific binding of retroviral envelope proteins to host cell receptors is the prerequisite for cell permissiveness to the infection. Retroviruses broaden their host range by mutations of the *env* gene; host cells develop resistance to retrovirus by mutations of genes encoding the specific receptors. We have described such an interesting semi-resistant phenotype in chicken line M and explained it by mutation of the receptor *Tvb*. Another defence mechanism used by the host cells is the inactivation of integrated invaders at the level of transcription via DNA methylation and modifications of adjacent histones. This is, however, an obstacle in using retroviruses as vectors for gene transfer and transgenesis. We have improved ASLV-based retroviral vectors by insertion of the core element from a CpG island between the promoter and the enhancer, which increases their resistance to transcriptional silencing and ensures long-term expression of transduced genes. We have successfully used a retroviral vector for transduction of reporter genes in the chicken male germ line, which opens the way to efficient transgenesis in chicken. We have also characterized the CpG methylation status in latent proviruses of HIV-1 and suggested a two-step model of HIV-1 latency. Finally, we have identified two genomic copies of porcine endogenous retroviruses as a potential risk factor in xenotransplantation of pig organs and tissues.

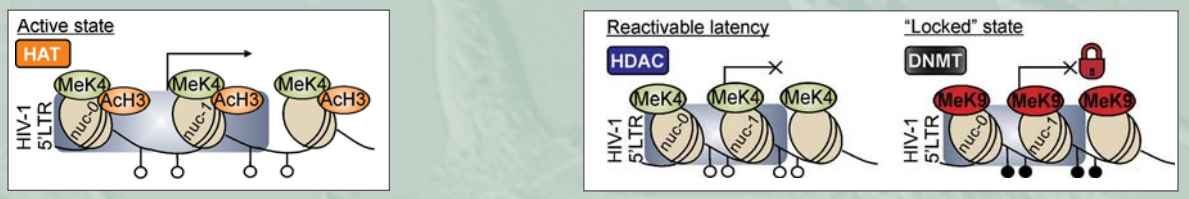
Current grant support

Ministry of Education, Youth and Sports (Center LC-06061), GACR (GA204/07/1030, GA523/07/1171, GA523/07/1282, GP204/08/P616), GA AS CR (IAA500520709), FP6 International project XENOME

Selected recent papers

1. Reinišová M, Šenigl F, Yin X, Plachý J, Geryk J, Elleder D, Svoboda J, Federspiel MJ, Hejnar J. A single amino acid substitution in the Tvb^{S1} receptor results in the semi-resistant phenotype of an inbred chicken line to infection by subgroup B and D avian sarcoma and leukosis viruses. **J Virol.** 2008;82:2097-2105.
2. Šenigl F, Plachý J, Hejnar J. The core element of a CpG island protects avian sarcoma and leukosis virus-derived vectors from transcriptional silencing. **J Virol.** 2008;82:7818-7827.
3. Reinišová M, Pavlíček A, Divina P, Geryk J, Plachý J, Hejnar J. Target site preference of subgroup C Rous sarcoma virus integration into the chicken DNA. **Open Genomics J.** 2008;1:6-12.
4. Mucksová J, Brillard J-P, Hejnar J, Poplštejn M, Kalina J, Bakst M, Yan H, Trefil P. Identification of various testicular cell populations in pubertal and adult cockerels. Accepted to **Anim Reprod Sci.**

DNA methylation and modification of histones associated with HIV-1 long terminal repeats in a two-step model of HIV-1 latency. Below, the active state. Right, the reactivable latency in line H12 and locked state in the 2D12 cell line.



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Laboratory of Transplantation Immunology

Transplantation imunity, cytokines, stem cells, immunoregulation

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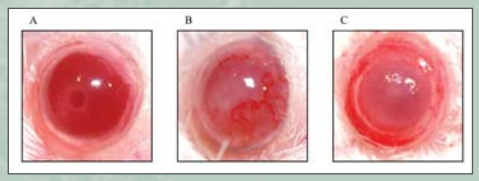
Research topics

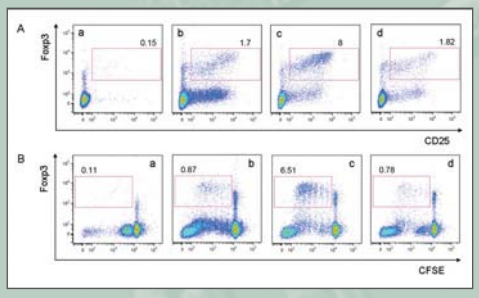
Transplantation of a damaged or non-functional organ often represents the only way to improve or even to rescue life. However, immunological rejection represents the major obstacle to further development of clinical transplantation. Therefore, deep knowledge of molecular and cellular mechanisms of the transplantation reaction is required. Using experimental models of corneal and limbal transplantation in mice we study regulatory mechanisms in the eye and the possibilities to treat corneal injuries by transplantation of limbal stem cells.

Using the model of immunological reaction to histocompatibility antigens we are focused on the study of activation and function of regulatory T cells in transplantation immunity and tolerance. On the model of orthotopic corneal and limbal transplantation we have analysed expression of genes for cytokines and other effector molecules during graft rejection and studied possibilities to prevent rejection of corneal and limbal grafts. Since successful treatment of damaged cornea requires transfer of limbal stem cells, we recently started to isolate, grow and characterize stem cells. We succeeded in isolating limbal stem cells in the mouse and using them for the repair of damaged corneal epithelium.

Well-established methods for monitoring the immune response enabled us, in co-operation with other laboratories, to study cytokine response in various experimental models of immunoregulation. The ultimate goal of our research is to get insights into the mechanisms of specific immune response, to isolate and transplant stem cells and to propose novel strategies for targeted immunoregulation.



Limbal transplantation in the mouse. A – syngeneic graft, B – allograft, C – xenograft



Induction of CD4⁺CD25⁺Foxp3⁺ regulatory T cells by alloantigens and TGF-β (A) and monitoring of cell proliferation using CSFE (B)

Current grant support

GA AS CR (KAN 200520804), GA CR (GA309/06/0121, GA206/08/0640, GD310/08/H077), 6th FP EC (018094), Ministry of Education, Youth and Sports (Center for Molecular and Cellular Immunology, 1M0506)

Selected recent papers

1. Tavandzi U, Procházka R, Usvald D, Hlučilová J, Vitásková M, Motlík J, Vítová A, Filipec M, Forrester JV, Holáň V. A new model of corneal transplantation in the miniature pig. Efficacy of immunosuppressive treatment. **Transplantation.** 2007;83:1401-1403.
2. Frič J, Marek M, Hrušková V, Holáň V, Forstová J. Cellular and humoral immune responses to chimeric EGFP-pseudocapsids derived from the mouse polyomavirus after their intranasal administration. **Vaccine.** 2008;26:3242-3251.
3. Piálek J, Vyskočilová M, Bímová B, Havelková D, Piálková J, Dufková P, Bencová V, Dureje L, Albrecht T, Hauffe HC, Macholán M, Munclinger P, Storchová R, Zajícová A, Holáň V, Gregorová S, Forejt J. Development of unique house mouse resources suitable for evolutionary studies of speciation. **J Hered.** 2008;99:34-44.
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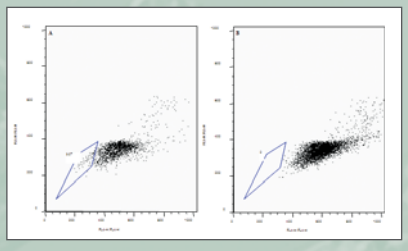

Detection of limbal stem cells as a "side population" based on the ability of stem cells to efflux DNA-binding dye Hoechst 33342 (A) and blocking the efflux by ABCG2 transporter inhibitor verapamil (B)

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Laboratory of Molecular Immunology

Transmembrane adaptor proteins, membrane rafts

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Eva Tvrzníková / Secretary

Research topics

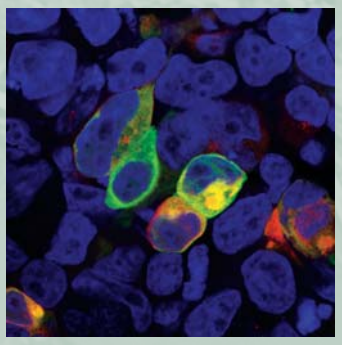
In recent years a major topic of our laboratory has been signalling molecules present in membrane rafts, namely several transmembrane adaptor proteins discovered previously by us (PAG/Cbp, NTAL/LAB, LIME) and their involvement in immunoreceptor signalling. In 2008 we worked on elucidation of the structure and function of an apparently novel type of "heavy" rafts, differing from the "classical" ones by higher protein-lipid ratio and containing a number of transmembrane proteins. We continued our studies on several novel raft-associated transmembrane adaptors (LST1A, PRR7, "Nvl"), on receptor phosphatase CD148, and collaborated on several studies concerning membrane rafts and their components. Furthermore, we produced a number of novel monoclonal antibodies as valuable research tools, e.g. those to TFG, H-Ras, CD148, mouse LIME, drebrin.

Current grant support

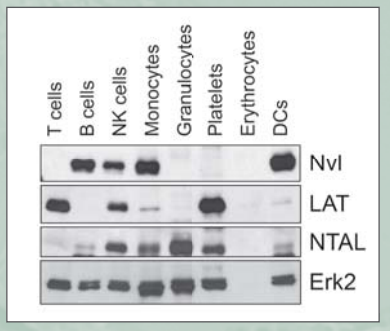
Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology, 1M0506; NPVII project 2B06064); FP6 EU (HYBLIB, NEST, 12919)

Selected recent papers

1. Gregoire C, Simova S, Wang Y, Sansoni A, Richelme S, Schmidt-Giese A, Simeoni L, Angelisova P, Reinhold D, Schraven B, Horejsi V, Malissen B, Malissen M. Deletion of the LIME adaptor protein minimally affects T and B cell development and function. **Eur J Immunol.** 2007;37:3259-3269.
2. Iwaki S, Spicka J, Tkaczyk C, Jensen BM, Furumoto Y, Charles N, Kovarova M, Rivera J, Horejsi V, Metcalfe DD, Gilfillan AM. Kit- and FcεRI-induced differential phosphorylation of the transmembrane adaptor molecule NTAL/LAB/LAT2 allows flexibility in its scaffolding function in mast cells. **Cell Signal.** 2008;20:195-205.
3. Khunkaewla P, Schiller HB, Paster W, Leksa V, Cermák L, Andera L, Horejsí V, Stockinger H. LFA-1-mediated leukocyte adhesion regulated by interaction of CD43 with LFA-1 and CD147. **Mol Immunol.** 2008;45:1703-1711.
4. Veracini L, Simon V, Richard V, Schraven B, Horejsi V, Roche S, Benistant C. The Csk-binding protein PAG regulates PDGF-induced Src mitogenic signaling via GM1. **J Cell Biol.** 2008;182:603-614.
5. Wu W, Slaastad HS, de la Rosa Carrillo D, Frey T, Tjonnfjord GE, Boretti E, Aasheim HC, Horejsi V, Lund-Johansen F. Antibody array analysis with label-based detection and resolution of protein size. **Mol Cell Proteomics.** Epub Sep 16, 2008.



Subcellular localization of a novel adaptor, PRR7 (red), as compared to PSD-95 (green)



Expression of transmembrane adaptors Nvl, LAT, NTAL in various types of blood cells

Scheme of receptor phosphatase CD148

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Laboratory of Biology of the Cell Nucleus

Regulation of gene transcription, nucleoskeleton, nuclear actin, myosin, ultrastructural methods

Research topics

In diploid mammalian cells, some $6x10^9$ base pairs of DNA fold as a nucleo-protein complex (i.e. chromatin) into higher-order arrays so as to fit in a nucleus measuring only 10 μm. The nucleus also contains machineries for transcription of genes and processing of RNA products, and for precise DNA replication, repair and recombination. Nuclear interior is therefore functionally highly compartmentalized, and the recent evidence points strongly to structure-related regulation of nuclear functions – however, the mechanisms forming the 3D-structure of the nucleus are still mostly obscure. We therefore employ a multi-disciplinary approach in order to study nuclear functions in relation to the higher-order nuclear structures, e.g. nuclear bodies, the nucleolus, and the nucleoskeleton. Our research concentrates on: (1) the relationship between nuclear compartmentalization and regulation of gene expression, (2) structure, dynamics, and function of the nucleoskeleton, which might direct nuclear compartmentalization, (3) functions of nuclear myosin I and actin in transcription and gene expression, (4) development of new microscopy methods for ultrastructural studies.

