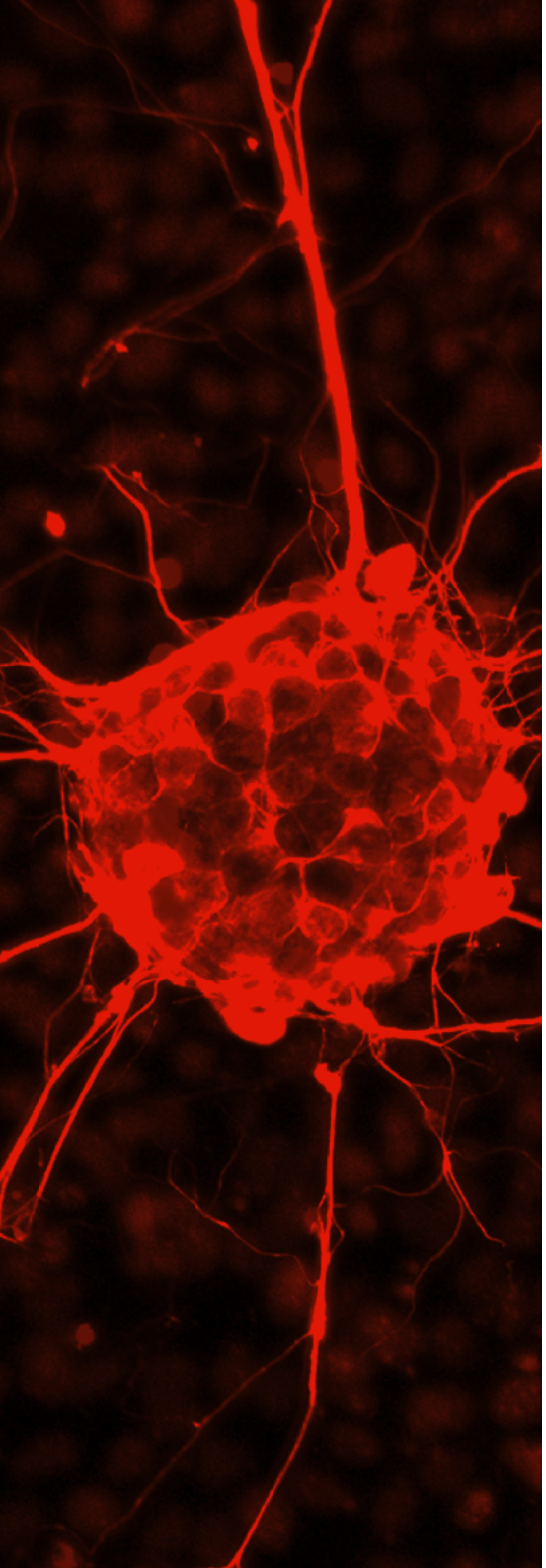

IMG

Institute of Molecular Genetics of the Czech Academy of Sciences

ANNUAL REPORT

2017–2019

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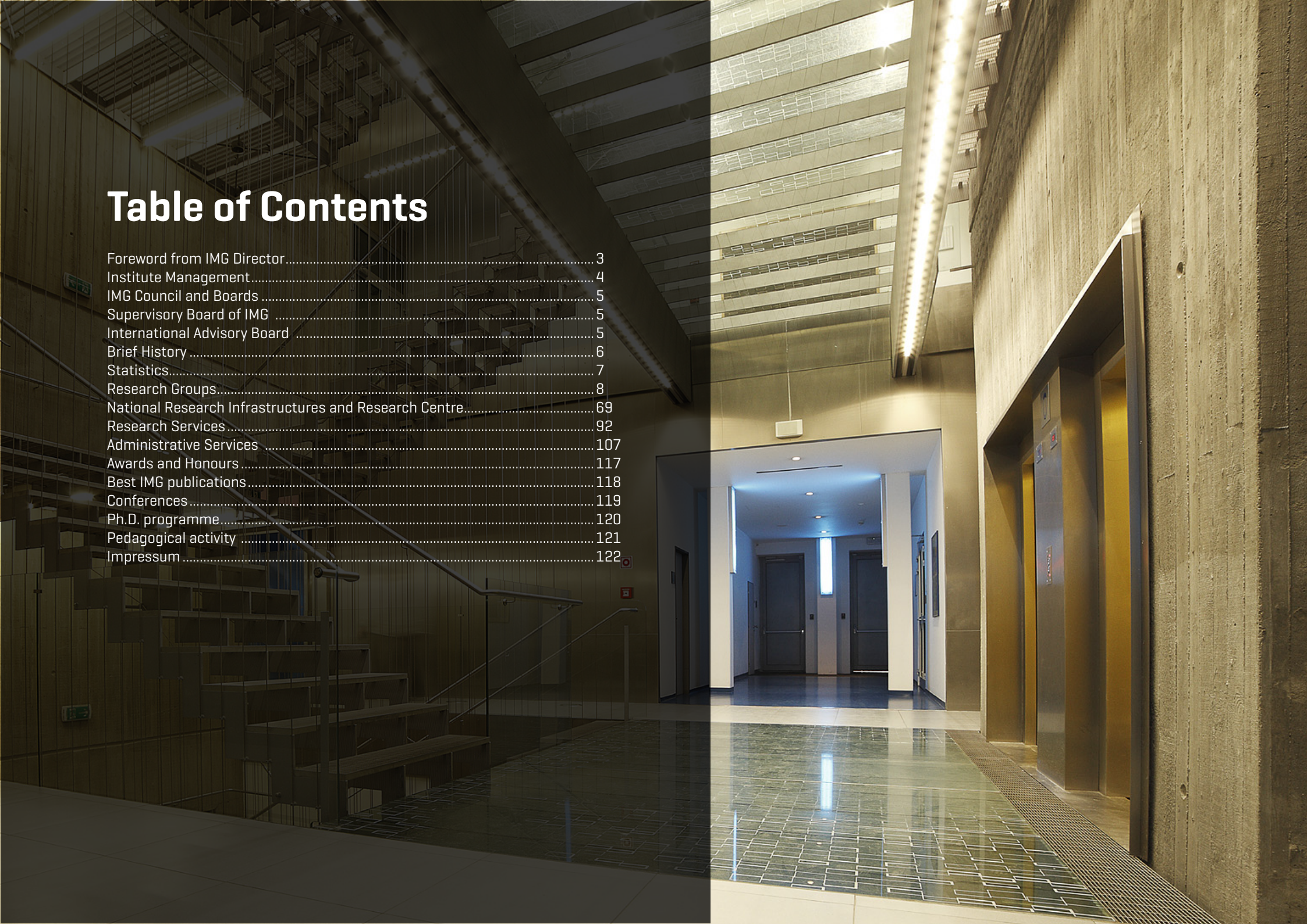

Foreword from IMG Director

Dear Colleagues,

The three-year Scientific Report of the Institute of Molecular Genetics of the Czech Academy of Sciences (IMG) summarizes the most remarkable results and activities we achieved in the years 2017-2019.

In this period, scientific research continued in 28 research groups (21 in Krč, six in Vestec within the framework of project BIOCEV, and one in Dejvice) and four large national research infrastructures (Czech-BioImaging, CZ-OPENSCREEN, and ELIXIR CZ in Krč, and Czech Centre for Phenogenomics in Vestec). In the period 2017-2019, the number of IMG employees increased from 565 to 607. About two-thirds of them worked in Krč and one third contributed to the project BIOCEV in Vestec; a minor part of employees worked in Dejvice and at the Koleč farm. The institute comprises 366 research scientists, including 121 Ph.D. students.

Our work resulted in numerous important research discoveries, which were presented at international conferences and symposia, including those organized by IMG researchers, and published in a number of respected international journals. The activity of our research groups also resulted in numerous application outputs and patents, which in many cases reflected cooperation with the business sphere and contributed considerable financial means to our Institute budget. To facilitate implementation of the application results, the Institute reinforced the technology transfer office and initiated cooperation with the iGi company. The applied research at IMG was also supported by the TACR Gamma project.

In that period, we obtained the major part of funding (~60 %) that sustained our basic research tasks in the form of specific grants from various grant agencies and other funding providers. The dependence on short-term grants (usually for about three years), however, caused that, on average, each group and infrastructure participated in more than four projects. This resulted in a sizeable bureaucratic burden for principal investigators. To improve conditions for preparing grant applications and getting information on possible grant funding, in 2017 we the established the Grant Department, which systematically monitored sources of specific funding, informed our researchers about grant options in Grant News, and helped our researchers to draft grant applications and manage grant inspections.

We also paid a lot of attention to the BIOCEV project in Vestec, of which our Institute is guarantor for the period of the compulsory sustainability phase (2016 – 2020). We had to ensure achievement of the set indicators and obtain finances for covering the operational costs. Thanks to the activity of our colleagues in Vestec, sustainability indicators were satisfactorily attained. However, we spent a lot of time to get a sufficient budget for the BIOCEV project, because the necessary support had to be obtained via a specific Academy competition. During the sustainability phase, we also intensively discussed the future of the BIOCEV project at the level of Academic Council and statutory representatives of all partner organizations (six Academy Institutes and two Faculties of Charles University).

Since 2017, we made significant changes in the administrative and technical services in Krč and in BIOCEV to increase more efficient and conceptual management of these services in both localities. We also initiated all necessary steps to switching to a new economic information system. The activity of our administrative supervision and the exemplary cooperation with the General Control Division of the Academy Head Office resulted in the purchase of the guesthouse in the Krč campus into our ownership.

During 2017-2019, we repaired the animal facility in Krč, initiated renovation of the key buildings in the detached site in Koleč, and completed extensive renovation of the electron microscopy facility in the main building in Krč, associated with installation of new modern electron microscopes.

We multiplied efforts in the popularization of our results and activities. To this end, we employed a new Ph.D. administrator, helping the IMG Ph.D. Committee to take care of the Ph.D. programme not only at the level of the Institute, but also of the entire Krč campus. As part of the yearly promotion, the Institute organized IMG Open Doors Days, and we launched the IMG Instagram, Twitter, and Facebook. A number of additional Institute activities have been recorded at our web pages.

In conclusion, in the years 2017-2019, our Institute continued in its growth of scientific excellence and importance, as documented in this Scientific Report. I am convinced that IMG, based on the people and equipment, services, presence of large national research infrastructures, animal facilities, and administrative team has all necessary prerequisites for further development and important contributions to the basic knowledge in the field of molecular cell biology and genetics, and also in transfer of new scientific findings and tools to their practical applications.

February 24, 2020

Petr Dráber

Institute Management

DIRECTOR OF THE INSTITUTE
Petr Dráber, Ph.D., D.Sc.

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Vladimír Kořínek, Ph.D.

DEPUTY DIRECTOR FOR ADMINISTRATION
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Institute for Molecular and Cell Biology
Porto, Portugal

Brief History

The history of our Institute ensues from 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.

In 1962, the Institute of Experimental Biology and Genetics of the Czechoslovak Academy of Sciences (IEBG) was founded, with Milan Hašek as its Director until 1970. The sixties of the last century mark, without doubt, the most memorable chapter of the Institute – the "Czechoslovak immunogenetic school" was born at that time, represented besides Hašek by such names as Pavol and Juraj Iványi, Jan Klein, Tomáš Hraba, Ivan Hilgert, Věra Hašková, Alena Lengerová, and others. It is generally known that Milan Hašek came close to the Nobel Prize (for the discovery of immunological tolerance, it was awarded to P. Medawar and M. Burnet); Pavol Iványi contributed significantly to the experiments whose results later brought the Nobel Prize to Jean Dausset; Jan Klein, after emigration to the U.S.A., in the seventies became probably the most eminent immunogeneticist worldwide (co-discoverer of the fundamental immunological significance of MHC proteins). During this period, great attention at IEBG was also paid to the development of the worldwide priority research of retroviruses (Jan Svoboda).

In the years 1964-2006, the major part of the Institute had its site in the building belonging to the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences (later Academy of Sciences of the Czech Republic) (IOCB) located at the address Flemingovo náměstí, Prague – Dejvice, and the minor part was situated in the complex of biological institutes of the Academy in Prague – Krč. Another important part of the Institute is the breeding and experimental farm in Koleč (about 20 km from Prague).

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), Milan Hašek was removed from the post of Director of the Institute, contacts with other countries were drastically limited.

After a short period during which the Institute was headed by Karel Heyberger, Prokop Málek served as Director of IEBG in 1970-1977.

In 1976, IEBG was joined with several biochemical laboratories of IOCB and renamed Institute of Molecular Genetics of the Czechoslovak Academy of Sciences (IMG). The post of Director of IMG was conferred on Josef Říman, (later appointed as President of the Czechoslovak Academy of Sciences for many years), who stayed in this position until 1991. Since that time, molecular biology has become the main topic of the Institute, but additional, traditional orientations have remained (immunogenetics, retrovirology, tumour immunology); these, however, also have gradually transferred to the molecular level. Other achievements from 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 continued the trend of enhancing the molecular biology approaches to the traditional as well as newly introduced topics. The Institute was first headed by Jan Svoboda (1991-1999) and then by Václav Pačes (1999-2005). In 2004, in the Krč site of the Academy, construction of a new building was started to house the Institute, in which since 2007 (for the first time in its history) a large majority of the Institute employees have finally gathered. After V. Pačes had been elected President of the Academy of Sciences of the Czech Republic, in 2005, Václav Hořejší became Director of the Institute.

In 2015 a new building of centre BIOCEV was finished and fully equipped in a nearby township Vestec, where several IMG research groups and a National Research Infrastructure "Czech Centre of Phenogenomics" is located.

In the same period, two other research infrastructures started operating in Krč, namely, CZ-OPENSCREN and Czech BioImaging hosted by the Krč part of IMG. In May 2017, Petr Dráber became IMG Director. At that time, the Institute included the central part on the Krč campus and three detached sites, one in Vestec (as part of the BIOCEV project), one in Dejvice and one in Koleč.

Statistics

The statistics correspond to the situation at the end of 2019

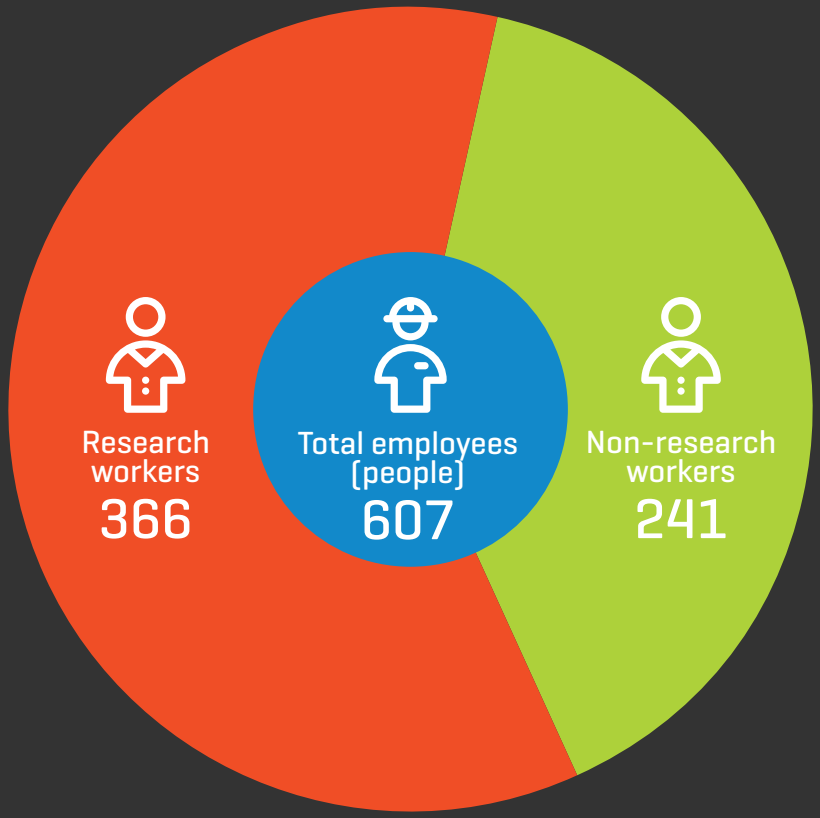
Research groups
28

Service groups
9

Administrative services
4

Large research infrastructures
4

Journal publications 2019
131



Ph.D. students
121

Total floor area IMG Krč m²
17 070

Total floor area IMG Vestec m²
7 368

Employees located in BIOCEV
193

Total floor area IMG Koleč m²
1 915

Total floor area IMG Dejvice m²
64

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LABORATORY OF

ADAPTIVE IMMUNITY

Tcells, signaling, immunity, disease, TCR

Ondřej Štěpánek

more information

e-mail

The Group of the Adaptive Immunity uncovers fundamental principles of how T cells elicite the protective immune response against pathogens and tumors, but maintain self-tolerance at the same time. One strong aspect of our research is the focus on the T-cell receptor signaling pathway and other signaling pathways that contribute to the fate decisions in T cells. To test physiological relevance of our hypotheses, we employ a battery of disease models including the models of autoimmune diabetes, cancer, or infection.

Besides the major direction, a part of the group focuses on the understanding of the biology of the BBSome, a protein complex, whose dysfunction can cause a multiorgan disease of Bardet-Biedl Syndrome.

