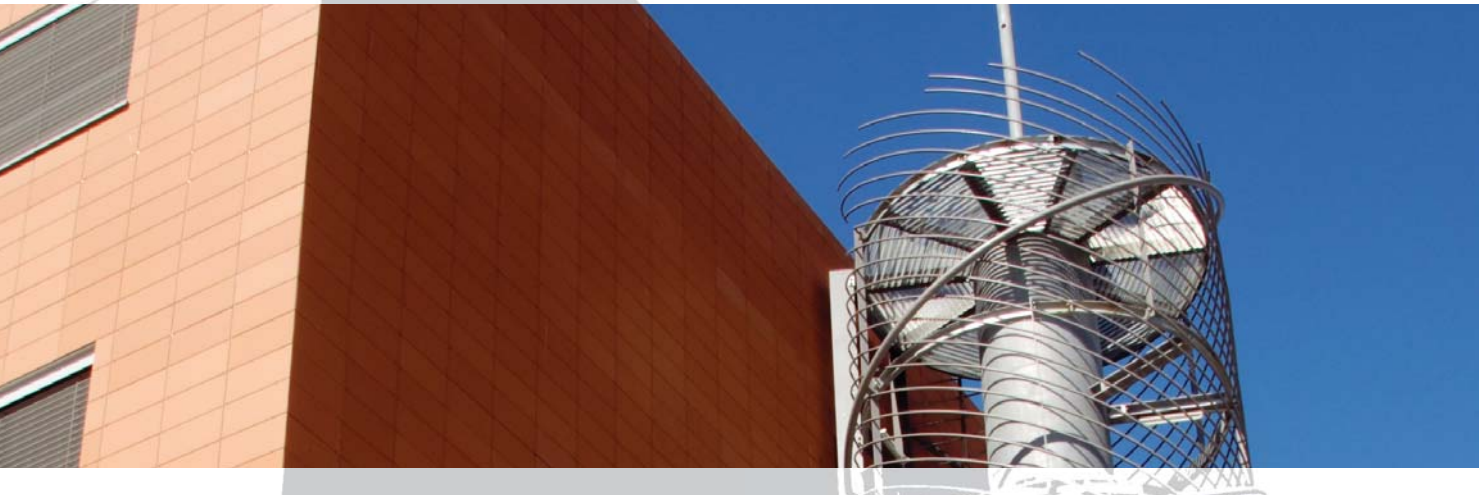
Institute of Molecular Genetics

Academy of Sciences of the Czech Republic



2007

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The previous research report of our Institute covered the years 2004 – 2005, so the present one should cover the next two years, 2006 – 2007. However, because of the major organizational changes of the Institute since January 2007, such a bi-annual report would be somewhat complicated and confusing. Therefore, publications for 2006 are given and some important events of 2006 are mentioned, but this report is for 2007 only and also in the future the reports will be annual.

CONTENS

Václav Hořejší
Director

Petr Dráber
Deputy Director

Jiří Špička
Deputy Director for Economy

Jiří Drahoš
Vice-President of AS CR
Chairman of the Supervisory Board

Jiří Forejt
Chairman of the Institute Council

Šárka Takáčová
Institute Secretary

Introduction

In 2007, our Institute literally entered a new era of its existence – at the beginning of this year we moved to our new building in the Krč Biomedical Institutes campus. Thus, the Institute finally starts to function as a standard scientific institution under one roof. We started working in a very nice, well equipped building and we are really happy about it – it is a fulfilment of a two generations' dream. In the autumn, we finished a new modern animal facility adjacent to the main building, and moved our mice there. We have started construction of the last part of our research complex – the conference building that will be finished in the Spring 2008 and will serve all biomedical institutes of the Krč biomedical research campus.

Just like all other Academy Institutes, in 2007, the Institute of Molecular Genetics became a Public Research Institution. This legal step brought about higher independence but also higher responsibility, and a number of administrative tasks. The Institute's Council was elected, the Supervisory Board was established, and the Director re-established. Most important, we performed a thorough re-organization of scientific groups – six previous groups were replaced by new ones led by younger and promising leaders selected in an international competition. Three additional groups will start in 2008 to fill the presently free laboratory space. A special „Biotechnology Division" has been established, comprising six research laboratories and sited in a neighbouring building. This part of the Institute will become independent in 2008 as a new sister institution, Biotechnology Institute AS CR.

Another important feature of the rejuvenation of the Institute has been establishment of several Service Departments, e.g. information technologies, microscopy and cytofluorometry, functional genomics and bioinformatics, media preparation, cryopreservation and monoclonal antibodies. A transgenic facility is being systematically developed to become fully functional in 2008. Several other service laboratories function well in other institutes of the campus and are being routinely used by us (e.g. mass spectrometry, DNA sequencing). In 2007 we bought several expensive microscopes and other instruments that bring our technical abilities again closer to currently highest standards.

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.

At present, 27 research groups of the Institute (including the Biotechnology Division) are dealing with the topics covering molecular and cellular immunology, functional genomics and bioinformatics, study of oncogenes, molecular biology of development, molecular basis of fertilization, structural biology and mechanisms of receptor signalling. An essential part of our Institute are 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. Several well prospering biotech spin-off companies have been born at the Institute in recent years based on such applied research products.

In 2007, the Institute scientists were again authors or co-authors of publications in a number of prestigious international journals (e.g. Nature Reviews Genetics, Trends in Genetics, EMBO Journal, Developmental Cell, Blood, Journal of Biological Chemistry, Journal of Immunology, Journal of Virology, Cancer Research, Journal of the American Chemical Society. Genome Research, Blood, Journal of Immunology, Journal of Biological Chemistry, Journal of Molecular Biology, Journal of Bacteriology, Journal of Cell Science, Nucleic Acids Research, Cancer Research).

The high standing of the Institute researchers is testified by awards and prizes; in 2007 Prof. Jiří Forejt was awarded the newly established most prestigious Preaemium Academiae of the Academy of Sciences (as one of four only awardees); Dr. Tomáš Brdička received Otto Wichterle Award for young Academy researchers; Dr. Petr Svoboda was awarded the Purkynje Fellowship and EMBO Installation Grant.

It is really exciting to see the potential opening for the Institute under the now much better conditions; it is only up to us whether the opportunity will be used properly . . .

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 1961, 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.

Ladislav Anděra

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Laboratory of Cell Signaling and Apoptosis

Death receptors, apoptosis, Daxx

Research topics

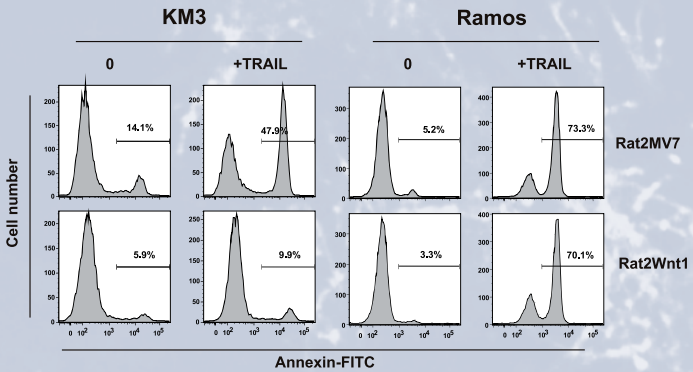
The laboratory deals with characterization and regulation of the signalling pathways triggered by pro-apoptotic TRAIL receptors (DR4 and DR5), by the Death Receptor 6 (DR6), or affected by apoptosis- and transcription-regulating adapter protein Daxx. In TRAIL-related projects we discovered a novel DR4-interacting protein ARAP1 that in a cell-specific manner affects DR4 membrane localization and we characterized Wnt1-transformed Rat2 fibroblast-mediated suppression of TRAIL-induced apoptosis of human pre-B leukaemia cells. At present we focus on the analysis of oncogenic transformation-induced sensitization of human cells to TRAIL-triggered apoptosis and on examination of TRAIL-induced signalling in tumour-initiating cells. In respect to DR6 signalling we dissected the role of DR6 glycosylation in DR6 membrane localization and currently we characterize molecular and functional properties of DR6(ICP)-interacting proteins. Novel interaction partners of Daxx (e.g. Brg1) were discovered by Y2H screening. These interactions apparently play important roles in regulation of transcription and apoptosis. Daxx associates with Brg1-Swi/Snf complex and is required for transactivation of several Brg1-dependent genes.

Current grant support

AS CR (AV0Z50520514), 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)

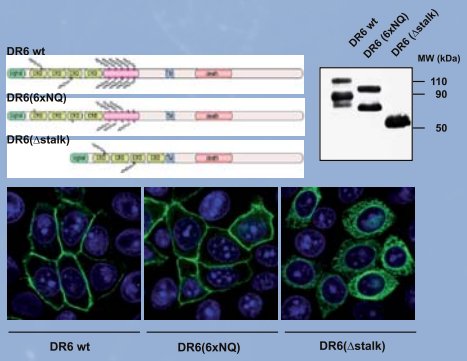
Selected recent papers

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;6:2591-9.
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. Neuzil J, Stantic M, Zobalova R, Chladova J, Wang X, Prochazka L, Dong L, Andera L, Ralph SJ. Tumour-initiating cells vs. cancer ‚stem' cells and CD133: what's in the name? **Biochem Biophys Res Commun.** 2007;355:855-9.
4. Tomasetti M, Andera L, Alleva R, Borghi B, Neuzil J, Procopio A. α-tocopheryl succinate induces DR4 and DR5 expression by a p53-dependent route: implication for sensitisation of resistant cancer cells to TRAIL apoptosis. **FEBS Lett.** 2006;580:1925-31.

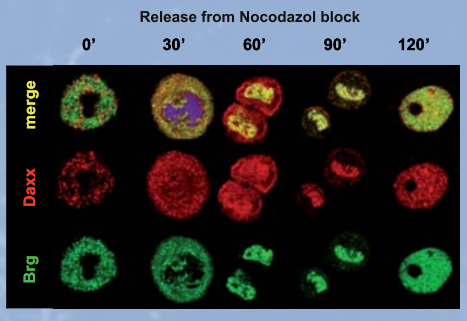


Rat2Wnt1 fibroblasts inhibit TRAIL-induced apoptosis of pre-B KM3 leukaemia cells but not of more differentiated Ramos Burkitt lymphoma.

Ladislav Anděra, PhD / Head of Laboratory
Michal Koc, PhD / Postdoc
Lukáš Čermák, PhD / Postdoc
Simona Benešová /Technician
Martin Klíma, MSc / PhD Student
Šárka Šímová, MSc / PhD Student
Vladimíra Šourková, MSc / PhD Student
Jan Švadlenka, MSc / PhD Student
Leonard Nevařil / Diploma Student
Jaromír Novák / Diploma Student
Tomáš Zikmund / Diploma Student



DR6 glycosylation mutants differ in their subcellular localization in transfected MDCK cells.



Daxx co-localizes with Brg1 in post-mitotic HeLa cells.

Petr Bartůněk

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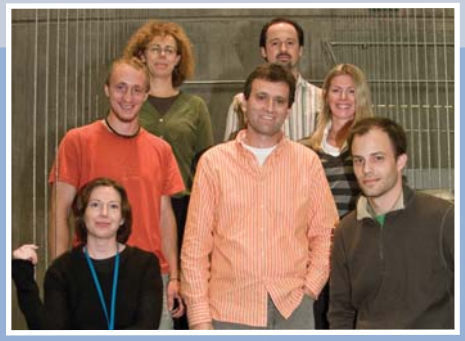
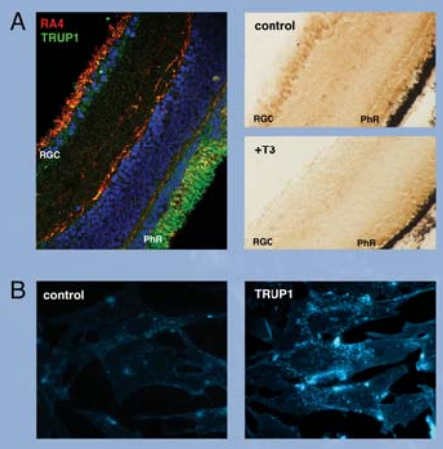
Laboratory of Cell Differentiation

Haematopoietic differentiation, nuclear hormone receptors



Petr Bartůněk, PhD / Head of Laboratory
Martina Zíková, PhD / Research Scientist
Alicia Corlett, PhD / Research Scientist
Olga Martínková / Technician
David Sedlák, MSc / PhD Student
Ondřej Svoboda / Diploma Student
Andre Kajlich / Diploma Student



(A) Expression of TRUP1 in chicken retina (left panel). TRUP1 is downregulated by T3 in vivo (right panels) RGC retinal ganglion cells, PhR photoreceptors. Immunohistochemical staining of chicken retina at embryonic day 15. (B) Ectopic expression of TRUP1 in fibroblasts leads to accumulation of cholesterol (stained with filipin) within the cell

Research topics

To date, we have concentrated on characterizing a novel sterol sensing domain-containing protein, TRUP1, that we cloned as a gene directly regulated by thyroid hormone. Evolutionary analysis demonstrates that TRUP1 is closely related to the *dispatched* family of proteins. Its expression predominates in the brain, retina and testis and corresponds with the tissues most profoundly affected by the inactivation of thyroid hormone receptor α and/or β. Over-expression of TRUP1 results in altered cholesterol distribution and accumulation, suggesting that it may regulate cholesterol trafficking/localization in the cell and as such may represent a new molecular link between thyroid hormone action and cholesterol metabolism (Fig. 1).

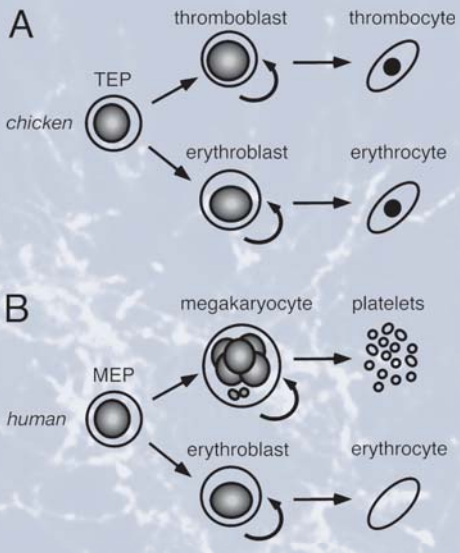
We have also identified, cloned and characterized the first non-mammalian Tpo, chicken thrombopoietin, and its receptor c-Mpl. Discovery of chicken Tpo and c-Mpl will greatly facilitate future studies regarding thrombocytic differentiation and haematopoietic stem cell development. Moreover, we have introduced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

Current grant support

EC FP6 (Integrated project CRESCENDO); GA AS CR (IAA500520705)

Selected recent papers

1. Bartunek P, Pajer P, Karafiat V, Blendinger G, Dvorak M, Zenke M. bFGF signaling and v-Myb cooperate in sustained growth of primitive erythroid progenitors. **Oncogene.** 2002;21:400-10.
2. Bartunek P, Kralova J, Blendinger G, Dvorak M, Zenke M. GATA-1 and c-myb crosstalk during red blood cell differentiation through GATA-1 binding sites in the c-myb promoter. **Oncogene.** 2003;22:1927-35.
3. 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;62:2516-25.



Schematic model of (A) thrombocytic (chicken) and (B) megakaryocyte (human) differentiation. Bi-potent thrombo/erythroid progenitor (TEP) and megakaryo/erythroid progenitor (MEP) cells represent a binary switch model to study cell fate determination.

Pavel Dráber

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Laboratory of Biology of Cytoskeleton

Modulation of microtubule organization, microtubule proteins

Research topics

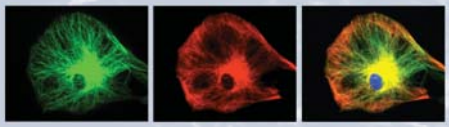
The long-term research programme of the laboratory has been focused on studying the structure-function relationships of microtubule (MT) proteins and their interactions with other cytoskeletal elements in cells under normal and pathological conditions. The organization of MT networks is controlled by 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. Our results demonstrate that non-receptor protein tyrosine kinase Fyn of the Src family plays an important role in MT nucleation both from MTOC and from membranes. We have also shown that ectopic cellular expression of γ-tubulin in gliomas may be significant in the context of centrosome dysfunction and may serve as a novel marker of anaplastic changes.

Current grant support

Ministry of Education, Youth and Sports (Center of Cell Functional Organization, LC545); GA CR (204/05/2375, 204/05/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;176:7243-53.
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 gamma-tubulin in diffuse astrocytic gliomas and human glioblastoma cell lines suggest centrosome protein amplification. **J Neuropathol Exp Neurol.** 2006;65:465-77.
3. Pěknicová J, Pexidrová M, Kubátová A, Koubek P, Teplá O, Sulimenko T, Dráber P. Expression of beta-tubulin epitope in human sperm with pathological spermiogram. **Fertil Steril.** 2007;88:1120-28.
4. Katsetos CD, Dráberová E, Šmejkalová B, Reddy G, Bertrand L, Chadarévian JP, Legido A, Nissanov J, Baas PW, Dráber P.: Class III beta-tubulin and gamma-tubulin are co-expressed and form complexes in human glioblastoma cells. **Neurochem Res.** 2007;2:1387-98.