Current grant support

AS CR (KAN200520704); GA CR (GA204/07/1592; GD204/05/H023); Ministry of Education, Youth and Sports (LC 545; LC06063; 2B06063)

Selected recent papers

1. Kahle M, Pridalova J, Spacek M, Dzijak R, Hozak P. Nuclear myosin is ubiquitously expressed and evolutionary conserved In vertebrates. **Histochem Cell Biol.** 2007;127:139-148.
2. Vlasakova J, Novakova Z, Rossmeislova L, Kahle M, Hozak P, Hodny Z. Histone deacetylase inhibitors suppress IFNα-induced up-regulation of promyelocytic leukemia protein. **Blood.** 2007;109:1373-1380.
3. Fulka H, John J C St, Fulka J, Hozak P. Chromatin in early mammalian embryos: achieving the pluripotent state. **Differentiation.** 2008;76:3-14.
4. Ogushi S, Palmieri CH, Fulka H, Saitou M, Miyano T, Fulka J Jr. The maternal nucleolus is essential for early embryonic development in mammals. **Science.** 2008; 319:613-616.
5. Strádalová V, Gaplovská-Kyselá K, Hozák P. Ultrastructural and nuclear antigen preservation after high-pressure freezing/freeze-substitution and low-temperature LR White embedding of HeLa cells. **Histochem Cell Biol.** 2008;130:1047-1052.

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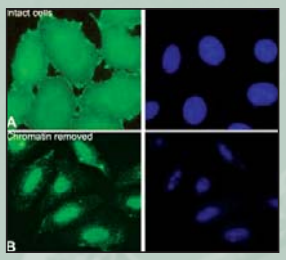
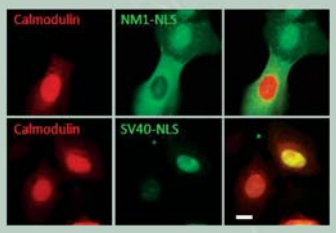
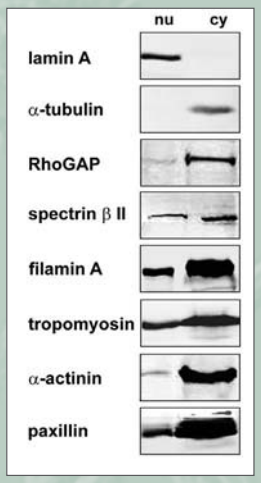
Lenka Pišlová / Secretary



Vinculin is an actin-binding protein which is considered to be exclusively cytoplasmic. We demonstrate for the first time nuclear localization of vinculin in intact cells (A). The intensity of the signal becomes stronger after the removal of chromatin (B). Green: anti-vinculin antibody; blue: DNA.



Nuclear transport mediated by NM1 nuclear localizing signal (NLS) is inhibited by calmodulin. This suggests that NM1 transport to the nucleus might be regulated by calcium levels.



Various actin-binding proteins were identified in nuclear extracts of Hela cells. Lamin and tubulin antibodies were used for control of purity of nuclear (nu) and cytoplasmic (cy) fractions. This information forms a basis for studying new components of nuclear structures.

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Laboratory of Chromosomal Stability

DNA damage response, DNA repair mechanisms, genomic instability syndromes

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Research topics

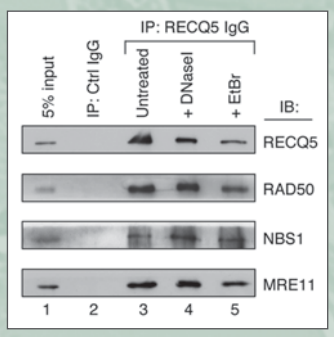
Cells are constantly under threat of the cytotoxic and mutagenic effects of DNA damage arising from DNA metabolism and following attack of endogenous and exogenous genotoxic agents. Failure to preserve genomic stability can lead to tumorigenesis. The research in our recently established laboratory is focused on understanding the mechanisms that control genomic stability in mammalian cells. Specifically, we study the role of human RecQ DNA helicases in DNA replication and DNA repair through analysis of their enzymatic activities and interactions with nuclear proteins. In humans, there are five RecQ homologues and deficiencies in three of them cause genetic disorders characterized by genomic instability, cancer predisposition, premature ageing and/or developmental abnormalities. Current studies in our laboratory address the function of the human RECQ4 protein, which is mutated in Rothmund-Thompson syndrome, a rare autosomal recessive disorder manifested by photosensitivity, skeletal abnormalities, aneuploidy, chromosomal rearrangements and predisposition to osteosarcomas. We also explore the cellular role of the RECQ5 helicase, whose deficiency in mice results in elevated level of homologous DNA recombination and increased incidence of cancer.

Current grant support

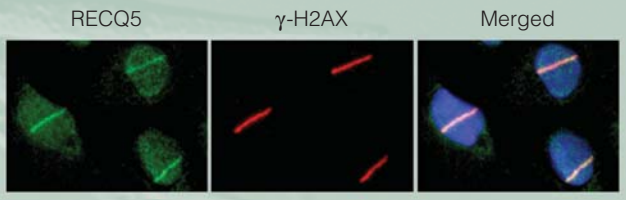
A start-up grant from the Institute of Molecular Genetics

Selected recent papers

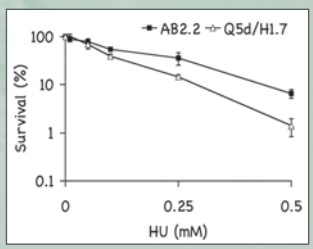
A new group, so far no publications with IMG affiliation



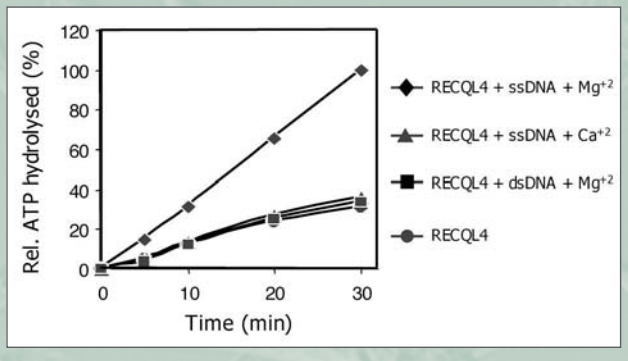
Co-immunoprecipitation of RECQ5 and the MRE11-RAD50-NBS1 complex from extract of human 293T cells



Accumulation of the human RECQ5 protein at chromosomal breaks generated by laser-microirradiation



Hypersensitivity of RECQ5-deficient cells to hydroxyurea (HU) that inhibits DNA replication



ATPase activity of purified human RECQL4 protein

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Laboratory of Cell and Developmental Biology

Wnt signalling, TCF/LEF transcription factors, colorectal cancer

Research topics

The main focus of the newly formed department lies on the molecular mechanisms of Wnt signalling in mammalian cells and signalling pathways influencing behaviour of normal and diseased intestinal epithelial cells.

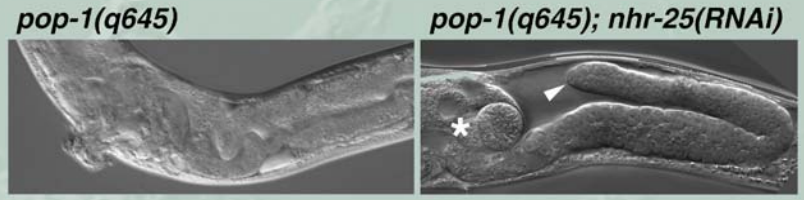
The most important result in the current years was the identification of the HIC1 (Hypermethylated In Cancer 1) tumour suppressor as a novel modulator of the Wnt signalling cascade. The *HIC1* gene is frequently epigenetically silenced or deleted in different types of solid tumours. When expressed, the HIC1 protein localizes into the nuclear dot-like structures called the HIC bodies. We showed that HIC1 interacts with the Wnt signalling effector TCF-4. Interestingly, HIC1 relocates TCF-4 to the HIC bodies and the effectiveness of this relocation is partly dependent on the structural function of CtBP (C-terminal binding protein). Furthermore, we demonstrated that HIC1 inhibits transcriptional activation of various Wnt-specific target genes. This inhibitory action is based just on the ability of HIC1 to sequestrate TCF-4 into the HIC bodies. Such sequestration results in uncoupling TCF-4/β-catenin complexes from the Wnt-responsive promoters and, ultimately, leaves these promoters irresponsive to the Wnt signals. In conclusion, we predict that the hyperactivity of the Wnt/β-catenin pathway might contribute to the development of tumours from cells in which the expression of HIC1 has been inactivated.

Current grant support

Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology 1M0506, NPV II Programme qCHIP/chip06, 2B06077), GA CR (GA204/06/1658, GA204/07/1567)

Selected recent papers

1. Valenta T, Lukas J, Doubravska L, Korinek V. HIC1 attenuates Wnt signaling by recruitment of TCF-4 and β-catenin to the nuclear bodies. **EMBO J.** 2006;25:2326-2337.
2. Asahina M, Valenta T, Šilhánkova M, Kořínek V, Jindra M. Crosstalk between a nuclear receptor and β-catenin signaling decides cell fates in the C..elegans somatic gonad. **Developmental Cell.** 2006;11:203-211.
3. Psahoulia FH, Drosopoulos KG, Doubravska L, Andera L, Pintzas A. Quercetin enhances TRAIL-mediated apoptosis in colon cancer cells by inducing the accumulation of death receptors in lipid rafts. **Mol Cancer Ther.** 2007;6:2591-2599.
4. Doubravská L, Šímová Š, Čermák L, Valenta T, Kořínek V, Anděra L. Wnt-expressing rat embryonic fibroblasts suppress Apo2L/TRAIL-induced apoptosis of human leukemia cells. **Apoptosis.** 2008;13:573-587.
5. Vojtechova M, Tureckova J, Kucerova D, Sloncova E, Vachtenheim J, Tuhackova Z. Regulation of mTORC1 signaling by Src kinase activity is Akt1-independent in RSV-transformed cells. **Neoplasia.** 2008;10:99-107.



Nuclear receptor NHR-25 counteracts β-catenin signalling during gonad development in C. elegans. The absence of gonadal arms caused in hermaphrodites by mutations in the pop-1/Tcf gene [pop-1(q645); left] can be reverted by nhr-25 knockdown (right). Arrowhead points to distal tip cell; asterisk indicates an embryo (Asahina et al., 2006).

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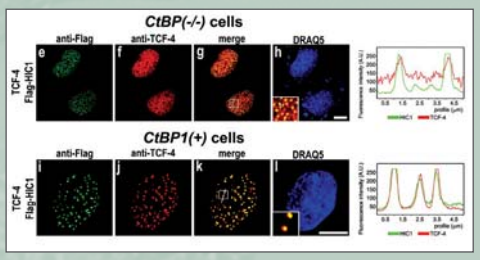
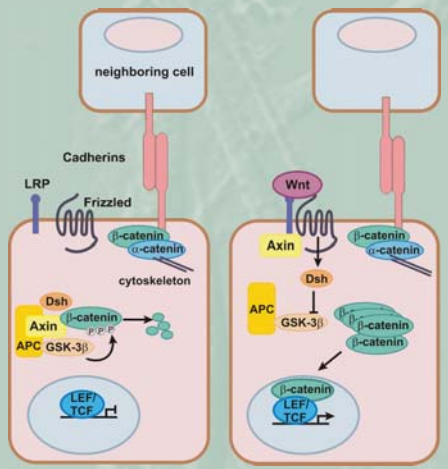


A simultaneous interaction between CtBP, TCF-4 and HIC1 is essential for the efficient nuclear sequestration of TCF-4 into the HIC1 bodies. *Confocal microscopy images of CtBP(-/-) (no CtBP expression, upper panel) and CtBP1(+) cells (expressing CtBP1, lower panel) transfected with the indicated constructs (left) and stained with anti-Flag and anti-TCF-4 antibody. The right panels show the overlap of fluorescence intensity peaks along profiles as indicated in the merged micrographs.*



The canonical Wnt/β-catenin signalling pathway (adopted from Reya and Clevers, Nature, 2005)

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Laboratory of Transcriptional Regulation

Eye development and evolution, Pax genes, Wnt signalling

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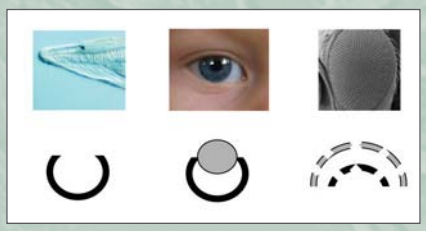
Research topics

We are interested in the genetic basis of mammalian eye and CNS development. Our focus is on the role of transcription factors and signalling cascades, especially on the role of *Pax* genes and Wnt/β-catenin pathway. A combination of gain-of-function (transgenic) and loss-of-function (conditional knock-outs) approaches is used.