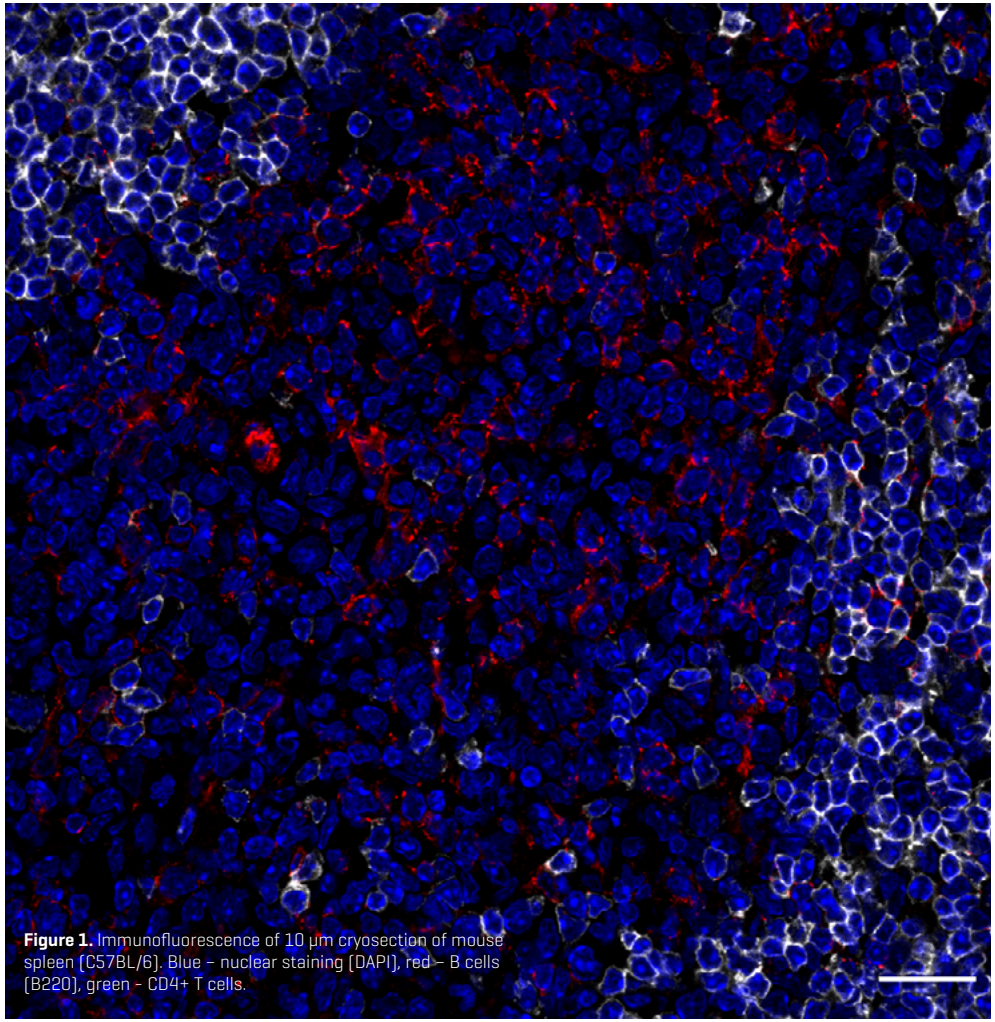


Figure 1. Immunofluorescence of 10 µm cryosection of mouse spleen (C57BL/6). Blue – nuclear staining (DAPI), red – B cells (B220), green - CD4+ T cells.

Selected publications:

1. Horkova V, Drobek A, Mueller D, Gubser C, Niederlova V, Wyss L, King CG, Zehn D, Stepanek O‡ (2020) Dynamics of the Coreceptor-LCK Interactions duringT Cell Development Shape the Self-Reactivity ofPeripheral CD4 and CD8 T Cells. *Cell Reports*, **30**:1504–1514.
2. Niederlova V, Modrak M, Tsyklauri O, Huranova M‡, Stepanek O‡ (2019) Meta-analysis of genotype-phenotype associations in Bardet-Biedl syndrome uncovers differences among causative genes. *Hum Mut*, **40**:2068-2087.
3. Drobek A, Moudra A, Mueller D, Huranova M, Horkova V, Pribikova M, Ivanek R, Oberle S, Zehn D, McCoy KD, Draber P, Stepanek O‡ (2018) Strong homeostatic TCR signals induce formation of self-tolerant virtual memory CD8 T cells. *EMBO J*, **37**(14). pii: e98518.
4. Lo WL, Shah NH, Rubin SA, Zhang W, Horkova V, Fallahee IR, Stepanek O, Zon LI, Kuriyan J, Weiss A (2019) Slow phosphorylation of a tyrosine residue in LAT optimizes T cell ligand discrimination. *Nat Immunol*, **20**:1481-1493.
5. Lo WL, Shah NH, Ahsan N, Horkova V, Stepanek O, Salomon AR, Kuriyan J, Weiss A (2018) Lck promotes Zap70-dependent LAT phosphorylation by bridging Zap70 to LAT. *Nat Immunol*, **19**:733-741.

In the picture: 1. Michálik Juraj | 2. Štěpánek Ondřej | 3. Přibíková Michaela | 4. Knížková Daniela | 5. Křížová Kateřina | 6. Drobek Aleš | 7. Horková Veronika | 8. Dráber Peter | 9. Tsyklauri Oksana | 10. Neuwirth Aleš | 11. Cupák Ladislav | 12. Janušová Šárka | 13. Paprčková Darina | 14. Prasai Avishek

LABORATORY OF

BIOLOGY OF CYTOSKELETON

Microtubules, γ-tubulin complexes, signal transduction

Pavel Dráber

more information

e-mail

The long-term research programme of the laboratory has been focused on studying the structure-function relationships of microtubule (MT) proteins in cells under normal and pathological conditions. The organization of dynamic MT networks is controlled by MT organizing centres (MTOCs). One of the key components of MTOCs is γ-tubulin, which is necessary for nucleation of MTs. Our current work focuses on understanding the modulation of MT organization by signal transduction molecules. Our results demonstrate that activation of bone marrow-derived mast cells (BMMCs) induces rapid and transient MT reorganization that is dependent both on protein tyrosine kinases and $Ca^{2+}$and diacylglycerol-regulated protein kinase C (cPKC). Suppression of MT formation in later stages of BMMC activation is regulated by protein tyrosine phosphatase 1 (SHP-1), which forms complexes with γ-tubulin ring complex proteins. MT regrowth and phenotypic rescue experiments showed that SHP-1 represents a negative regulator of MT nucleation. The modulation is due to the changes in γ-tubulin accumulation on the centrosomes. We have shown that two human γ-tubulins (genes *TUBG1, TUBG2*) differ in their properties, but both associate with mitochondrial membranes. Although γ-tubulin 2 accumulates in the adult brain, γ-tubulin 1 remains the major isotype in various brain regions. Differentiation of SH-SY5Y human neuroblastoma cells or oxidative stress induced by mitochondrial inhibitors resulted in upregulation of γ-tubulin 2, while the expression of γ-tubulin 1 was unchanged. These data indicate that in the face of predominant γ-tubulin 1 expression, the accumulation of γ-tubulin 2 in mature neurons and neuroblastoma cells during oxidative stress may denote a prosurvival role of γ-tubulin 2 in the neurons. We have also shown that *TUBG1* missense variants linked with malformations of cortical development disrupt microtubule dynamics but not neurogenesis. Finally, we were the first to report that the self-assembly of tubulin can be controlled by intense nanosecond pulsed electric fields, which modulate tubulin conformations.

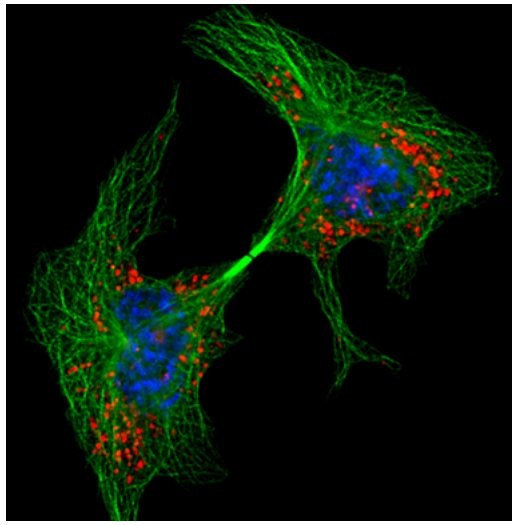


Figure 1. Rat basophilic RBL-2H3 cells stained for microtubules (green), serotonin granules (red) and nuclei (blue).

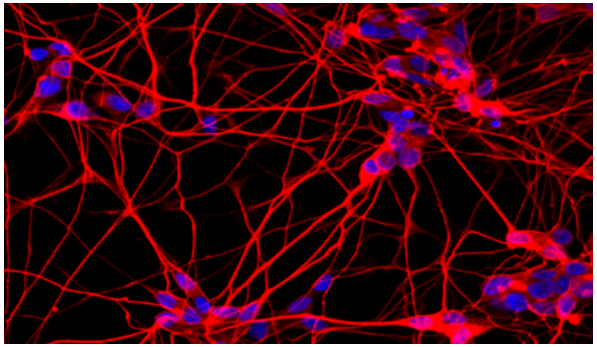


Figure 2. Human neuroblastoma SH-SY5Y cells differentiated by all-trans retinoic acid. Staining for βIII-tubulin (red) and nuclei (blue).

Selected publications:

1. Klebanovych A, Sládková V, Sulimenko T, Vosecká V, Rubíková Z, Čapek M, Dráberová E, Dráber P*, Sulimenko V* (2019) Regulation of microtubule nucleation in mouse bone marrow-derived mast cells by protein tyrosine phosphatase SHP-1. ***Cells*, 8**:e345.
2. Chafai DE*, Sulimenko V, Havelka D, Kubínová L, Dráber P, Cifra M* (2019) Reversible and irreversible modulation of tubulin self-assembly by intense nanosecond pulsed electric fields. ***Adv Mater*, 31**:e1903636.
3. Ivanova E, Gilet JG, Sulimenko V, Duchon A, Rudolf G, Runge K, Collins SC, Asselin L, Broix L, Drout N, Tilly, P, Nusbaum P, Vincent A, Magnant W, Skory V, Birling MC, Pavlovic G, Godin JD, Yalcin B, Herault Y, Dráber P, Chelly J, Hinckelmann MV* (2019) *TUBG1* missense variants underlying cortical malformations disrupt neuronal locomotion and microtubule dynamics but not neurogenesis. ***Nat Commun*, 10**:e2129.
4. Rubíková Z, Sulimenko V, Paulenda T, Dráber P* (2018) Mast cell activation and microtubule organization is modulated by miltefosine through protein kinase C inhibition**.** ***Front Immunol*, 9**:e1563.
5. Dráberová E, Sulimenko V, Vinopal S, Sulimenko T, Sládková V, D'Agostino L, Sobol M, Hozák P, Křen L, Katsetos CD, Dráber P*(2017) Differential expression of human γ-tubulin isotypes during neuronal development and oxidative stress points to γ-tubulin 2 prosurvival function. ***FASEB J*, 31**:1828-1848.

In the picture: 1. Sulimenko Vadym | 2. Rubíková Zuzana | 3. Vosecká Věra | 4. Sládková Vladimíra | 5. Sulimenko Tetyana | 6. MIchová Irena | 7. Klebanovych Anastasiya | 8. Dráberová Eduarda | 9. Dráber Pavel

LABORATORY OF

BIOLOGY OF THE CELL NUCLEUS

Nucleus, nucleoskeleton, transcription, phospholipids, lamin

Pavel Hozák

more information

e-mail

Cell nucleus, regulation of gene expression, nucleoskeleton, nuclear myosins and phospholipids, microscopy

In diploid mammalian cells, some 6×10^9 base pairs of DNA fold as a nucleoprotein complex (i.e., chromatin) into higherorder 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. The nuclear interior is therefore functionally highly compartmentalized, and recent evidence points strongly to structurerelated regulation of the nuclear functions – however, the mechanisms forming the 3Dstructure of the nucleus are still mostly obscure. We therefore employ a multidisciplinary approach in order to study the nuclear functions in relation to the higherorder nuclear structures, e.g., nuclear bodies, the nucleolus, and the nucleoskeleton.

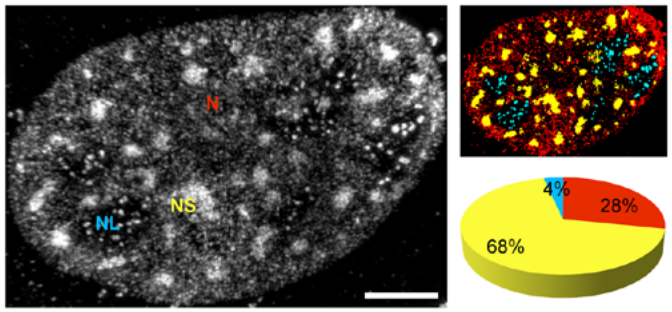
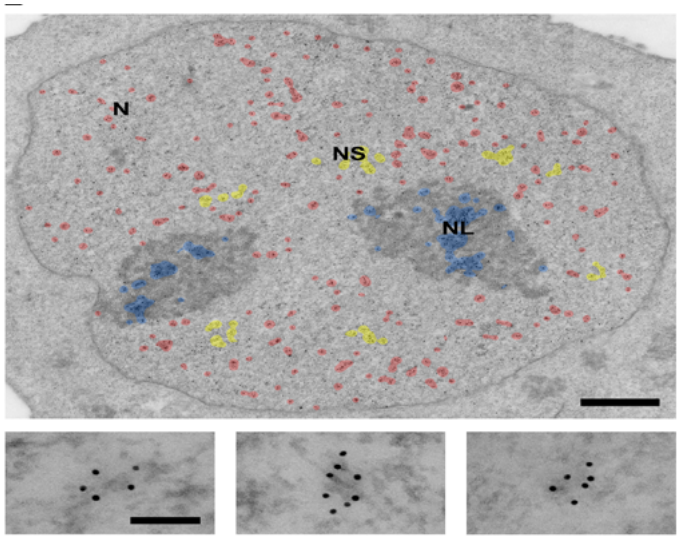


Figure 1. Super-resolution image showing PtdIns(4,5)P2 antibody staining in nuclear speckles (NS), nucleoli (NL) and the nucleoplasm (N). Scale bar: 1 μm. The distribution of PtdIns(4,5)P2 pools in colour-coded original image and intensity quantification chart are shown on the right.

Our research concentrates on: (1) the relationship between nuclear compartmentalization and regulation of gene expression, (2) the structure, dynamics, and function of the nucleoskeleton, which contributes to the nuclear compartmentalization, (3) the molecular mechanisms of laminopathies, (4) the functions of nuclear lipids, (5) development of new microscopy methods.

Figure 2. A TEM image of nuclear PtdIns(4,5)P2 labelling on the surface of an ultrathin section. The abbreviations and colour-coding are the same as above. NLIs of 40–100 nm are shown in a magnified view below. Scale bars: 1 μm (main panel), 100 nm (magnified views)



Selected publications:

1. Fišerová J, Maninová M, Sieger T, Uhlířová J, Šebestová L, Efenberková M, Čapek M, Fišer K, Hozák P* (2019) Nuclear pore protein TPR associates with lamin B1 and affects nuclear lamina organization and nuclear pore distribution. *Cell Mol Life Sci*, **76**:21992216.
2. Sztacho M, Sobol M, Balaban C, Escudeiro Lopes SE, Hozák P* (2019) Nuclear phosphoinositides and phase separation: Important players in nuclear compartmentalization. *Adv Biol Regul*, **71**:111117.
3. Ulicna L, Rohozkova J, Hozak P* (2018) Multiple aspects of PIP2 involvement in C. elegans gametogenesis. *Int J Mol Sci*, **19**(9).
4. Sobol M, Krausová A, Yildirim S, Kalasová I, Fáberová V, Vrkoslav V, Philimonenko V, Marášek P, Pastorek L, Čapek M, Lubovská Z, Uličná L, Tsuji T, Lísa M, Cvačka J, Fujimoto T, Hozak P * (2018) Nuclear phosphatidylinositol 4,5bisphosphate islets contribute to efficient RNA polymerase IIdependent transcription. *J Cell Sci*,**131**(8).
5. Ulicna L, Kalendova A, Kalasova I, Vacik T, Hozák P* (2018) PIP2 epigenetically represses rRNA genes transcription interacting with PHF8. *Biochim Biophys Acta Mol Cell Biol Lipids*, **1863**:266275.

In the picture: 1. Hozák Pavel | 2. Sztacho Martin | 3. Kříž Pavel | 4. Jelínková Iva | 5. Fišerová Jindřiška | 6. Amlerová Zuzana | 7. Filimoněnko Vlada | 8. Miladinović Ana | 9. Maystorova Rositsa | 10. Šebestová Lenka | 11. Uhlířová Jana | 12. Pišlová Lenka | 13. Biddle Veronika

LABORATORY OF

CANCER BIOLOGY

Ubiquitin ligase, cell cycle, stress, mouse model, cancer

Lukáš Čermák

BIOCEV

more information

e-mail

Protein degradation via the proteasome-ubiquitin system (UPS) plays a crucial role in cellular homeostasis. Defects in this system are often associated with pathologic states such as cancer or developmental abnormalities. E3-ubiquitin ligases are responsible for substrate recognition and subsequent degradation. Despite this fact, many of them have not been paired with any specific substrate yet. In our projects, we focused on Cullin-dependent ubiquitin ligases. To discover novel substrates of these multisubunit enzymes, we perform state-of-art affinity purification of protein complexes associated with these enzymes. Detailed biochemical analysis of the interaction between potential substrates and ubiquitin ligases helps us to reveal novel mechanisms of substrate recognition and signalling pathways involved in cellular growth, survival and stress response. Besides the cancer cell line environment, we aspire to confirm novel roles of selected ubiquitin ligases in a physiologic context. In collaboration with the Czech Centre for Phenogenomics (CCP), we are developing mouse models of their deficiency and dysregulation.