IMicrotubules (green) and intermediate filaments (red) in primary astrocytes.

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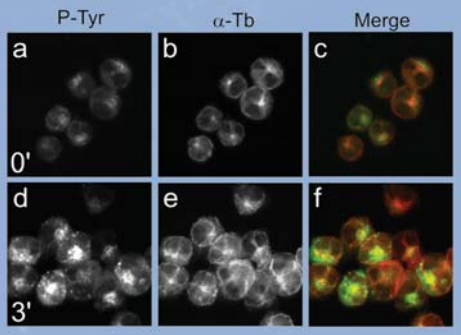
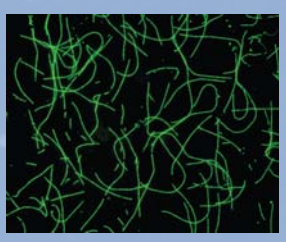
Vadym Sulimenko, PhD / Research Scientist
Věra Richterová, MSc / Research Assistant
Ladislav Cupák / Technician
Irena Mlchová / Technician
Barbora Šmejkalová, MSc / PhD Student
Stanislav Vinopal, MSc / PhD Student
Zuzana Hájková / Diploma Student
Tetyana Sulimenko / Maternity Leave



Immunofluorescence localization of tyrosine-phosphorylated proteins (green) and α-tubulin (red) in resting (a-c) and activated (d-e) Lyn$^{-/-}$ bone marrow mast cells.



Microtubules prepared in vitro from purified tubulin.

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Laboratory of Signal Transduction

Plasma membrane in mast cell signaling

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Filip Franko, MSc / PhD Student
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Pavel Lebduška, MSc / PhD Student
Iva Polakovičová, MSc / PhD Student
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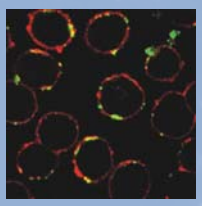
Martin Machyna, Bc / Diploma Student
Michal Šimíček / Diploma Student

Telemetry used for continuous measurement of body temperature in the course of allergy reaction



Non-apoptotic phosphatidylserine (PS) externalization induced by aggregation of GPI-anchored glycoprotein Thy-1. RBL cells were treated with anti-Thy-1 monoclonal antibody for 15 min. Externalized PS was detected with FITC-labelled annexin V (green) and Thy-1 with cyanine 3-labelled secondary antibody (red). PS was distributed in distinct patches showing only partial overlap with Thy-1.

Research topics

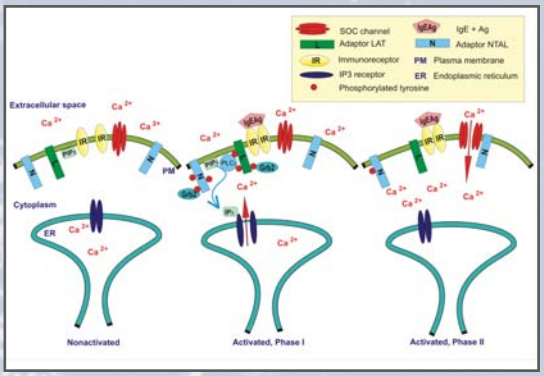
Our current studies are focused on understanding the role of plasma membrane components and actin cytoskeleton in initial stages of mast cell activation induced by engagement of the high affinity IgE receptor (FcεRI) and/or cytokine receptor, c-Kit. Using bone marrow-derived mast cells from mice deficient in the transmembrane adaptor proteins LAT and/or NTAL and mast cell lines with enhanced or decreased amount of NTAL and/or another adaptor protein Grb2 we analyzed the role of these proteins in tyrosine phosphorylation of the FcεRI and other substrates, and calcium response. Furthermore, we analyzed topography of these and other plasma membrane components, including GPI-anchored proteins, using immunofluorescence microscopy, FRET and electron microscopy on isolated membrane sheets. Interestingly, aggregation of GPI-anchored proteins induced externalization of phosphatidylserine (PS) which was not dependent on secretory response or apoptosis. We have proposed that this mechanism could contribute to „inside-out" signaling in response to pathogens and other external activators. Furthermore, we have produced several antibodies specific for signaling molecules, including LAT, PLSCR1, STIM1 and PTP20.

Current grant support

Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology, 1M0506); GA CR (301/06/0361); GA AS CR (KAN200520701)

Selected recent papers

1. Heneberg P, Lebduška P, Dráberová L, Korb J, Dráber P. Topography of plasma membrane microdomains and its consequences for mast cell signaling. **Eur J Immunol.** 2006;36:2795--806.
2. Smrž D, Dráberová L, Dráber P. Non-apoptotic phosphatidylserine externalization induced by engagement of glycosylphosphatidylinositol-anchored proteins. **J Biol Chem.** 2007;282:10487-97.
3. Dráberová L, Shaik G M, Volná P, Heneberg P, Tůmová M, Ledbuška 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;179:5169-80.
4. Dráber P, Dráberová L, Henberg P, Šmíd F, Farghali H, Dráber P. Preformed STAT3 transducer complexes in human HepG2 cells and rat hepatocytes. **Cell Signal**. 2007;19:2400-12.
5. Lebduška P, Korb J, Tůmová M, Heneberg P, Dráber P. Topography of signaling molecules as detected by electron microscopy on plasma membrane sheets isolated from non-adherent mast cells. **J Immunol Methods.** 2007;328:139-151.



The role of transmembrane adaptor NTAL in early and late stages of mast cell signalling

Michal Dvořák

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Laboratory of Molecular Virology

Carcinogenesis, cell differentiation, EGR4

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.

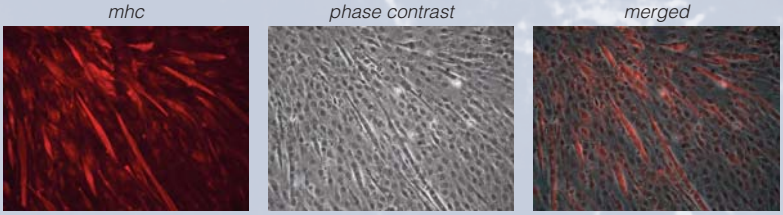
In studies on cell fate determination, differentiation and malignant transformation of haematopoietic and neural cells (collaboration with the Institute of Anatomy, Prague), c-*myb* and v-*myb* genes are used as tools to modulate development of avian cells and tissues. In studies on the nephrogenic blastema 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 egr and myb families serve as tools to affect epithelial and mesenchymal cell phenotypes.

Current grant support

Ministry of Education, Youth and Sports of the Czech Republic (Center of Cell Invasiveness in Embryonic Development and Tumour Metastases, LC06061; Center of Chemical Genetics, LC06077); Grant Agency of the Czech Republic (204/06/1728, 203/06/1038); Academy of Sciences of the Czech Republic (AV0Z50520514, IAA500520608)

Selected recent papers

1. Kral V, Lang K, Kralova J, Dvorak M, Martasek P, Chin A, Andrievsky A, Lynch V, Sessler JL. Polyhydroxylated sapphyrins: multisite non-metallic catalysts for activated phosphodiester hydrolysis. **J Am Chem Soc.** 2006;128:432-437.
2. Kralova J, Synytsya A, Pouckova P, Koc M, Dvorak M, Kral V. Novel porphyrin conjugates with a potent photodynamic antitumor effect: differential efficacy of mono- and bis-β-cyclodextrin derivatives *in vitro* and *in vivo*. **Photochem Photobiol.** 2006;82:432-438.
3. Nanka O, Valášek P, Dvořáková M, Grim M. Experimental hypoxia and embryonic angiogenesis. **Dev Dyn.** 2006;235:723-733.
4. 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.
5. 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.
6. Kaspar P, Dvorak M. Involvement of phosphatidylserine externalization in the down-regulation of c-myb expression in differentiating C2C12 cells. **Differentiation**. Epub Oct 9,2007.



Differentiation of myogenic cells to myotubes. Myosin heavy chain (mhc) expression (red fluorescence) in differentiating muscle cell line C2C12.

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Petr Kašpar, PhD / Research Scientist
Jarmila Králová, PhD / Research Scientist
Vladimír Čermák, MSc / PhD Student
Jan Kosla, MSc / PhD Student
Petr Pajer, MSc / PhD Student
Václava Škopová, MSc / PhD Student
Michaela Starostová, MSc / PhD Student
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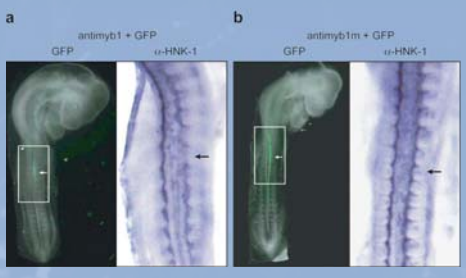
Detection of FoxP1 transcription factor (brown) in nuclei or cytoplasm of chicken nephroblastoma cells. Tissue microarrays were prepared from clonal tumours.



c-Myb is required for the formation of migratory neural crest cells. a) electroporated antimyb1 morpholino oligonucleotides reduce the amount of neural crest cells (detected by HNK-1 antibody - violet) emigrating from the neural tube of the chick embryo in the area depicted by the arrow. b) Control antimyb1m oligonucleotides have no inhibitory effect.

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Laboratory of Mouse Molecular Genetics

Meiotic silencing, aneuploidy, genomics, hybrid sterility genes

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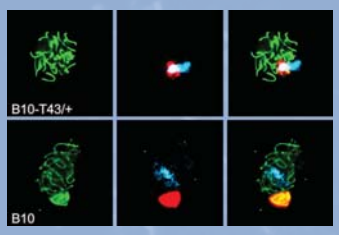
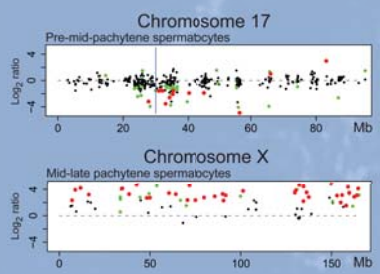


Meiotic synapsis and XY body in pachytene spermatocytes of B10-T43/+ sterile males and B10 controls. Synaptonemal complexes are green, phosphorylated histone H2AX is red and chromosome 17 is light blue.



Distribution of gene expression changes (Log2 scale) along chromosome 17 and X between sterile and fertile males. Expression differences significant at P<0.05 in green, at P<0.01 in red

Research topics

We study **Meiotic X-chromosome inactivation** by genome-wide expression profiling and by monitoring X-chromosome histone modifications in meiotic and postmeiotic 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 in a systems genetics project with the Max-Planck-Institute for Molecular Genetics in Berlin (Dr. H. Lehrach).

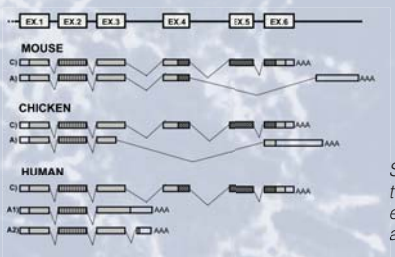
We analyse **Haplotype structure and conserved synteny** in the *Hst1* region of mouse chromosome 17 by sequencing 33 loci from 80 chromosomes of five (sub)species of mice. Conservation of a complex pattern of alternative and antisense transcripts at the *Pdcd2* locus in the *Hst1* region suggests its biological importance.

Current grant support

Ministry of Education, Youth and Sports (Center of Applied Genomics, 1M0520); GA CR (301/05/0738, 301/06/1334, 301/07/1264, 301/07/1383); GA AS CR (IAA5052406); National Institutes of Health, USA (1 R01 HG003183-01); 6th FP EC (037627)

Selected recent papers

1. Mihola O, Forejt J, Trachtulec Z. Conserved alternative and antisense transcripts at the programmed cell death 2 locus. **BMC Genomics.** 2007;8:20.
2. Homolka D, Ivanek R, Capkova J, Jansa P, Forejt J. Chromosomal rearrangement interferes with X-chromosome inactivation. **Genome Res.** 2007;17:1431-7.
3. Pialek J, Vyskočilova 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 Heredity.** Epub Oct 26,2007.
4. Pravenec M, Kazdova L, Landa V, Zidek V, Mlejnek P, Simakova M, Jansa P, Forejt J, Kren V, Qi N, Wang J-M, Chan D, Aitman T, Kurtz TW. Identification of mutated Srebf1 as a QTL influencing risk for hepatic steatosis in the spontaneously hypertensive rat. **Hypertension.** 2008;51:148-153.



Schematic representation of the constitutive (C) and alternative (A) transcripts encoding PDCD2 in the mouse, chicken and human.

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Laboratory of Molecular Immunology

Transmembrane adaptor proteins, membrane rafts

Research topics

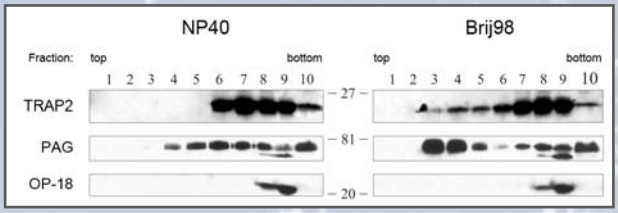
In recent years a major topic of our laboratory has been signalling molecules present in membrane rafts, namely several transmembrane adaptor proteins discovered previously by us (PAG/Cbp, NTAL/LAB, LIME) and their involvement in immunoreceptor signalling. In 2006-2007 we participated in characterization of mice deficient in the transmembrane adaptor protein NTAL and LIME (gene knock-out); based on these studies, both these proteins appear to be mainly negative regulators of immunoreceptor signalling. Furthermore, we have been working on elucidation of structure and function of four other novel transmembrane adaptors (LST1A, PRR7, "TRAP2", "Nvl") and collaborated on several studies concerning membrane rafts and their components. Also, we identified blood plasma protein vitronectin as a major opsonin of late apoptotic cells. Additionally, we produced a number of novel monoclonal antibodies as valuable research tools, e.g. those to the above-mentioned novel TRAPs, Sos1, H-Ras, SHIP, caprin-1, or ectoenzyme glutamate carboxypeptidase II (GCPII) and related GCPIII and PSMA-L.

Current grant support

Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology, 1M0506; international project EUREKA, RECAN, 1P04OE190); FP6 EU (HYBLIB, NEST, 12919)

Selected recent papers

1. Tessarz AS, Weiler S, Zanzinger K, Angelisova P, Horejsi V, Cerwenka A. Non-T cell activation linker (NTAL) negatively regulates TREM-1/DAP12-induced inflammatory cytokine production in myeloid cells. **J Immunol.** 2007;178:1991-9.
2. Meraner P, Horejsi V, Wolpl A, Fischer GF, Stingl G, Maurer D. Dendritic cells sensitize TCRs through self-MHC-mediated Src family kinase activation. **J Immunol.** 2007;178:2262-71.
3. Kitaura J, Kawakami Y, Maeda-Yamamoto M, Horejsi V, Kawakami T. Dysregulation of Src family kinases in mast cells from epilepsy-resistant ASK versus epilepsy-prone EL mice. **J Immunol.** 2007;178:455-62.
4. Smida M, Posevitz-Fejfar A, Horejsi V, Schraven B, Lindquist JA. A novel negative regulatory function of the phosphoprotein associated with glycosphingolipid-enriched microdomains: blocking Ras activation. **Blood.** 2007;110:596-625.
5. Hong H, Kitaura J, Xiao W, Horejsi V, Ra C, Lowell CA, Kawakami Y, Kawakami T. The Src family kinase Hck regulates mast cell activation by suppressing an inhibitory Src family kinase Lyn. **Blood.** 2007;110:2511-9.
6. 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;37:3259-69.