Our second main interest is eye evolution. Several model systems including mouse, amphioxus, scallop, medaka and jellyfish are used in the laboratory. Early morphological studies have suggested that eye has evolved multiple times during the course of evolution. In contrast, more recent genetic data indicate a central role of Pax6 in eye development in most animals. In fact, eye assembly always relies on the same basic principle, i.e. photoreceptors located in the vicinity of dark shielding pigment. Cnidaria as the likely sister group to the Bilateria are the earliest branching phylum with a well-developed visual system. We have shown that camera-type eyes of the Cubozoan jellyfish, *Tripedalia cystophora*, use genetic building blocks typical of vertebrate eyes, namely a ciliary phototransduction cascade and melanogenic pathway. Our findings indicative of parallelism provide a new insight into eye evolution.



Morphological diversity among animal eyes is in contradiction to the conserved nature of Pax6 transcription factor. Three major eye designs represented by the cup-like frontal eye of amphioxus (left), camera-type eye of vertebrates (middle) and the compound eye of insects (right). A highly conserved transcription factor Pax6 implicated in formation of the three eye types (Kozmik, 2008).

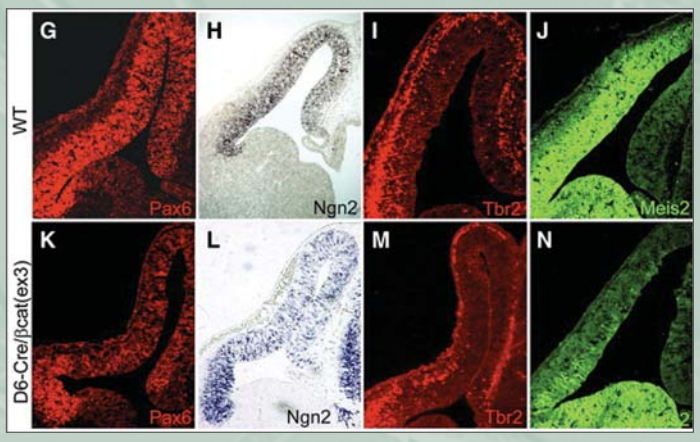
Current grant support

Ministry of Education, Youth and Sports (Center for Applied Genomics 1M0520), GA CR (GA204/08/1618), GA AS CR (IAA500520604)

Selected recent papers

1. Machon O, Backman M, Machonova O, Kozmik Z, Vacik T, Andersen L, Krauss S. A dynamic gradient of Wnt signaling controls initiation of neurogenesis in the mammalian cortex and cellular specification in the hippocampus. **Dev Biol.** 2007;311:223-237.
2. Kozmik Z, Ruzickova J, Jonasova K, Matsumoto Y, Vopalensky P, Kozmikova I, Strnad H, Kawamura S, Piatigorsky J, Paces V, Vlcek C. Assembly of the cnidarian camera-type eye from vertebrate-like components. **Proc Natl Acad Sci USA.** 2008;105:8989-8993.
3. Kozmik Z, Swamynathan SK, Ruzickova J, Jonasova K, Paces V, Vlcek C, Piatigorsky J. Cubozoan crystallins: evidence for convergent evolution of pax regulatory sequences. **Evol Dev.** 2008;10:52-61.
4. Kozmik Z. The role of Pax genes in eye evolution. **Brain Res Bull.** 2008;75:335-339.
5. Jonášova K, Kozmik Z. Eye evolution: lens and cornea as an upgrade of animal visual system. **Semin Cell Dev Biol.** 2008;19:71-81.

Assembly of the cnidarian eye from vertebrate-like components (Kozmik et al. 2008; ref. 2)



Permanent activation of canonical Wnt/β-catenin signalling inhibits expression of neurogenic genes (Machon et al., 2007).

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Functional gene mapping, leishmaniasis, atopy

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Yahya Sohrabi, MSc / PhD Student
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Klára Podzimková / Bachelor Student
Matyáš Šíma / Diploma Student

Research topics

The laboratory is dealing with two main topics:

- Mapping and functional analysis of genes that control resistance to infection
- Genetic and environmental influence on atopy

We study the genetic regulation of interaction between the immune system and the infectious agent in leishmaniasis. The disease is caused by protozoan parasites of genus *Leishmania* that multiply in macrophages. Different species of *Leishmania* induce different symptoms, but even the patients infected by the same species develop different clinical manifestations. Many phenomena observed in human leishmaniases can be investigated in *Leishmania major* infection in mouse. Our work is aimed at identification and functional analysis of genes influencing the course of *L. major* infection in mouse. Our approach uses a combination of genetic dissection with screening of a large set of immunological and clinical parameters of the disease. We found that *Lmr (Leishmania major response)* gene effects on disease symptoms were organ-specific and heterogeneous. Thus, these studies revealed a network-like complexity of the combined effects of multiple functionally diverse QTLs (quantitative trait loci).

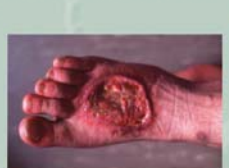
Interestingly, six of nine *Lmr* that influence serum IgE level after *Leishmania major* infection were mapped in the regions homologous with the human chromosomal segments that control total serum IgE in human atopic diseases. Genetic analysis in the mouse can therefore help identify in these regions the unknown genes that control atopic response in humans.

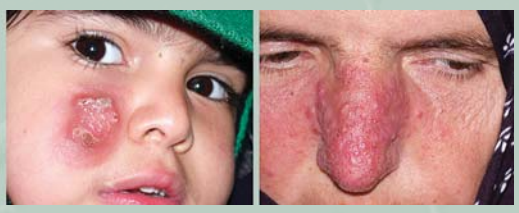
Current grant support

GA CR (GA310/06/1745, GA310/08/1697), FP6 EC EU (INTAS Genomics 05-1000004-7761), GA AS CR (IAA500520606), Ministry of Education, Youth and Sports (LC 06009)

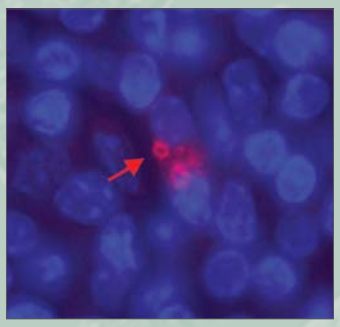
Selected recent papers

1. Gusareva ES, Bragina EJ, Deeva EV, Kazakevich NV, Puzyrev VP, Ogorodova LM, Lipoldová M. Cat is a major allergen in patients with asthma from west Siberia, Russia. **Allergy.** 2006;61: 509-510.
2. Havelková H, Badalová J, Svobodová M, Vojtíšková J, Kurey I, Vladimirov V, Demant P, Lipoldová M. Genetics of susceptibility to leishmaniasis in mice: four novel loci and functional heterogeneity of gene effects. **Genes Immun.** 2006;7:220-233.
3. Lipoldová M, Demant P. Genetic susceptibility to infectious disease: lessons from mouse models of leishmaniasis. **Nat Rev Genet.** 2006;7:294-305.
4. Gusareva ES, Ogorodova LM, Chernyak BA, Lipoldová M. Relationship between total and specific IgE in patients with asthma from Siberia. **J Allergy Clin Immunol.** 2008;121:781.

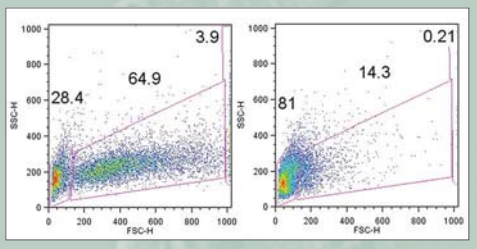




Cutaneous leishmaniasis



Leishmania tropica



Flow cytometry analysis of different growth forms of Leishmania major promastigotes
Left. Third day of cultivation (logarithmic phase of growth). Left frame – procyclics, central frame – nectomonades, right frame – other forms
Right. Seventh day of cultivation (stationary phase of growth). Left frame – metacyclics and haptomonades, central frame – nectomonades, right frame – other forms

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Laboratory of Tumour Immunology

Anti-tumour immunotherapy, immunoediting, immunoepigenetics

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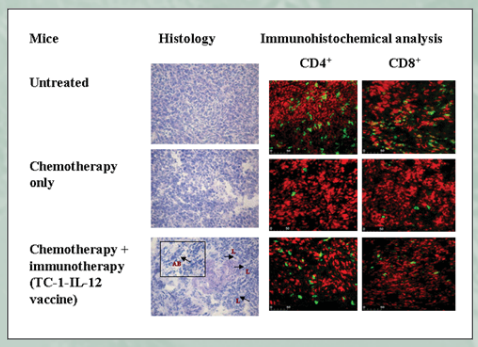
Romana Kalenská / Diploma Student
Jakub Novák / Diploma Student

Research topics

The long-term research programme of the Laboratory is focused on the mechanisms involved in induction, regulation and suppression of the anti-tumour immunity. The murine model for tumours associated with human papilloma virus (aetiologic agent of the cervical carcinoma) has been employed in most of our studies. Special attention has been paid to the clinically relevant setting of the minimal residual tumour disease treatment after primary tumour resection or chemotherapy. We have investigated mechanisms of immunosuppression in the course of the tumour growth, with the final goal to include the blockage of the negative signals into the immunotherapeutic schemes. We have also investigated the mechanisms of the anti-tumour immune responses against tumours mediated by MHC class I-restricted and unrestricted mechanisms, and immunologic cross-reactivity between tumours of the same aetiology but distinct MHC class I expression.
We have found that epigenetic agents induce expression of genes involved in antigen-processing machinery and surface expression of MHC class I molecules on the tumour cells, as well as selected co-stimulatory and co-inhibitory molecules.



Tumour-infiltrating leukocytes during TC-1/A9 tumour growth and chemo- and immunotherapy
In figures showing the immunohostochemical analysis, T helper ($CD4^+$) and cytotoxic T lymphocytes ($CD8^+$) are green while tumour cells are red.
Magnification: 400x or 630x

Current grant support

GA CR (GD310/05/H533, GA301/06/077, GA301/07/1410); GA AS CR (IAA500520605, IAA500520807); the European Clinical Gene Transfer Advisory Network (Clinigene, EC-NoE, FP6+7)

Selected recent papers

1. Reinis M, Simova J, Indrova M, Bieblova J, Bubenik J. CpG oligodeoxynucleotides are effective in therapy of minimal residual tumour disease after chemotherapy or surgery in a murine model of MHC class I-deficient, HPV16-associated tumours. **Int J Oncol.** 2007;30:1247-1251.
2. Reinis M, Simova J, Indrova M, Bieblova J, Pribylova H, Moravcova S, Jandlova T, Bubenik J. Immunization with MHC class I-negative but not -positive HPV16-associated tumour cells inhibits growth of MHC class I-negative tumours. **Int J Oncol.** 2007;30:1011-1017.
3. Manning J, Indrova M, Lubyova B, Pribylova H, Bieblova J, Hejnar J, Simova J, Jandlova T, Bubenik J, Reinis M. Induction of MHC class I molecule cell surface expression and epigenetic activation of antigen-processing machinery components in a murine model for human papilloma virus 16-associated tumours. **Immunology.** 2008;123:218-227.
4. Indrová M, Bieblová J, Bubeník J, Reinis M. IL-12 immunotherapy of minimal residual disease in murine models of HPV16-associated tumours: induction of immune responses, cytokine production and kinetics of immune cell subsets. **Int J Oncol.** 2008;32:499-507.
5. Bubenik J. Genetically modified cellular vaccines for therapy of human papilloma virus type 16 (HPV 16)-associated tumours. **Curr Cancer Drug Targets.** 2008;8:180-186.

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Laboratory of Structural Biology

Protein crystallography, HIV protease, antibody engineering

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Research topics

The Laboratory carries out structural work with various proteins of biological or medicinal interest. Among them, HIV protease, antibody fragments and galectins take a prominent position.