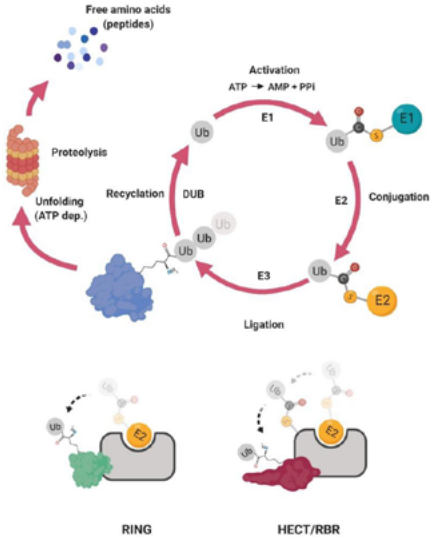


Figure 1. UPS system

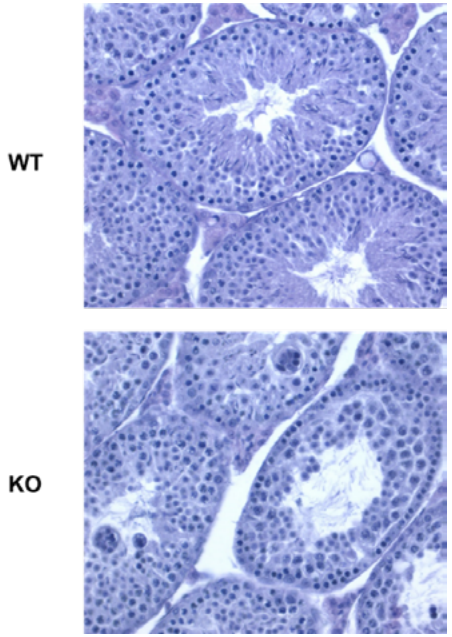


Figure 2. Inactivation of E3 ubiquitin ligase in the mouse model and its effect on spermatogenesis

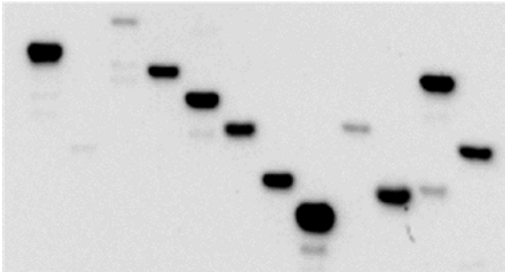
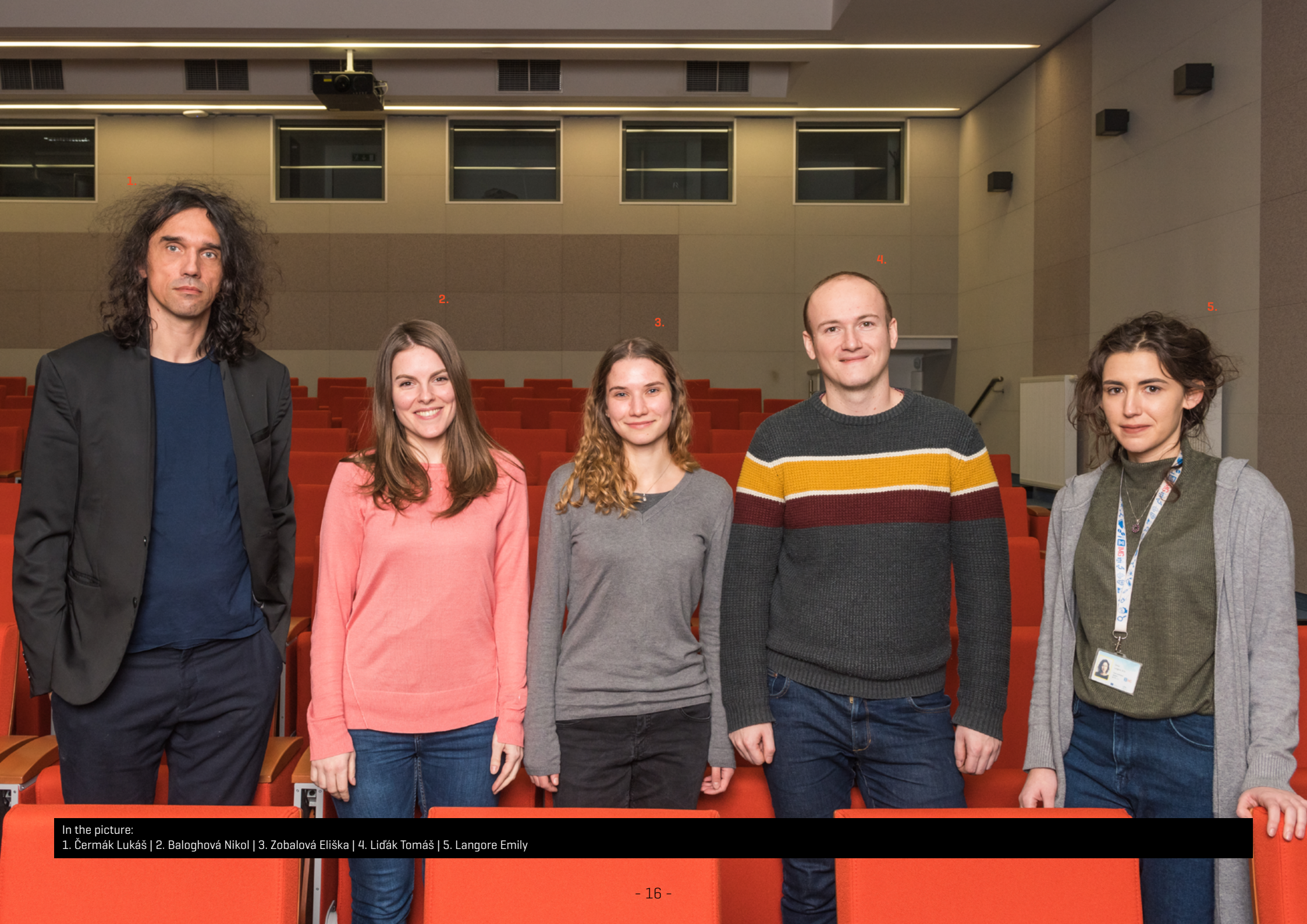


Figure 3.: Expression of various E3 ubiquitin ligases isolated for mass-spectrometry analysis of their potential substrates

Selected publications:

1. Baloghova N, Lidak T, Cermak L* (2019) Ubiquitin ligases involved in the regulation of Wnt, TGF-β, and Notch signaling pathways and their roles in mouse development and homeostasis. Genes. 2019 Oct 16;10(10)
2. Horn M, Geisen C, Cermak L, Becker B, Nakamura S, Klein C, Pagano M, Antebi A. DRE-1/FBXO11-dependent degradation of BLMP-1/BLIMP-1 governs C. elegans developmental timing and maturation. Developmental Cell. 2014 Mar 31;28(6):697-710
3. Duan S, Cermak L, Pagan JK, Rossi M, Martinengo C, di Celle PF, Chapuy B, Shipp M, Chiarle R, Pagano M (2012) FBXO11 targets BCL6 for degradation and is inactivated in diffuse large B-cell lymphomas. Nature. 2011 Nov 23



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1. Čermák Lukáš | 2. Baloghová Nikol | 3. Zobalová Eliška | 4. Liďák Tomáš | 5. Langore Emily

LABORATORY OF

CANCER CELL BIOLOGY

Cancer, cell cycle, checkpoint, oncogene, tumour suppressor

Libor Macůrek

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In the laboratory of Cancer Cell Biology, we study the cellular responses to genotoxic stress. We focus on the mechanisms that maintain genome integrity in healthy cells and on the defects that allow cancer cells to escape the surveillance mechanisms. In particular, we focus on protein phosphatase PPM1D/WIP1, which negatively regulates tumour suppressor p53. We employ cell biology, CRISPR-mediated gene editing, molecular biology and biochemical approaches to decipher the mechanisms that control the PPM1D/WIP1 function. In addition, we use mouse models to investigate the oncogenic properties of PPM1D/WIP1. We also explore PPM1D/WIP1 as a potential pharmacological target in cancers with wild-type p53. Finally, we screen cancer patients for mutations in cancer-predisposing genes to identify new prognostic biomarkers.

Figure 1. Working model for the role of PPM1D/Wip1 in cancer development | Upon genotoxic stress, healthy cells activate tumor suppressor p53 and stop transmission through cell cycle. Cells with abnormally high levels of PPM1D/Wip1 fail to stop in the checkpoint and continue proliferation despite the presence of damaged DNA. Accumulation of genetic abnormalities can eventually lead to cell transformation.

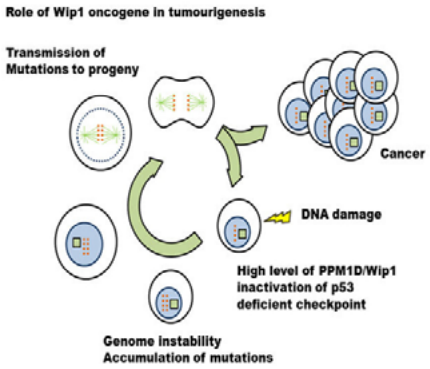


Figure 2. Mutation of PPM1D/Wip1 impairs cell cycle checkpoint | Healthy cells do not divide in the presence of DNA damage and arrest in G1 phase of the cell cycle (red). Cells carrying mutation in PPM1D gene continue progression through the cell cycle also in the presence of DNA damage and start replicating their genome (orange). Mutation in PPM1D does not affect cells in the G2 phase of the cell cycle.

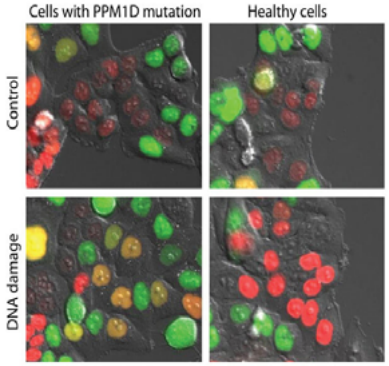
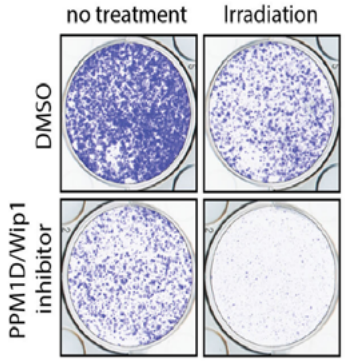


Figure 3. Suppression of cancer cell growth by combination of PPM1D/Wip1 inhibitor and radiotherapy | Breast cancer cells were treated or not with small-molecule PPM1D/Wip1 inhibitor and exposed to ionizing radiation. Colony formation (blue dots) was evaluated after 2 weeks.



Selected publications:

1. Burocziova M, Burdova K, Martinikova AS, Kasparek P, Kleiblova P, Danielsen SA, Borecka M, Jenikova G, Janečková L, Pavel J, Zemankova P, Schneiderova M, Schwarzova L, Ticha I, Sun XF, Jiraskova K, Liska V, Vodickova L, Vodicka P, Sedlacek R, Kleibl Z, Lothe RA, Korinek V, Macurek L (2019) Truncated PPM1D impairs stem cell response to genotoxic stress and promotes growth of APC-deficient tumors in the mouse colon. ***Cell Death Dis*, 10**:818.
2. Burdova K, Storchova R, Palek M, Macurek L (2019) WIP1 Promotes homologous recombination and modulates sensitivity to PARP inhibitors. ***Cells*, 8**:1258.
3. Jaiswal H, Benada J, Müllers E, Akopyan K, Burdova K, Koolmeister T, Helleday T, Medema RH, Macurek L, Lindqvist A (2017) ATM/Wip1 activities at chromatin control Plk1 re-activation to determine G2 checkpoint duration. ***EMBO J*, 36**:2161-2176.
4. Kleiblova P, Stolarova L, Krizova K, Lhota F, Hojny J, Zemankova P, Havranek O, Vocka M, Cerna M, Lhotova K, Borecka M, Janatova M, Soukupova J, Sevcik J, Zimovjanova M, Kotlas J, Panczak A, Vesela K, Cervenkova J, Schneiderova M, Burocziova M, Burdova K, Stranecky V, Foretova L, Machackova E, Tavandzis S, Kmoch S, Macurek L, Kleibl Z (2019) Identification of deleterious germline CHEK2 mutations and their association with breast and ovarian cancer. ***Int J Cancer*, 145**:1782-1797.

In the picture: 1. Gui Wentao | 2. Palek Matouš | 3. Karri Sirish | 4. Štorchová Radka | 5. Vieru Andra Stefania | 6. Aquino Perez Cecilia | 7. Císařová Natálie | 8. Macůrek Libor | 9. Pavel Jozef | 10. Stolařová Lenka

LABORATORY OF

CELL AND DEVELOPMENTAL BIOLOGY

Stem cells, signalling pathways, intestinal epithelium, cancer, haematological disorders

Vladimír Kořínek

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Tissues in the adult organism contain a population of tissue-specific stem cells that provide the cellular basis for homeostatic maintenance of adult tissues. The stem cell behaviour is controlled by multiple signalling pathways that regulate stem cell renewal and the balance between cell proliferation and differentiation. Genetic alterations in tumour suppressors and proto-oncogenes lead to deregulation of these cascades, resulting in cellular transformation and tumour formation. Our research is focused on three scientific themes:

Research theme 1 – Tumour-initiating programme in the intestine

Since the fate of intestinal stem cells is determined by the Wnt signalling pathway, our aim is to find genes that are regulated by Wnt signalling. Advanced colorectal tumours display high heterogeneity; however, tumour-initiating mutation in the Apc tumour suppressor underlies the origin of the vast majority of them. Our recent results indicate that depending on the position in the intestine, the transformed cell activates a specific transcriptional programme to ensure its long-term survival in the tissue.

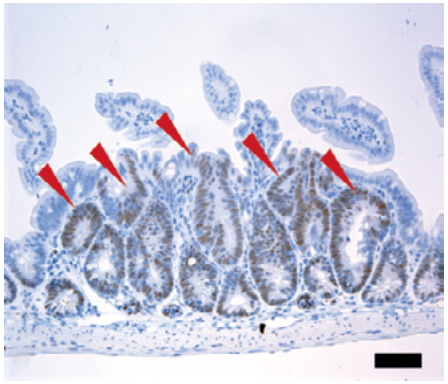

Figure 1. Microadenomas (red arrowheads) arising in the Apc-deficient small intestine. Immunohistochemical localization of proliferating cell nuclear antigen (PCNA; brown cell nuclei) in the small intestine of ApccKO/cKO Lgr5-EGFP-IRES-CreERT2 mice 21 days after tamoxifen administration. Sections were counterstained with haematoxylin (blue nuclear signal); scale bar: 0.3 mm.

Research theme 2 – Adult somatic stem cell niche

The identity of somatic stem cells is determined by a specific microenvironment, so-called stem cell niche, which promotes a strict control over tissue homeostasis. Our aim is to depict the complex interactions between the stem cell niche and stem cells during epithelial renewal and in colon cancer. Recently, we have discovered that sub-epithelial mesenchymal cells constitute the intestinal stem cell niche by secreting Wnt ligands that promote the stem cell renewal.

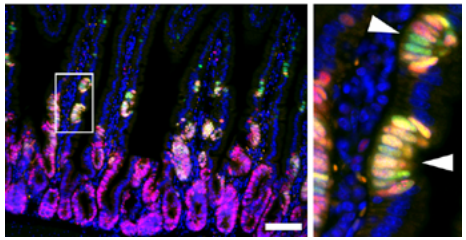

Figure 2. Msx1 marks ectopic crypts formed on the small intestinal villi upon Apc loss. Fluorescent microscopy images of Msx1 (green fluorescent signal) and PCNA (red florescent signal) protein localization in ApccKO/cKO Villin-CreERT2 small intestine 4 days after tamoxifen administration. Ectopic crypts containing Msx1- and PCNA-positive cells are formed on the villi (white arrowheads in inset). Some of these cells co-express Msx1 and PCNA (yellow fluorescence). Specimens were counterstained with DAPI (nuclear blue florescent signal). Notice that the purple colour results from the coalescence of the blue and red fluorescent signal. Scale bar: 0.15 mm.

Research theme 3 – Genetic basis of haematological malignancies

Myeloproliferative neoplasms (MPN) represent a group of disorders arising due to the genetic defect(s) in haematopoietic stem cells. While the concept of somatic driver mutations in MPNs is well established, the contribution of other factors, such as germ-line variants that modulate the risk of MPN development by promoting acquisition of additional somatic mutations, is less understood. Our aim is to identify the new genetic predispositions to MPN and characterize them. We have demonstrated that a germ-line (or acquired) mutation in the gene encoding kinase JAK2 enhances oncogenic JAK2/STAT signalling and causes a specific clinical course of the disease in MPN patients.

Selected publications:

1. Babosova O, Kapralova K, Raskova Kafkova L, Korinek V, Divoky V, Prchal JT, Lanikova L* (2019) Iron chelation and 2-oxoglutarate-dependent dioxygenase inhibition suppress mantle cell lymphoma's cyclin D1. *J Cell Mol Med*, **23**:7785-7795.
2. Horazna M, Janeckova L, Svec J, Babosova O, Hrckulak D, Vojtechova M, Galuskova K, Sloncova E, Kolar M, Strnad H, Korinek V* (2019) Msx1 loss suppresses formation of the ectopic crypts developed in the Apc-deficient small intestinal epithelium. *Sci Rep*, **9**:1629.
3. Degirmenci B, Valenta T*, Dimitrieva S, Hausmann G, Basler K* (2018) GLI1-expressing mesenchymal cells form the essential Wnt-secreting niche for colon stem cells. *Nature*, **558**:449-453.
4. Mambet C, Babosova O, Defour JP, Leroy E, Necula L, Stanca O, Tatic A, Berbec N, Coriu D, Belickova M, Kralova B, Lanikova L, Vesela J, Pecquet C, Saussoy P, Havelange V, Diaconu CC, Divoky V*, Constantinescu SN* (2018) Cooccurring V617F and R1063H mutations increase JAK2 signaling and neutrophilia in myeloproliferative neoplasms. *Blood*, **132**:2695-2699.
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LABORATORY OF

CELL DIFFERENTIATION

Chemical biology, hematopoietic and neural cell differentiation, signalling pathways, zebrafish

Petr Bartůněk

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The main interest of the laboratory lies in the study of the molecular mechanism of cell fate determination. We have established systems to get insight into the self-renewal and differentiation of haematopoietic and neural stem cells.

Neural stem cells (NSCs) are defined by their dual ability to self-renew through mitotic cell division or differentiate into the varied neural cell types. DISP3/PTCHD2 is a sterol-sensing domain-containing protein, which is highly expressed in neural tissues. We demonstrated that NSC differentiation triggered significant reduction in DISP3 expression in the resulting astrocytes, neurons and oligodendrocytes. Moreover, when DISP3 expression was disrupted, the NSC "stemness" was suppressed, leading to a larger population of cells undergoing spontaneous neuronal differentiation. Conversely, overexpression of DISP3 resulted in increased NSC proliferation and impaired cell differentiation (Konirova et al. 2017).