Distribution of a novel transmembrane adaptor protein TRAP2 in fractions of density gradient ultracentrifugation

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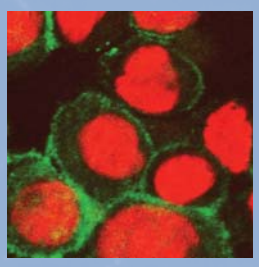
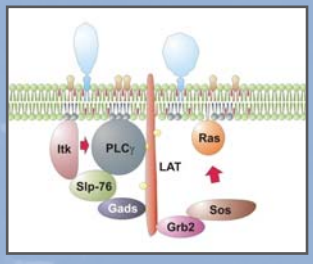
Peter Dráber, MSc / PhD Student
Lukáš Chmátal, Bc / Diploma Student
Ivana Vonková / Diploma Student
Eva Tvrzníková / Secretary



Subcellular localization of a novel transmembrane adaptor, LST1A



Hypothetical organization of a signalosome organized around the pivotal T cell transmembrane adaptor LAT

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Laboratory of Viral and Cellular Genetics

Receptors for retroviruses, retroviral vectors, endogenous retroviruses

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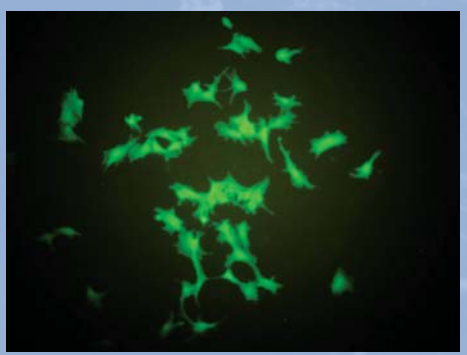
Anton A Buzdin / Visiting Scientist



Retroviral vector transduces GFP reporter gene into chicken testicular cells including the spermatogonial stem cells

Research topics

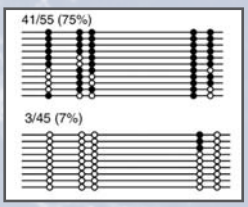
The main scientific interest of our group has been traditionally focused on the interactions of retroviruses with the host cells. Retroviruses enter their natural host cells via specific receptors, integrate into the host genome, and use the cell transcription machinery to express their structural or enzymatically active proteins. At the level of whole organism, retroviruses induce various pathologies and may even penetrate the germ lines being thereafter transmitted vertically as endogenous retroviruses. Human endogenous retroviruses do not replicate themselves but some of them are inevitable for our health and some of them may be harmful by inadvertent activation. Host cells inactivate the integrated invaders by their transcriptional silencing via DNA methylation and modifications of adjacent histones. This is, however, an obstacle in using retroviruses as vectors for gene transfer and transgenesis. In the years 2006 and 2007, we have identified a novel semiresistant variant of chicken receptor for ASLV-B and described the ASLV-induced wasting disease in chicken. We have described that insertion of a core element from CpG island into retroviral vectors improves their resistance to transcriptional silencing and ensures long-term expression of such vectors. We have successfully used a retroviral vector for transduction of reporter genes in chicken male germ line, which opens the way to efficient transgenesis in chicken. We have also characterized the CpG methylation patterns of human syncytins, endogenous retroviruses involved in differentiation of human placenta syncytiotrophoblast. Furthermore, we are intersted in porcine endogenous retroviruses as a potential risk factor in xenotransplantation of pig organs and tissues.

Current grant support

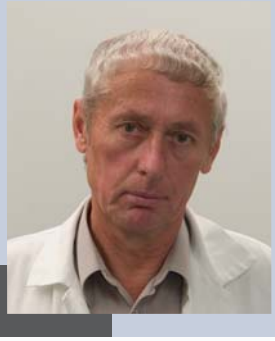
Ministry of Education, Youth and Sports (Center LC-06061), GA CR (204/05/0939, 204/07/1030, 523/07/1171, 523/07/1282), GA AS CR (A500520709), FP6 International project XENOME

Selected recent papers

1. Matoušková M, Blažková J, Pajer P, Pavlíček A, Hejnar J. CpG methylation suppresses transcriptional activity of human syncytin-1 in non-placental tissues. **Exp Cell Res.** 2006;312:1011-1020.
2. Průková D, Vernerová Z, Pilčík T, Stepanets V, Indrová M, Geryk J, Plachý J, Hejnar J, Svoboda J. Differences in pathogenicity among ALV strains belonging to the same subgroup. **Avian Pathol.** 2007;36:15-27.
3. Kalina J, Šenigl F, Mičáková A, Mucksová J, Blažková J, Poplštein M, Hejnar J, Trefil P. Retrovirus-mediated in vitro gene transfer into chicken male germ line cells. **Reproduction.** 2007;134:445-453.
4. 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 TvbS1 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**; in press.



Comparison of the CpG methylation within syncytin-1 LTR in HeLa (upper part) and BeWo (lower part) cells



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Laboratory of Transplantation Immunology

Transplantation immunity, cytokines, immunoregulation

Research topics

Immunological rejection represents the major obstacle for further development of clinical transplantation. Therefore, the insight into the cellular and molecular mechanisms of immunological reaction and the search for possibilities to manipulate with the immune response are the main tasks of the group.

Using the model of skin grafting in mice we characterized the role of nitric oxide produced by graft-infiltrating macrophages after allo- or xenotransplantation. Recent research is focused on the study of activation and function of regulatory T cells in transplantation immunity and tolerance. Using the model of orthotopic corneal transplantation we have analysed expression of genes for cytokines and other effector molecules during graft rejection and studied possibilities to prevent rejection of corneal grafts.

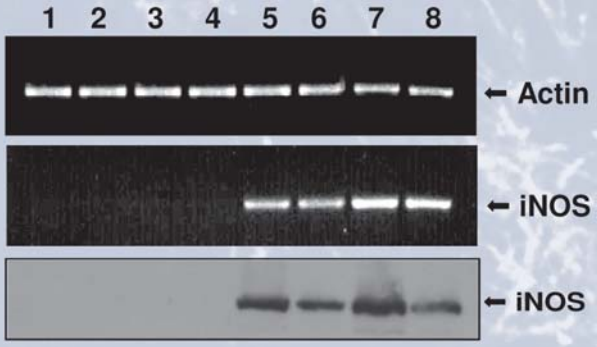
Well-established methods for monitoring the immune response enabled us, in co-operation with other laboratories, to study cytokine response in various experimental models of immunoregulation. The ultimate goal of our research is to get insights into the mechanisms of specific immune response and to propose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

Current grant support

GA CR (309/06/0121, 310/03/H147), IGA Ministry of Health (NR/8340), 6th FP EC (018094), Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology, 1M0506)

Selected recent papers

1. Holáň V, Pindjáková J, Krulová M, Neuwirth A, Zajícová A, Frič J. Production of nitric oxide during graft rejection is regulated by the Th1/Th2 balance, the arginase activity and L-arginine metabolism. **Transplantation.** 2006;81:1708-1715.
2. Holáň V. Corneal stromal cells selectively inhibit the production of certain anti-inflammatory cytokines. **Expert Rev Clin Immunol.** 2006;2:101-108.
3. Havelková H, Holáň V, Kárník I, Lipoldová M. Mouse model for analysis of non-MHC genes influencing allogeneic response: recombinant congeneic strains of OcB/Dem series that carry identical H-2 locus. **Central Eur J Biol.** 2006;1:16-28.
4. Kubera M, Roman A, Basta-Kaim A, Budziszewska B, Zajicova A, Holan V, Rogoz Z, Skuza G, Leskiewicz M, Regulska M, Jogla G, Nowak G, Lason W. Effect of acute and repeated treatment with mirtazapine on the immunity of noradrenaline transporter knockout C57BL/6J mice. **Pharmacol Biochem Behaviour.** 2006:85,813-819.
5. 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.



Expression of gene for iNOS and production of iNOS protein in normal mouse skin (1,2), syngeneic skin graft (3,4), rejected allograft (5,6) and rejected xenograft (7,8).

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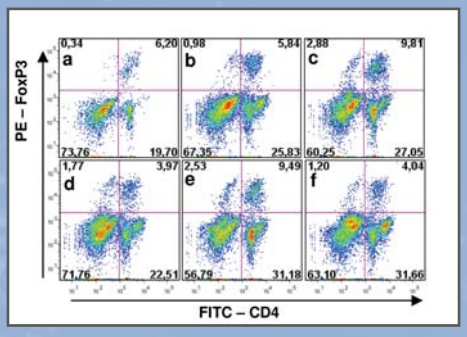
Orthotopic corneal transplantation in mice. A – healthy mouse eye, B – surviving corneal allografts, C – rejected corneal allografts.



Flow cytometry analysis of mouse spleen cells expressing Foxp3, a marker of regulatory T cells.

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Laboratory of Transcriptional Regulation

Eye development and evolution, Pax genes

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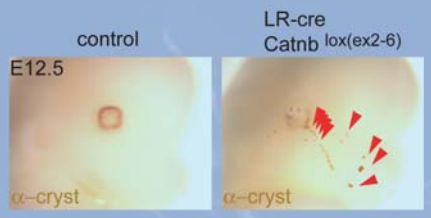
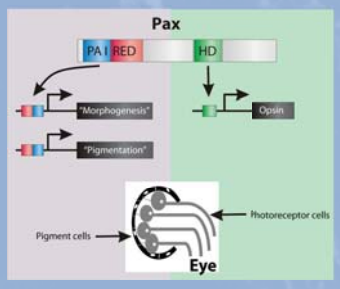
Daniela Gurská / Diploma Student



Ectopic lens formation in the absence of β-catenin gene function (Kreslova et al., 2007)



The´Paxcentric´ (bipartite, PD-HD) model proposes an evolutionarily conserved function for paired domain in pigmentation (and morphogenesis) and for homeodomain in opsin gene regulation, respectively. The fascinating feature of the proposed model is that the morphological unity found in the eye, a photoreceptor linked to the shading pigment, is mirrored at the molecular level, by uniting two independent DNA-binding domains in one regulatory protein: Pax.

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 are used.

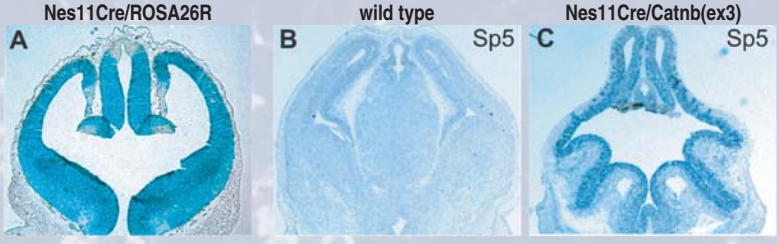
Our second main interest is eye evolution. Several model systems including mouse, amphioxus, scallop, medaka and jellyfish are used in the laboratory. Early morphological studies have suggested that eye has evolved multiple times during the course of evolution. In contrast, more recent genetic data indicate a central role of Pax6 in eye development in most animals. We have recently proposed a model that two independent DNA-binding domains within a single Pax transcription factor have been co-opted for two essential features of the proto-eye: production of a dark pigment and production of a photopigment. Experiments are under way to test this bipartite model. In addition, we are looking at the role of other genes acting dowstream of *Pax* in the regulatory cascade (e.g. *Six, Eya* or *Dach* genes), which are highly evolutionarily conserved.

Current grant support

AS CR (AV0Z50520514), Ministry of Education, Youths and Sports (Center for Applied Genomics 1M0520), GA AS CR (IAA500520604)

Selected recent papers

1. Kozmik Z, Holland ND, Kreslova J, Oliveri D, Schubert M, Jonasova K, Holland LZ, Pestarino M, Benes V, Candiani S. Pax-Six-Eya-Dach network during amphioxus development: conservation in vitro but context specificity in vivo. **Dev Biol.** 2007;306:143-59.
2. Kreslova J, Machon O, Ruzickova J, Lachova J, Wawrousek EF, Kemler R, Krauss S, Piatigorsky J, Kozmik Z. Abnormal lens morphogenesis and ectopic lens formation in the absence of beta-catenin function. **Genesis.** 2007;45:157-68.
3. Fujimura N, Vacik T, Machon O, Vlcek C, Scalabrin S, Speth M, Diep D, Krauss S, Kozmik Z. Wnt-mediated down-regulation of Sp1 target genes by a transcriptional repressor Sp5. **J Biol Chem.** 2007;282:1225-37.
4. Jonášova K, Kozmik Z. Eye evolution: lens and cornea as an upgrade of animal visual system. **Semin Cell Dev Biol;** Epub Oct 13,2007.
5. 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;311:223-37.



Sp5 gene is activated by canonical Wnt/β-catenin signalling (Fujimura et al., 2007).

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Laboratory of Molecular and Cellular Immunology

Functional gene mapping, leishmaniasis, atopy

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).

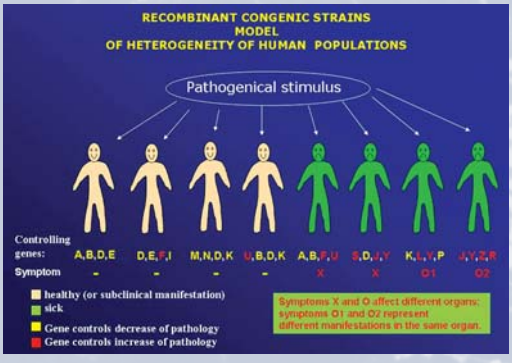
Interestingly, six of nine *Lmr* that influence serum IgE level after *Leishmania major* infection were mapped in the regions homologous with the human chromosomal segments that control total serum IgE in human atopic diseases. Genetic analysis in the mouse can therefore help identify in these regions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

Current grant support

GA CR (310/06/1745, 310/03/H147), 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, Russia. **J Allergy Clin Immunol**; in press.



Genotype influences on manifestations of infectious diseases

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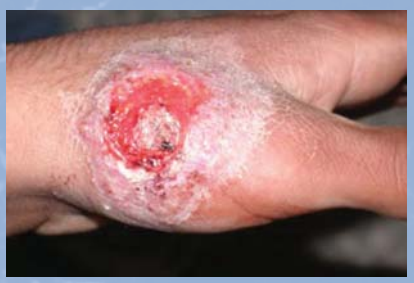
Mitotic Leishmania major, red - tubulin, green - vimentin
Photo: E. Dráberová



Cutaneous leishmaniasis
Photo: Y. Sohrabi

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Laboratory of Tumour Immunology

Anti-tumour immunotherapy, immunoediting, immunoepigenetics

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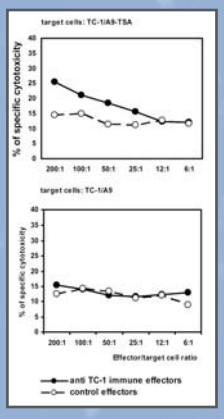


Cytotoxic T lymphocyte-mediated lysis of TC-1/A9 cells after induction of MHC class I surface expression by Trichostatin A.
Spleen cells from mice immunized with irradiated MHC class I-positive TC-1 cells were used in a chromium release microcytotoxicity assay. The targets were TC-1/A9 Tricostatin A (TSA)-treated and untreated TC-1/A9 cells. Control effector cells were spleen cells from non-immune animals. Only TSA-treated TC-1/A9 target cells were significantly lysed with spleen cells from the immune mice. The critical role of cytotoxic T lymphocytes was determined by experiment in which depletion of $CD8^+$ effector cells with a specific antibody blocked the cytotoxic effects.

Research topics

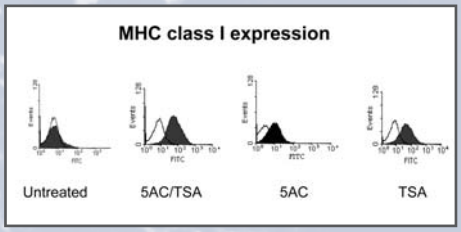
The long-term research programme of the Laboratory is focused on the mechanisms involved in induction and regulation of the anti-tumour immunity. The murine model for tumours associated with human papilloma virus (aetiologic agent of the cervix carcinoma) has been employed in most of our studies. This model has been used for analysis of the missing signals important for effective immune responses and their delivery in the optimal form in order to induce or restore effective anti-tumour responses. 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 immunosupression 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 induced expression of genes involved in antigen processing machinery and surface expression of MHC class I molecules on the tumour cells, which consequently became susceptible to the lysis by cytotoxic T lymphocytes.

Current grant support

GA CR (310/05/H533, 301/06/077, 301/07/1410); GA AS CR (IAA500520605); League against Cancer, Prague; the European Clinical Gene Transfer Advisory Network (Clinigene, EC-NoE, FP6+7)

Selected recent papers

1. Indrova M, Bieblova J, Jandlova T, Vonka V, Pajtasz-Piasecka E, Reinis M. Chemotherapy, IL-12 gene therapy and combined adjuvant therapy of HPV 16-associated MHC class I-proficient and -deficient tumours. **Int J Oncol.** 2006;28:253-9
2. Reinis M, Simova J, Bubenik J. Inhibitory effects of unmethylated CpG oligodeoxynucleotides on MHC class I-deficient and -proficient HPV16-associated tumours. **Int J Cancer.** 2006; 118:1836-42
3. 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;30:1247-51
4. 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;30:1011-7
5. 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.** Epub Aug 28,2007.



MHC class I expression on MHC class I-deficient TC-1/A9 cells was induced after 5-azacytidine (5-azaC) and Trichostatin A (TSA) treatments, as determined by flow cytometry

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Laboratory of Genomics and Bioinformatics

Genomics, transcriptome analysis, expression profiling

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.

The genome project of *Rhodobacter capsulatus* has been completed. The tools of bioinformatics were developed in order to analyse nucleotide sequences generated in the lab as well as those available in the international databases.

We now begin to characterize genomes and genes of at least three different cnidarian species, hydrozoan *Cracpedacusta sowerbyi*, cubozoan *Tripedalia cystophora* and anthozoan *Aitplasia pulchella*. To understand the evolution of higher metazoan genomes and the developmental processes that they regulate, it is necessary to make comparisons with an appropriate outgroup. 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. Cnidarian genomes are a potential key to understanding many aspects of animal evolution.