The HIV protease (HIV PR) research is focused on development of novel potent inhibitors as well as on understanding the structural basis of drug resistance acquired by mutations in HIV PR itself, in its target sites and elsewhere in the HIV polyproteins.

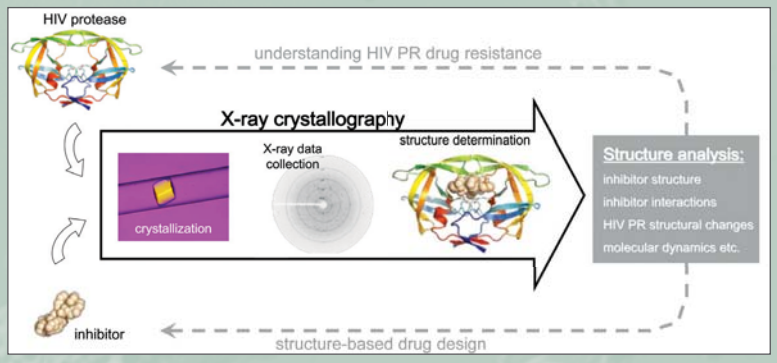
The antibodies include the antibody M75 (in Fab or scFv formats) specific to human carbonic anhydrase IX, a carcinoma marker. Several other antibody fragments of potential diagnostic and/or immunotherapeutic use (e.g. against CD20, CD44, CD3) have been cloned, expressed, purified and characterized in our laboratory with the aim to improve their radionuclide labelling or to introduce further useful properties.

Current grant support

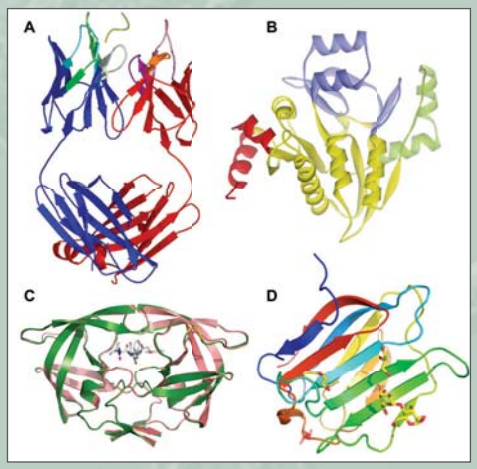
Ministry of Education, Youth and Sports (Center of Targeted Therapeutics, 1M0505; international project EUREKA, OE290); FP6 HIV protease inhibitor resistance by enzyme-substrate co-evolution (EU, LSHP-CT-2007-037693); Ministry of Industry and Commerce (2A-2TP1/076); GA CR (GA301/07/0600)

Selected recent papers

1. Krejčiříková V, Fábry M, Marková V, Malý P, Řezáčová P, Brynda J. Crystallization and preliminary X-ray diffraction analysis of mouse galectin-4 N-terminal carbohydrate recognition domain in complex with lactose. **Acta Cryst F.** 2008;64:665-667.
2. Řezáčová P, Kožíšek M, Moy SF, Sieglová I, Joachimiak A, Machius M, Otwinowski Z. Crystal structures of the effector-binding domain of repressor CggR from Bacillus subtilis reveal ligand-induced structural changes upon binding of several glycolytic intermediates. **Mol Microbiol.** 2008;69:895-910.
3. Kožíšek M, Šašková KG, Řezáčová P, Brynda J, van Maarseveen NM, De Jong D, Boucher C, Kagan R, Nijhuis M, Konvalinka J. Ninety nine is not enough: molecular characterisation of drug-resistant HIV-protease mutants with insertions in the flap region yielding resistance to protease inhibitors. **J Virol.** 2008;82:5869-5878.
4. Bartoňová V, Král V, Sieglová I, Brynda J, Fábry M, Hořejší M, Kožíšek M, Šašková KG, Konvalinka J, Sedláček J, Řezáčová P. Potent inhibition of drug-resistant HIV protease variants by monoclonal antibodies. **Antiviral Res.** 2008;78:275-277.
5. Král V, Mader P, Collard R, Fábry M, Hořejší M, Řezáčová, P, Kožíšek M, Závada J, Sedláček J, Rulíšek L, Brynda J. Stabilization of antibody structure upon association to a human carbonic anhydrase IX epitope studied by X-ray crystallography, microcalorimetry, and molecular dynamics simulations. **Proteins.** 2008;71:1275-1287.



A schematic depicting of individual steps involved in structural studies of HIV PR-inhibitor complexes. X-ray crystallography method is used to determine three-dimensional structures of HIV PR in complex with inhibitory compounds. Structural information is used to explain the mechanism of HIV resistance as well as for the structure-based drug design of novel inhibitory compounds.



*Selected crystal structures published in 2008: **A.** Fab fragment of anti-carbonic anhydrase IX antibody [ref. 5], **B.** the effector-binding domain of repressor CggR from Bacillus subtilis [2], **C.** HIV-1 protease with insertion E35EE [3], **D.** mouse galectin-4 carbohydrate recognition domain [1].*

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Laboratory of Transgenic Models of Diseases & Transgenic Unit

Cell-extracellular matrix interactions, proteases and their inhibitors, transgenesis & embryo manipulations

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Inken M Beck, PhD / Research Scientist
Šárka Suchanová, PhD / Research Scientist
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Jana Ježková, Ing / Technical Assistant
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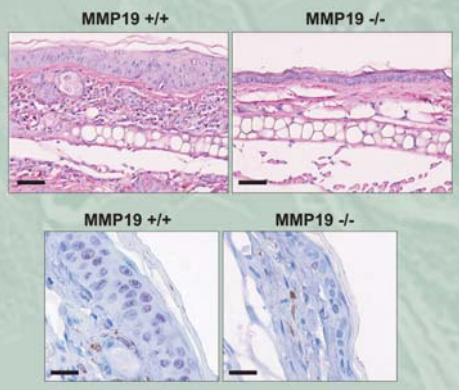
Alexandra Mayer, Bc / Diploma Student
Haĺka Buryová / Bachelor Student

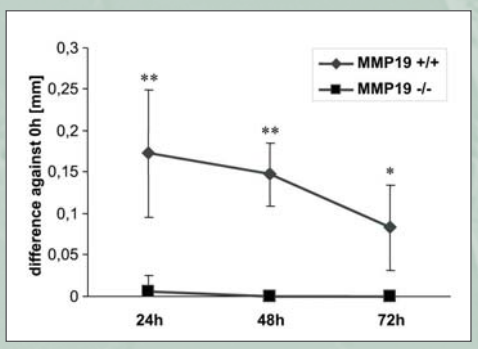
Research topics

Interactions of cells with their surroundings, i.e. the extracellular matrix, is essential for development and functional organization of specialized tissues and organs. The cell-matrix interactions control cell differentiation, survival, migration, and activation via cell surface receptors and adhesion molecules. Especially adhesion molecules sense changes in the composition of extracellular matrix that is affected by proteases and their inhibitors. Balance between these two molecule classes determines if tissues and organ architecture are to be built up or disrupted. Thus, this balance is pivotal for tissue homeostasis and its disturbance leads to development of various pathologies such as cancer, chronic inflammation, or fibrosis.

Our current research focuses on investigating the role of selected metallo- and serine proteases, and their inhibitors in two biological compartments: liver and epidermis/epithelium. Regulated expression of proteases in the epidermis and many epithelia is crucial not only to maintain the body and organ barriers, but also for regulation of local inflammatory reactions. To further the understanding of development and progression of liver fibrosis and inflammation processes, our research in this area analyses the effects and consequences of metalloproteinase-mediated turnover of extracellular matrix and the release of regulatory molecules from the cellular surfaces, a process that is mediated by shedding proteases.

In addition to the research activities we have set up, in the middle of 2008, a Transgenic Unit that offers embryo manipulating services including DNA pronuclear microinjections, sperm freezing and archiving, *in vitro* fertilization (IVF), embryo isolations, rederivation of mouse lines/strains, vasectomy, etc.





MMP19-deficient mice show impaired contact hypersensitivity model (CHS) reaction: influx of inflammatory cells (upper panel), keratinocyte proliferation (middle panel), and ear swelling (lower panel).

Current grant support

AS CR (J. E. Purkyně Fellowship to R.Sedláček); GA AS CR (IAA500520812); GA CR (GC301/08/J053)

Selected recent papers

Beck IM, Rückert R, Brandt K, Mueller MS, Sadowski T, Brauer R, Schirmacher P, Mentlein R, Sedlacek R. MMP19 is essential for T cell development and T cell-mediated cutaneous immune responses. **PLoS ONE.** 2008;3:e2343.

Generation of transgenic mice. DNA microinjection into pronucleus of murine zygote: left, zygote before insertion of microcapillary; middle, zygote during microinjection; right, two-cell stage embryos developing from the manipulated eggs.

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Laboratory of RNA Biology

pre-mRNA splicing, small nuclear ribonucleoproteins

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Viola Hausnerová / Diploma Student
Petr Těšina / Diploma Student
Jana Křížová / Technician

Research topics

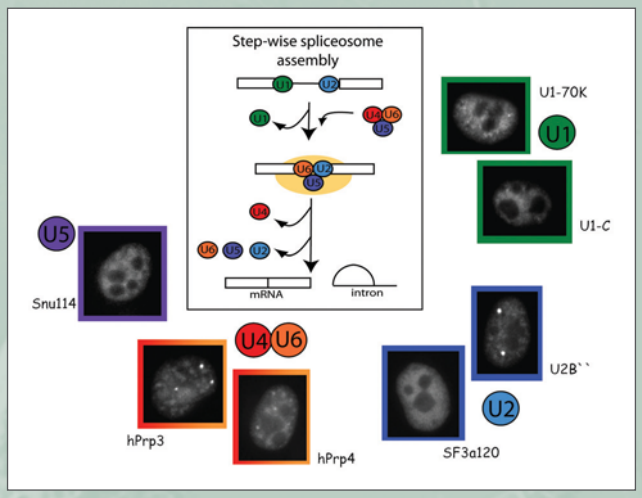
RNA molecules are not just messengers acting between DNA and proteins but rather required factors that play an active role in the expression of genes encoded in our genome. An RNA processing step called splicing can dramatically increase the diversity of proteins in human cells and tissues. RNA splicing is catalysed by a large macromolecular complex, the spliceosome, which is formed from several RNA-protein complexes called snRNPs. In our group we are interested in spliceosome assembly and the organization of RNA splicing in the cell nucleus. Using advanced microscopy techniques (e.g. live cell imaging, FRET, FCS) we explore where and when the spliceosome assembles in the cell nucleus. Experimental data are then used for modelling spliceosome assembly in the 3D space of the nuclear landscape. We identified the conserved nuclear compartment, the Cajal body, as the site of snRNP assembly and recycling, and we proposed a model stating that the presence of Cajal bodies increases the efficiency of snRNP formation. We also aim to determine how mutations in splicing factors can cause *retinitis pigmentosa*, a human genetic disease characterized by photoreceptor cell degeneration.

Current grant support

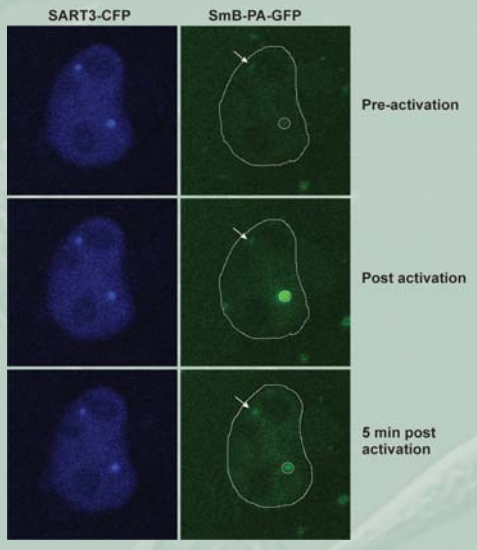
MPI-partner group grant, GA CR (GA204/07/0133), GA AS CR (KAN200520801)

Selected recent papers

1. Klingauf M, Staněk D, Neugebauer KM. Enhancement of U4/U6 snRNP association in Cajal bodies predicted by mathematical modeling. **Mol Biol Cell.** 2006;17:4972-4981.
2. Staněk D, Neugebauer KM. Cajal bodies: a meeting place for snRNP in the nuclear maze. **Chromosoma.** 2006;115:343-354.
3. Staněk D, Přidalová-Hnilicová J, Novotný I, Huranová J, Blažíková M, Wen X, Sapra, A.K., Neugebauer, K.M. Spliceosomal snRNPs repeatedly cycle through Cajal bodies. **Mol Biol Cell.** 2008;19:2534-2543.
4. Cvačková Z, Albring KF, Koberna K, Ligasová A, Huber O, Raška I, Staněk D. Pontin is localized in nucleolar fibrillar centers. **Chromosoma**. 2008;117:487-497.