In brain cancer treatment, radiotherapy plays a significant role; however, the use of this therapy is often accompanied by neurocognitive decline that is, at least partially, a consequence of radiation-induced damage to NSC populations. Our new findings describe features that define the response of neural stem cells to ionizing radiation. We investigated the effects of irradiation on NSCs isolated from the mouse brain. We show that most cells do not undergo apoptosis after irradiation but rather cease proliferation and start a differentiation programme (Konirova et al. 2019).

Our studies on vertebrate haematopoietic development have been extended by establishing *ex vivo* cultures of zebrafish haematopoietic cells. Recently, we have produced several recombinant zebrafish growth factors (Epo, Gcsfa/b, Tpo, IL34, Mcsfa/b and SCFa/b) that allow us to establish, for the first time, zebrafish haematopoietic clonal assays in semisolid media. Our findings bring information on how haematopoietic cytokines had evolved following the diversification of teleosts and mammals from a common ancestor (Oltova et al. 2018).

Moreover, these tools enabled us to reveal the clonogenic and proliferation capacity of bi-potent thrombo/erythropoietic progenitors with respect to their mammalian haematopoietic counterparts. Despite obvious phenotypic differences between fish and mammalian thrombocytes and erythrocytes, our results strongly demonstrate the evolutionary conservation of the basic processes and molecular mechanisms of erythro/thrombopoiesis in the vertebrates.

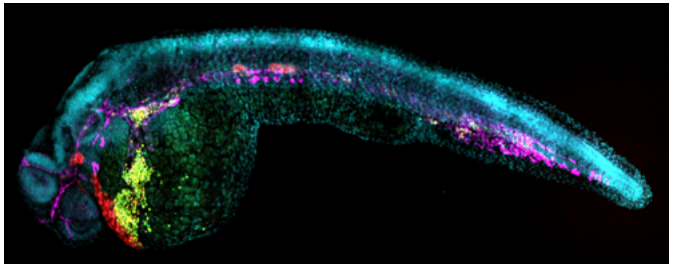

Figure 1. Whole-mount multiplexed RNA fluorescence in situ hybridization of 30 hpf zebrafish embryo. RNA was stained using hybridization chain reaction technology (Molecular Instruments). Zebrafish erythrocytes were detected using gata1a (green) and klf17 (red) probes, endothelial cells were stained using etv2 probe (magenta), and nuclei were visualized using DAPI (cyan).

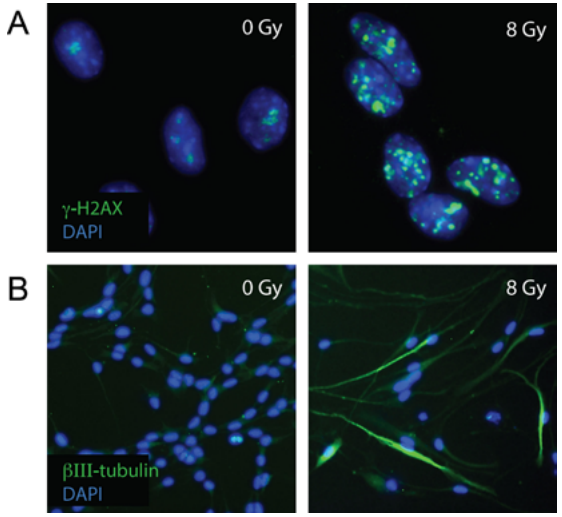

Figure 2. The response of neural stem cells to ionizing radiation. (A) DNA damage response is induced by irradiation. Neural stem cells after irradiation stained with γH2AX antibody (green) and DAPI (blue). (B) Radiation promotes NSC differentiation. Neural stem cells after irradiation stained with βIII-tubulin antibody (green) and DAPI (blue).

Selected publications:

1. Konířová J, Oltová J, Corlett A, Kopycińska J, Kolář M, Bartůněk P, Zíková M* (2017) Modulated DISP3/PTCHD2 expression influences neural stem cell fate decisions. *Sci Rep*, **7**:41597.
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6. Oltova J, Svoboda O, Bartunek P. Front Cell Dev Biol. 2018 Dec 20;6:174. doi: 10.3389/fcell.2018.00174. eCollection 2018. Review

In the picture: 1. Bartůněk Petr | 2. Zíková Martina | 3. Jarošová Šárka | 4. Machoňová Olga | 5. Oltová Jana | 6. Svoboda Ondřej | 7. Mikulášová Tereza | 8. Klementová Jana | 9. Kovář Martin | 10. Dvořák Michal 11. Jovičić Jovana | 12. Dobiášovská Ivana | 13. Hojerová Tereza | 14. Vondráková Zuzana | 15. Dvořáková Marta

LABORATORY OF

CELL MOTILITY

Cytoskeleton, trypanosome flagellum, mammalian cilium, processes of flagellum formation

Vladimír Varga

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Our research focuses on the eukaryotic flagellum and cilium, fascinating organelles with motility, sensory and signalling functions. Malfunctions of these organelles in humans cause pleiotropic diseases collectively called ciliopathies. There is little understanding of how these complex organelles with a highly organized cytoskeleton are formed. We leverage the unique experimental tractability of parasitic flagellate *Trypanosoma brucei* to identify proteins involved in the processes of flagellum formation and length regulation.

To gain an insight into the activities of the identified proteins, we employ a broad range of molecular biology, biochemistry, and advanced light and electron microscopy approaches. Taking advantage of the high degree of evolutionary conservation of the cilia, we search for mammalian orthologues of the *T. brucei* proteins and study those in mammalian models. We believe that understanding the processes of the flagellum formation will be informative as to the causes of individual ciliopathies.

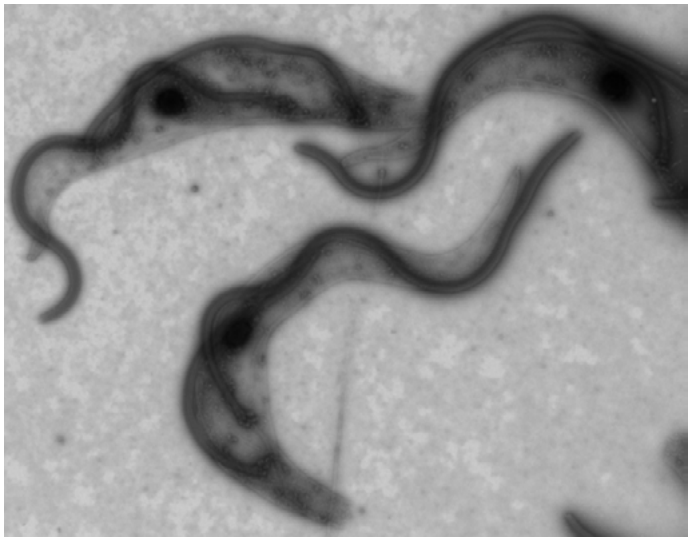

Figure 1. A transmission electron microscopy image of detergent-extracted whole-mount negatively stained cells of Trypanosoma brucei. (Image taken by Miroslava Šedinová)

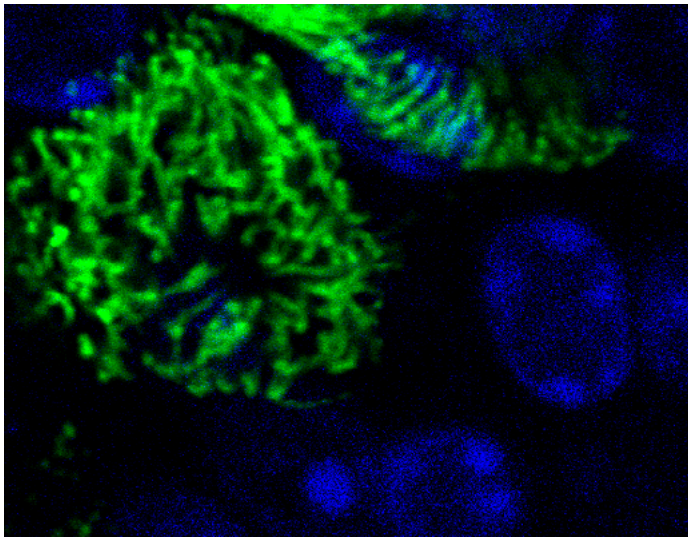

Figure 2. A fluorescence microscopy image of multiciliated tracheal epithelial cells. Cilia in green, cell nuclei in blue. (Image taken by Peter Gorilák)

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1. Varga V*, Moreira-Leite F, Portman N, Gull K* (2017) Protein diversity in discrete structures at the distal tip of the trypanosome flagellum. *Proc Natl Acad Sci USA* **114**:E6546-E6555.
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LABORATORY OF

EPIGENETIC REGULATIONS

Oocyte-to-embryo transition, RNA degradation, RNAi, miRNA, retrotransposon

Petr Svoboda

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We study the mechanisms governing gene expression during mammalian oocyte-to-embryo transition (OET). OET is an orchestrated process where a highly specialized cell – the oocyte – is transformed into cells that are able to give rise to a new organism. This transformation is accompanied by extensive reprogramming of gene expression, which includes extensive post-transcriptional control of maternal mRNAs. Maternal mRNAs that are no longer needed are eliminated, while mRNAs whose products are needed for zygotic genome activation (ZGA) are maintained and translated. Our recent research focused on induction of selective mRNA degradation during resumption of meiosis, fertilization, and zygotic genome activation. Our current work aims at understanding the evolving role of small RNAs during OET.

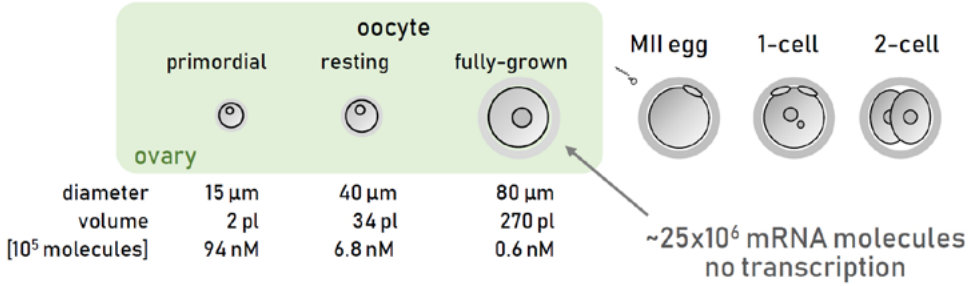

Figure 1. Oocyte-to-embryo transition in mice. Ovarian oocyte development is followed by ovulation, completion of meiosis, fertilization, and zygotic genome activation, which takes place at the 2-cell stage in mouse zygotes. An important aspect of OET is management of the massive maternal transcriptome in the large cytoplasmic volume.

Small RNAs guiding repressive ribonucleoprotein complexes represent a unique layer of control of gene expression and retrotransposon activity. Our research focuses on the role of three classes of small RNAs (microRNAs, short interfering RNAs (siRNAs) and PIWI-associated RNAs (piRNAs)) in the mammalian female germline. Mammalian oocytes offer an excellent opportunity to study the evolving co-existence of all three classes of small RNAs. While only siRNAs acting in the RNA interference (RNAi) pathway are essential for OET in mice, it is unclear whether this is exceptional or common in mammals.

We particularly focus on the molecular foundation of highly active RNAi in mouse oocytes: a unique maternal isoform of Dicer, which is responsible for highly efficient siRNA production, and an evolving set of long non-coding RNAs carrying antisense pseudogene sequences, which give rise to siRNAs, which in turn suppress complementary mRNA. Research questions we wish to answer include: Which molecular mechanisms are controlled by RNAi in mouse oocytes? How small RNA pathways operate in oocytes of other mammals, such as rat, hamster, cow, and pig? What are the consequences of ectopically enhanced RNAi in somatic cells?

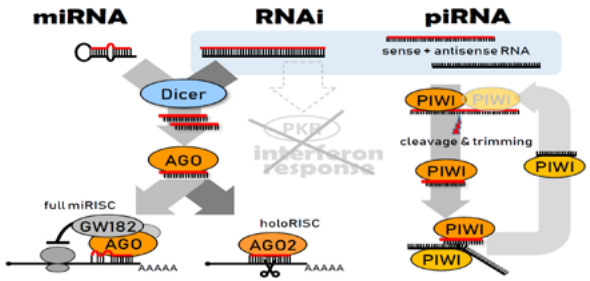

Figure 2. Schematic depiction of the three small RNA pathways that are present in mammalian oocytes. While all three pathways are present, their physiological relevance in the female germline may vary.

Selected publications:

1. Taborska E, Pasulka J, Malik R, Horvat F, Jenickova I, Jelić Matošević Z, Svoboda P* (2019) Restricted and non-essential redundancy of RNAi and piRNA pathways in mouse oocytes. *PLoS Genet*, **15**:e1008261. doi:10.1371/journal.pgen.1008261.
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3. Horvat F, Fulka H, Jankele R, Malik R, Jun M, Solcova K, Sedlacek R, Vlahovicek K, Schultz RM, Svoboda P* (2018) Role of Cnot6l in maternal mRNA turnover. *Life Sci Alliance*, **1**:e201800084. doi: 10.26508/lsa.201800084.
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LABORATORY OF

EPIGENETICS OF THE CELL NUCLEUS

Chromosomal dynamics, Vinculin/DEB-1, gametogenesis, C. elegans, M. musculus

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Identification of new players affecting meiosis during gametogenesis is clearly a very important, timely endeavour as the chromosomal dynamics and possible complications during meiotic divisions still remain incompletely understood. Yet, inaccuracies during meiotic stages are connected to chromosomal aberrations leading to severe genetic disorders as well as to male infertility.

In our experiments, we showed that vinculin/DEB-1 participates in meiotic prophase progression. Depletion of DEB-1 impacts chromosomal pairing stabilization, attachment of chromosomes to cytoskeletal forces, and formation of synaptonemal complex during prophase I, resulting in meiosis delay and increased presence of chromosome univalents. Our study thus revealed an unsuspected role of DEB-1 in the progression of meiotic prophase, including chromosome dynamics and pairing that have been shown to be essential meiotic components.
So far, nuclear functions of vinculin/DEB-1 have not been described at all, and we suggest accomplishing a systematic study using a panel of structural, molecular and genetic methods in order to reveal details about its biological functions in the cell nucleus, and in meiosis in particular. We plan to achieve two main aims: 1/ Mapping of vinculin at meiosis-specific structures in cell nuclei; 2/ Deciphering the meiosis-specific roles of vinculin and associated proteins.
Meiosis is a key process in sexual reproduction contributing to the genetic variability of organisms. Deciphering the roles of novel components of the synaptonemal complex would therefore significantly contribute to our understanding of the molecular mechanisms and dynamics of meiotic events, and may possibly also help to explain some of the fertility deficiencies, which are a prominent medial problem affecting 10 % of humans.

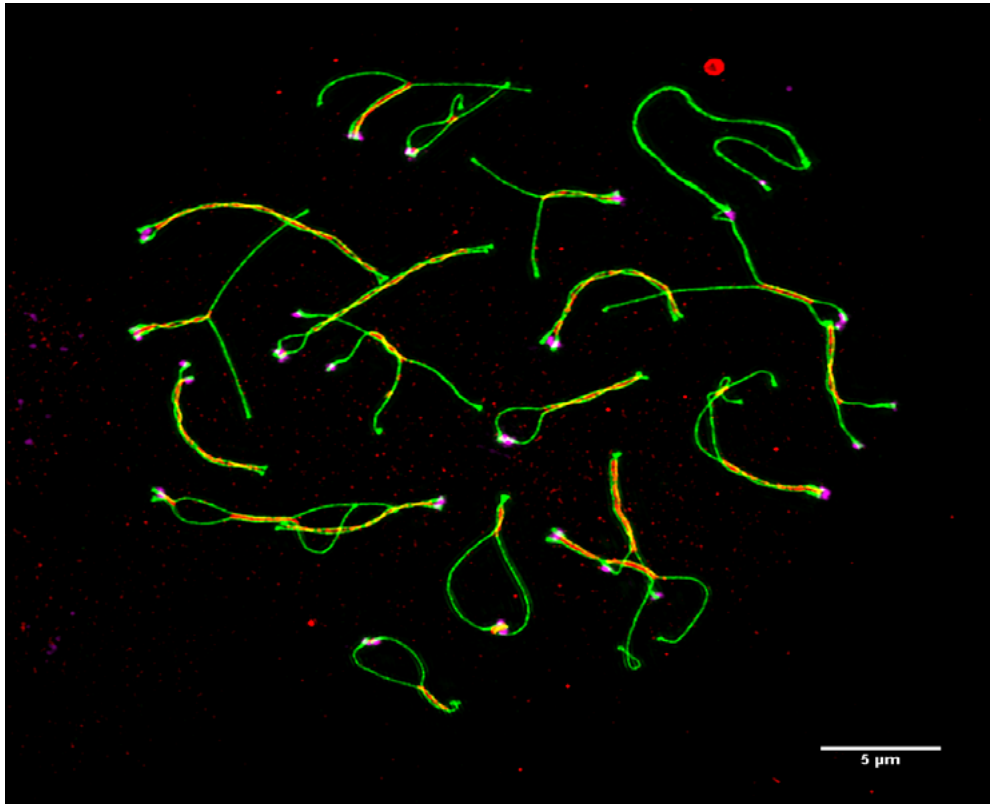

Figure 1. Spread mouse primary spermatocyte of an adult fertile male in the diplotene stage of meiotic cell division. Meiotic synaptonemal-complex (SC) proteins of the pairing chromosomes are marked by indirect immunofluorescence technique. SYCP3 – the lateral element of SC in green colour; SYCP1 - the central element of SC in red colour; in magenta, centromeres – the structural part of chromosomes essential for the proper pairing and segregation of homologous chromosomes.