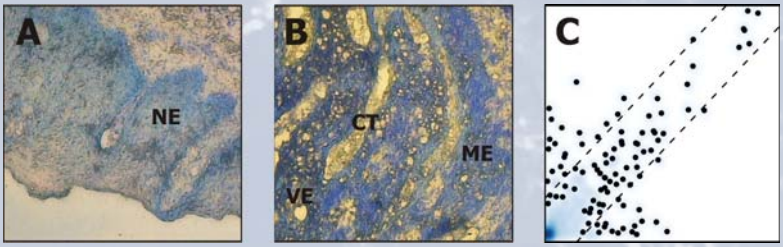
A second major project of our group is directed towards identification of specific markers in cancer tissue with potential applications in medical diagnosis. We use Illumina microarray chip analysis for detection of appropriate gene sets.

Current grant support

Ministry of Education, Youth and Sports (Center for Applied Genomics, 1M0520; NPV II, project No.: 1M0520)

Selected recent papers

1. Bukovská G, Klučar L, Vlček Č, Adamovič J, Turňa J, Timko J. Complete nucleotide sequence and genome analysis of bacteriophage BFK20 - A lytic phage of the industrial producer Brevibacterium flavum. **Virology.** 2006;348:57-71.
2. Pavlíček A, Gentles, AJ, Pačes J, Pačes V, Jurka, J. Retroposition of processed pseudogenes: the impact of RNA stability and translational control. **Trends Genet.** 2006;22:69-73.
3. Drábková L, Vlček Č. The phylogenetic position of Oxychloe (Juncaceae): evidence from morphology, nuclear and plastid DNA regions. **Taxon.** 2007;56:95-102.
4. Fujimura N, Vacík T, Machoň O, Vlček Č, Scalabrin S, Speth M, Diep D, Krauss S, Kozmik Z. Wnt-mediated down-regulation of Sp1 target genes by a transcriptional repressor Sp5. **J Biol Chem.** 2007;282:1225-1237.



Oral cancer (B) is believed to have developed through a progression of pre-malignant histopathological changes in normal epithelium (A, NE). Like other cancers, oral cancers have heterogeneous cell population in addition to the malignant epithelium (ME): connective tissue / fibroblasts (CT) and vascular epithelium (VE). Comparison of transcription profiles (C) can help find genes that are specific for cancer progression.

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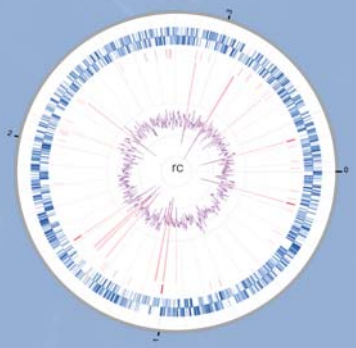
Zdeněk Krejčík, MSc / PhD Student
Radek Zíka, MSc / PhD Student
Miluše Hroudová, MSc / PhD Student
Daniel Panchártek / Diploma Student



Rhodobacter chromosome: [a] blue and gray: predicted genes in forward and reverse orientation [b] red: t-rna, [c] violet: gc content (window 5kb); [d] light red: highlits denote gc < 50%

Hydrozoan medusa Craspedacusta sowerbyi is a genomic model important for the study of metazoan

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Laboratory of Structural Biology

Protein crystallography, HIV protease, antibody engineering

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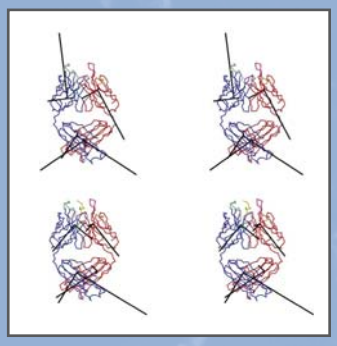


Global stabilization of the complex structure: changes in principal axes of the libration tensors for Fab M75 domains (VH, VL, CH, and CL) superimposed to stereo views of the crystal structures. Shown are Cα traces of the free Fab (upper block) and of the complex (lower block). The heavy chain is coloured mainly blue, the light chain mainly red, the epitope peptide yellow, the libration axes black.

Research topics

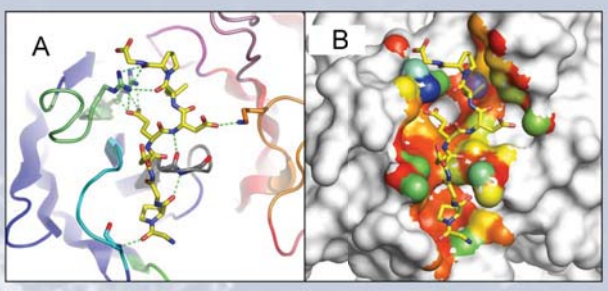
The Laboratory carries out structural work with various proteins and their complexes of biological or medicinal interest. Among them, HIV protease, antibodies and galectins take a prominent position. The HIV protease (HIV PR) research is focused onto the structural basis of drug resistance acquired by 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. Also carried out is protein engineering work with therapeutic antibodies aimed 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 EU (037693); Ministry of Industry and Commerce (2A-2TP1/076); GA CR (301/07/0600)

Selected recent papers

1. Cígler P, Kožíšek M, Řezáčová P, Brynda J, Otwinowski Z, Pokorná J, Plešek J, Grüner B, Dolečková-Marešová L, Máša M, Sedláček J, Bodem J, Kraeusslich H-G, Král V, Konvalinka J. From non-peptide towards non-carbon protease inhibitors: metallacarboranes as specific and potent inhibitors of HIV protease. **Proc Natl Acad Sci USA.** 2005;102:15394-9.
2. Dušková J, Dohnálek J, Skálová T, Petroková H, Vondráčková E, Hradílek M, Konvalinka J, Souček M, Brynda J, Fábry M, Sedláček J, Hašek J. On the role of the R configuration of the reaction-intermediates isostere in HIV-1 protease-inhibitor binding: X-ray structure at 2.0 A resolution. **Acta Crystallogr D Biol Crystallogr.** 2006;62(Pt 5):489-497.
3. Ondráček J, Mesters JR. An ensemble of crystallographic models enables the description of novel bromate-oxonian species trapped within a protein crystal. **Acta Crystallogr D Biol Crystallogr.** 2006;69 (Pt 9):996-1001.
4. Carey J, Brynda J, Wolfova J, Grandori R, Gustavsson T, Ettrich R, Smatanova IK. WrbA bridges bacterial flavodoxins and eukaryotic NAD(P)H:quinone oxidoreductases. **Protein Sci.** 2007;10:2301-5.
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.** Epub Nov 27,2007.



Structure of the antibody M75 combining site; the carbonic anhydrase IX epitope peptide, PGEEDLPGEEDL, is shown with the sticks model coloured yellow. Panel A: Hydrogen bonds formed between the antibody and the epitope peptide. Respective CDR loops are coloured blue/green for the heavy chain and magenta/mauve for the light chain. Panel B: Areas of protein surface at van der Waals radii buried upon the peptide binding; rainbow colouring from yellow (0<Å²) to blue (40 Å²); white (0 Å²).

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Laboratory of Molecular Pharmacology

G-protein coupled receptors, neurotransmitters, allosteric modulators

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.

Current grant support

AS CR (1M0505); Ministry of Education, Youth and Sports (LC06063 „FLUMBIOL", EUREKA project „BRAINSTAIN"); GA CR (204/05/0920); FP6 RTD EC („SYNSCAFF"), GA AS CR (IAA400400621, IAA500390701)

Selected recent papers

1. Hlavackova V, Kniazeff J, Goudet C, Zikova A, Maurel D, Vol C, Trojanova J, Prézeau L, Pin J-P, Blahos J. Evidence for a single heptahelical domain being turned on upon activation of a dimeric GPCR. **EMBO J.** 2005;24,499–509.
2. Goudet C, Kniazeff J, Hlavackova V, Malhaire F, Maurel D, Acher F, Blahos J, Prezeau L, Pin J-P. Asymmetric functioning of dimeric metabotropic glutamate receptors disclosed by positive allosteric modulators. **J Biol Chem.** 2005;280:24380-5.
3. Sinagra M, Verrier D, Frankova D, Korwek KM, Blahos J, Weeber EJ, Manzoni O, Chavis P. Reelin. Very-low-density lipoprotein receptor, and apolipoprotein E receptor 2 control somatic NMDA receptor composition during hippocampal maturation *in vitro*. **J Neurosci.** 2005;25:6127-36.
4. Brock C., Boudier L, Maurel D, Blahos J, Pin J-P. Assembly-dependent surface targeting of the heterodimeric GABAB receptor is controlled by COPI, but not 14-3-3. **Mol Biol Cell.** 2005;16:5572–5578.
5. 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;99:288-98.

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Zdeňka Syrová PhD / Research Scientist
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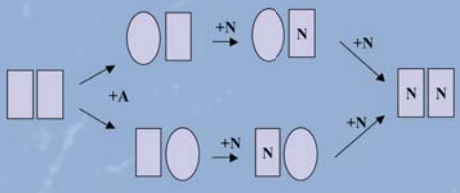
In dimeric Metabotropic Glutamate receptor, upon competitive agonist binding only one of two identical subunits reaches activated state. Thus, modulation of a single heptahelical domain by allosteric enhancer is sufficient to exert full effect. Accordingly, both heptahelical domains have to be blocked by a negative allosteric modulator.



Heptahelical domain (HD) activation of mGlu receptor, schematically. Upon activation of the receptor by an agonist (A) either heptahelical domain can reach the active state (square=inactive state, oval=active HD conformation). Interaction of the negative allosteric modulator (N) with a single HD results in no apparent change in the receptor activity, as the adjacent subunit is still capable to activate G-proteins. The inhibitory effect of such compound is reached only when both HDs are occupied. The conformational changes of the HDs and association of the adjacent G-proteins upon various pharmacological treatments are currently studied using the FRET (Forster's Resonance Energy Transfer) approach.

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Laboratory of Biology of the Cell Nucleus

Regulation of gene transcription, nucleoskeleton, nuclear actin, myosin

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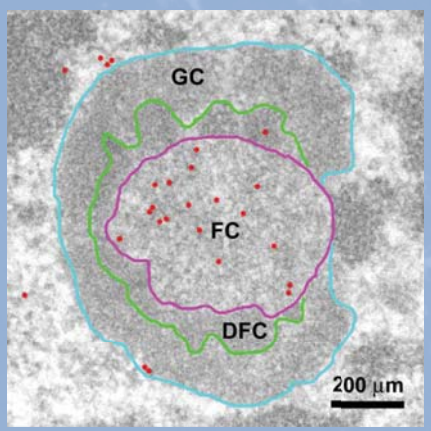
Anatolij Philimonenko, MSc / PhD Student
Miloslava Maninová, MSc / PhD Student
Sukriya Yildirim, MSc / PhD Student
Jakub Kukla / Diploma Student
Tomáš Chum / Diploma Student
Lenka Pišlová / Secretary



Ultrastructural detection of actin molecules (red dots) in the nucleolus of resting human lymphocyte

Research topics

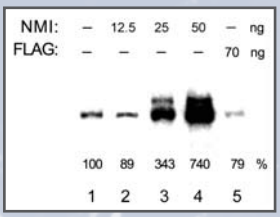
In diploid mammalian cells, some $6x10^9$ base pairs of DNA fold as a nucleoprotein complex (i.e. chromatin) into higher-order arrays so as to fit in a nucleus measuring only 10 µm. The nucleus also contains machineries for transcription of genes and processing of RNA products, and for precise DNA replication, 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

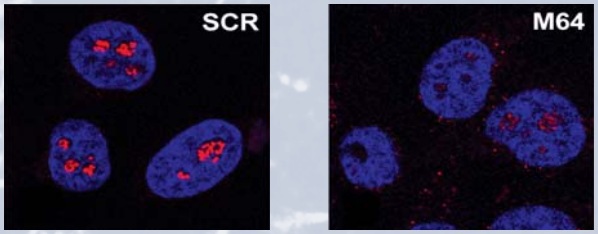
GA AS CR (IAA500390501); AS CR (KAN200520704); GA CR (204/07/1592, 204/05/H023); ESF/GA CR (DYN/04/E002); Ministry of Education, Youth and Sports (LC 545; LC06063; 2B06063)

Selected recent papers

1. Philimonenko AA, Hodny Z, Jackson DA, Hozak P. The microarchitecture of DNA replication domains. **Histochem Cell Biol.** 2006;125:103-17.
2. Janderova-Rossmeislova L, Novakova Z, Vlasakova J, Philimonenko V, Hozak P, Hodny Z. PML protein association with specific nucleolar structures differs in normal, tumor and senescent human cells. **J Struct Biol.** 2007;159:56-70.
3. Vlasakova J, Novakova Z, Rossmeislova L, Kahle M, Hozak P, Hodny Z. Histone deacetylase inhibitors suppress IFNalpha-induced up-regulation of promyelocytic leukemia protein. **Blood.** 2007;109:1373-80.
4. Kahle M, Pridalova J, Spacek M, Dzijak R, Hozak P. Nuclear myosin is ubiquitously expressed and evolutionary conserved In vertebrates. **Histochem Cell Biol.** 2007;127:139-48.



Addition of nuclear myosin I accelerates transcription of ribosomal genes in vitro (Northern blot, visualization of rRNA transcripts)



Depletion of NMI by siRNAs reduces rDNA transcription (red – transcripts, blue – DNA)

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Laboratory of Immunobiology

Innate immune receptors, TCR signalling, Fyn, Lck

Research topics

The main research interest of our recently established group is focused on two independent topics:

- Molecular and functional characterization of innate immune receptors (IIRs) and signalling molecules involved in the processes of sterile inflammation, developmental tissue remodelling and chronic inflammatory diseases. Our main effort is focused on Toll-like receptors (Fig. 1) and the identification of their putative endogenous, self-derived ligands. Data accumulated in this study point to spatially and temporarily regulated expression of IIRs in early stages of mammalian embryogenesis (Fig. 2) and suggest their role in the process of embryonic homeostasis.

- Characterization of molecular mechanisms underpinning temporal and spatial coordination of two Src-family tyrosine kinases, Lck and Fyn, during the initiation of membrane proximal T-cell signalling (Fig. 3 and 4). Previous data provided a basis for formulation of the Lck-dependent Fyn activation model featuring the translocation of activated Lck into lipid rafts and subsequent activation of lipid rafts-resident Fyn. Our recent structure-function analysis identified *cis*-acting structural elements of Lck critical for partitioning to LR and transphosphorylation of Fyn kinase domain when co-localized in LR.

Current grant support

GA AS CR (IAA500520707)

Selected recent papers

So far no papers (a newly formed group)

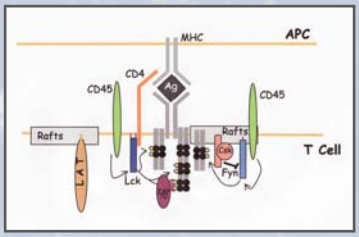

Fig. 3. A hypothetical scheme of functional interrelation of Lck and Fyn kinases during the process of TcR/CD4-induced proximal signalling

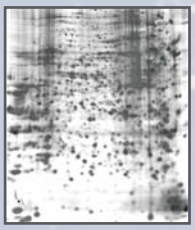

Fig. 4. 2-D gel electrophoresis approach allows us to identify putative targets of Src-family tyrosine kinase Lck which could play an essential role in an active process of Lck translocation to lipid rafts.

Dominik Filipp, PhD / Head of Laboratory
Jana Jelínková, PhD / Research Scientist
Aleš Neuwirth, MSc / Research Assistant
Anežka Fišerová, MD / Research Assistant
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Tereza Vavrochová / Diploma Student

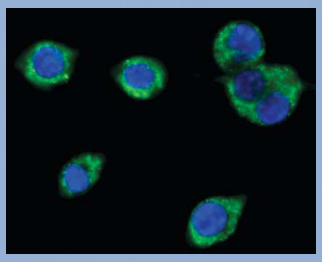
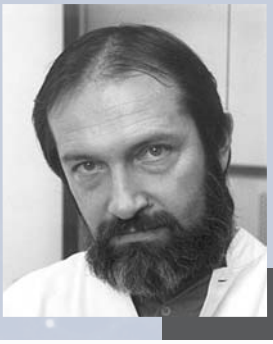


Fig. 1. Fluorescent microscopy of innate immune cells stained with DAPI (blue, nuclei) and Alexa 488-conjugated antibody specific for Toll-like receptor 4 (green)

Fig. 2. Wholemount in situ hybridization of 8.5-day-old mouse embryo with an antisense probe specific for TLR4 revealing the expression in embryonal head structures



Jiří Bartek

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Laboratory of Genome Integrity

DNA damage response, cell cycle, oncogenic transformation

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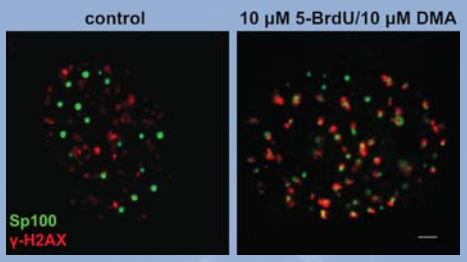
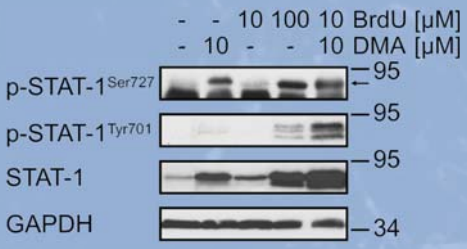


Foci of DNA damage (γ-H2AX) colocalize with PML nuclear bodies (Sp100) in prematurely senescent cells



Activated markers of JAK/STAT signalling pathway in HeLa cells forced to premature senescence by 5-bromodeoxyuridine and/or distamycin A

Research topics

The newly established group will be centered on the mechanisms of maintenance of genomic integrity, which is a fundamental biological mechanism that guards against genetic diseases including cancer. Orchestration of DNA damage signalling with cell cycle checkpoints, DNA repair, chromatin modulation and cell death pathways relies on regulatory protein post-translational modifications. The key role of protein phosphorylation in DNA damage response (DDR) is well established, however, the significance of ubiquitylation, sumoylation and neddylation is only emerging. We will focus on human genes involved in regulatory ubiquitylation, sumoylation and neddylation within the DDR machinery. We will study the molecular basis and biological role of such protein modifications in DNA damage signalling and cell fate decisions including cell cycle arrest, DNA repair and cell survival.