Assembly of the spliceosome in vivo. Currently, it is unknown how splicing machinery assembles in the cell nucleus. To analyse this problem we created a battery of splicing-specific proteins tagged with fluorescent proteins. These constructs are used for FRET, FRAP and FCS to measure interactions and dynamics of individual proteins directly in living cells.



Cycling of spliceosomal snRNPs between Cajal bodies. Specific marker of snRNPs - the SmB protein - was tagged with photoctivatable GFP, expressed in the cell and specifically activated in one Cajal body (circle). SART3-CFP serves as a marker of Cajal bodies. This and other experiments helped us to reveal the role of Cajal bodies in snRNP recycling.

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Laboratory of Epigenetic Regulations

RNA degradation, dsRNA, mobile DNA

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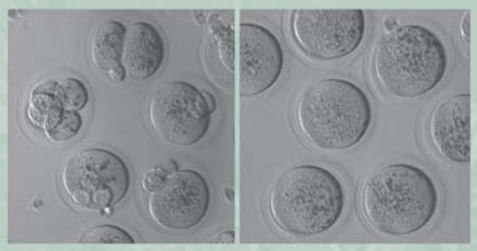
Kateřina Podolská, MSc / PhD Student
Lenka Sarnová / Diploma Student

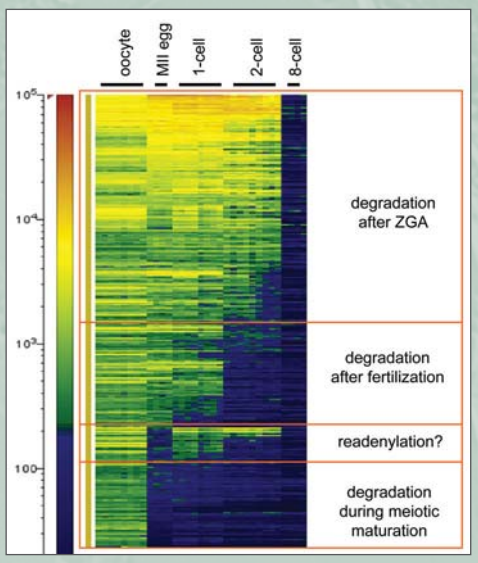
Research topics

Our lab explores research topics related to RNA silencing and repression of mobile elements in mammals. Current running projects include studies of activity and silencing of L1 retrotransposons, analysis of stability of maternal mRNAs in the oocyte, characterization of effects of long double-stranded RNA (dsRNA) and further analysis of RNA silencing. A representative example of our work is the study of effects of long dsRNA expression. Long dsRNA presence in mammalian cells can induce sequence-specific silencing as well as a number of sequence-independent effects resulting in general inhibition of proteosynthesis, non-specific mRNA degradation, activation of interferon-response genes, and, eventually, apoptosis. In order to understand effects of long dsRNA expression in mammalian cells, we have generated transgenic mice ubiquitously transcribing a long inverted repeat, which gives rise to a long dsRNA hairpin. We also developed a cell culture system allowing more detailed analysis of long dsRNA expression. We are currently addressing known mechanisms involving long dsRNA such as interferon pathway activation, adenosine deamination of the long dsRNA, and RNA silencing.



CagMosIR (F1 317.3 #4) **WT** (F1 317.3 #6)

Mos null phenotype (parthenogenetic activation of MII oocytes) in oocytes isolated from transgenic animals carrying the CagMosIR transgene, which ubiquitously produces dsRNA with Mos sequence.



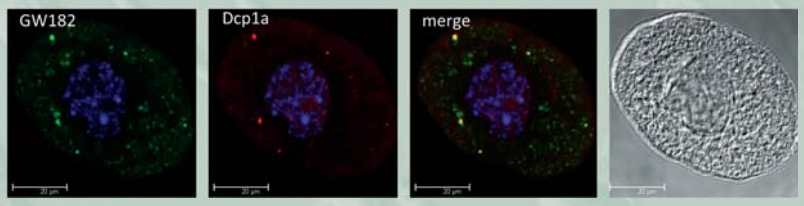
Microarray analysis of maternal mRNA degradation

Current grant support

AS CR (Purkyně Fellowship); EMBO Installation Grant, GA AS CR (IAA501110701)

Selected recent papers

1. Schmitter D, Filkowski J, Sewer A, Pillai RS, Oakeley EJ, Zavolan M, Svoboda P, Filipowicz W. Effects of Dicer and Argonaute down-regulation on mRNA levels in human HEK293 cells. **Nucleic Acids Res.** 2006;34:4801-4815.
2. Svoboda P. Off-targeting and other non-specific effects of RNAi experiments in mammalian cells. **Curr Opin Mol Ther.** 2007;9:248-257.
3. Grosshans H, Svoboda P. miRNA, siRNA, piRNA – Kleine Wiener Ribonukleinsauren. **Bioessays.** 2007;29:940-943.
4. Svoboda P. RNA silencing in mammalian oocytes and early embryos. **Curr Top Microbiol Immunol.** 2008;320:225-256.
5. Sinkkonen L, Hugenschmidt T, Berninger P, Gaidatzis D, Mohn F, Artus-Revel CG, Zavolan M, Svoboda P, Filipowicz W. MicroRNAs control de novo DNA methylation through regulation of transcriptional repressors in mouse embryonic stem cells. **Nat Struct Mol Biol.** 2008;15:259-267.
6. Svoboda P, Stein P. (2008) RNAi experiments in mouse oocytes and early embryos. **CSH Protocols.** 2009;4(10.1101/pdb.top56).



Co-localization of p-body components in meiotically incompetent oocytes. P-bodies are centres of mRNA metabolism, including degradation and storage.

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Laboratory of Genomics and Bioinformatics

Genomics, next-generation sequencing, transcriptome analysis

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Michal Kolář, PhD / Research Scientist
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Miluše Hroudová, MSc / PhD Student
Jakub Rídl, MSc / PhD Student
Petr Vojta / Diploma Student

Research topics

Our laboratory was amongst the first to complete genome projects. Information generated in these projects was used in evolutionary studies and recently also in biotechnological applications.

Using the 454 next-generation sequencing facility (GS FLX/Titanium), we begin to characterize metagenomic samples and genomes of evolutionarily interesting species. To understand the evolution of higher metazoan genomes and the developmental processes that they regulate, it is necessary to make comparisons with appropriate outgroups. Cnidaria, a group of lower Metazoa, are the natural outgroup for comparative genomics and developmental studies. The availability of the model animal genomic sequences will allow inferences to be made about the gene complement of the common bilaterian ancestor. Two cnidarian genomes, hydrozoan *Cracpedacusta sowerbyi* and cubozoan *Tripedalia cystophora*, are surveys for genome analysis. Unicellular protozoa, especially their genome content and structure, can unveil where the root of the eukaryotic tree lies. Genome sequencing of several protozoan species is planned. The metagenomic approach to the environmental samples and unculturable microbes is under way, too.

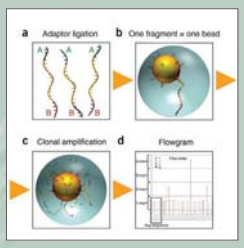
A second major project of our group is directed towards identification of specific markers in cancer tissue with potential applications in medical diagnosis. We use Illumina microarray chip analysis for detection of appropriate gene sets.

Current grant support

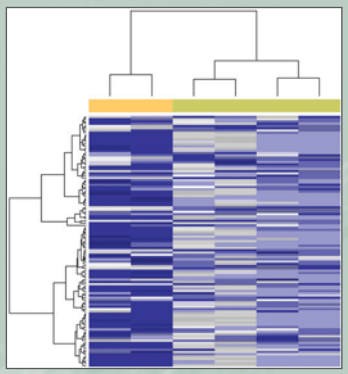
Ministry of Education, Youth and Sports (Center for Applied Genomics, 1M0520; NPV II, project 1M0833)

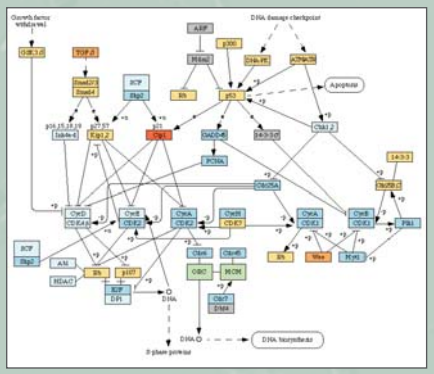
Selected recent papers

1. Kozmik Z, Růžičková J, Jonášová K, Matsumoto Y, Vopálenský P, Kozmiková I, Strnad H, Kawamura S, Piatigorsky J, Pačes V, Vlček Č. Assembly of the cnidarian camera-type eye from vertebrate-like components. **Proc Natl Acad Sci USA.** 2008;105:8989-8993.
2. Jenčová V, Strnad H, Chodora Z, Ulbrich P, Vlček Č, Hickey WJ, Pačes V. Nucleotide sequence, organization and characterization of the (halo)aromatic acid catabolic plasmid pA81 from Achromobacter xylosoxidans A8. **Res Microbiol.** 2008;159:118-127.
3. Kozmik Z, Swamynathan SK, Růžičková J, Jonášová K, Pačes V, Vlček Č, Piatigorsky J. Cubozoan crystallins: evidence for convergent evolution of pax regulatory sequences. **Evol Dev.** 2008;10:52-61.

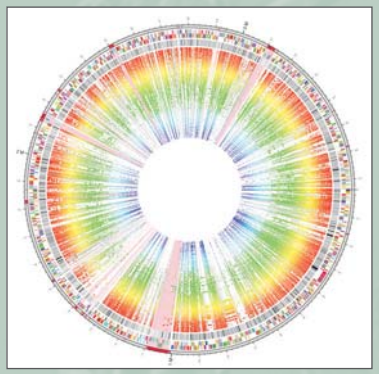


The Genome Sequencer FLX supports a number of formats, allowing users to customize the number of samples per instrument run and the number of reads per sample.
Genome Sequencer process: A and B adaptors are appended to each fragment (a) to allow binding to DNA capture beads (b). Fragments are amplified on the beads in emulsion (c). When sequenced in the Genome Sequencer FLX, each clonally amplified fragment generates its own unique sequence read (d).





Arrest of the cell cycle after exposure of human cell lines to statins. [a] The cell cycle network is suppressed by up-regulation of p53 and TGF-β pathways (up-regulated genes in orange, down-regulated in blue). [b] Expression profiles of cell cycle-related transcripts show the same pattern in several biological and technical replicates (two leftmost columns: no statins administered, the other four columns: replicated samples exposed to statins).



Rhodobacter genome - homologues in bacterial genomes: genes on forward and reverse strand are coloured according to their function, more inside is similarity heatmap with homologues in selected bacterial genomes.

SERVICES - INFORMATION TECHNOLOGIES

Head: **Petr Divina**

People:

Petr Divina, PhD, Miroslav Indra, PhD, Petr Janků, MSc, Tomáš Drexler, Michal Kůs, Michal Rolník, Jakub Šimon

The IT department provides innovative, reliable, and integrated information technology solutions to support various needs within the Institute. Ensuring seamless operation and administration of LAN and wireless network and providing basic networking services such as e-mail, web, DNS and VPN are major tasks. Great emphasis is placed on the network security and data protection using firewall and anti-virus solutions. The IT department offers hardware purchase consultancy, computer ordering, software installation and application support for Windows and Macintosh users. For commonly used software in the Institute, volume and site licensing options are negotiated. Additionally, the IT department provides special support for other technical and scientific departments, e.g. developing simple on-line tools and maintaining dedicated databases, such as animal tracking system. The IT department also operates audio-visual equipment in the new conference hall and provides computers for courses and conferences organized at the Institute. The important systems of the network infrastructure are housed in a modern data centre room equipped with controlled air-conditioning, uninterrupted power supply, temperature and humidity monitoring and fire protection system. In 2008, a secondary data centre room was built to provide additional housing for data storage and backup.