Selected publications:

1. Rohožková J, Hůlková L, Fukalová J, Flachs P, Hozák P* (2019) Pairing of homologous chromosomes in C. elegans meiosis requires DEB-1 – an orthologue of mammalian vinculin. *Nucleus*, **10**:93-115. doi: 10.1080/19491034.2019.1602337
2. Fišerová J, Maninová M, Sieger T, Uhlířová J, Šebestová L, Efenberková M, Čapek M, Fišer K, Hozák P* (2019) Nuclear pore protein TPR associates with lamin B1 and affects nuclear lamina organization and nuclear pore distribution. *Cell Mol Life Sci*, **76**:2199-2216. doi: 10.1007/s00018-019-03037-0

In the picture: 1. Hozák Pavel | 2. Flachs Petr | 3. Darášová Alžběta | 4. Hůlková Lenka | 5. Pišlová Lenka

LABORATORY OF

EYE BIOLOGY

Development, eye, brain, mouse, genetics

Zbyněk Kozmik

BIOCEV

more information

e-mail

We are interested in studies of embryonic development of the mammalian eye and brain. Our focus is on the role of transcription factors, epigenetic regulators and signalling cascades. We use the mouse as a versatile laboratory model that allows us to combine powerful genetics, embryology and cell biology approaches. Conditional inactivation of individual genes is achieved using the Cre/loxP system within the developing retina or brain of the mouse embryo.

Figure 1. Expression of transcription factor Pax6 in embryonic mouse eye

Selected publications:

1. Fujimura N, Kuzelova A, Ebert A, Strnad H, Lachova J, Machon O, Busslinger M, Kozmik Z* (2018) Polycomb repression complex 2 is required for the maintenance of retinal progenitor cells and balanced retinal differentiation. *Dev Biol*, **433**:47-60. doi: 10.1016/j.ydbio.2017.11.004. Epub 2017 Nov 12.
2. Chodelkova O, Masek J, Korinek V, Kozmik Z, Machon O* (2018) Tcf7L2 is essential for neurogenesis in the developing mouse neocortex. *Neural Dev*, **13**:8. doi: 10.1186/s13064-018-0107-8.

In the picture: 1. Dupačová Naoko | 2. Láchová Jitka | 3. Kozmik Zbyněk | 4. Antošová Barbora | 5. Sunny Sweetu Susan | 6. Kreplová Michaela | 7. Smolíková Jana

LABORATORY OF

GENOME DYNAMICS

DNA strand breaks, RNA processing, neurodegeneration

Keith W. Caldecott

more information

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The main research of our group is focused on Poly-ADP-Ribose Polymerases (PARPs); a class of DNA repair enzymes that detect DNA single-strand breaks (SSBs) and signal their presence by catalysing the rapid synthesis of poly(ADP-ribose). In the last few years, we have successfully developed a highly sensitive poly(ADP-ribose) assay for detecting SSBs that arise in the cells. This helped us to publish our conceptually ground-breaking discovery that the neurological disease that is triggered by unrepaired SSBs is caused in part by excessive activation of the DNA damage sensor protein, PARP1. This discovery identifies PARP1 as a plausible new therapeutic target in the treatment of neurological disease; a truly exciting concept in which novel and/or existing PARP1 inhibitors might be repurposed beyond their current use in the cancer clinic. Excitingly, excessive PARP activity has now also been implicated in several common neurological diseases including Alzheimer's, Parkinson's and Huntington's disease, expanding the possible translational significance of our finding. Ultimately, we suggest that SSBs might even be an aetiological factor in normal human ageing.

Importantly, our work in the field of PARP biology extends beyond the molecular mechanisms of human disease in postmitotic cells to include disease mechanisms in proliferating cells. In particular, we have recently identified that the primary source of endogenous SSBs that are detected by PARP1 during normal cell division are not stochastic DNA lesions, but instead are normal Okazaki fragment intermediates of DNA replication. This unexpected and striking discovery implicates PARP-dependent DNA repair as an alternative pathway for the processing of canonical DNA replication intermediates; a paradigm-shifting discovery that challenges the "text book" view of how DNA is replicated. This work has major implications for cancer research, because it identifies these obligatory DNA replication intermediates as the likely source of synthetic lethality that is triggered in certain cancer cells by PARP1 inhibition.

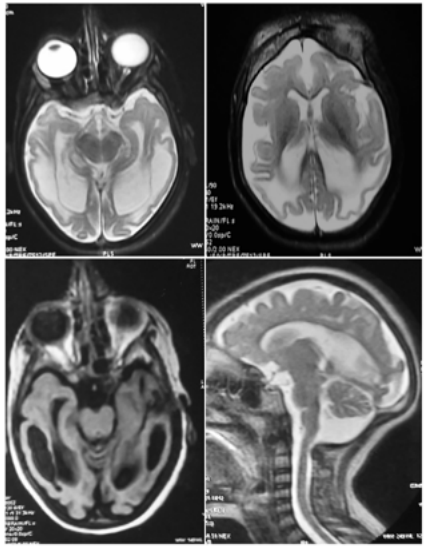

Figure 1. A magnetic resonance imaging (MRI) scan of a patient with microcephaly, an abnormally small head circumference.

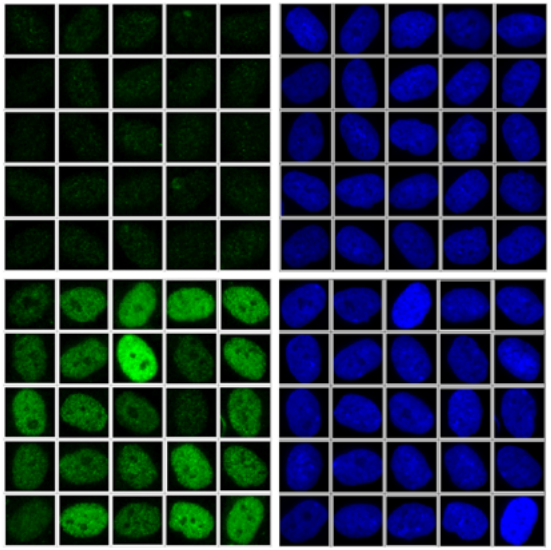

Figure 2. A fluorescence image obtained by high-throughput microscopy showing an accumulation of a DNA single-strand break marker ADP-ribose (green) in individual cell nuclei. After application of a DNA damage-inducing agent, the patient-derived cells (bottom) accumulate ADP-ribose compared to the healthy control (top).

Selected publications:

1. Hanzlikova H*, Kalasova I, Demin AA, Pennicott LE, Cihlarova Z, Caldecott KW* (2018) The importance of Poly(ADP-Ribose) Polymerase as a sensor of unligated Okazaki fragments during DNA replication. *Mol Cell*, **71(2)**:319-331.e3.
2. Hanzlikova H*, Caldecott KW* (2019) Perspectives on PARPs in S phase. *Trends Genet*, **35**:412-422.
3. Caldecott KW (2019) XRCC1 protein; form and function. *DNA Repair*, **81**:102664.
4. Kalasova I, Hanzlikova H*, Gupta N*, Li Y, Altmüller J, Reynolds JJ, Stewart GS, Wollnik B, Yigit G, Caldecott KW* (2019) Novel PNKP mutations causing defective DNA strand break repair and PARP1 hyperactivity in MCSZ. *Neurol Genet*, **5**:e320.
5. Mahjoub A, Cihlarova Z, Tétreault M, MacNeil L, Sondheimer N, Caldecott KW, Hanzlikova H*, Yoon G* (2019) Homozygous pathogenic variant in associated with nonprogressive cerebellar ataxia. *Neurol Genet*, **5**:e359.

In the picture: 1. Hanzlíková Hana | 2. Sobol Margarita | 3. Kalasová Ilona | 4. Krejčíková Kateřina | 5. Havelková Jarmila | 6. Caldecott Keith | 7. Cihlářová Zuzana

LABORATORY OF

GENOME INTEGRITY

DNA damage response, carcinogenesis, ageing, R-loops, gold nanoparticles

Jiří Bartek

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The long-term research interest of our group is focused on cellular responses to DNA damage, namely complex and/or difficult to repair DNA lesions resulting in permanent block of cell division termed cellular senescence. Cellular senescence, by its impact on the tissue microenvironment mediated by secretion of specific factors involving proinflammatory cytokines, is emerging as key of multiple factors contributing to ageing and ageing-associated diseases including cancer. We are specifically interested in 1) highlighting the nature of complex and irreparable DNA lesions characteristic of senescent cells; 2) deciphering the role of ribosomal DNA instability in development of cellular senescence and the function of promyelocytic leukaemia protein (PML) in DNA repair of ribosomal DNA loci; 3) unravelling the phenotypic changes occurring during cellular senescence that contribute to resistance of senescent cells to cell death and oxidative stress; 4) mechanisms how senescent cells contribute to radioresistance and chemoresistance of cancer cells and cancer cell phenotypic plasticity in general, including function of specific signalling pathways (namely interferon and TGF-β) in these processes; 5) mechanisms resolving collisions between replication and transcription machineries and associated RNA:DNA hybrids referred to as R-loops; and 6) involvement of the above mechanisms in pathological changes manifested as cancer and ageing with the goal to develop novel therapeutic means, such as development of new drugs specifically targeting senescent cells (termed senolytics) and nanotechnology-based approaches, for instance, thermotherapy utilising targeted gold nanoparticles.

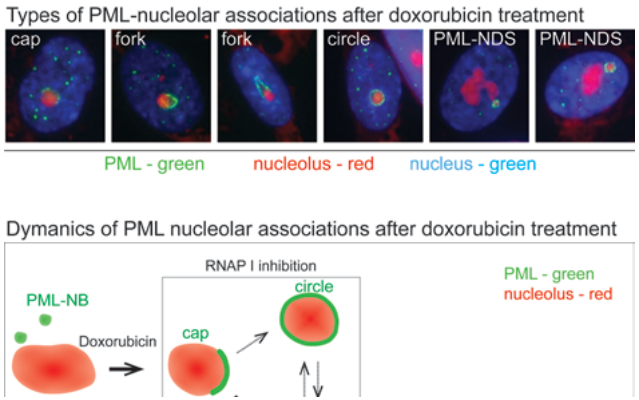

Figure 1. Promyelocytic leukaemia protein (PML) is a core and essential component of PML nuclear bodies (PML-NBs) that are functionally involved in the regulation of cell cycle, apoptosis and cellular senescence. We found that after specific treatments causing drug-induced senescence, PML interacts with the surface of the nucleolus, as shown in the upper microscopic image where PML (green) was detected by indirect immunofluorescence; the nucleolus and nucleus are marked by TOTO3 (red) and DAPI (blue). Schematic depiction (bottom part) of doxorubicin-induced dynamic transitions of nucleolar PML compartments obtained by long-term following cells expressing fluorescent proteins EGFP-PML IV (green) and nucleolar marker RFP-B23 (red) by time lapse microscopy in relation to nucleolar activity of RNA polymerase I (RNAP I). PML-NDS, PML nucleolus-derived structure; PML-NB, PML nuclear body.

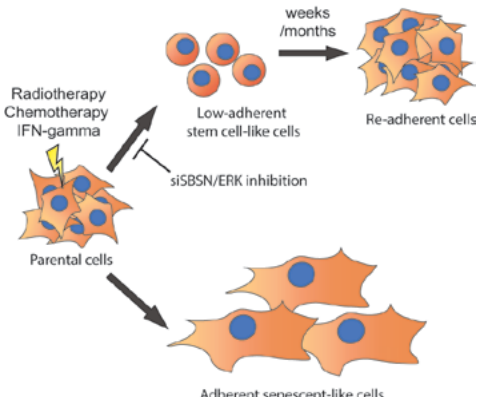

Figure 2. Most cancer patients experience tumour recurrence and metastatic dissemination even after radio- or chemo-therapy. Transcriptome profiling of cancer cells surviving radiation or chemotherapy revealed that, in low-adherent stem-like cells, an IFN- and MAPK/ERK-driven transcription programme mediated expression of a novel oncoprotein, suprabasin, that is functionally involved in the survival of low-adherent cells.

Selected publications:

1. Hubackova S, Pribyl M, Kyjacova L, Moudra A, Dzijak R, Salovska B, Strnad H, Tambor V, Imrichova T, Svec J, Vodicka P, Vaclavikova R, Rob L, Bartek J*, Hodny Z* (2019). Interferon-regulated suprabasin is essential for stress-induced stem-like cell conversion and therapy resistance of human malignancies. *Mol Oncol*, **13**:1467-1489.
2. Imrichova T, Hubackova S, Kucerova A, Kosla J, Bartek J*, Hodny Z*, Vasicova P* (2019) Dynamic PML protein nucleolar associations with persistent DNA damage lesions in response to nucleolar stress and senescence-inducing stimuli. *Aging*, **11**:7206-7235.
3. Vajrychova M, Salovska B, Pimkova K, Fabrik I, Tambor V, Kondelova A, Bartek J*, Hodny Z* (2019) Quantification of cellular protein and redox imbalance using SILAC-iodoTMT methodology. *Redox Biol*, **24**:101227.
4. Vancurova M, Hanzlikova H, Knoblochova L, Kosla J, Majera D, Mistrik M, Burdova K, Hodny Z*, Bartek J* (2019) PML nuclear bodies are recruited to persistent DNA damage lesions in an RNF168-53BP1 dependent manner and contribute to DNA repair. *DNA Repair (Amst)*, **78**:114-127.
5. Zarska M, Sramek M, Novotny F, Havel F, Babelova A, Mrazkova B, Benada O, Reinis M, Stepanek I, Musilek K, Bartek J, Ursinyova M, Novak O, Dzijak R, Kuca K*, Proska J*, Hodny Z* (2018) Biological safety and tissue distribution of (16-mercaptohexadecyl)trimethylammonium bromide-modified cationic gold nanorods. *Biomaterials*, **154**:275-290.

In the picture: 1. Přibyl Miroslav | 2. Šalovská Barbora | 3. Andrš Martin | 4. Salajková Šárka | 5. Imrichová Terezie | 6. Cuchalová Lucie | 7. Žárská Monika | 8. Boleslavská Barbora | 9. Kondelová Alexandra | 10. Vašicová Pavla | 11. Kubíková Iva | 12. Naščáková Zuzana | 13. Oravetzová Anna | 14. Ryšánek David | 15. Vančurová Markéta | 16. Opravilová Magdaléna

LABORATORY OF

GENOMICS AND BIOINFORMATICS

Bioinformatics, functional genomics, cancer microenvironment, ancient mtDNA, endogenous retroviruses

Michal Kolář

more information

e-mail

Activity of our laboratory is based on advanced applications of genomics, transcriptomics and bioinformatics, the most vigorously developing disciplines of contemporary life sciences. Since 2017, we have been equipped with the Illumina NextSeq next-generation sequencer, which replaced outdated microarray technology. From 2019, we have been using single cell transcriptomics and epigenomics technology (10x Genomics). As a part of our know-how, we develop sophisticated bioinformatical tools and pipelines to analyse produced data sets as well as those available in public databases. We use all these high-throughput and bioinformatic tools to conduct our own scientific projects, for long term collaborations with our colleagues and clinicians, and to support other scientific groups at the Institute.

Cancer transcriptomics. We have been involved in a long term-project focused on head and neck squamous cell carcinoma and skin cancers. We focus on tumour microenvironment and interactions between cancer associated fibroblasts and tumour cells. Recently, we have published a summary of this collaborative work [1]. We have collected a large data set of patient samples (>100 patients) and cancer associated fibroblasts that are being analysed in the recently awarded project Centre for Tumor Ecology supported by the Operational Programme Research, Development and Education.

Bioinformatics and databases, genomics. The laboratory forms the local node of the Pan-European ELIXIR bioinformatics research infrastructure. We curate and maintain the database of mitochondrial sequences coming from the ancient DNA samples AmtDB [2] and the database of human endogenous retroviruses HERVd. In collaboration with the Laboratory of Viral and Cellular Genetics, we study endogeneous retroviruses also in other species [3]. In collaboration with other groups of the Institute, members of the Laboratory became involved in functional genomics research of several models of malignant and immune diseases [4,5].

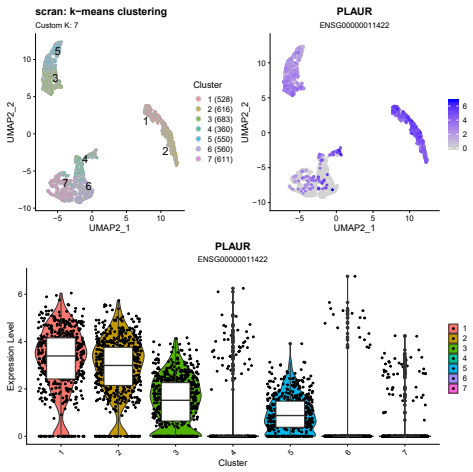

Figure 1. Clustering of single-cell transcriptomic data with emphasized expression of the marker gene PLAUR.

Figure 2. Example output from the AmtDB search engine (A) and visualization of the results on a map (B).

Selected publications:

1. Plzák J, Bouček J, Bandúrová V, Kolář M, Hradilová, M, Szabo P, Lacina L, Chovanec M, Smetana, K Jr.* (2019) The head and neck squamous cell carcinoma microenvironment as a potential target for cancer therapy. Cancers **11**(4):440 (https://doi.org/10.3390/cancers11040440)
2. Ehler E*, Novotný J, Juras A, Chylenski M, Moravčík O, Pačes J* (2019) AmtDB: a database of ancient human mitochondrial genomes. Nucleic Acids Res **47**(D1):D29-D32. (https://academic.oup.com/nar/article/47/D1/D29/5106144)
3. Farkašová H, Hron T, Pačes J, Hulva P, Benda P, Gifford RJ*, Elleder D* (2017) Discovery of an endogenous Deltaretrovirus in the genome of long-fingered bats (Chiroptera: Miniopteridae). Proc Natl Acad Sci U S A **114**(12):3145-3150.
4. Yamano T, Dobeš J, Vobořil M, Steinert M, Brabec T, Ziętara N, Dobešová M, Ohnmacht C, Laan M, Peterson P, Benes V, Sedláček R, Hanayama R, Kolář M, Klein L*, Filipp D* (2019) Aire-expressing ILC3-like cells in the lymph node display potent APC features. J Exp Med **216**(5):1027-1037.
5. Horázná M, Janečková L, Švec J, Babošová O, Hrčkulák D, Vojtěchová M, Galušková K, Šloncová E, Kolář M, Strnad H, Kořínek V* (2019) Msx1 loss suppresses formation of the ectopic crypts developed in the Apc-deficient small intestinal epithelium. Sci Rep **9**(1):1629.