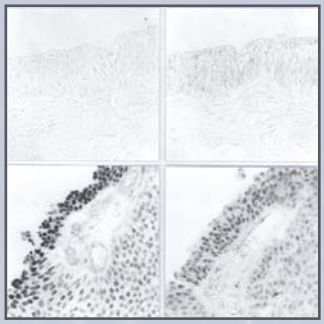
The second aim of our work will be focused on the mechanisms of cellular senescence, the regulatory pathways involved in specific secretion phenotype of senescent cells and pathophysiological role of senescent cells in tumour and ageing tissues. We will be addressing specific functions of PML and PML nuclear bodies in development of senescent phenotype, the role of interferons in transcription regulation of *PML* gene and other interferon-stimulated genes in senescent cells.

Current grant support

GA AS CR (IAA50039050), GA CR (204/08/1418, 301/08/0353).

Selected recent papers

So far no papers (a newly formed group)



Immunohistochemical section of normal bladder mucosa (top row) and early bladder cancerous lesion (Ta stadium; bottom row) stained by activated form of Chk2 kinase (left) and heterochromatin marker HP1γ (right).

Nucleoli-associated PML nuclear bodies are characteristic for replicatively senescent untransformed cells and can be induced in prematurely senescent tumour cell lines by 5-bromodeoxyuridine and distamycin A.

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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 are molecular mechanisms of Wnt signalling in mammalian cells and signalling pathways influencing behaviour of normal and diseased intestinal epithelial cells.

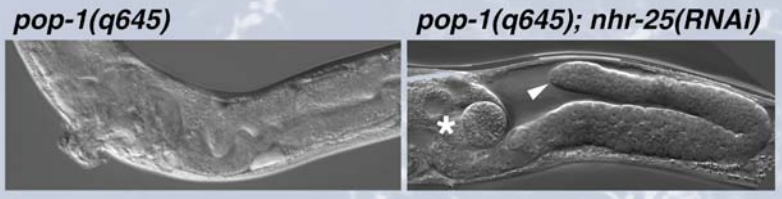
The most important result in the current years was the identification of the HIC1 (Hypermethylated In Cancer 1) tumour suppressor as a novel modulator of the Wnt signalling cascade. The *HIC1* gene is frequently epigenetically silenced or deleted in different types of solid tumours. When expressed, the 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 Program qCHIP/chip06, 2B06077), GA CR (204/06/1658, 204/07/1567)

Selected recent papers

1. Valenta T, Lukas J, Doubravska L, Korinek V. HIC1 attenuates Wnt signaling by recruitmentof 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. Stokrova J, Sloncova E, Sovova V, Zila V, Tureckova J, Vojtechova M, Korb J, Tuhackova Z. Characterization of four clones derived from human adenocarcinoma cell line, HT29, and analysis of their response to sodium butyrate. **Int J Oncol.** 2006;28:559-65.
4. 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;6:2591-9.



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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Lenka Doubravská, MSc / PhD Student
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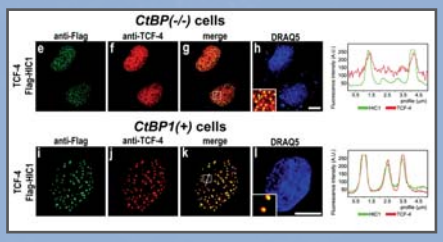
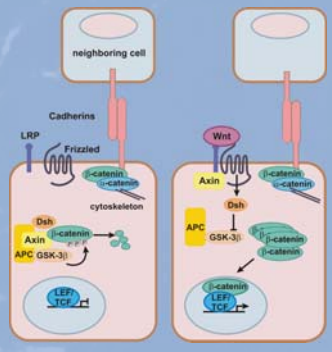
Michaela Krausová, MSc / PhD Student
Vendula Pospíchalová, Bc / Diploma Student
Zuzana Brinská, Bc / Diploma Student



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 RNA biology

pre-mRNA splicing, small nuclear ribonucleoproteins

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Viola Hausnerová / Diploma Student

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 catalyzed 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.

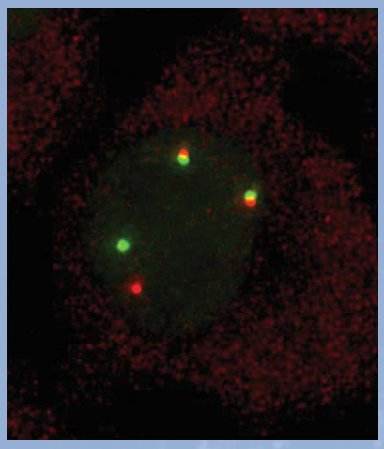
Current grant support

GA CR (301/05/0601, 204/07/0133) MPI-partner group 2006-2008: Pre-mRNA splicing and organization of the cell nucleus

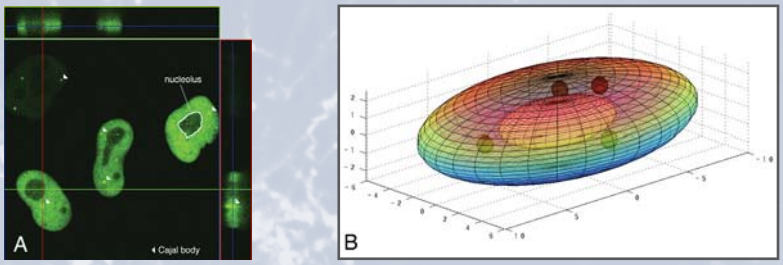
Selected recent papers

A new group, so far no papers from IMG; below papers of D.S. from the previous laboratory are shown:

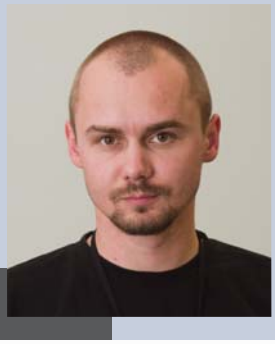
1. Staněk D, Rader SD, Klingauf M, Neugebauer KM. Targeting of U4/U6 small nuclear RNP assembly factor SART3/p110 to Cajal Bodies. **J Cell Biol.** 2003;160:505-516.
2. Staněk D, Neugebauer KM. Detection of snRNP assembly intermediates in Cajal bodies by FRET. **J Cell Biol.** 2004;166:1015-25.
3. Dundr M, Hebert MD., Karpova TS, Staněk D, Xu H, Shpargel KB, Meier TU, Neugebauer KM, Matera AG, Misteli T. In vivo kinetics of Cajal body components. **J Cell Biol.** 2004;164: 831-842.
4. Klingauf M, Staněk D, Neugebauer, KM. Enhancement of U4/U6 snRNP association in Cajal bodies predicted by mathematical modeling. **Mol Biol Cell** 2006;17:4972-81.
5. Staněk D, Neugebauer KM. Cajal bodies: a meeting place for snRNP in the nuclear maze. **Chromosoma** 2006;115:343-54.



Localization of two proteins involved in spliceosome assembly in a human HeLa cell. Green – SART3 distributed throughout the nucleus and concentrated in Cajal bodies; red – SMN localized in nuclear gems and in the cytoplasm.



Modelling of nuclear space. Distribution of a splicing factor in the nucleus of live cells (A) and a derived mathematical model of the nucleus used for mathematical analysis (B).



Petr Svoboda

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Laboratory of Epigenetic Regulations

RNA degradation, dsRNA, mobile DNA

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 a 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.

Current grant support

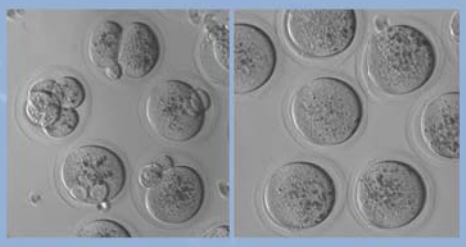
AS CR (Purkynje Fellowship); EMBO Installation Grant, GA AS CR (IAA501110701)

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;34:4801-15.
2. Svoboda P. Off-targeting and other non-specific effects of RNAi experiments in mammalian-cells. **Curr Opin Mol Ther.** 2007;9:248-57.
3. Grosshans H, Svoboda P. miRNA, siRNA, piRNA – Kleine Wiener Ribonukleinsauren. **Bioessays.** 2007; 29:940-3.
4. Svoboda P. RNA silencing in mammalian oocytes and early embryos. **Curr Top Microbiol Immunol**; in press.
5. Sinkkonen L, Hugenschmidt T, Berninger P, Gaidatzis D, Mohn F, Artus-Revel C, Zavolan M, Svoboda P, Filipowicz W. MicroRNAs control de novo DNA methylation in mouse embryonic stem cells. **Nat Struct Mol Biol**; in press.

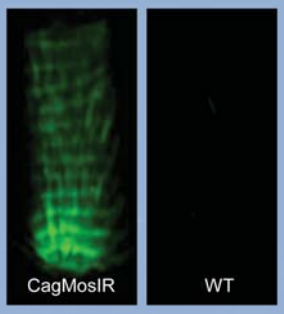
Long dsRNA expression in transgenic mice.
Structure of the CagMosIR transgene used for ubiquitous expression of a long RNA hairpin with the Mos sequence.

Petr Svoboda, PhD / Head of Laboratory
Matyáš Flemr, MSc / PhD Student
Jana Nejepínská, MSc / PhD Student
Lenka Sarnová, MSc / Diploma Student

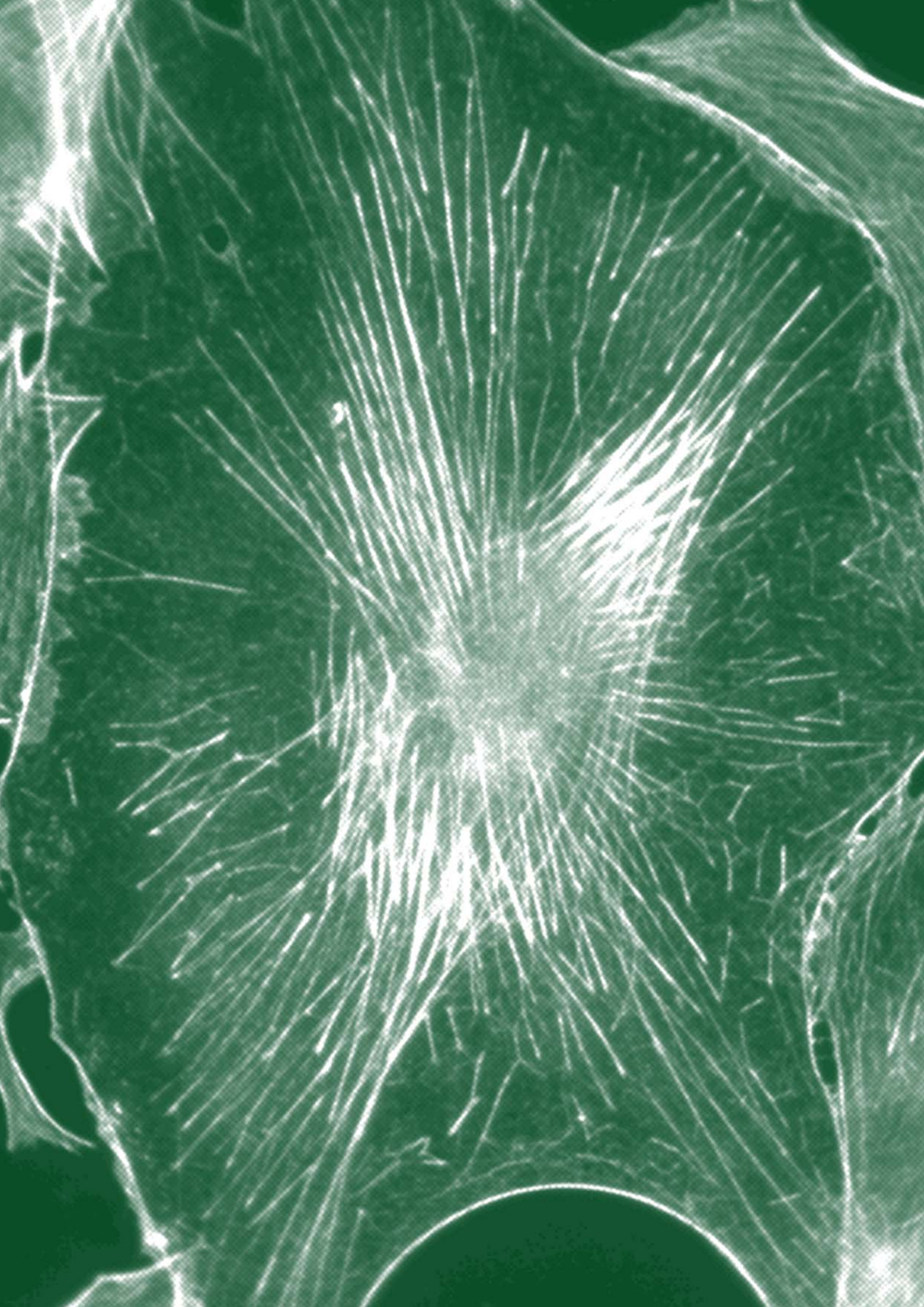


CagMosIR (F1 317.3 #4) **WT** (F1 317.3 #6)

Mos null phenotype (parthenogenetic activation of MII oocytes) in oocytes isolated from transgenic animals carrying the CagMosIR.



EGFP expression in somatic cells of CagMosIR transgenic mice (fluorescence of the tail tip).



Mikael Kubista

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Biotechnology Division
Laboratory of Gene Expression

Research topics

The laboratory develops techniques for and applications of real-time RT-PCR to studies of biological phenomena. Examples include early development of *Xenopus laevis*, formation of teeth, and cell heterogeneity. Among recent accomplishments we determined the temporal expression profiles of 16 developmental genes in 16 stages of *Xenopus laevis* and, in collaboration with Professor S. Bustin's laboratory in London, we developed qPCR tomography to determine expression profiles of biological processes. Another objective of the department is to develop advanced multivariate statistical methods for analysis of spatio-temporal qPCR expression profiles. The work is collaboration with the company MultiD Analyses (www.multid.se). We also support the Prague TATAA Biocenter (www.tataa.com) in their real-time PCR courses with know-how.

Selected recent papers

1. Kubista M, Andrade JM, Bengtsson M, Forootan A, Jonák J, Lind K, Šindelka R, Sjöback R, Sjögreen B, Strömbom L, Ståhlberg A, Zoric N. The real-time polymerase chain reaction. **Mol Asp Med.** 2006;27:95-125.
2. K. Lind, A.Ståhlberg, N. Zoric, M. Kubista. Combining sequence-specific probes and DNA binding dyes in real-time PCR for specific nucleic acid quantification and melting curve analysis. **Biotechniques.** 2006;40:315-18.
3. Kubista M, Sjogreen B, Forootan A, Sindelka R, Jonak J, Andrade JM. Real-time PCR gene expression profiling. **Eur Pharmaceut Rev.** 2007, Vol. 1.
4. R. Sindelka, J. Jonák, R. Hands, S. A. Bustin, M. Kubista, Intracellular expression profiles measured by real-time PCR tomography in the Xenopus laevis oocyte. **Nucleic Acids Res.** Epub Nov 26;2007.

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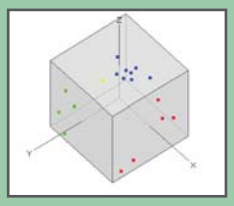
Vlasta Čtrnáctá, PhD / Postdoc
Radek Šindelka, MSc / PhD Student
David Švec, MSc / PhD Student



Multivariate profiling analysis of Xenopus laevis developmental expression profiles reveals that develoment goes through three main phases charcaterized by the expression of different genes.