Computer classroom

Main data centre room

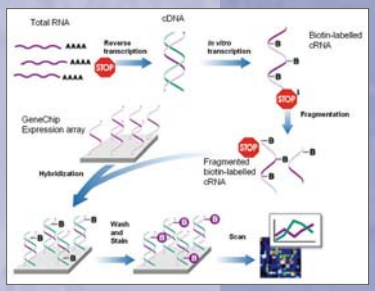
Tape library and disk storage

SERVICES - GENOMICS AND BIOINFORMATICS

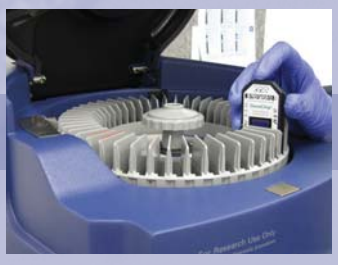
Head: **Robert Ivánek**

People:

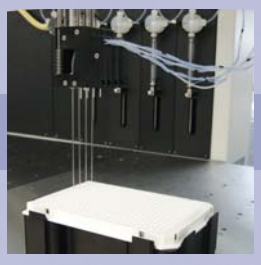
Robert Ivánek, MSc, Martina Chmelíková, MSc, Veronika Klatovská, MSc



The facility was established in late 2005 after purchase of the Affymetrix GeneChip System and was initially operated by the staff from the Department of Mouse Molecular Genetics. Since January 2007, it has become an independent unit which provides full chip microarray services, real-time quantitative PCR service and high-throughput methods using the robotic equipment. The services are provided not only to the research groups at the Institute of Molecular Genetics, but also to other academic institutions in the Czech Republic as well as abroad. The core facility is equipped with two microarray platforms: Affymetrix GeneChip System and Illumina BeadStation 500, real-time PCR cycler Roche LC480 and JANUS robots from PerkinElmer, and also with instruments for assessment of quality and quantity of processed samples (spectrophotometer Nanodrop and capillary electrophoresis Agilent Bioanalyzer 2100). The facility represents one of the European certified Affymetrix core labs.



Affymetrix GeneChip Scanner



PerkinElmer Janus

Agilent Bioanalyzer

SERVICES - CRYOBANK AND MONOCLONAL ANTIBODIES

Head: **Dobromila Matějková**

People:
Dobromila Matějková, MSc, Hana Gondová, Šárka Šilhánková, Hana Korábová

The new cryobank (capacity over 350,000 samples) was established in January 2007 and is used for storage of cell lines, mouse sperm, and embryos in liquid nitrogen. The storage containers are supplied with liquid nitrogen from a tank (capacity of 6,000 litres). It is equipped with an independent power supply in case of emergency. The samples can be stored in liquid nitrogen or nitrogen vapour. The operation, diagnostics and maintenance of storage containers is under fully automated control. The operating parameters of storage containers and safety of the whole unit are checked by a monitoring system with GSM and web interface outputs.
The monoclonal antibody service laboratory performs mycoplasma cell culture testing and provides complete service for preparation of new monoclonal antibodies, including: immunization of mice, fusion of mouse spleen cells with myeloma tumour cells, primary antibody production screening (using ELISA test), cloning by limiting dilution or agar cloning, secondary antibody production screening (using e.g. ELISA), production of monoclonal antibodies into the cell culture supernatants, generation of a hybridoma cell bank.

Liquid nitrogen storage vessels


mAb production laboratory

SERVICES – FLOW CYTOMETRY AND LIGHT MICROSCOPY

Head: **Ondrej Horváth**

People:
Ondrej Horváth, MD, Zdeněk Cimburek

The facility provides methodological and instrumental background for flow cytometric and fluorescence microscopic techniques. At present, the facility is equipped with two analysers – BD FACSCalibur and BD LSRII cytometers. The LSRII instrument has been upgraded with the yellow 561-nm laser and is now a four-laser (405-nm, 488-nm, 561-nm and 633-nm) instrument with 14 fluorescence detectors. This upgrade, together with a large set of dichroic mirrors and bandpath filters, made this instrument very flexible and capable to cover most of the flow cytometry applications. Both instruments possess an HTS loader for high-throughput analysis of samples directly from 96- or 384-well plates. The facility is also equipped with an AutoMACS Pro (Miltenyi Biotec) magnetic separator for automatic rapid sorting of cells, as well as cell culture facilities.
The facility is running three microscopes: confocal microscope with superfast scanner (Leica TCS SP5 AOBS TANDEM), Leica inverted fluorescent microscope with TIRF ilumination (Leica), wide-field inverted fluorescence microscope with laser excitation (DeltaVision Core). This state-of-art instrumentation allows facility users to use a wide range of microscopy techniques including FRET, FRAP, time-lapse experiments, membrane studies, vesicle transport studies, etc.
Several offline analysis workstations are also available in the facilty, for analysis of flow cytometric (FlowJo) and image data (SoftWorx Suite, Imaris, Leica Application Suite Advanced Fluorescence, ImageJ).

SERVICES – MEDIA, GLASS WASHING

Head: **Hana Marxová**

People:

Hana Marxová, Lucie Janská, Zuzana Wolfová, Jitka Škopová, Miluše Alferiová, Stanislava Bendová

SERVICES – ANIMAL HOUSE (MICE)

Head: **Jan Honetschläger**

People:

Jan Honetschläger DVM, Jana Kopkanová MSc, Zuzana Bakešová, Renáta Cihelková, Kateřina Formánková, Pavla Kameníková, Daniela Kratochvílová, Jarmila Krestová, Miloslava Kudličová, Michaela Lišáková, Kamila Malá, Libuše Mayerová, Kateřina Ševčíková, Hana Vaňková, Alena Zachardová

The IMG animal (mouse) facility has recently been housed in two buildings on the Krč campus and is accredited for work with genetically modified animals, with total capacity up to 8,000 cages. To date, we have available about 150 mice strains; most of them are unique. All animals are housed under standard pathogen-free conditions required for high-quality research. We built a new quarantine with a capacity up to 400 cages, allowing us to import animals from cooperating institutes more easily. The animal facility also hosts a newly established transgenic unit that will produce various types of transgenic and gene knock-out mice and perform re-derivation from the quarantine.

SERVICES – ANIMAL HOUSE (CHICKEN)

Head: **Milena Vilhelmová**

People:

Milena Vilhelmová, PhD, Eva Bernášková, Alena Eisensteinová, Petra Faloutová, Ladislava Hachová, Zdena Koptová, Alena Porazilová, Radomíra Skoková, Jaroslava Strnadelová, Milena Vaverková, Jaroslava Vlasáková

This facility is located in the village Koleč, north of Prague, about 45 km from the main campus in Praha-Krč. It takes mainly care of breeding of genetically defined inbred, congenic and outbred chicken lines (and one duck line). The facility produces eggs, embrya and chickens needed for several research groups dealing mostly with chicken models. Before laboratories for this type of work are reconstructed on the Krč campus, the facility is also used for experimental laboratory work with these models.

SERVICES – BUILDING MAINTENANCE

Head: **Tomáš Němec**

People:
Tomáš Němec, Bc, Dana Macková

SERVICES – FINANCES AND ADMINISTRATION

Head: **Zdeňka Sokolová**

People:
Zdeňka Sokolová, Věra Bálková, Petr Blahout, Ivana Brabencová, Leopold Cillich, Milena Dobrá, Kateřina Drastilová, Jitka Emanuelová, Jan Hladký, Hana Nezbedová, Milena Petríková, Jaroslava Samohylová, Renata Schönová, Miloslava Šnajbergová, Emílie Štorchová, Hana Švestková

DIRECTOR'S OFFICE

Head: **Šárka Takáčová**

People:
Šárka Takáčová, MSc, Leona Krausová, Gabriela Marešová, Zdeňka Schuhová, Lucie Tykalová

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The groups cancelled or translocated to the Institute of Biotechnology

(papers produced still under the IMG affiliation)

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Seminar Speakers

JANUARY

04/01/08 Adam Pavlíček (Pfizer Global R&D Computational Biology, San Diego, CA, USA)

FEBRUARY

21/02/08 Hynek Wichterle (Columbia University, New York, NY, USA)

MARCH

18/03/08 Daniel Zicha (London Research Institute, London, UK)

APRIL

28/04/08 Laurent Prezeau (CNRS/INSERM, Montpellier, France)
29/04/08 Leonid B. Margolis (National Institute of Child Health and Human Development, NIH, Bethesda, MD, USA)

MAY

02/05/08 Maria Li Lung (Department of Biology, Centre for Cancer Research, The Hong Kong University of Science and Technology, Hong Kong, China)
06/05/08 Linda Scobie (Division of Biological and Biomedical Sciences, Glasgow Caledonian University, UK)
29/05/08 Zsuzsanna Izsvak (Max-Delbrück-Center for Molecular Medicine, Berlin, Germany)

JUNE

20/06/08 Paolo Salomoni (MRC, Toxicology Unit, Leicester, UK)
24/06/08 Hetty J. Bontkes (Department of Haematology, Vrije Universiteit Medical Centre, Amsterdam, Netherlands)
24/06/08 Radmila Hrdličková and Jiří Nehyba (University of Texas, Austin, TX, USA)

JULY

03/07/08 Martin Hrabe de Angelis (Helmholzt Zentrum München, Institute of Experimental Genetics, München, Germany)
07/07/08 Antonella Viola (Instituto Clinico Humanitas, IRCCS, Milano, Italy)
11/07/08 Gerald Schumann (Paul-Ehrlich-Institut, Federal Agency for Sera and Vaccines, Langen, Germany)
15/07/08 Peter Sutovsky (Animal Science and Clinical Obstetrics & Gynecology University of Missouri-Columbia, Columbia, MO, USA)
18/07/08 Maja Bucan (Department of Genetics, University of Pennsylvania, Medical School, Philadelphia, PA, USA)
18/07/08 Stefan Moisyadi (Institute for Biogenesis Research, Department of Anatomy, Biochemistry and Physiology, University of Hawai'i at Manoa, HI, USA)
23/07/08 Paula Stein (Department of Biology, University of Pennsylvania, Philadelphia, PA, USA)
31/07/08 Bernd Giebel (Heinrich-Heine-Universität Düsseldorf, Institut für Transplantationsdiagnostik und Zelltherapeutika, Klinik für Hämatologie, Onkologie und klinische Immunologie, Düsseldorf, Germany)

AUGUST

27/08/08 Ramnik Xavier (Massachussetts General Hospital-Harvard University, Boston, MA, USA)

SEPTEMBER

26/09/08 Wieland B. Huttner (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany)
26/09/08 Josef Jiricny (Institute of Molecular Cancer Research, University of Zurich, Switzerland)
26/09/08 Hans Lehrach (Max Planck Institute for Molecular Genetics, Berlin, Germany)
26/09/08 Iain Mattaj (EMBL Heidelberg, Germany)
26/09/08 Joram Piatigorsky (National Eye Institute, National Institutes of Health, Bethesda, MD, USA)
26/09/08 Kai Simons (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany)
30/09/08 Bruce W.S. Robinson (School of Medicine and Pharmacology, Sir Charles Gairdner Hospital, Nedlands, Perth, Australia)

OCTOBER

14/10/08 Jean-Marie Buerstedde (Helmholtz Zentrum Münich, Institute for Molecular Radiobiology, Münich, Germany)
16/10/08 Milan Vašák (Department of Biochemistry, University of Zürich, Switzerland)
20/10/08 Leslie M. Turner (Max Planck Institute for Evolutionary Biology, Dresden, Germany)

NOVEMBER

07/11/08 Kenneth Paigen (The Jackson Laboratory, Bar Harbor, Maine, ME, USA)
07/11/08 Beverly Paigen (The Jackson Laboratory, Bar Harbor, Maine, ME, USA)
27/11/08 Etienne Joly (Molecular Neuro-Immunogenetics Group, INSERM, CHU Purpan, Toulouse, France)
27/11/08 Lubomír Turek (University of Iowa, Department of Pathology, Iowa City, IA, USA)

DECEMBER

01/12/08 Paul V. Lehmann (Case Western Reserve University, Cleveland, OH, USA)
08/12/08 Nicholas D. Holland (Scripps Institution of Oceanography, University of California, San Diego, CA, USA)

Highlights of 2008

A daughter Institute established

The former Biotechnology Division became independent as a new Institute of Biotechnology AS CR, v. v. i., in the neighbouring building. However, we continue a close relationship between the IMG and its "daughter Institute".