In the picture: 1. Ehler Edvard | 2. Novotný Jiří | 3. Kubovčiak Jan | 4. Čápová Alice | 5. Pfeiferová Lucie | 6. Pačes Jan | 7. Kolář Michal | 8. Hradilová Miluše | 9. Svatoňová Petra | 10. Pačes Václav | 11. Kocourková Šárka | 12. Krausová Martina

GENOMICS AND BIOINFORMATICS (CORE FACILITY)

Functional genomics, next-generation sequencing, single-cell sequencing, bioinformatics, sample preparation

Michal Kolář

more information

e-mail

The core facility operates instruments for functional genomics and provides next-generation sequencing and single-cell transcriptomics services including consultations on project considerations and experimental design. The laboratory also performs primary bioinformatical analyses. The services are provided to the research groups at the Institute, to other academic institutions, and also to commercial entities.

The core facility is equipped with an Illumina NextSeq 500 next-generation sequencer, two single-cell technologies (10x Genomics Chromium Controller and Bio-Rad ddSEQ), two real-time PCR cyclers (Roche LC480), two legacy microarray platforms (Affymetrix GeneChip System and Illumina BeadStation 500) and an EnVision Plate Reader from PerkinElmer. The laboratory also operates instruments for assessment of the quality and quantity of processed samples (Nanodrop spectrophotometer, Qubit fluorometer, capillary electrophoreses Agilent Bioanalyzer 2100 and Agilent Fragment Analyzer 5200). Two ultrasonicators (Covaris ME 220 and Bioruptor) are available as shared equipment.

Figure 1. Illumina NextSeq 500 sequencer

Figure 2. Single-cell isolators 10x Genomics Chromium Controller and Bio-Rad ddSEQ

In the picture: 1. Kubovčiak Jan | 2. Čápová Alice | 3. Kolář Michal | 4. Krausová Martina | 5. Kocourková Šárka

LABORATORY OF

GERM CELL DEVELOPMENT

Fertility, sterility, spermatogenesis, meiosis, recombination initiation

Zdeněk Trachtulec

BIOCEV

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Genetic recombination is the quintessence of gametogenesis; it ensures not just the reshuffling of parental alleles and thus higher variability among the offspring, but first of all the proper segregation of chromosomes during the meiotic cell divisions and thereby fertility. The sites of meiotic double strand DNA breaks, and thus the sites of recombination, are determined in many mammals by the PRDM9 (PR/SET-domain carrying 9) protein, an epigenetic factor that carries histone-3-methyltransferase and DNA-binding activities. This protein is essential for fertility in the classical laboratory mouse, but not in the dog. In addition, a fertile human subject carrying both copies of *PRDM9* inactivated was found.
In our study published in 2019, we described the identification of male mice that produced sperm and/or offspring regardless of lacking functional PRDM9. Despite hotspots in the default sites including promoters, some spermatocytes (but no oocytes) lacking PRDM9 completed synapsis and repaired these sites to crossovers. These cells displayed a crossover rate similar to the wild type that was higher than in the wild-type spermatocytes from the previously studied mice. Fertility parameters of *Prdm9*-deficient F1 male hybrids of two mouse subspecies depended on the locus of chromosome X that also controls hybrid sterility and crossover rate. We speculated that one of the mechanisms that could rescue the effect of PRDM9 absence might be an increased efficiency of the hotspot repair.
Our mice that tolerate the loss of PRDM9 can serve as an improved model of human meiosis.

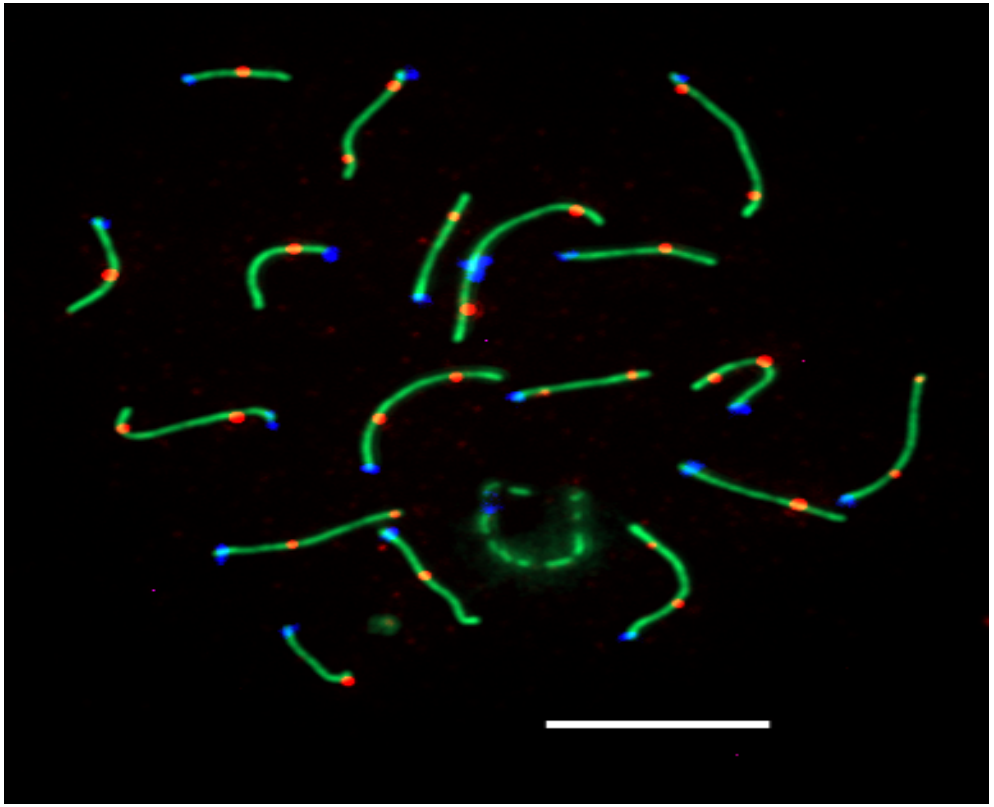
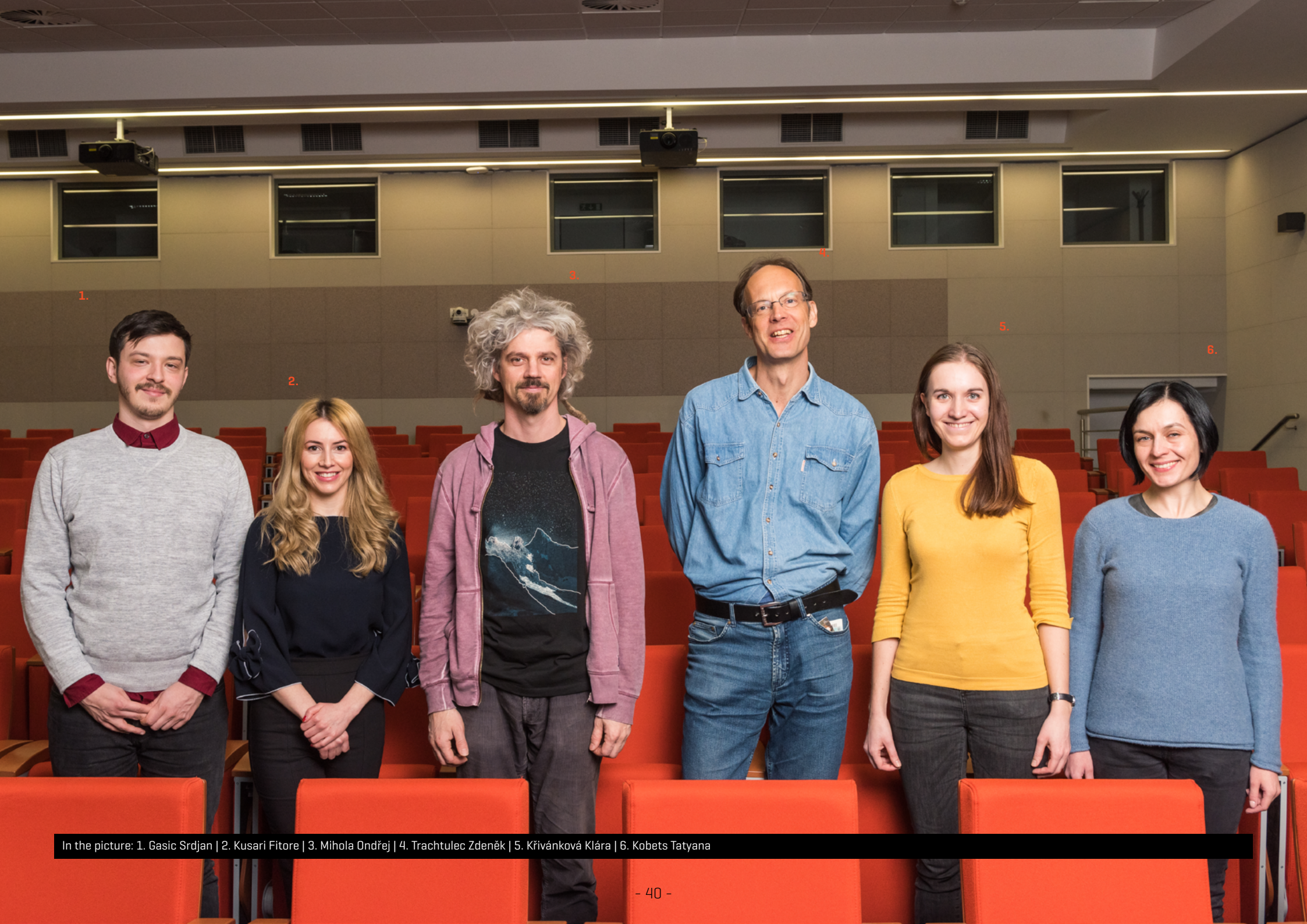


Figure 1. Immature spermatogenic cell (pachytene spermatocyte) from a *Prdm9*-deficient mouse (background strain PWD/Ph); this cell is immunolabelled for chromosomal axis protein SYCP1 (green), crossover site factor (red), and centromeres (blue); the bar represents 10 micrometers. One of the images that was used to count recombination (crossover) rates per cell.

Selected publication:

1. Mihola O, Pratto F, Brick K, Linhartova E, Kobets T, Flachs P, Baker CL, Sedlacek R, Paigen K, Petkov PM, Camerini-Otero RD, Trachtulec Z* (2019) Histone methyltransferase PRDM9 is not essential for meiosis in male mice. *Genome Res*, **29**:1078–1086.



In the picture: 1. Gasic Srdjan | 2. Kusari Fitore | 3. Mihola Ondřej | 4. Trachtulec Zdeněk | 5. Křivánková Klára | 6. Kobets Tatyana

LABORATORY OF

HAEMATOONCOLOGY

Haematopoietic stem cell, self-renewal, myeloid differentiation, leukaemia, inflammation

Meritxell Alberich Jorda

more information

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In our research group we investigate the regulation of haematopoietic stem cell (HSC) maintenance and fate by transcription factors and their target genes, determine whether these elements are altered in human leukaemias (in particular acute myeloid leukaemia, AML), and elucidate their contribution to leukaemogenesis. In addition, we investigate how cell extrinsic factors regulate HSC self-renewal and how they impact myeloid commitment. Our three main research lines are:

1. To determine the function of C/EBPα target genes in normal and malignant haematopoiesis;
2. To define the role of the β-catenin-TCF/LEF transcription-mediating complex in normal and aberrant haematopoiesis;
3. To assess the effects of chronic inflammation in HSC fitness and leukaemogenesis.

To reach these goals we employ murine and human primary cells, as well as murine models. We perform a variety of *in vitro* assays to assess cell proliferation, apoptosis, colony-forming potential, replating ability, differentiation, and migration. Further, we carry out murine bone marrow cell transplantation assays, challenge mice with infectious agents, and perform HSC mobilization assays *in vivo*. Using primary cells from patients suffering from AML, we generate PDX models. To get novel insights into the molecular mechanism of stem cell regulation and transformation, we employ molecular biology approaches including CRISPR technology, RNAseq, and ChIP-seq/qPCR.

Together, we aim at understanding the mechanisms that control HSC maintenance and fate, and determine cell intrinsic and extrinsic factors that contribute to the development of leukaemia. Ultimately, our work will contribute to establishing the knowledge for the development of better AML therapies.

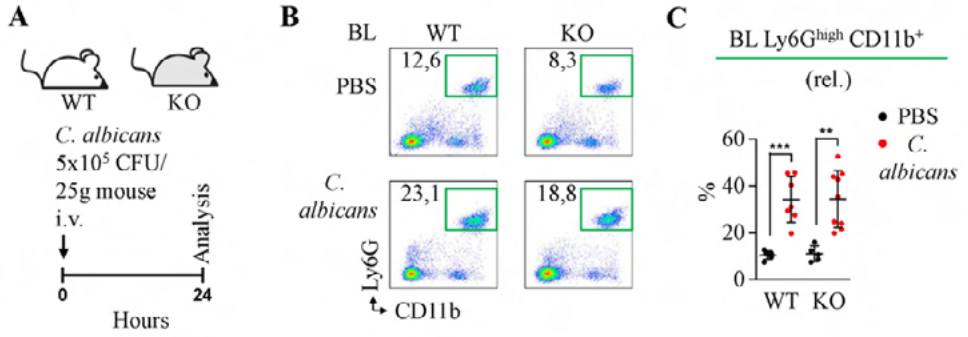

Figure 1. Candida albicans infection in WT and Cebpg KO mice. (A) Graphical representation of the infection protocol. (B) Representative flow cytometry plots from WT and Cebpg KO blood from mice treated with PBS or C. albicans. Green boxes indicate percentage of CD11b+Ly6G+ neutrophils. (C) Quantification of panel B.

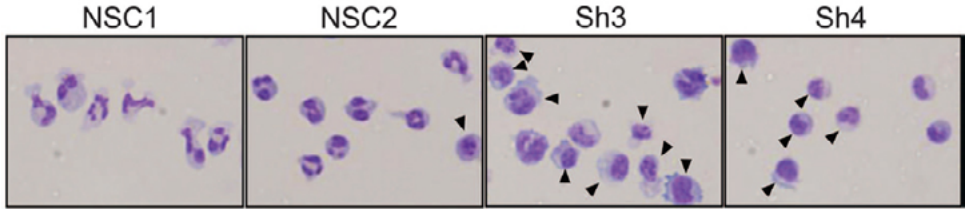

Figure 2. Evi2b knockdown blocks granulocytic differentiation of 32D/G-CSF-R cells. 32D/G-CSF-R cells were infected with shRNAs targeting and downregulating expression of the transmembrane protein Evi2b (sh3 and sh4) or non silencing control shRNA (NSC1 and NSC2). Cell morphological analysis was assessed on May-Grunwald Giemsa stained cytospins.

Selected publications:

1. Zjablovskaja P, Kardosova M, Danek P, Angelisova P, Benoukraf T, Wurm AA, Kalina T, Sian S, Balastik M, Delwel R, Brdicka T, Tenen DG, Behre G, Fiore F, Malissen B, Horejsi V, Alberich-Jorda M* *(2017)* EVI2B is a C/EBPα target gene required for granulocytic differentiation and functionality of hematopoietic progenitors. ***Cell Death Differ*, 24**:705-716.
2. Wurm AA, Zjablovskaja P, Kardosova M, Gerloff D, Bräuer-Hartmann D, Katzerke C, Hartmann JU, Benoukraf T, Fricke S, Hilger N, Müller AM, Bill M, Schwind S, Tenen DG, Niederwieser D, Alberich-Jorda M, Behre G* (2017) Disruption of the C/EBPα-miR-182 balance impairs granulocytic differentiation. ***Nat Commun*, 8**:46.
3. Gonzalez D, Luyten A, Bartholdy B, Zhou Q, Kardosova M, Ebralidze A, Swanson KD, Radomska H, Zhang P, Kobayashi SS, Welner RS, Levantini E, Steidl U, Chong G, Collombet S, Choi MH, Friedman AD, Scott LM, Alberich-Jorda M*, Tenen DG* (2017) ZNF143 is an important regulator of the myeloid transcription factor C/EBPα. ***J Biol Chem*, 292**:18924-18936.
4. Zjablovskaja P, Danek P, Kardosova M, Alberich-Jorda M* (2018) Proliferation and differentiation of murine myeloid precursor 32D/G-CSF-R cells. ***J Vis Exp*, (132).**
5. Kardosova M, Zjablovskaja P, Danek P, Angelisova P, Lobo de Figueiredo-Pontes L, Welner RS, Brdicka T, Lee S, Tenen DG, Alberich-Jorda M* (2018): C/EBPγ is dispensable for steady-state and emergency granulopoiesis. ***Haematologica*, 103**: e331-e335 .

In the picture: 1. Vaníčková Karolína | 2. Karkoulia Elena | 3. Kuzmina Maria | 4. Daněk Petr | 5. Alberich Jorda Meritxell | 6. Grušanović Srdjan

LABORATORY OF

IMMUNOBIOLOGY

Central and peripheral immune tolerance, T cell signalling, embryonic haematopoiesis, toll-like receptors

Dominik Filipp

more information

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An overarching theme of our research is the cellular, molecular and signalling processes underpinning immune homeostasis.

Central and peripheral tolerance. To eliminate self-reactive T-cells, transcription regulator Aire promotes expression of tissue-restricted antigens in the medullary thymic epithelial cells (mTECs). In this context, we have shown that if not removed in the thymus, self-reactive enteric α-defensin-recognizing T cells in the periphery can destroy Paneth cells, leading to intestinal microbiome dysregulation and enhanced inflammatory Th17 responses.[1] Using single-cell RNA-sequencing, we have also studied the process of cooperative antigen transfer and its importance for the generation of T-regulatory cells (*Voboril et al, Nature Communications, in revision*).