Petr Bartůněk

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Biotechnology Division
Laboratory of Chemical Genetics

Research topics

This newly formed laboratory is a Screening Unit for the Center for Chemical Genetics (www.chemgen.cz), a consortium of five academic institutions, consisting of 10 integrated teams of biologists and chemists that is funded by the Ministry of Education, Youth and Sports, Czech Republic. The mission of the Center is to identify small molecules that perturb important signalling pathways within the cell and as such influence processes that include cell proliferation, differentiation, and programmed cell death. The laboratory is well equipped to perform high-throughput screening (HTS) using cell-based assays.

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Michael-Robin Witt, PhD / Sr Research Scientist
Eva Bartoňová, MSc / Research Assistant
Antonio Pombinho, MSc / Research Assistant
David Sedlák, MSc / PhD Student

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Biotechnology Division
Laboratory of Molecular Therapy

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Jana Novotná, PhD / Research Scientist
Jakub Rohlena, PhD / Research Scientist
Karel Vališ, MSc / Research Scientist
Jaromíra Chladová, MSc / PhD Student
Renata Zobalová, MSc / PhD Student
Katarina Kľučková, MSc / PhD Student
Zuzana Bancíková, MSc / PhD Student
Ľubica Škultétyová, MSc / PhD Student

Research topics

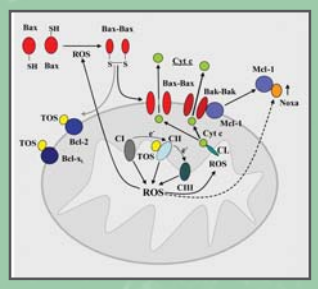
The laboratory deals with the design and development of anti-cancer drugs from the newly defined group of mitocans, small molecules that induce apoptosis by way of mitochondrial destabilization. We are in particular interested in pro-apoptotic analogues of vitamin E (VE), such as α-tocopheryl succinate (α-TOS) that act by interfering with the mitochondrial redox chain. Recently, our focus has shifted to the biology and therapy of cancer stem cells. We are interested in identifying the molecular mechanism of action of VE analogues, in particular how they induce apoptosis and inhibit angiogenesis. Our goal is to develop an efficient and selective anti-cancer drug based on VES. At present, in collaboration with Griffith University in Australia, we are starting phase I/II clinical trials with the currently non-treatable mesothelioma patients, with positive results (tumour reduction) in one experimental patient.

Current grant support

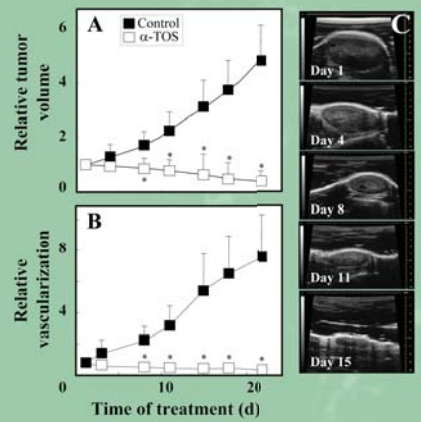
GA CR (305/07/1008), GA AS CR (IAA500520702, IAA500520602), AS CR (Programme Nanotechnology for Society KAN200520703)

Selected recent papers

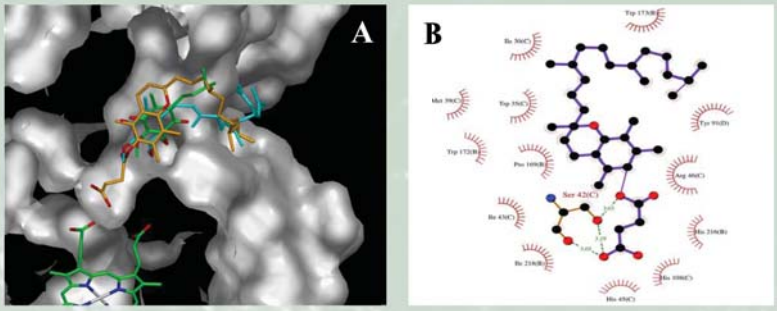
1. Stapelberg M, Gellert N, Swettenham E, Tomasetti M, Witting PK, Procopio A, Neuzil J. α-Tocopheryl succinate inhibits malignant mesothelioma by disrupting the FGF autocrine loop: The role of oxidative stress. **J Biol Chem.** 2005;280:25369-25376.
2. Wang XF, Birringer M, Dong LF. Veprek P, Low P, Swettenham E, Stantic M, Yuan LH, Zobalova R, Wu K, Ralph SJ, Ledvina M, Neuzil J. A peptide adduct of vitamin E succinate targets breast cancer cells with high erbB2 expression. **Cancer Res.** 2007;67:3337-3344.
3. Neuzil J, Dyason JC, Freeman R, Dong LF, Prochazka L, Wang XF, Scheffler I, Ralph SJ. Mitocans as anti-cancer agents targeting mitochondria: Lessons from studies with vitamin E analogues, inhibitors of complex II. **J Bioenerg Biomembr**. 2007;39:65-72.
4. Neuzil J, Stantic M, Zobalova R. Chladova J, Wang X, Prochazka L, Dong L, Andera L, Ralph SJ. Tumour-initiating cells vs. cancer 'stem' cells and CD133: What's in the name? **Biochem Biophys Res Commun.** 2007;355:855-859.



Model of apoptosis induction by α-TOS, resulting in generation of reactive oxygen species (ROS) and mitochondrial destabilization.



Effect of α-TOS on tumour growth (A) and angiogenesis (B) in FVB/N c-neu transgenic mice with spontaneous formation of HER2-high breast carcinomas. Panel C - temporal change in breast carcinoma in a representative animal.



Model of interaction of α-TOS with the proximal coenzyme Q (ubiquinone, CoQ) binding site in the mitochondrial complex II (succinate dehydrogenase)

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Biotechnology Division

Laboratory of Diagnostics for Reproductive Medicine

Sperm and seminal plasma proteins, detection of sperm quality

Research topics

The long-term research programme of the laboratory (formerly Laboratory of Biology and Biochemistry of Fertilization) concentrates on studying the molecular mechanism of fertilization, especially in connection with the male reproductive tract and spermatozoa. The recent results include characterization of several novel sperm and seminal plasma proteins. Newly developed monoclonal antibodies were used for differential diagnostics of sperm pathology and for selection of useful methods of assisted reproduction in human and veterinary medicine.

Current grant support

GA CR (303/04/P070, 204/05/HO23, 303/05/0614, 303/06/0895, 305/06/0427, 524/06/0817); IGA Ministry of Health (NR/7838-3, NR/8932-3), Ministry of Education, Youth and Sports (Center of Molecular Methods for Monitoring the Diffuse Pollution of the Environment (1M06011); NPVII: (Project 2B06151), international collaboration project EUREKA No OE211 EKDEQ)

Selected recent papers

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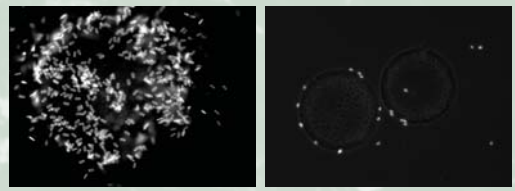
2. Jonáková V, Maňásková P. Tichá M. Separation, characterization and identification of boar seminal plasma proteins. **J Chromatogr B**. 2007;849:307-314.
3. Maňásková P, Pěknicová J, Elzeinová F, Tichá M, Jonáková V. Origin, localization and binding abilities of boar DQH sperm surface protein tested by specific monoclonal antibodies. **J Reprod Immunol.** 2007;74:103-113.
4. Čapková J, Elzeinová F, Novák P. Increased expression of secretory actin-binding protein (SABP) on human spermatozoa is associated with poor semen quality. **Hum Reprod.** 2007;22:1396-1404.
5. Peknicova J, Pexidrova M, Kubatova A, Koubek P, Tepla O, Sulimenko T, Draber P. Expression of β-tubulin epitope in human sperm with pathological spermiogram. **Fertil Steril.** 2007;88:1120-28.



Sperm surface protein *(DQH) (Immunofluorescence with monoclonal antibodies)*

Sperm-egg binding. *Hoechst staining of control spermatozoa (A) and sperm treated with antibody against sperm surface protein (DQH) (B) to zona pellucida of oocyte. Reduced sperm binding (B).*

Jana Pěknicová, PhD / Head of Laboratory
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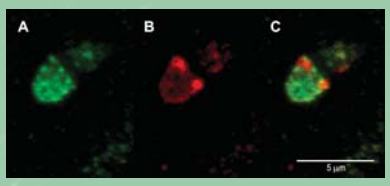
Jana Čapková, PhD / Research Scientist
Pavla Maňásková, PhD / Research Scientist
Pavel Koubek, MSc / PhD Student
Alena Králová, MSc / PhD Student
Eva Cibulková, MSc / PhD Student
Andriy Dorosh, MSc / PhD Student
Fatima Elzeinová, MSc / Research Assistant
Hasmik Margaryan, MSc / Research Assistant
Alena Kubátová, MSc / Research Assistant
Lukáš Děd, MSc / Research Assistant
Helena Líbalová / Diploma Student
Petr Páral / Diploma Student
Nina Davidová / Diploma Student
Věra Doušová /Technician
Jitka Jelínková / Technician



Double staining of acrosomal and cytoskeletal proteins in the human sperm head. *Immunofluorescence with monoclonal antibodies Hs-14 against acrosome proteins (green) – **(A)**, TU-12 against β-tubulin (red) – **(B)** and co-localization with both antibodies **(C)**.*

Šárka Růžičková

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Biotechnology Division
Laboratory of Diagnostics of Autoimmune Diseases

Šárka Růžičková, RNDr / Head of Laboratory
Irena Veselá / Technician
Alena Halouzková / Technician
Martina Bajziková / Diploma Student
Lucie Nováková / Diploma Student

Research topics

The research of this newly established laboratory is focused on: (1) humoral and genetic aspects of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematodes and myositis; (2) identification of target molecules for therapy of these diseases; (3) development and design of new diagnostics for autoimmune diseases. Single-cell RT-PCR is used as a unique technique in our research.

Current grant support

GA CR (310/06/0477), IGA Ministry of Health (NR 9106-3)

Peter Šebo

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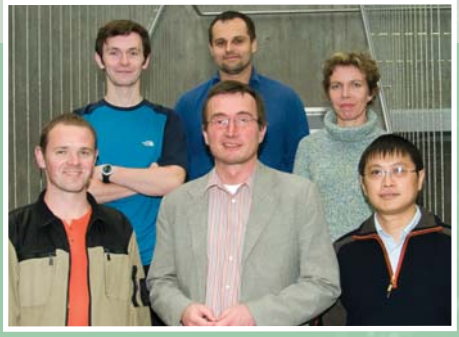
Biotechnology Division
Laboratory of Recombinant Ligand Engineering



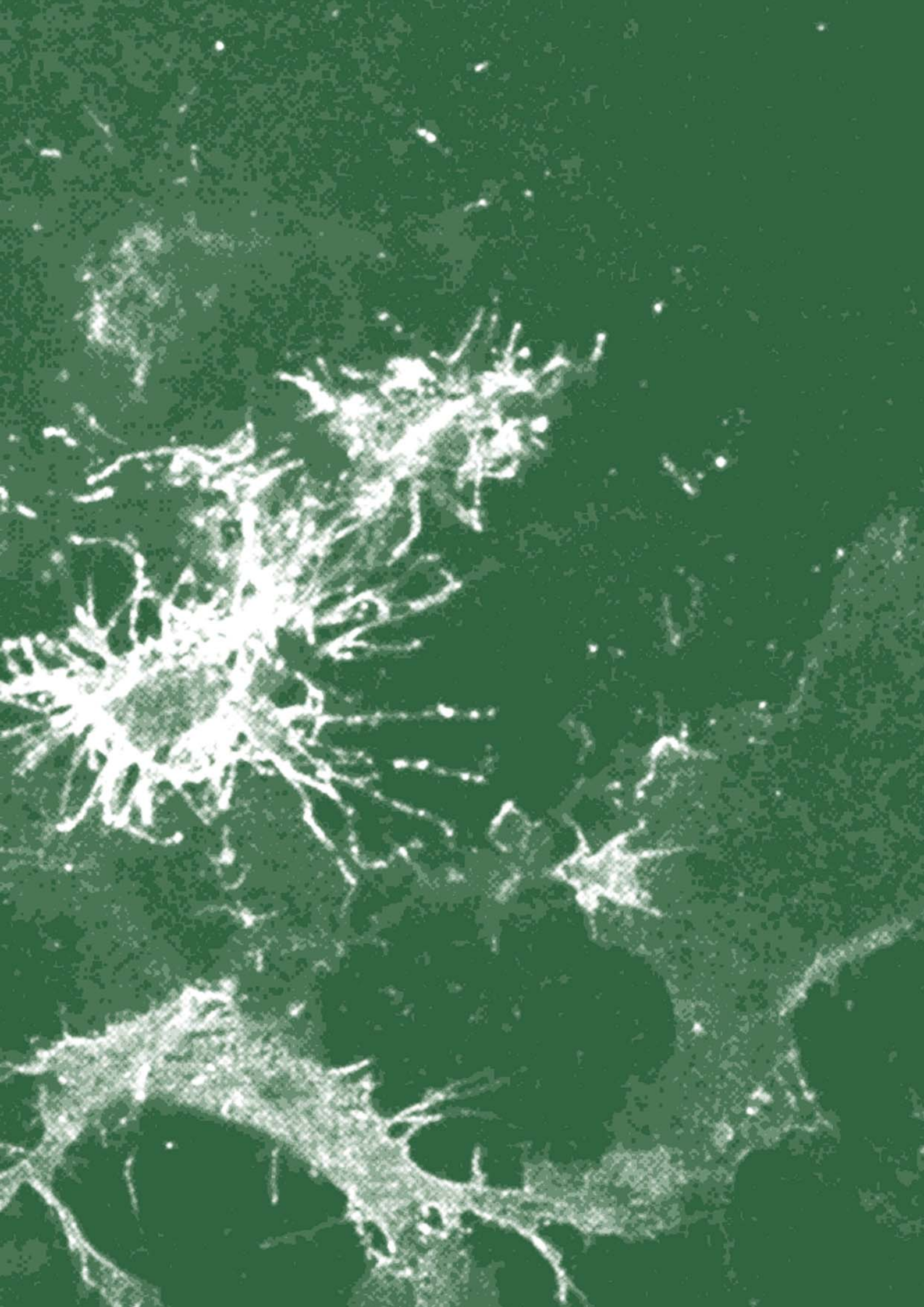
Peter Šebo, PhD / Head of Laboratory
Jingjing Li, PhD / Postdoc
Milan Kuchař, PhD / Postdoc
Hana Petroková, PhD / Postdoc
Petr Jeřábek, MSc / PhD Studentt

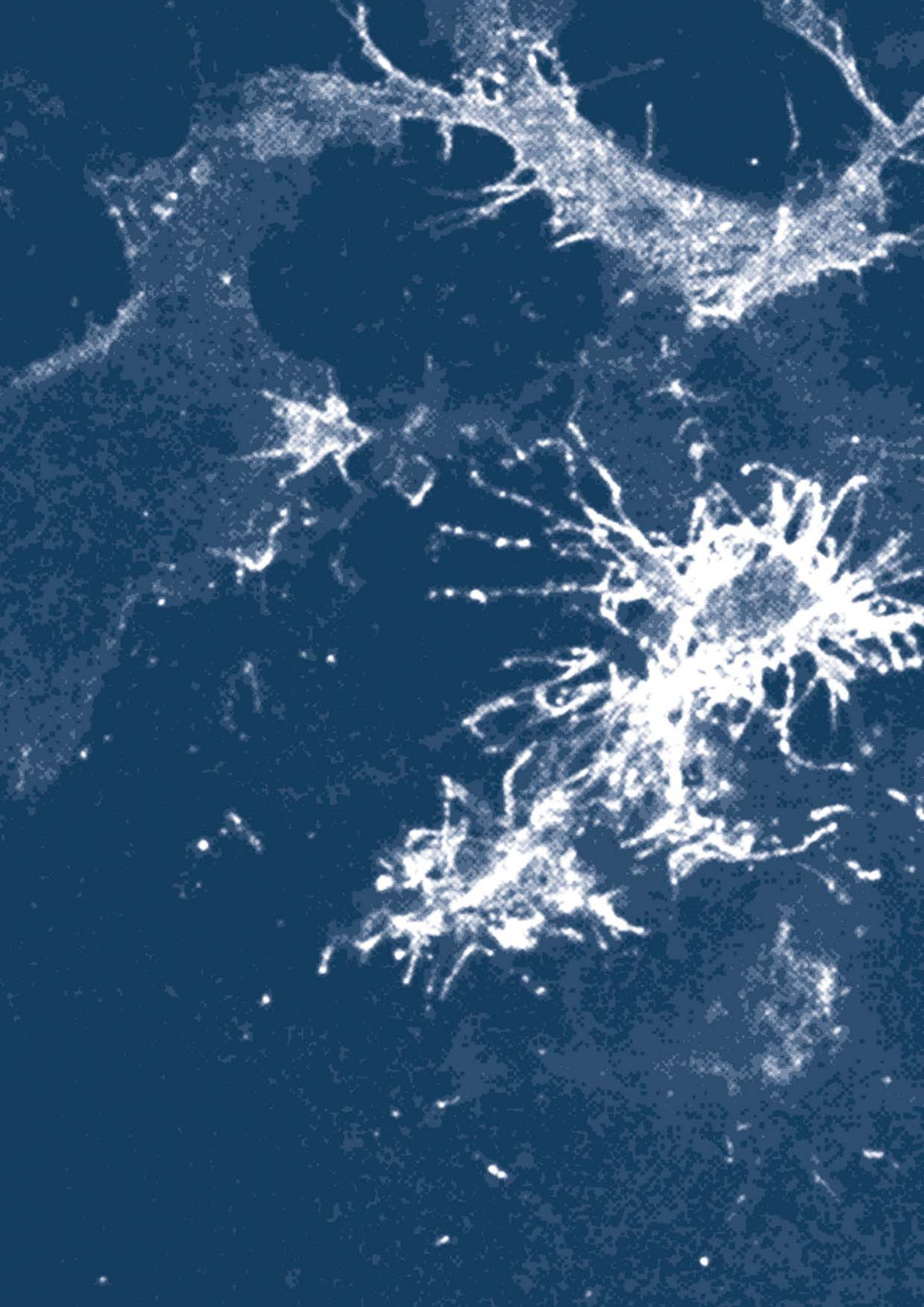
Research topics

The research of this newly established laboratory will be focused on structural biology and protein engineering of novel scaffolds of small non-immunoglobulin type recombinant binding proteins, aiming to deepen our understanding of structure-function relationships that underlie high-affinity protein-protein interactions. The acquired knowledge and generated novel binding protein tools are expected to be useful in various research and diagnostic applications, including design of microfluidic nanoimmunosensors for detection of cytokines.