New research groups established

Two new groups were established in 2008, led by Radislav Sedláček and Pavel Janščák (see pp. 18 and 24).

New service facility established

A transgenic facility became functional (as a part of the group of Radislav Sedláček), but so far was mostly absorbed with servicing the embryo transfers into the new animal facility.

New lecture hall

Construction of the last part of our research complex – the conference hall with adjacent dining hall – was completed in May 2008. The new lecture hall for almost 300 people will serve the entire Krč biomedical research campus.
On January 6, 2009, the lecture hall was officially named "Milan Hašek Auditorium" to honour the founder of the Institute.

Other construction activities

A nice park, including a small pond, was created on a land plot adjacent to the Institute.

Reconstruction of pavilion CH started in November 2008; after finishing in May 2009 it will host a non-mouse (mainly chicken) experimental animal facility.

In order to reduce our operational costs and contribute to the clean energy policy, company *České teplo s.r.o.* installed, in September 2008, a photovoltaic power unit at the roof of our Institute.

New instruments

In 2008 we started operation of a state-of-art FEI electron microscope for ultrastructural, tomographic, cryo-ultrastructural and analytic observations close to native conditions (operated by the group of Pavel Hozák) and new-generation high-throughput sequencer (operated by the group of Čestmír Vlček).

Interim evaluation of the Institute

Interim evaluation for the period 2005-2007 by the "Commission for evaluation of research activities of AS CR institutes" ranked the Institute into the top category „A".

Institute conferences, seminars

The official opening of the new conference hall took place on September 26, with a one-day international conference. Wieland B. Huttner (Dresden), Josef Jiricny (Zurich), Ian Mattaj (EMBL, Heidelberg), Joram Piatigorsky (NIH, Bethesda, MD), Kay Simons (Dresden) and Hans Lehrach (Berlin) were the invited speakers.

The 1st PhD Student Conference took place on October 17. The speakers were Jiří Bartek (keynote speaker), Matyáš Flemr, Pavel Vopálenský, Jakub Rídl, Ondřej Štěpánek, Martina Huranová, Sukriye Yildirim, Pavel Otáhal, Vladimír Čermák, Bohumil Fafílek, Michal Kahle, Rena Brauer, Igor Grekov.

On November 2 – 5, the Institute hosted the 22nd International Mammalian Genome Conference. The Conference was organized by a local organizing committee led by Jiří Forejt and included more than 250 participants. Among the prominent speakers were Johnathan Flint (Oxford), Lee Niswander (Boulder), Tim Aitman (London), Diethard Tautz (Cologne), Stylianos Antonarakis (Geneva), Wolf Reik (Cambridge), Philip Avner (Paris) and Barbara Wold (Pasadena).

The 2008 Annual Institute Conference took place on December 19 in the IMG Milan Hašek Auditorium. The speakers were: Čestmír Vlček, Petr Svoboda, Radislav Sedláček, Igor Shevelev, Lenka Doubravská, Michal Dvořák, Dominik Filipp, Vladimír Holáň, Petr Bartůněk, Pavel Dráber, Gabriela Pavlínková and Jakub Rohlena.

An important part of the Institute's scientific life are regular Wednesday afternoon seminars in which advanced students or postdocs present topics of individual laboratories. The speakers were: Elena Gusareva, Martina Huranová, Zdeněk Trachtulec, Anna Kofferová, Martin Klíma, Lukáš Chmátal, Vlada Filimonenko, Iryna Kozmiková, Barbora Hořejší, Petr Svoboda, Michal Kolář, Jakub Rohlena (IBT), Petr Pajer, Aleš Neuwirth, Pavlína Řezáčová, Hana Blažková, Radislav Sedláček, Lada Biedermannová (IBT), Alicia Corlett, Šárka Růžičková (IBT), Mikael Kubista (IBT), Andriy Dorosh (IBT), Milan Reiniš, Igor Grekov, Jan Lukáš, Magda Matoušková, Kateřina Pokorná, Jiří Kumpošt, Jarmila Hnilicová, Ondřej Mihola, Gouse M. Shaik, Rastislav Dzijak, Tereza Havlová, Michal Koc.

Prizes and honours

Lubica Dráberová – Arnold Beckman Publication Prize of Immunotech, a. s. and Czech Society for Biochemistry and Molecular Biology for the best publication in cell biology and imunology; Milan Pospíšil Award of the Czech Immunological Society for the best scientific report in the field of innate and tumour immunology

Petr Heneberg – Award of the Czechoslovak Microscopy Society for the best PhD thesis and J. V. Koštíř Prize of Biotech, a. s. and of the Czech Society for Biochemistry and Molecular Biology for collection of papers on new aspects of cell submembrane signalling

Daniel Smrž – Award of the Czech Immunological Society for the best scientific report presented by a young immunologist

Václav Hořejší – Award of the Czech Immunological Society for life-long merits in the progress of immunology

Václav Pačes – Medal of Merit by the President of the Czech Republic

New Associate Professor

Jaroslav Blahoš, Medical Pharmacology, Faculty of Medicine Hradec Králové, Charles University

PhD programme

A significant part of our scientific community is represented by over 70 PhD students (11 international), who strongly contribute to the scientific output and reputation of the Institute. Therefore, one of our priorities is to offer a competitive PhD programme that will attract the best students and will provide them with high-quality training for a career in molecular, cell and developmental biology, immunology, genetics, and virology.

We established a committee for PhD studies (Dominik Filipp, Pavel Hozák, Robert Ivánek (PhD student representative), David Staněk, and Petr Svoboda (current head of the committee)) that takes care of all matters concerning PhD students. The committee created Czech and English PhD websites and restructured the system for selection of candidates for PhD studies. The selection process starts with an online application where students provide their data in a uniform format in English and the group leaders later get a chance to meet with candidates during the PhD Interview Day.

Over thirty applicants came for the first PhD Interview Day on February 12, 2008. Applicants gave short English presentations of thesis research, were briefly interviewed and ranked by a three-member committee, and then they were interviewed by group leaders. At the end, eleven candidates joined the PhD programme. PhD interviews were well received and they will become a standard procedure for selecting PhD students in the future.

We also aim to foster training of our existing PhD students. We enlarged the selection of PhD courses taught in English. Most of these courses take place at our Institute: Acquisition and Processing of the Image in Microscopy (one-week practical course organized by P. Hozák), Advances in Immunology (K. Drbal, D. Filipp, R. Špíšek, P. Otáhal, T. Brdička, V. Hořejší), Advances in Molecular Biology and Genetics (two-week lecture course organized by J. Jonák and P. Svoboda), Basic Immunology (P. Otáhal, V. Hořejší), Epigenetics (P. Svoboda), Innate Immunity (D. Filipp), Cell Nucleus and Gene Expression (P. Hozák, Z. Hodný).

In order to make the PhD studies more effective, English classes for our students were moved directly to the IMG building. PhD students routinely present in English during labmeetings, journal clubs, and during institutional weekly seminars, which are almost exclusively given by PhD students now. PhD students also proposed and organized the first IMG PhD conference on October 17, 2008. With twelve student talks and a keynote lecture by Jiří Bartek, the conference brought together students and other researches in an informal atmosphere and laid foundations for a new tradition.

Further information on PhD studies at the IMG can be found at: http://www.img.cas.cz.

Teaching (Semestral Courses)

Molecular Mechanisms of Apoptosis, Ladislav Anděra, Faculty of Science, Charles University

Pharmacology, Jaroslav Blahoš, 2nd Faculty of Medicine, Charles University, Prague, and Faculty of Medicine Hradec Kralové, Charles University

Molecular Modelling and Bioinformatics, Jiří Brynda and Pavlína Řezáčová, Institute of Chemical Technology

Three-Dimensional Structure Solution of Macromolecules, Jiří Brynda and Pavlína Řezáčová, Faculty of Science, Charles University

Anti-tumour Immunity, Jan Bubeník, Faculty of Science, Charles University

Immunology and Gene Therapy of Tumours, Jan Bubeník, 1st Faculty of Medicine, Charles University

Molecular Mechanisms of Morphogenesis, Lukáš Čermák, Faculty of Science, Charles University

Structure and Function of the Cytoskeleton, Pavel Dráber, Faculty of Science, Charles University

Strategy and Tactics of Grant Proposal, Petr Dráber, Faculty of Science, Charles University

Molecular Immunology, Karel Drbal, Faculty of Science, Charles University

Advances in Immunology, Dominik Filipp, Karel Drbal, Pavel Otáhal, Tomáš Brdička, Radek Špíšek (2nd Faculty of Medicine, Charles University) and Václav Hořejší, Faculty of Science, Charles University

Innate Immunity, Dominik Filipp, Faculty of Science, Charles University

Molecular Genetics of the Mammalian Organism, Jiří Forejt, Faculty of Science, Charles University

Regulation Mechanisms of Immunity, Vladimír Holáň, Faculty of Science, Charles University

Immunology, Václav Hořejší, Faculty of Science, Charles University

Cell Nucleus and Gene Expression, Pavel Hozák, Faculty of Science, Charles University

Image Acquisition and Processing in Biomedical Microscopy, Pavel Hozák, Czechoslovak Microscopy Society

Gene Expression, Jiří Jonák, 1st Faculty of Medicine, Charles University

Seminars „Biological Oxidation“, Jiří Jonák, 1st Faculty of Medicine, Charles University

Molecular Pathology, Vladimír Kořínek, Faculty of Science, Charles University

Model Organisms in Developmental Biology, Zbyněk Kozmik, Faculty of Science, Charles University

Advances in Immunology of Infectious Diseases. Molecular Mechanisms of Defence against Infection, Marie Lipoldová, 3rd Faculty of Medicine, Charles University

Basic Immunology, Pavel Otáhal, 3rd Faculty of Medicine, Charles University

Bioinformatics, Jan Pačes (with Jiří Vondrášek from the Institute of Organic Chemistry and Biochemistry AS CR), Faculty of Science, Charles University

Bioinformatics, Jan Pačes, University of Perugia, Perugia, Italy

Gene Engineering, Václav Pačes (with Tomáš Ruml from the Institute of Chemical Technology), Institute of Chemical Technology

Molecular Genetics, Václav Pačes, Institute of Chemical Technology

Advances in Cell Biology, David Staněk (1 lecture), 1st Faculty of Medicine, Charles University

RNA Structure and Function, David Staněk, 1st Faculty of Medicine, Charles University

Molecular and Cellular Oncology, Jan Svoboda and Jiří Hejnar, Faculty of Science, Charles University

Developmental Biology, Petr Svoboda, Faculty of Science, Charles University

Epigenetics, Petr Svoboda, Faculty of Science, Charles University

Biotechnology of Monoclonal Antibodies, Vladimír Viklický, Faculty of Science, Charles University

System of Funding Research and Development in the Czech Republic, Vladimír Viklický, Faculty of Science, Charles University

Soluble Mediators in the Immune System, Jarmila Vojtíšková, 3rd Faculty of Medicine, Charles University

Theses Defended in 2008

Bachelor Theses

Antošová Barbora The role of connexins Cx46 and Cx50 in eye lens and their role in cataractogenesis
(Supervisor: Zbyněk Kozmik; Faculty of Science, Charles University, Prague)

Auxt Miroslav Epigenetic mechanisms of retrovirus transcriptional silencing
(Supervisor: Jiří Hejnar; Faculty of Science, Charles University, Prague)

Dušková Eva Pre-mRNA splicing regulation by antisense oligonucleotides
(Supervisor: David Staněk; Faculty of Science, Charles University, Prague)

Hájková Zuzana Participation of proteins of γ-tubulin complexes in the regulation of plus-end microtubule dynamics
(Supervisor: Pavel Dráber; Faculty of Science, Charles University, Prague)

Chum Tomáš Regulators of actin dynamics profilin and β-thymosin have nuclear functions
(Supervisor: Pavel Hozák; Faculty of Science, Charles University, Prague)

Kukla Jakub Localization of actin and actin-binding proteins in the cell nucleus
(Supervisor: Pavel Hozák; Faculty of Science, Charles University, Prague)

Pitule Pavel Functional importance of short protein linear motifs and their bioinformatic analysis
(Supervisor: Karel Drbal; Faculty of Science, Charles University, Prague)

Sarnová Lenka siRNA design
(Supervisor: Petr Svoboda; Faculty of Science, Charles University, Prague)