Interestingly, AIRE is not exclusively expressed in mTECs, but also in extrathymic cells present in the lymph nodes, spleen and testes. To enable cell type-specific ablation of the *Aire* gene, we generated transgenic mice with a LoxP-flanked *Aire* locus.[2] We have also identified Aire-expressing cells in lymph nodes with typical group 3 innate lymphoid cell (ILC3) characteristics. They express MHCII, costimulatory molecules, and present antigens to CD4⁺ T cells. These findings define a novel type of ILC3-like cells with potent APC features.[3]

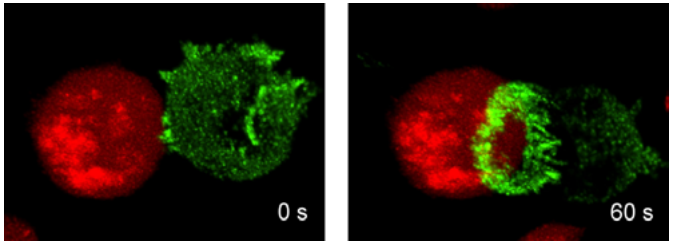

Figure 1. Expression of TLR2 in the embryo
Immunofluorescence of E7.5 embryo. TLR2⁺ cells are in green. Nuclei were stained by DAPI (blue). YS, yolk sac, EP, embryo proper, PPS, posterior primitive streak. E, day of embryonic development.

Toll-like receptors and embryonic haematopoiesis. We have shown that TLRs are expressed during early embryogenesis (Fig. 1). The expression of TLR2 on E7.5 c-kit⁺ cells mark the emergence of precursors of erythro-myeloid progenitors (EMPs). Using *in vivo* fate mapping, we demonstrated that at E8.5, the *Tlr2* locus is already active in emerging EMPs and in progenitors of adult haematopoietic stem cells (HSC). Together, we showed that the activation of the *Tlr2* locus tracks the earliest events in the process of EMP and HSC specification.[4]

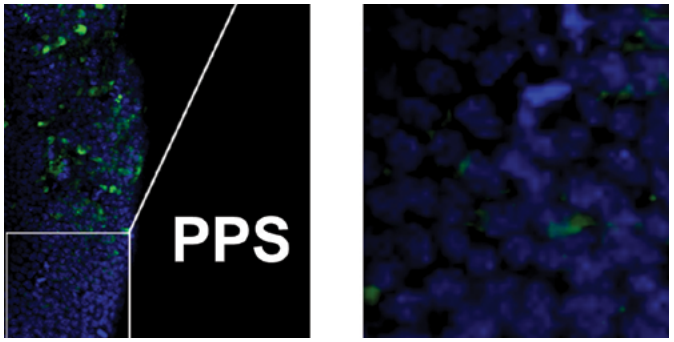

Figure 2. Early T cell activation
Live-cell imaging of immunological synapse formation between RAJI B cell (red) and Jurkat T cell expressing α-actinin-1 (green).

TCR proximal signalling. We continue in our effort to understand the earliest events leading to the activation of T cells (Fig. 2). Toward this end, we have contributed to studies on membrane heterogeneities in T cells.[5]

Selected publications:

1. Filipp D*, Brabec T, Vobořil M, Dobeš J (2019) Enteric α-defensins on the verge of intestinal immune tolerance and inflammation. *Semin Cell Dev Biol*, **88**:138-146.
2. Dobeš J, Edenhofer F, Vobořil M, Brabec T, Dobešová M, Čepková A, Klein L, Rajewsky K, Filipp D* (2018) A novel conditional Aire allele enables cell-specific ablation of the immune tolerance regulator Aire. *Eur J Immunol*, **48**:546-548.
3. Yamano T†, Dobes J†, Voboril M, Steinert M, Brabec T, Zietara N, Dobesova M, Ohnmacht C, Laan M, Peterson P, Benes V, Sedlacek R, Hanayama R, Kolar M, Klein L†*, Filipp D‡* (2019) Aire-expressing ILC3-like cells in the lymph node display potent APC features. *J Exp Med*, **216**:1027-1037. † *equal contribution*
4. Balounová J, Šplíchalová I, Dobešová M, Kolář M, Fišer K, Procházka J, Sedláček R, Jurisicova A, Sung, Alberich-Jorda M, Filipp D* (2019) Toll-like receptor 2 expression on c-kit± cells tracks the emergence of definitive hematopoietic progenitors in a pre-circulation embryo. *Nat Commun*, **10:**5176**.**
5. Angelisova P, Ballek O, Sykora J, Benadfa O, Cajka T, Pokorna J, Pinkas D, Horejsi V* (2019) The use of styrene-maleic acid copolymer (SMA) for studies on T cell membrane rafts. *Biochim Biophys Acta Biomembr*, **186**:130-141.

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LABORATORY OF

IMMUNOLOGICAL AND TUMOUR MODELS

Experimental cancer therapy, tumour immunology, murine models, JAK/STAT signalling, cellular senescence

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Research

Our long-term research interest are interactions between tumour cells and the immune system, as well as the impacts of anti-tumour therapies on these interactions. We are focused on experimental anti-tumour therapy, using murine models and investigating chemo- and immunotherapies and their combinations. We also pay attention to the mechanisms by which tumour cells can escape from specific immune responses, as well as to the mechanisms of immune suppression development in the tumour microenvironment (e.g., myeloid-derived suppressor cells; [**Fig. 1**]. At present, we concentrate on the impacts of genotoxic stress and cellular senescence induction by chemotherapeutic agents or cytokines and on mutual interactions between stressed/senescent cells and the immune system [**Fig. 2**]. We hypothesize that, despite the fact that cellular senescence represents an important barrier against cancer development, the presence of senescent cells or cells in genotoxic stress in general can influence the development of age-related diseases, and also cancer. Thus not only senescence induction, but also elimination of the effects of these cells are important for effective anti-cancer therapy. The JAK/STAT signalling pathways play important roles in the processes mentioned above. Recently, we have concentrated on the role of STAT1 in cellular stress/senescence induction. Further, we suppose that the STAT3 signalling pathway inhibition can be an important tool for elimination of the negative effects of chemotherapy, and it can also increase its efficacy. Therefore, we study novel and existing STAT3 inhibitors and their potential clinical usage in murine preclinical models.

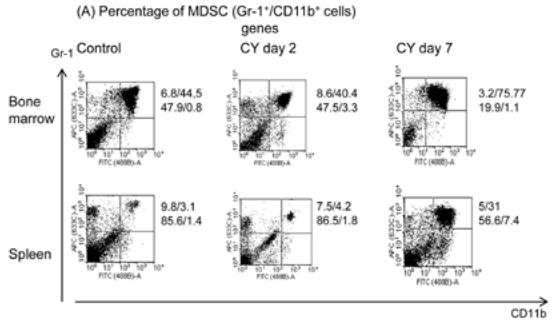

Figure 1. Cyclophosphamide increased the percentage of CD11b+/Gr-1+ cells in the spleens and bone marrow of treated animals.
Bone marrow and spleen after administration of cyclophosphamide (CY), 200 mg/kg i.p. C57Bl/6 mice were injected with 200 mg/kg i.p. and their spleens and bone marrow cells were analysed by flow cytometry 2 and 7 days after injection. Myeloid-derived suppressor cells in the spleen were detected as CD11b+/Gr-1+ cells.

Contractual research and services

We perform analyses of the experimental tumour development and anti-tumour immune responses and we test the efficacy of experimental therapies (not only immunotherapy). We use both tumours induced by syngeneic tumour cell transplantation and transgenic mice as orthotopic models that develop spontaneous tumours. We routinely use experimental models of minimal residual tumour disease after surgery or chemotherapy. Indeed, we are open to more future collaborations and contractual research.

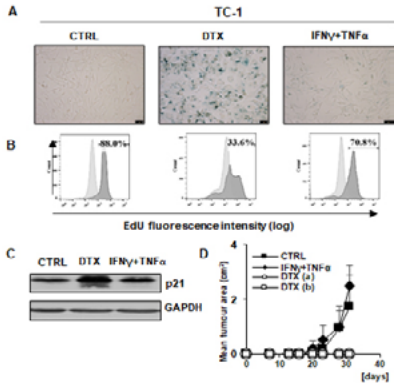

Figure 2. Docetaxel (DTX) but not IFNγ+TNFα induces senescence in TC-1 cells. Senescence-associated β-galactosidase activity in TC-1 cells (A) treated with DTX or IFNγ+TNFα for 4 days. (B) Cell proliferation block after the DTX treatment was detected by 5-Ethynyl-2′-deoxyuridine (EdU), using flow cytometry analysis. Western blot quantification of p21 in control, DTX-, IFNγ+TNFα-treated TC-1 cells (C). Docetaxel-treated TC-1 senescent cells, unlike the IFNγ+TNFα-treated cells or untreated cells (3x104 cells were transplanted s.c.), do not form tumours in mice (D). Mice were injected either with 3x104 or with 3x105 docetaxel-treated cells (DTX (a) and DTX (b), respectively).

Selected publications:

1. Mikyskova R, Indrova M, Stepanek I, Kanchev I, Bieblova J, Vosahlikova S, Moserova I, Truxova I, Fucikova J, Bartunkova J, Spisek R, Sedlacek R, Reinis M* (2017) Dendritic cells pulsed with tumor cells killed by high hydrostatic pressure inhibit prostate tumor growth in TRAMP mice. *Oncoimmunology*, **6**:e1362528.
2. Mikyšková R, Štěpánek I, Indrová M, Bieblová J, Šímová J, Truxová I, Moserová I, Fučíková J, Bartůňková J, Špíšek R, Reiniš M* (2016) Dendritic cells pulsed with tumor cells killed by high hydrostatic pressure induce strong immune responses and display therapeutic effects both in murine TC-1 and TRAMP-C2 tumors when combined with docetaxel chemotherapy. *Int J Oncol*, **48**:953-964.
3. Hubackova S, Kucerova A, Michlits G, Kyjacova L, Reinis M, Korolov O, Bartek J*, Hodny Z* (2016) IFNγ induces oxidative stress, DNA damage and tumor cell senescence via TGFβ/SMAD signaling-dependent induction of Nox4 and suppression of ANT2. *Oncogene*, **35**:1236-1249.
4. Sapega O, Mikyšková R, Bieblová J, Mrázková B, Hodný Z, Reiniš M* (2018) Distinct phenotypes and 'bystander' effects of senescent tumour cells induced by docetaxel or immunomodulatory cytokines. *Int J Oncol*, **53**:1997-2009.

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LABORATORY OF

INTEGRATIVE BIOLOGY

Cytoskeleton, cytolinker proteins, cell junctions, simple epithelia, mechanobiology

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In recent years, our main research interests have been 1) cytoskeleton-dependent regulation of cell-cell contacts in simple epithelia, 2) regulation of cell-matrix adhesions, and 3) cytoskeleton and adhesion-mediated signalling in epithelial-mesenchymal transition, cell migration and invasiveness. We mainly focus on cytoskeletal linker proteins, in particular plectin, and we study the functional consequences of cytoskeletal organization in cell/tissue mechanics and mechanotransduction, i.e., conversion of physical cues into intracellular mechanosignalling pathways. To fulfil our aims in the complexity of biological systems, we use a combination of *in vitro* (primary cells and CRISPR/Cas9-targeted cell lines) and *in vivo* (transgenic models) approaches. Beside conventional molecular biology techniques, we also employ methods that enable us to measure and apply physiologically relevant forces and deformations, such as traction force and atomic force microscopy, magnetic tweezer rheology, and FRET-based tension sensors . Our findings provided a novel perspective on the exclusivity of actomyosin-mediated contractility for integrin activation and provided the basis for a more in-depth investigation of the role of intermediate filaments in mechanosignalling.

Our long-term interest includes mouse models for studying the physiology and pathophysiology of digestive epithelia. We strive to 1) identify genes with unique and essential functions in simple epithelia; 2) generate mouse models with targeted selected genes; and 3) characterize phenotypes of the generated mouse models, addressing gene functions in healthy and diseased simple epithelia. For example, we generated a mouse model recapitulating the symptoms of *Epidermolysis bullosa* (*EB*) in the liver. Analysis of this model showed that *EB*-associated genes play a crucial role in the liver adaptation to cholestasis. Mutated mice failed to rearrange bile ducts in experimental cholestasis, and bile retention caused significant liver damage (Jirouskova et al., *J. Hepatol.*, 2018). This study highlights the risks in patients with *EB* in combination with bile formation and excretion defects. Our research also has a profound effect on understanding liver fibrosis, inflammatory bowel diseases, and carcinogenesis.

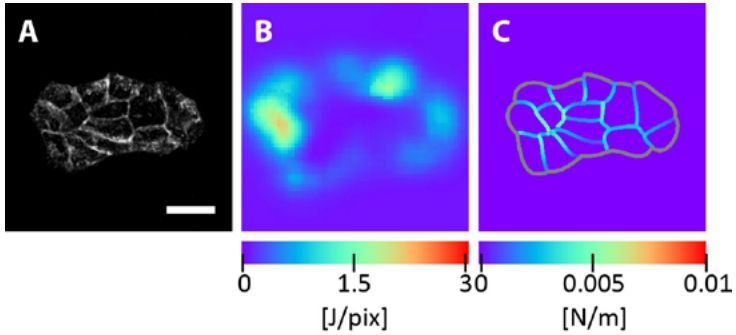

Figure 1. 2D traction force microscopy in cell colonies. **(A)** Colony of MDCK cells labelled with tdTomato-Farnesyl. **(B,C)** Distributions of contractile energy (B) and line tension at cell-cell borders (C) shown as pseudo-colour images. Bar, 30 μm.

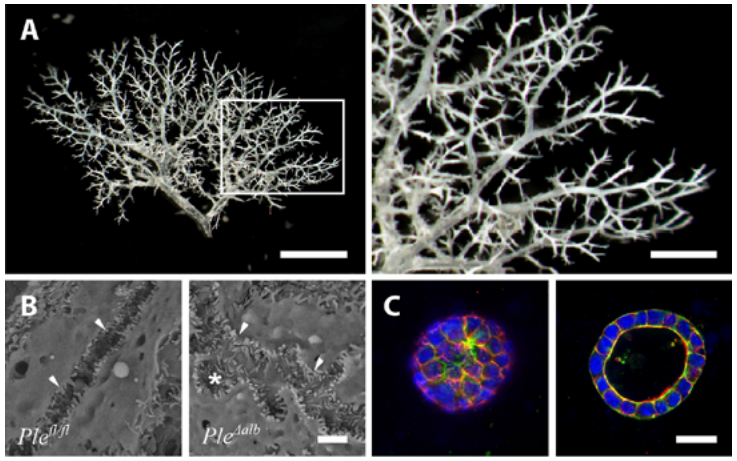

Figure 2. Visualization of biliary tree architecture. **(A)** Acrylic resin cast of biliary tree in the liver lobe of adult mice. Bar, 3 mm. **(B)** Scanning electron images of bile canaliculi in wild-type (*Ple*$^{fl/fl}$; left) and liver-specific plectin knockout (*Ple*$^{•alb}$; right) mouse. Arrowheads, bile canaliculi; asterisk, blind loop in *Ple*$^{•alb}$ canaliculi only. Bar, 1 μm. **(C)** 3D spheroid grown from biliary epithelial cells and immunolabelled using antibodies to pan-keratin (green) and plectin (red). Nuclei stained with DAPI (blue). Bar, 10 μm.

Selected publications:

1. Jirouskova M, Nepomucka K, Oyman-Eyrilmez G, Kalendova A, Havelkova H, Sarnova L, Chalupsky K, Schuster B, Benada O, Miksatkova P, Kuchar M, Fabian O, Sedlacek R, Wiche G, Gregor M* (2018) Plectin controls biliary tree architecture and stability in cholestasis. *J Hepatol*, **68**:1006-1017.
2. Taylor SRA, Malone J, Zhang Y, Prechova M, Kaczmarek LK* (2019) Phactr1 regulates Slack (KCNT1) channels via protein phosphatase 1 (PP1). *FASEB J*, **34**:1591-1601. https://doi.org/10.1096/fj.201902366R
3. Korelova K, Jirouskova M, Sarnova L, Gregor M* (2019) Isolation and 3D collagen sandwich culture of primary mouse hepatocytes to study the role of cytoskeleton in bile canalicular formation in vitro. *J Vis Exp*, **154**. doi: 10.3791/60507.

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LABORATORY OF

LEUKOCYTE SIGNALLING

Leukocyte signalling, membrane adaptor proteins, autoinflammation, haematopoiesis, myeloid cells

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The Laboratory of Leukocyte Signalling is studying the molecular mechanisms of signal transduction downstream of various leukocyte surface receptors. For a long time, our interest has been focused on membrane adaptor proteins and on the roles of these proteins in the regulation of leukocyte signalling and in leukocyte-driven pathologies. We also study plasma membrane separation into various micro or nanodomains and their relationship to the membrane protein distribution and function. In the recent years we have paid most attention to several so far poorly characterized membrane adaptor proteins. Among the most interesting was OPAL1, a membrane adaptor that is aberrantly expressed in childhood leukaemia. We found that it inhibits the activity of an important bone marrow homing receptor, CXCR4, in leukaemic cells as well as in myeloid progenitors. We also found that it regulates haematopoietic stem and progenitor cell mobilization and curtails bone marrow transplantation efficiency. These data helped us to better understand the regulation of these clinically important processes. Another interesting membrane adaptor is PSTPIP2. Its deficiency in mice results in an autoinflammatory disorder characterized by sterile inflammation of the bones and surrounding soft tissues. It is similar to several human bone diseases. We have discovered that the absence of PSTPIP2 results in exaggerated production of reactive oxygen species by neutrophil granulocytes early in the disease in the positions of future inflammatory bone lesions. Production of these toxic compounds then critically contributes to the bone damage accompanying this disease. We believe that this discovery will help in improving future treatment strategies for this class of disorders. Finally, within a long-lasting collaboration with the group of Marek Cebecauer at J. Heyrovsky Institute of Physical Chemistry, we also contribute to understanding the relationships between the structure and subcellular/nanoscopic localization of membrane adaptors and other membrane proteins.