Current grant support

AS CR „Nanotechnologies for the Society“ (KAN200520702)





SERVICES INFORMATION TECHNOLOGIES

Head: Petr Divina

People: Petr Divina, PhD, Miroslav Indra, PhD, Petr Janků, MSc, Marek Kubát, Michal Kůs, Jakub Šimon

Data centre room: racks, enclosed hot aisle and UPS Symmetra PX

The IT department provides innovative, reliable, and integrated information technology solutions to support various needs within the Institute. It ensures seamless operation and administration of LAN and wireless network including mail, web, DNS and secure VPN access. Great emphasis is placed on the network security and data protection using firewall and anti-virus solutions. The IT department also 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. Additionally, 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, the IT department negotiates volume and site licensing options. All 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. The room was designed to accommodate future expansion as the information technology advances. Currently, there are up to 40 devices with total 50 TB disk storage capacity and additional tape storage capacity for data backup.

SERVICES GENOMICS AND BIOINFORMATICS

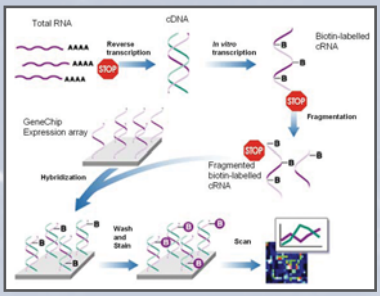
Head: Robert Ivánek

People: Robert Ivánek, MSc, Martina Chmelíková, MSc

Affymetrix GeneChip System

Illumina BeadStation 500

The facility was established in late 2005 after purchase of the Affymetrix GeneChip System and was initially operated by staff from the Department of Mouse Molecular Genetics. Since January 2007 it became 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).



SERVICES CRYOBANK AND MONOCLONAL ANTIBODIES

Head: Dobromila Matějková

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

Liquid nitrogen storage vessels

Monoclonal antibody production laboratory

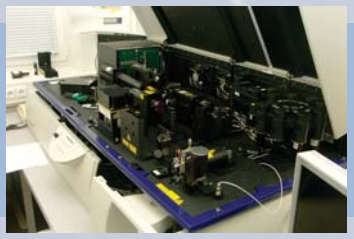
The new cryobank (capacity over 350 000 samples) was established in January 2007 and is used for storage of cell lines, mouse sperm, and embryos in liquid nitrogen. The storage containers are supplied with liquid nitrogen from a tank {capacity of 6000 litres}. It is equipped with an independent power 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 fully automated and controlled. 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 clonation, secondary antibody production screening (using e.g. ELISA), production of monoclonal antibodies into the cell culture supernatants, generation of a hybridoma cell bank.

SERVICES FLOW CYTOMETRY AND LIGHT MICROSCOPY

Head: Ondrej Horváth

People: Ondrej Horváth, MD, Zdeněk Cimburek



Cytofluorometer LSRII

Leica Microscope with TIRF

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 561nm laser and is now a four laser (405nm, 488nm, 561nm and 633nm) 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 have HTS loader for high throuput analysis of samples directly from 96- or 384-well plates. The facility is also provided with AutoMACS Pro (Miltenyi Biotec) magnetic separator for automatic rapid sorting of cells, as well as cell culture equipment.

The following microscopes have been installed very recently and will be in routine use soon: confocal microscope with superfast scanner (Leica TCS SP5 AOBS TANDEM), Leica inverted fluorescent microscope with TIRF illumination (Leica), wide-field inverted fluorescence microscope with laser excitation (DeltaVision). This state of art instrumentation allows facility users to use a wide range of microscopy techniques includibg FRET, FRAP, time-lapse experiments, membrane studies, vesicle transport studies, etc.

SERVICES MEDIA, GLASS WASHING

Head: **Hana Marxová**

People: Hana Marxová, Miluše Alferiová, Stanislava Bendová, Lucie Jánská, Jitka Škopová

SERVICES ADMINISTRATIVE AND TECHNICAL SERVICE OF THE BIOTECHNOLOGY DIVISION

Head: **Jan Škoda**

People: Jan Škoda, MSc, Jan Rajnoch, MD, Hana Boháčková, Věra Chaloupková, Marie Chmelíková, Jiřina Kočová, Renáta Koubová, Zdeňka Kšírová

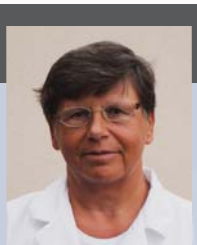
SERVICES ANIMAL HOUSE (MICE)

Head: **Michael Boubelík**

People: Michael Boubelík, PhD, Lukáš Jebavý, Assoc Prof, PhD, Zuzana Žižková, MSc, Dana Koukalová, Kateřina Formánková, Pavla Kameníková, Daniela Kratochvílová, Jarmila Krestová, Miloslava Kudličová, Michaela Lišáková, Veronika Lorincová, Ludmila Martínková, Libuše Mayerová, Kateřina Ševčíková, Ludmila Šimečková, Hana Vaňková, Alena Zachardová

The animal (mouse) facilities of the IMG were for many years localized mainly in building "G" in the Krč campus, belonging to the Institute of Physiology, with the capacity of about 3000 cages and more recently also in building "V" accredited for work with genetically modified animals (capacity reserved for IMG about 2000 cages). In October 2007, a new modern animal house (building "C", capacity up to 6000 cages) was finished, located immediately next to the new main building of the Institute. Mice kept formerly in the building G were moved to the new facility in building C. The new animal house will continue to breed unique mice strains under standard pathogen-free conditions, mostly prepared at the Institute. The new animal house will also host a newly established transgenic facility that will produce various types of transgenic and gene KO mice.

SERVICES ANIMAL HOUSE (CHICKEN)



Head: **Milena Vilhelmová**

People: Milena Vilhelmová, PhD, Eva Bernášková, Alena Eisensteinová, Petra Faloutová, Eva Fišerová, Zdena Koptová, Alena Porazilová, Radomíra Skoková, Jaroslava Strnadelová, Milena Vaverková, Jaroslava Vlasáková

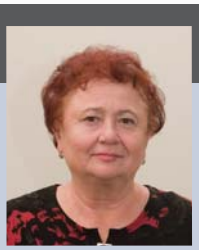
This facility is located in the village Koleč, north of Prague, about 45 km from the main campus in Praha-Krč. It takes mainly care of breeding of genetically defined inbred, congenic and outbred chicken lines (and one duck line). The facility produces eggs, embrya and chickens needed for several research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

SERVICES BUILDING MAINTENANCE

Head: Tomáš Němec

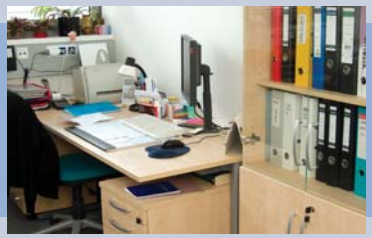
People: Tomáš Němec, Bc, Ludmila Boukalová, Dana Macková, Dana Martínková, Dagmar Urbanová

SERVICES FINANCES AND ADMINISTRATION



Head: Zdenka Sokolová

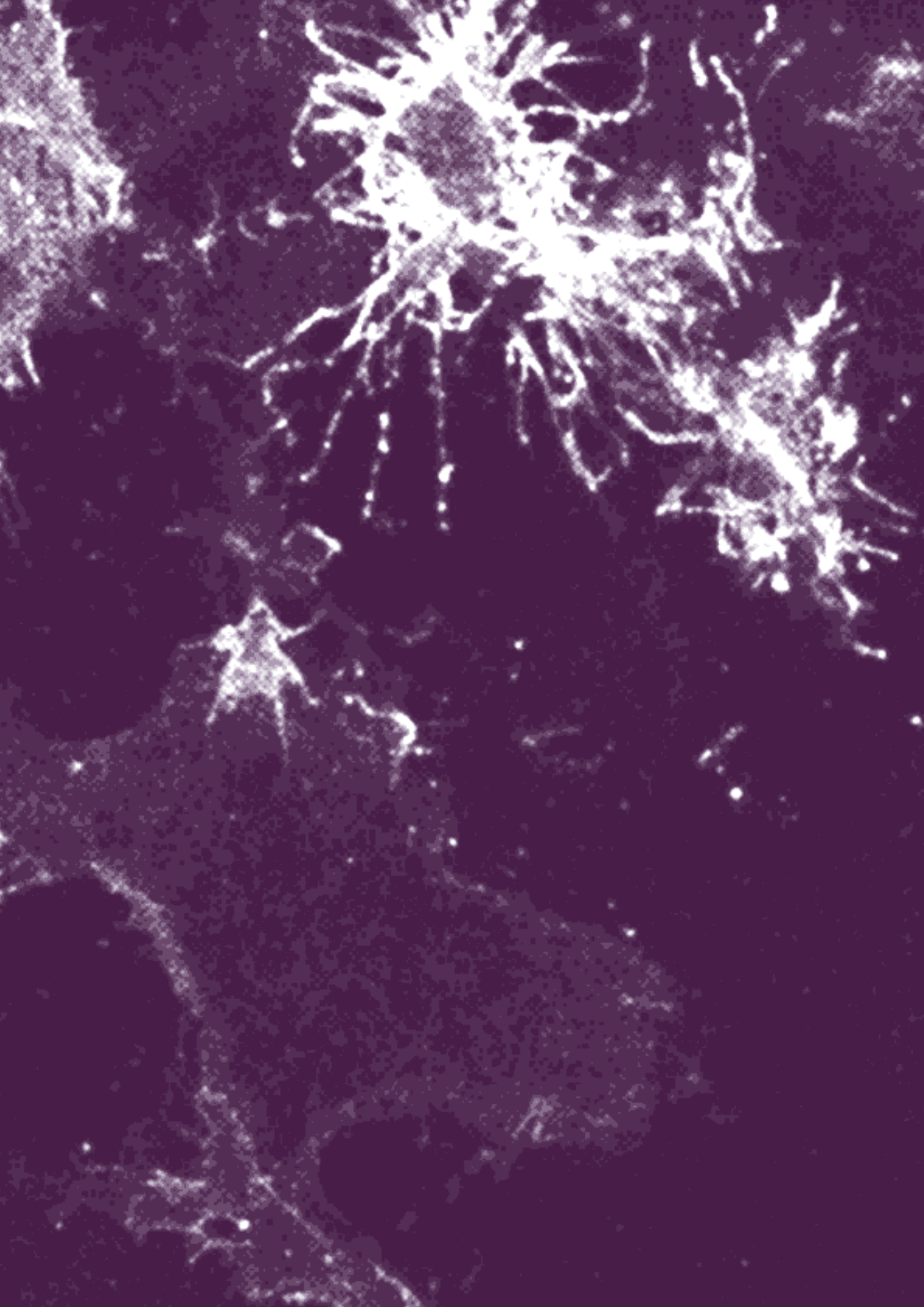
People: Zdenka Sokolová, Věra Bálková, Ivana Brabencová, Milena Dobrá, Kateřina Drastilová, Jitka Emanuelová, Jan Hladký, Hana Nezbedová, Milena Petríková, Jaroslava Samohylová, Miloslava Šnajbergová, Emílie Štorchová, Hana Švestková



DIRECTOR´S SECRETARIATE

Head: Šárka Takáčová

People: Šárka Takáčová , MSc, Leona Krausová, Gabriela Marešová, Lucie Tykalová, Vladimír Viklický, MD, PhD (Institute Secretary for Biotechnologies)



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Seminar Speakers

MARCH

02/03/07	Boris Zhivotovsky (Karolinska Institutet, Stockholm, Sweden)
02/03/07	Jürgen Brosius (University of Münster, Germany)
29/03/07	Kazuo Inaba (University of Tsukuba, Japan)
29/03/07	Jacky Cosson (CNRS, University Pierre et Marie Curie, Paris, France)
29/03/07	Andrzej Ciereszko (Instit. of Animal Reprod. Food Res., Olsztyn, Poland)

APRIL

05/04/07	Markéta Jiroušková (The Rockefeller University, New York, NY, USA)
17/04/07	Ivan Hirsch (Institut Paoli-Calmettes, Marseille, France)
24/04/07	Hannes Stockinger (Medical University Vienna, Austria)

MAY

10/05/07	Fridtjof Lund-Johansen (Inst. of Immunology, University of Oslo, Norway)
24/05/07	Miroslava Uhlířová (University of Rochester, NY, USA)
24/05/07	Georges Calothy (Institute Curie, Orsay, France)
28/05/07	Gabriela Pavlínková (University of Nebraska, Omaha, NE, USA)

JUNE

07/06/07	Zdeněk Hel (University of Alabama, Birmingham, AL, USA)
11/06/07	Toshiaki Kawakami (La Jolla Inst. for Allergy and Immunology, La Jolla, CA, USA)

JULY

09/07/07	Lyn Griffith (Griffith University, Southport, Qld, Australia)
11/07/07	Jean-Luc Gatti (INRA-CNRS-Université de Tours-Haras, Nouzilly, France)
20/07/07	Ronald Naumann (MPI for Cell Biology and Genetics, Dresden, Germany)
30/07/07	Burkhart Schraven (Otto von Guericke University, Magdeburg, Germany)

SEPTEMBER

18/09/07	Stanislav Tomarev (National Eye Institute, NIH, Bethesda, MD, USA)
20/09/07	Eduard Bitto (University of Wisconsin-Madison, Madison, WI, USA)

OCTOBER

02/10/07	Antonio Caldarelli (Max Planck Institute for Cell Biology and Genetics, Dresden, Germany)

NOVEMBER

09/11/07	Petra Hájková (Gurdon Institute, University of Cambridge, England)
22/11/07	Wilhelm Ansorge (Institute of Advanced and Emerging Technology, Lausanne, Switzerland)
22/11/07	Fabio Malavasi (Universita Degli Studi Di Torino, Torino, Italy)

DECEMBER

04/12/07	Igor Shevelev (University of Toronto, Canada, and University of Zurich, Switzerland)

Highlights of 2006 – 2007

Major organizational changes

The Institute of Molecular Genetics has profoundly changed in the previous two years. In preparation for the moving into the brand new modern building we made major organizational changes. Several laboratories were terminated or reorganized by the end of 2006; several of their heads achieved retirement age:

- Laboratory of Intracellular Communications (Zdena Tuháčková) was cancelled; several of its members joined the newly formed laboratory led by Vladimír Kořínek.
- Laboratory of Cell Biology (Eva Matoušková) has moved to the 1st Medical Faculty, Charles University
- Laboratory of Gene Expression (Jiří Jonák) was cancelled; several of its members were relocated as a new group led by Libor Krásný to the Institute of Microbiology AS CR.
- Laboratory of Micromorphology of Biopolymers (Jan Korb) was cancelled.
- Laboratory of Biology and Biochemistry of Fertilization (Jana Pěknicová) was transformed into Laboratory of Diagnostics for Reproductive Medicine within the newly established Biotechnology Division.
- Laboratory of Biochemistry of Reproduction (Věra Jonáková) was cancelled and most of its members joined the above new laboratory led by Jana Pěknicová in the Biotechnology Division
- Laboratory of Recombinant Expression and Structural Biology (Juraj Sedláček) was partially relocated to the Institute of Organic Chemistry and Biochemistry AS CR (IOCB) and partially transformed into Laboratory of Structural Biology (provisional head Jan Konvalinka; closely collaborating with the IOCB part and located as a detached laboratory at the IOCB)

Other changes involved the change of head of the Laboratory of Transplantation Immunology (now Vladimír Holáň).