Šulcová Jitka The use of RNA interference for inhibition of mammalian gene expression
(Supervisor: Karel Drbal; Faculty of Science, Charles University, Prague)

Těšina Petr Mutations of splicing factors in hereditary eye disease - retinitis pigmentosa. Regulation of alternative splicing
(Supervisor: David Staněk; Faculty of Science, Charles University, Prague)

Vavrochová Tereza Embryonal phagocytes: their identification, origin and functions
(Supervisor: Dominik Filipp; Faculty of Science, Charles University, Prague)

Vávrová Kateřina Genetic impacts on atopic disease development
(Supervisor: Marie Lipoldová; Faculty of Science, Charles University, Prague)

Diploma Theses

Brinská Zuzana Wnt signalling in the liver
(Supervisor: Vladimír Kořínek; Faculty of Science, Charles University, Prague)

Gabanová Veronika Gene expression analysis of cnidarian larvae Tripedalia cystophora
(Supervisor: Zbyněk Kozmik; Faculty of Science, Charles University, Prague)

Chmátal Lukáš Biochemical and functional characterization of a transmembrane adaptor protein LST1/A
(Supervisor: Václav Hořejší; Faculty of Science, Charles University, Prague)

Jonášová Kristýna Refractive index gradient in the cubozoan eye: gene expression analysis
(Supervisor: Zbyněk Kozmik; Faculty of Science, Charles University, Prague)

Kalenská Romana Induction of the immune response against HPV16-associated tumours with experimental vaccines
(Supervisor: Milan Reiniš; Faculty of Science, Charles University, Prague)

Moravcová Simona Regulation of the expression of MHC class I molecules and other immunoactive molecules on tumour cells
(Supervisor: Milan Reiniš; Faculty of Science, Charles University, Prague)

Svoboda Ondřej Cloning, expression, and characterization of recombinant growth factors
(Supervisor: Petr Bartůněk; Faculty of Science, Charles University, Prague)

Štěpánek Ivan Unmethylated CpG oligodeoxynucleotides and their function in differentiation of murine dendritic cells
(Supervisor: Milan Reiniš; Faculty of Science, Charles University, Prague)

Tománková Tereza Regulation of alternative splicing
(Supervisor: David Staněk; Faculty of Science, Charles University, Prague)

Valentová Vanda Genetic control of cytokine production
(Supervisor: Marie Lipoldová; Faculty of Science, Charles University, Prague)

PhD Theses

Frič Jan New strategies for antigen delivery and modulation of specific immune response
(Supervisor: Vladimír Holáň; Faculty of Science, Charles University, Prague)

Heneberg Petr New aspects of the cell submembrane signalling
(Supervisor: Petr Dráber; 3rd Faculty of Medicine, Charles University, Prague)

Král Vlastimil Recombinant antibody fragments
(Supervisor: Juraj Sedláček; Faculty of Science, Charles University, Prague)

Mihola Ondřej Positional cloning of Hst1 gene (Hybrid sterility 1) and molecular analysis of candidate genes
(Supervisor: Zdeněk Trachtulec; Faculty of Science, Charles University, Prague)

Mikasová Lenka Lateral diffusion of CB1 receptor
(Supervisors: Olivier Manzoni and Jaroslav Blahoš; University of Bordeaux, 2nd Faculty of Medicine, Charles University, Prague)

Pilčík Tomáš Mapping of genes for quantitative trait loci and establishment of their epistases in recombinant congenic mouse strains
(Supervisor: Marie Lipoldová; Faculty of Science, Charles University, Prague)

Průková Dana Pathogenic effects of avian leukosis viruses in chicken
(Supervisor: Josef Geryk; Faculty of Science, Charles University, Prague)

Stepanets Volodymyr Avian leukosis virus subgroup C (ALV-C): pathogenic consequences of virus heterotransmission to duck host; the cellular receptor cloning and functional determinants identification
(Supervisor: Jan Svoboda; Faculty of Science, Charles University, Prague)

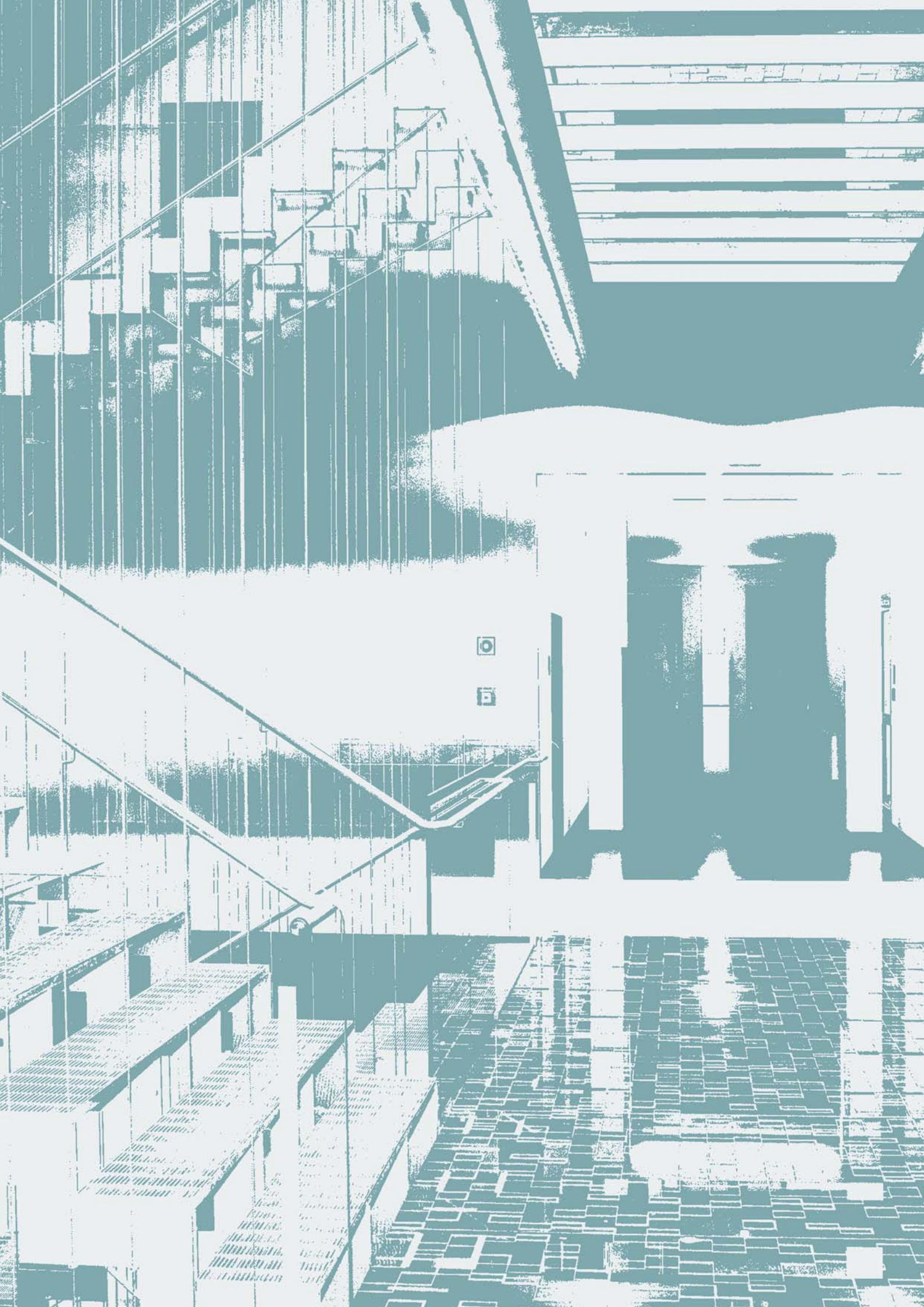
Šenigl Filip Improvement of retroviral vectors for efficient gene transfer
(Supervisor: Jiří Hejnar; Faculty of Science, Charles University, Prague)

Šímová Šárka Regulation of TRAIL-induced apoptosis
(Supervisor: Ladislav Anděra; 3rd Faculty of Medicine, Charles University, Prague)

Vlasáková Jana Regulation of promyelocytic leukaemia protein expression
(Supervisor: Zdeněk Hodný; Faculty of Science, Charles University, Prague)

Habilitation

Blahoš Jaroslav Study of the signalling of metabotropic glutamate and GABAb receptors (Faculty of Medicine Hradec Králové, Charles University)



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Development of the IMG Complex

Newly Opened Animal House

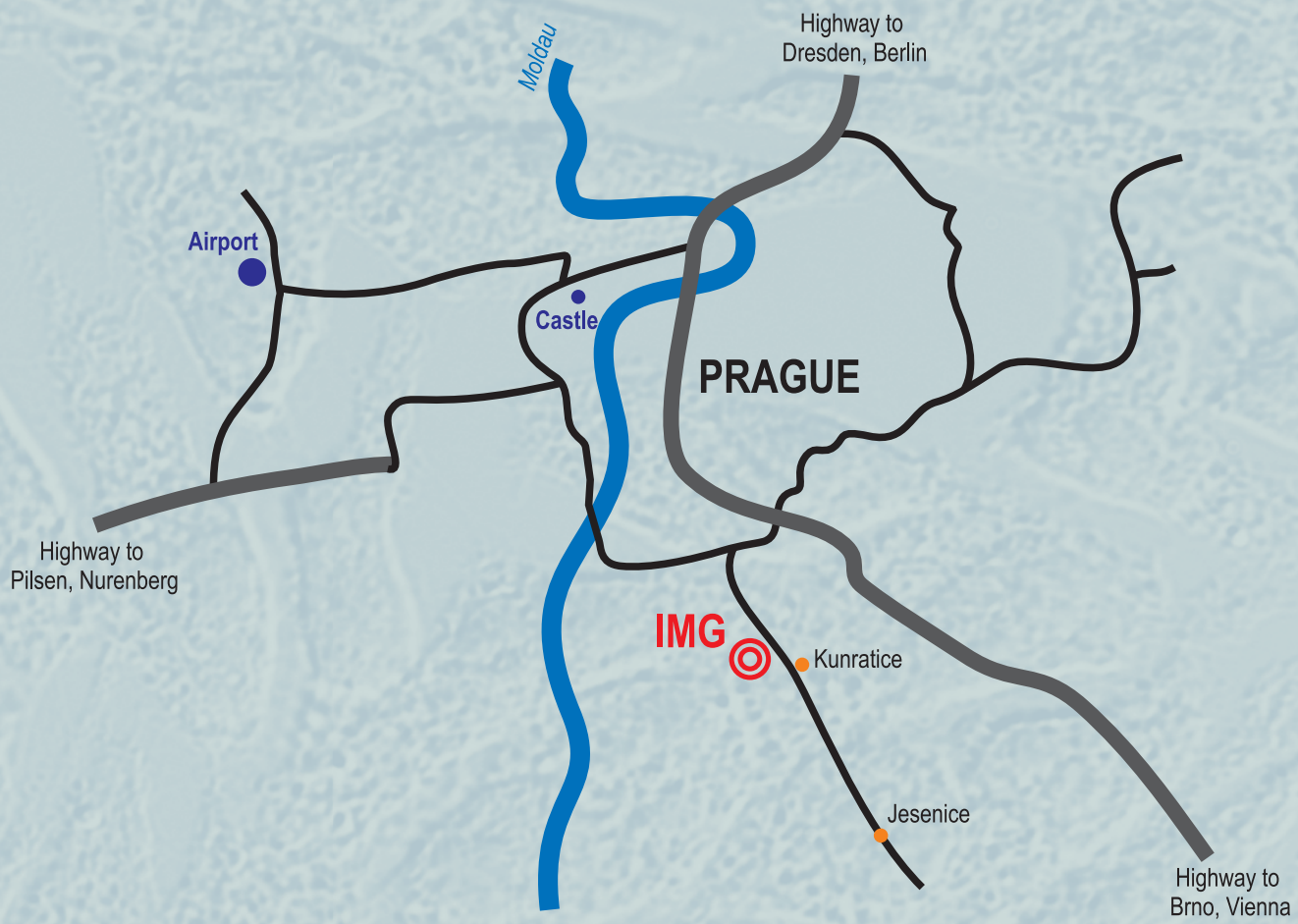
Newly Opened Conference Hall

Newly Opened Cafeteria and Terrace

New Park

FINAL VIEW OF THE ENTIRE COMPLEX

Where We Are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