New groups established

Several new laboratories were established led by group leaders selected in an international competition. These laboratories (heads David Staněk, Pavel Hozák, Vladimír Kořínek, Petr Svoboda, Jaroslav Blahoš, Dominik Filipp, and Jiří Bartek) are featured in the previous pages. Other new group leaders selected in the competition were Radek Sedláček, Igor Vořechovský and Pavel Tolar, whose groups will be established in 2008.

A special „Biotechnology Division" has been established, comprising six research laboratories and sited in a neighbouring building („Lb"). This part of the Institute will become independent since January 1st, 2008, as a new sister institution, Biotechnology Institute AS CR. These laboratories are featured on previous pages (27-31).

New service facilities established

In addition to the already existing service facilities (Animal facilities, Media preparation and glass washing, Finances and administration), several new ones were established (Information technologies, Genomics and bioinformatics, Cryobank, Monoclonal antibody facility, Cytofluorometry and light microscopy) (see pp. 32-36). Furthermore, we participate in the work of the Proteomics facility of the Institute of Microbiology.

Legal status changed

On January 1st, 2007, the Institute became a Public Research Institution. This legal step brought about higher independence but also higher responsibility, and a number of administrative tasks. At the beginning of 2007, the Institute's Council was elected, Supervisory Board was established and director re-stablished.

Moving into the new buildings

We moved into the main new building in the course of December 2006 and January 2007 and mice were transferred into the new animal house in November 2007. These major logistic operations were well managed and we became fully operational within a few weeks.

Official opening of the new building

The official opening of the main building took place on April 19th, 2007, with participation of Dana Kuchtová (Minister of Education), Miroslava Kopicová (vice-chairperson of the Council for Research and Development), Václav Pačes (President of the Academy of Sciences of the Czech Republic) and a number of directors of research institutes, deans of faculties, journalists, TV and other guests.

Cutting the ribbon – from left to right: Miroslava Kopicová, former Minister of Education, Václav Pačes, AS CR President, Dana Kuchtová, Minister of Education

Opening address by AS CR President Václav Pačes (left – Václav Hořejší, Director of IMG, middle, Dana Kuchtová, Minister of Education)

New instruments

Moving into the new building and establishment of the new service facilities was also connected with purchase of new modern equipment and technology such as: modern central IT equipment, Illumina BeadStation 500, real-time PCR cycler Roche LC480, JANUS robots from PerkinElmer, spectrophotometer Nanodrop, capillary electrophoresis Agilent Bioanalyzer 2100, modern liquid nitrogen storage containers for cryopreservation of cells and other biomaterials, confocal microscope with superfast scanner (Leica), TIRF microscope (Leica), wide-field fluorescence microscope with laser excitation (DeltaVision), two FEI electron microscopes for ultrastructural, tomographic, cryo-ultrastructural and analytic observations close to native conditions, micromanipulator, several specialized fluorescence microscopes, etc.

Institute conferences, seminars

The 2006 Annual Institute Conference took place on October 13th in Hotel Krystal, Prague. The speakers were: Jaroslav Blahoš, David Staněk, Pavel Lebduška (laboratory od Petr Dráber), Vladimír Kořínek, Petr Svoboda, and Miluše Hroudová (laboratory od Čestmír Vlček).

The 2007 Annual Conference took place on November 23rd in the Institute of Clinical and Experimental Medicine, Prague. The speakers were: Ladislav Anděra, Jiří Forejt, Jiří Hejnar, Pavel Hozák, Michael Kubista, and Peter Šebo.

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.

Prizes and honours

Petr Dráber – 2006 - Prize of the Learned Society of the Czech Republic

Jiří Forejt – 2007 - the newly established most prestigious Praemium Academiae of the AS CR (as one of four only awardees);

Tomáš Vacík – 2006 - Arnold Beckman Publication Prize (Sigma-Aldrich)

Tomáš Brdička – 2007 - Otto Wichterle Award for young AS CR researchers;

Petr Svoboda – 2006 Purkynje Fellowship of the AS CR and EMBO Installation Grant.

Radek Sedláček – 2006 Purkynje Fellowship of the AS CR

New Professors

Jiří Forejt, Genetics, Molecular Biology and Virology, Faculty of Science, Charles University, Prague, November 2006

Jiří Jonák, Medical Chemistry and Biochemistry, 1st Faculty of Medicine, Charles University, Prague, April 2007

Pavel Hozák, Medical Biology 3rd Faculty of Medicine, Charles University, Prague, November 2007

Teaching (Semestral Courses)

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

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

Advances in Immunology, Jan Černý, Karel Drbal, Pavel Otáhal, Tomáš Brdička, Radek Špíšek, Faculty of Science, Charles University

Structure and Function of the Cytoskeleton, Pavel Dráber, 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

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

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

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

Biochemistry of Animal Reproduction, Věra Jonáková, Faculty of Science, Charles University

Mechanisms of Cell Proliferation, Jan Kovář, 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

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

Molecular Genetics, Václav Pačes, Institute of Chemical Technology

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

Molecular Mechanisms of Fertilization, Jana Pěknicová, Faculty of Science, Charles University

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

Cell Biology, David Staněk, 1st Faculty of Medicine, 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

Theses Defended in 2006 – 2007

Diploma Theses

2007

Bražina Jan Characterization of a novel panel of monoclonal antibodies for study of microtubule-associated proteins
(Supervisor: Pavel Dráber, Faculty of Science, Charles University, Prague)

Handrková Helena Involvement of protein-tyrosine phosphorylation in the regulation of translation
(Supervisor: Zdena Tuháčková, Faculty of Science, Charles University, Prague)

Havlová Tereza Characterization of a novel transmembrane adaptor protein TRAP2 in human leukocytes
(Supervisor: Václav Hořejší, Faculty of Science, Charles University, Prague)

Svobodová Martina Src family thyroxin-kinases in early developmental stages of *Xenopus laevis*
(Supervisor: Jiří Jonák, Faculty of Science, Charles University, Prague)

Tišerová Hana Thermostability of elongations factors Tu from *E. coli* and *B. stearothermophilus* studied by targeted point mutagenesis
(Supervisor: Jiří Jonák, Faculty of Science, Charles University, Prague)

Turková Linda Structure and function of a novel transmembrane adaptor protein LST-1
(Supervisor: Václav Hořejší, Faculty of Science, Charles University, Prague)

Žíla Vojtěch Electron microscopy in the analysis of interactions of polyomavirus and cellular structures
(Supervisor: Jitka Štokrová, Faculty of Science, Charles University, Prague)

2007

Dráber Peter Characterization of transmembrane adaptor protein PRR7 in the cells of immune system
(Supervisor: Václav Hořejší, Faculty of Science, Charles University, Prague)

Procházková Jana Regulatory mechanisms of the effector phase of transplantation reaction
(Supervisor: Vladimír Holáň, Faculty of Science, Charles University, Prague)

Přibylová Hana Changes in the expression and presentation of antigens during progression of experimental tumours associated with Human papilloma virus 16; analysis of defects and their influence on immune response
(Supervi-sor: Milan Reiniš, Faculty of Science, Charles University, Prague)

Starostová Michaela Study of the v-Myb oncoprotein variable region.
(Supervisor: Michal Dvořák. Faculty of Science, Charles University, Prague)

Vanišová Marie Mapping genes that modify susceptibility to *Leishmania major* infection
(Supervisor: Marie Lipoldová, Faculty of Science, Charles University, Prague)

PhD Theses

2006

Blažková Jana Role of DNA methylation in transcriptional regulation of retroviral genome expression
(Supervisors: Jiří Hejnar, Faculty of Science, Charles University, Prague, Ivan Hirsch, Université de la Méditerranée, Aix-Marseille II, Marseille)

Brožová Markéta Characterization of a novel progenitor cell line, EM-G3, of human mammary carcinoma
(Supervisor: Eva Matoušková, Faculty of Science, Charles University)

Hořejší Zuzana Role of the DNA damage checkpoint in normal and cancer cell cycle
(Supervisors: Jiří Bartek, Institute of Cancer Biology and Centre for Genotoxic Stress Research, Danish Cancer Society, Michal Dvořák, Faculty of Science, Charles University, Prague)

Kahle Michal Toward the function of nuclear myosin I
(Supervisor: Pavel Hozák, Faculty of Science, Charles University, Prague)

Krásná Luboslava Biological behaviour and selected molecular characteristics of epithelial cells propagated *in vivo* from normal and tumour tissue of mammary gland in women
(Supervisor: Eva Matoušková, Faculty of Science, Charles University, Prague)

Qunyan Yu G1 cyclins and their role in oncogenesis
(Supervisor: Pavel Veselý, 1st Faculty of Medicine, Charles University, Prague)

Rossmeislová Lenka Promyelocytic leukaemia protein function in normal, tumour and senescent human cells
(Supervisor: Pavel Hozák, Faculty of Science, Charles University, Prague)

Storchová Radka Evolution of sex chromosomes and their role in speciation
(Supervisor: Jiří Forejt, Faculty of Science, Charles University, Prague)

Strnad Hynek Restriction-modification systems of bacterium *Rhodobacter capsulatus* SB100
(Supervisor: Václav Pačes, Institute of Chemical Technology, Prague)

Sulimenko Vadym Distribution and functions of γ-tubulin and its complexes
(Supervisor: Pavel Dráber, Faculty of Science, Charles University, Prague)

Vítová Andrea Cellular and molecular mechanisms of corneal transplant rejection
(Supervisor: Vladimír Holáň, Faculty of Science, Charles University, Prague)

2007

Čermák Lukáš Regulation of epithelial plasticity and apoptotic signalling from cell surface receptors
(Supervisor: Ladislav Anděra, Faculty of Science, Charles University, Prague)

Divina Petr Gene order in eukaryotic genomes: an analysis using sequence-based gene expression data
(Supervisor: Jiří Forejt, Faculty of Science, Charles University, Prague)

Macůrek Libor Molecular characterization of γ-tubulin interactions with signalling molecules
(Supervisor: Pavel Dráber, Faculty of Science, Charles University, Prague)

Pindjáková Jana The role of T lymphocytes and macrophages in experimental models of allo- and xenograft rejection
(Supervisor: Vladimír Holáň, Faculty of Science, Charles University, Prague)

Smrž Daniel Phosphatidylserine and phospholipid scramblase in mast cell signalling
(Supervisor: Petr Dráber, Faculty of Science, Charles University, Prague)

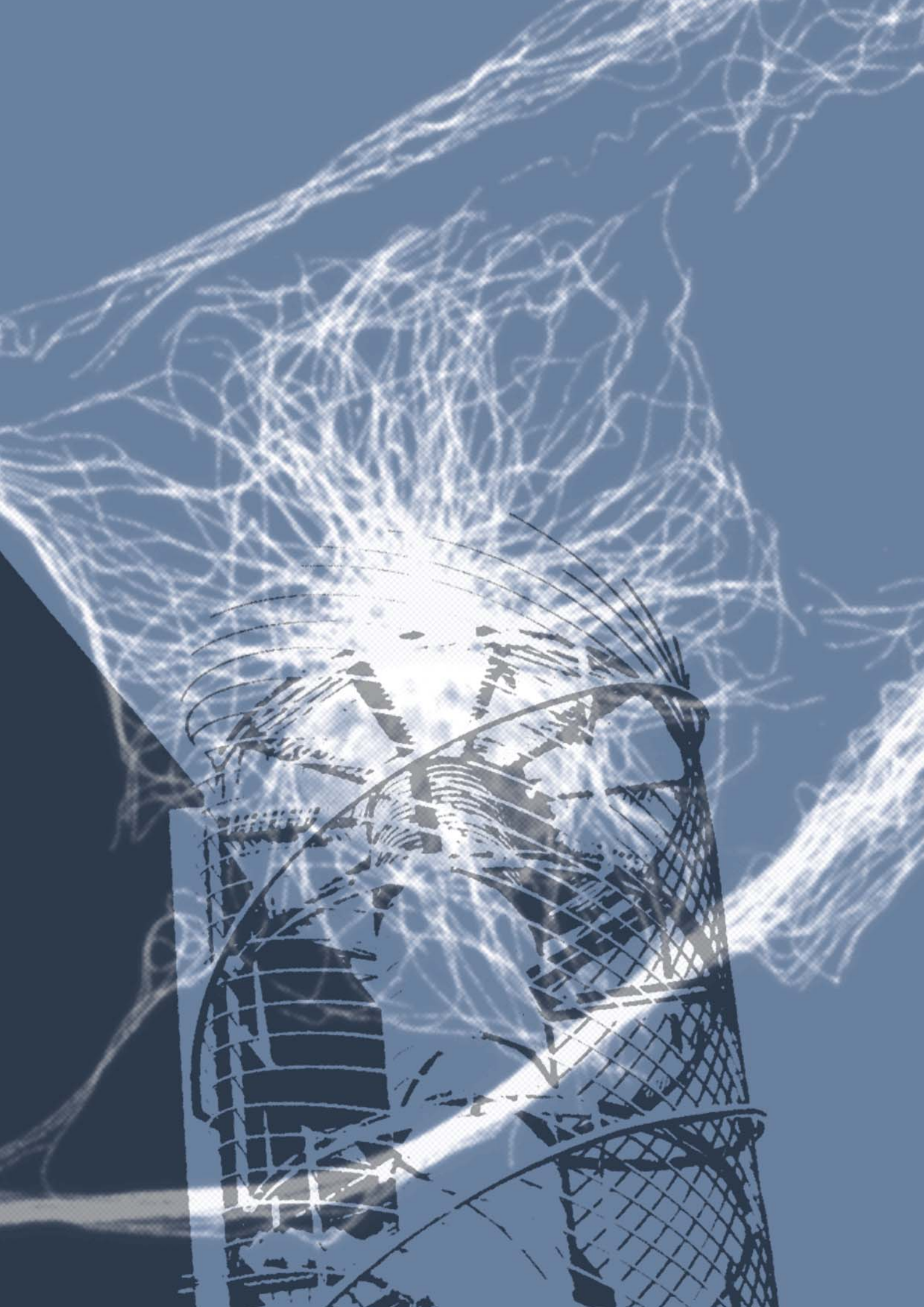
Valenta Tomáš New components of the Wnt signalling pathway
(Supervisor: Vladimír Kořínek, Faculty of Science, Charles University, Prague)

Habilitations

2006

Brynda Jiří Determination of biological macromolecule structure by the X-ray structural analysis method (Technical University, Liberec)

Dráber Pavel Molecular mechanisms of nucleation and heterogeneity of microtubules (Charles University, Prague)

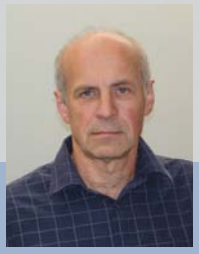


IMG Council

Chairman: Jiří Forejt, Prof, PhD, DSc (IMG)

Vice-Chairman: Jiří Hejnar, PhD (IMG)

Petr Dráber, PhD, DSc (IMG)



Michal Dvořák, PhD (IMG)

Václav Hořejší, Prof, PhD (IMG)

Pavel Hozák, Prof, PhD, DSc (IMG)

Vladimír Kořínek, PhD (IMG)

Peter Šebo, PhD (IMG)

Vladimír Havlíček, Assoc Prof, PhD
(Institute of Microbiology AS CR)

Marek Moša, PhD
(Sevapharma, a.s.)

Marek Jindra, Assoc Prof, PhD
(Institute of Parasitology AS CR)

Jan Tachezy, Assoc Prof, PhD
(Faculty of Science, Charles University, Prague)

The Council of the Institute serves as an advisory organ to the Director and decides on essential scientific and organizational issues. Its members are appointed by election.

Supervisory Board

Chairman: Jiří Drahoš, Prof, PhD, DSc
(Academic Council AS CR)

Vice-Chairman: Jiří Špička, MSc
(Deputy Director, IMG)

Martin Fusek, Assoc Prof, PhD
(Life Sciences Capital)

David Štůla
(lawyer)

Jaroslav Kuneš, PhD, DSc
(Institute of Physiology AS CR)

The main task of the Supervisory Board is to monitor the financial and legal matters connected with the Institute administration. Its members have been selected by the Academy of Sciences from Academy and business sphere representatives.

Construction of the New Building


18. 3. 2005


11. 5. 2005


13. 6. 2005


1. 7. 2005


18. 7. 2005


19. 8. 2005


8. 9. 2005


19. 9. 2005


12. 10. 2005


9. 11. 2005


3. 1. 2006


20. 3. 2006


26. 5. 2006


1. 8. 2006


22. 1. 2007

Where We Are


Moldau
Highway to
Dresden, Berlin
Airport
Castle
PRAGUE
Highway to
Pilsen, Nurenberg
IMG
Kunratice
Jesenice
Highway to
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