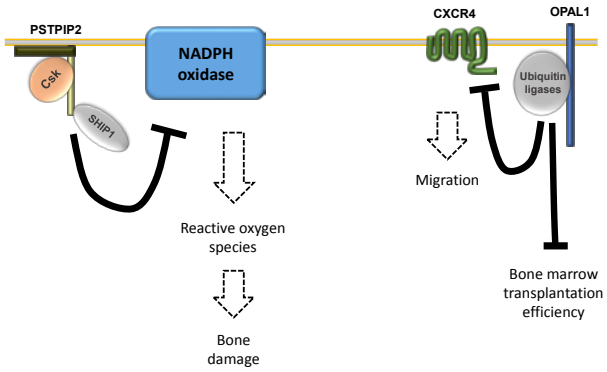

Figure 1. Schematic representation of the function of two membrane adaptor proteins, PSTPIP2 and OPAL1. PSTPIP2 (left) inhibits NADPH oxidase activity and consequently suppresses reactive oxygen species production and autoinflammatory bone damage. OPAL1 (right) recruits Nedd4-family ubiquitin ligases and negatively regulates CXCR4-driven migration and bone marrow transplantation efficiency.

Selected publications:

1. Kralova J, Drobek A, Prochazka J, Spoutil F, Fabisik M, Glatzova D, Borna S, Pokorna J, Skopcova T, Angelisova P, Gregor M, Kovarik P, Sedlacek R, Brdicka T* (2020) Dysregulated NADPH oxidase promotes bone damage in murine model of autoinflammatory osteomyelitis. *J Immunol*. doi: 10.4049/jimmunol.1900953. [Epub ahead of print]
2. Borna S, Drobek A, Kralova J, Glatzova D, Splichalova I, Fabisik M, Pokorna J, Skopcova T, Angelisova P, Kanderova V, Starkova J, Stanek P, Matveichuk OV, Pavliuchenko N, Kwiatkowska K, Protty MB, Tomlinson MG, Alberich-Jorda M, Korinek V, Brdicka T* (2020) Transmembrane adaptor protein WBP1L regulates CXCR4 signalling and murine haematopoiesis. *J Cell Mol Med*, **24**:1980-1992.
3. Angelisova P, Ballek O, Sykora J, Benada O, Cajka T, Pokorna J, Pinkas D, Horejsi V* (2019) The use of styrene-maleic acid copolymer (SMA) for studies on T cell membrane rafts. *Biochim Biophys Acta Biomembr*, **1861**:130-141.
4. Lukeš T, Glatzová D, Kvíčalová Z, Levet F, Benda A, Letschert S, Sauer M, Brdička T, Lasser T, Cebecauer M*(2017) Quantifying protein densities on cell membranes using super-resolution optical fluctuation imaging. *Nat Commun*, **8**:1731.

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LABORATORY OF

MOLECULAR AND CELLULAR IMMUNOLOGY

Leishmaniasis, genetic control, complex disease, disease mechanisms, leishmanicidal compounds

Marie Lipoldová

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The research programme of the laboratory aims to identify the genes and molecular mechanisms involved in the control of immune response and susceptibility to complex infectious diseases. Complex diseases, in contrast to diseases caused by mutations in a single gene, are responsible for the largest part of human morbidity and mortality. These diseases are controlled by multiple genes – QTL (quantitative trait loci) – and hence their pathogenesis cannot be explained by effects of a single gene with omission of others. The variation in these QTLs causes a large part of inter-individual differences in the course and severity of the disease. These differences strongly affect individual susceptibility to a disease, manifestation of specific pathogenic pathways and symptoms in individual patients, individual responsiveness to therapy, and the final outcome of the process. Leishmaniasis is a prototypical complex disease and it has served as a major paradigm of immune response to an infectious agent. In the years 2017-2019, we aimed to define important regulators and mechanisms of leishmaniasis (2,3,5), find shared components of leishmaniasis and other complex diseases (4), and to develop translational applications (1). We described a novel potential mechanism influencing *Leishmania major* infection – interferon-induced GTPases. Co-localization of the GBP2b protein with most *L. major* parasites in the skin of resistant and intermediate strains, but not in highly susceptible BALB/c mice, suggests that this molecule might play a role in defence against leishmaniasis (2). We were the first to combine the genetic mapping of susceptibility to leishmaniasis with the detailed analysis of pathology, immunology, and parasite load of individual mice. We performed a first systematic a genome-wide search, which led to the description of a network-like structure of genes that regulate dissemination of the parasite inside a mammalian organism. The host genes revealed a wide variety of heterogeneous effects that included distinct organ-specific control, single-gene effects, gene-gene interactions, and sex-dependent control (5). We also found a novel compound, diphenyleneiodonium, which demonstrates potent leishmanicidal activity both *in vitro* and *in vivo*. We patented this compound both in EU (Grekov et al. EP3054941, 2017) and in USA (Grekov et al. US 10350176).

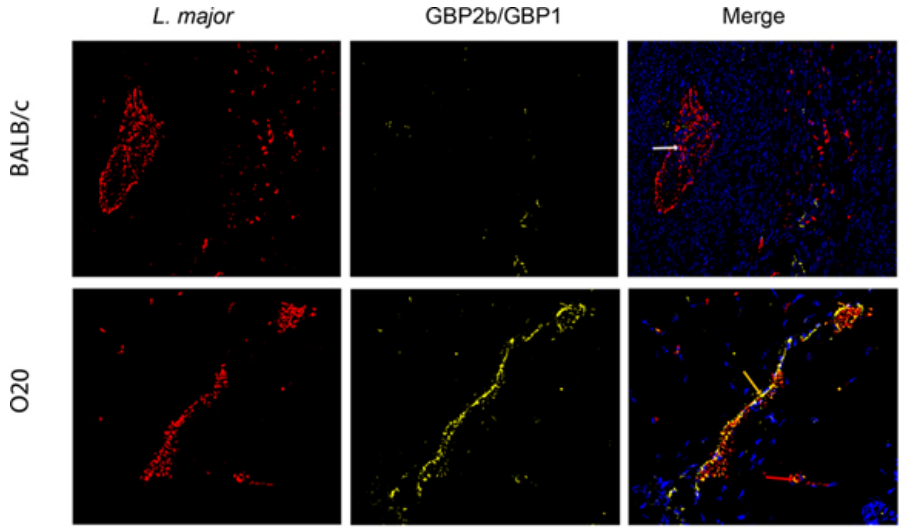

Figure 1. GBP2b/GBP1 protein and *L. major* parasites in the skin of infected mice BALB/c and O20. (Adapted from Sohrabi et al. Front. Immunol. 2018). White arrow shows *L. major* amastigotes (red colour), red arrows point to amastigotes co-localized with GBP2b/GBP1, whereas yellow arrows show a stretch of parasites and GBP2b/GBP1. Cell nuclei are stained in blue.

Selected publications:

1. Grekov I, Pombinho AR, Kobets T, Bartůněk P, Lipoldová M* (2017) Calcium ionophore, calcimycin, kills *Leishmania* promastigotes by activating parasite nitric oxide synthase. Biomed Res Int, **2017**:1309485.
2. Sohrabi Y, Volkova V, Kobets T, Havelková H, Krayem I, Slapničková M, Demant P, Lipoldová M* (2018) Genetic regulation of guanylate binding proteins 2b and 5 during leishmaniasis in mice. Front Immunol, **9**:130.
3. Sohrabi Y*, Lipoldová M* (2018) Mannose receptor and the mystery of nonhealing *Leishmania major infection*. Trends Parasitol, **34**: 354-356.
4. Palus M, Sohrabi Y, Broman KW, Strnad H, Šíma M, Růžek D, Volkova V, Slapničková M, Vojtíšková J, Mrázková L, Salát J, Lipoldová M* (2018) A novel locus on mouse chromosome 7 that influences survival after infection with tick-borne encephalitis virus. BMC Neurosci, **19**:39.
5. Kobets T, Čepičková M, Volkova V, Sohrabi Y, Havelková H, Svobodová M, Demant P, Lipoldová M* (2019) Novel loci controlling parasite load in organs of mice Infected with *Leishmania major*, their interactions and sex influence. Front Immunol, **10**:1083.

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LABORATORY OF

MOLECULAR PHARMACOLOGY

Cannabinoid receptor 1, endocannabinoid signalling, nociception, pain, synaptic plasticity

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Studies on the dimeric structure of mGluRs were approached by several laboratories including ours; this research was conducted as a continuing collaboration with the CNRS laboratory in Montpellier. Briefly, we revealed in studies using pharmacological tools combined with functional assays and DNA recombination technology that the mGluRs are obligatory dimers, and that within the dimer only one subunit activates G-proteins. This was recently supported by crystallographic studies conducted by Brian Kobilka.

In another venue we discovered that distinct splice variants of mGluR1 combine in dimers with important functional outcomes. Therefore, a fraction of mGluR1 receptors exist as heterodimers with respect to their splice variants.

More recently, we detected the Src homology 3-domain growth factor receptor-bound 2-like (endophilin) interacting protein 1 (SGIP1) as a novel CB1R interacting partner. SGIP1 is functionally linked to clathrin-mediated endocytosis and its overexpression in the hypothalamus leads to an energy regulation imbalance resulting in obesity in rodents. We reported that SGIP1 prevents the endocytosis of activated CB1R and that it alters signalling via the CB1R in a biased manner. CB1R – β2 arrestin-associated signalling is profoundly changed, most likely as a consequence of the prevention of the receptor's internalization, an inhibition mediated by SGIP1. To study the role of SGIP1 *in vivo*, we developed SGIP1 knockout mice to explore their phenotype. In a recently submitted manuscript, we report alterations in emotionality of SGIP1 knockout mice based on open field, elevated plus maze, and light/dark box tests. We discovered that a mouse coping with despair in an inescapable situation is enhanced by SGIP1 deletion. In the tail immersion test, the antinociceptive effects of CB1R agonists were significantly enhanced in the SGIP1 knockout mice. In evaluating responses to Δ9-tetrahydrocannabinol in cannabinoid tetrad tests, interesting differences were revealed compared to wild-type mice, including modification of responses in several models of pain.

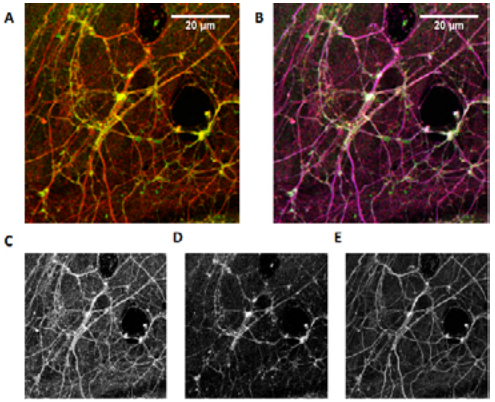

Figure 1. CB1R, SGIP1 and Piccolo are colocalized in autaptic hippocampal neurons.
Autaptic neurons were stained with a-CB1R (red), a-SGIP1 (green) and a-Piccolo (blue) antibodies. The pictures shows the overlay of CB1R and SGIP1 (A) and also and overlay with synaptic marker Piccolo (B). The split channels depict a-CB1R (C), a-SGIP1 (D) and a-Piccolo (E) staining separately. The colocalization of the three proteins is visible in synaptic buttons.

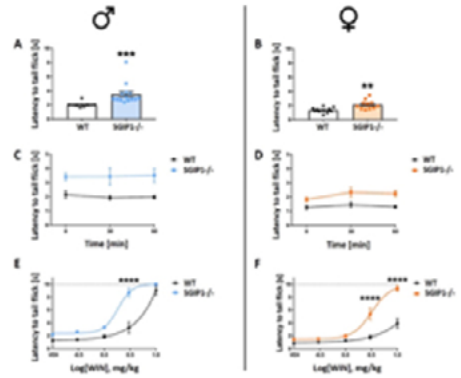

Figure 2. Male and female SGIP1-/- mice have prolonged latencies in the tail immersion test and are more sensitive to cannabinoid agonist WIN55,212-2.
A, B) To assess acute analgesia, we used the tail immersion test. C, D) The tip of the animal's tail was immersed into a water bath of 52°C and the latency to flick the tail was measured in three trials with 30 min inter-trial intervals and averaged. Both sexes of SGIP1-/- had prolonged latencies to flick the tail (E,F). To assess the analgesic effect of cannabinoid receptor agonist WIN 55,212-2 (WIN), the mice were injected with increasing doses of WIN (0, 0.3, 1, 3, 10 mg/kg i. p.) 1 hour apart and the tail flick was measured 1 hour after the application. WIN provides increased analgesia in SGIP1-/- mice of both sexes compared to WT control.

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1. Hlavackova V, Goudet C, Kniazeff J, Zikova A, Maurel D, Vol C, Trojanova J, Prézeau L, Pin JP, Blahos J* (2005) Evidence for a single heptahelical domain being turned on upon activation of a dimeric GPCR. *EMBO J*, **24**:499–509.
2. Hlavackova V, Zabel U, Frankova D, Bätz J, Hoffmann C, Prezeau L, Pin JP *, Blahos J *, Lohse MJ* (2012) Sequential inter- and intrasubunit rearrangements during activation of dimeric metabotropic glutamate receptor 1. *Science Signal*, **5**:ra59.

Shared senior co-authorship:

1. Techlovská S, Chambers JN, Dvořáková M, Petralia RS, Wang YX, Hájková A, Nová A, Franková D, Prezeau L, Blahos J * (2014) Metabotropic glutamate receptor 1 splice variants mGluR1a and mGluR1b combine in mGluR1a/b dimers in vivo. *Neuropharmacology*, **86**:329-336.
2. Hájková A, Techlovská S, Dvořáková M, Chambers JN, Kumpošt J, Hubálková P, Prézeau L, Blahoš J* (2016) SGIP1 alters internalization and modulates signaling of activated cannabinoid receptor 1 in a biased manner. *Neuropharmacology*, **107**:201-214.

In the picture: 1. Blahoš Jaroslav | 2. Dvořáková Michaela | 3. Pejšková Lucie | 4. Durydivka Oleh | 5. Gazdarica Matej

LABORATORY OF

MOUSE MOLECULAR GENETICS

Meiosis, Prdm9, genetics of hybrid sterility, meiotic sex chromosome inactivation, chromosome substitution mouse strains

Jiří Forejt

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The group focuses on genetic factors affecting the first meiotic prophase in mouse hybrids between related subspecies. The lab identified the first hybrid sterility gene, *Prdm9*, in a vertebrate species. *Prdm9* (*Meisetz*), encoding a meiotic histone H3 lysine-4 and lysine-36 tri-methyltransferase, revealed its dual role as a single factor determining positions of the meiotic recombination hotspots and as a major hybrid sterility gene possibly involved in speciation.[5] The second hybrid sterility gene showing Dobzhansky-Muller incompatibility with *Prdm9* was mapped to a 2.7 Mb *Hstx2* locus on chromosome X.[1] The same interval includes a major gene regulator of meiotic recombination rate (*Balcova et al., PLoS Genet. 2016*). The third prerequisite for complete meiotic arrest and male infertility of the laboratory model of hybrid sterility (mouse strains PWD of *Mus m. musculus* and B6 of *Mus m. domesticus* subspecies) is the *musculus/domesticus* heterozygosity of the genetic background. To understand the effect of genetic background in more detail, strains of hybrid mice were constructed where a pair of chromosomes of one subspecies was substituted by the corresponding pair from the other subspecies using chromosome substitution strains. This generated hybrids with stretches of DNA that came entirely from a single subspecies. Having such a stretch of 27 million or more DNA base pairs fully restored synapsis in a given pair of chromosomes during meiosis. Hybrid sterility was reversed when synapsis was restored in the four chromosomes that were most strongly affected by asynapsis.[2] Chromosome substitution strains prepared by the group (*Gregorova et al., Genome Res. 2008*) were also employed for identification of meiotic DNA DSBs repaired by noncrossovers (gene conversion). NGS sequencing of 10 mouse chromosome substitution strains revealed 94 noncrossovers with the mean length of a conversion tract of 32 base pairs. The finding of a significant deficit of noncrossovers descending from asymmetric DSBs has implications for the molecular mechanism of hybrid sterility in mice from crosses between closely related subspecies (*Gergelits et al., Genetics, in review 2020*).

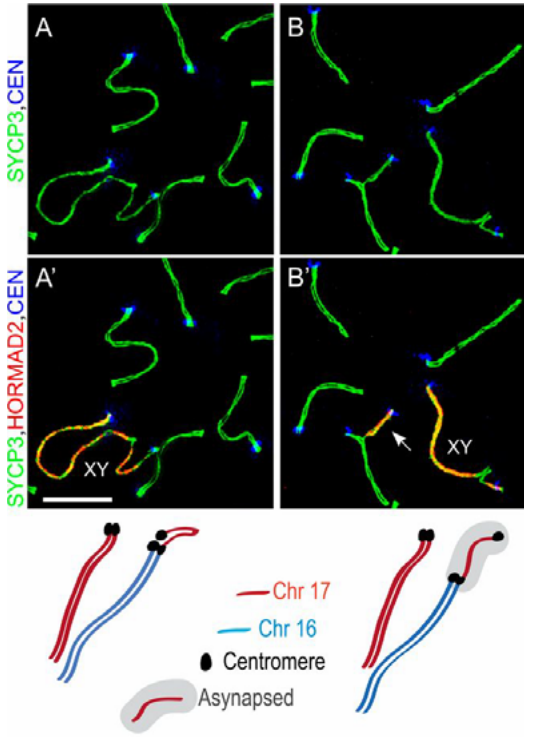

Figure 1. Super-resolution microscopy of synaptonemal complexes decorated by anti-SYCP3 antibody in pachytene spermatocytes of mice with T43Ts partial trisomy. The unsynapsed supernumerary copy of proximal chromosome 17 is folding to itself in the left cell or is left unpaired as a univalent decorated by HORMAD2 (arrow) on the right. Sex chromosomes are labelled XY. From Jansa et al., Biol Reprod. 124:1-9, 2014.

Selected publications:

1. Lustyk D, Kinsky S, Ullrich KK, Yancoskie M, Kasikova L, Gergelits V, Sedlacek R, Chan YF, Odenthal-Hesse L, Forejt J*, Jansa P* (2019) Genomic structure of *Hstx2* modifier of *Prdm9*-dependent hybrid male sterility in mice. *Genetics*, **213**:1047-1063.
2. Gregorova S, Gergelits V, Chvatalova I, Bhattacharyya T, Valiskova B, Fotopulosova V, Jansa P, Wiatrowska D, Forejt J* (2018) Modulation of *Prdm9*-controlled meiotic chromosome asynapsis overrides hybrid sterility in mice. *Elife*, **7**:pii: e34282. doi: 10.7554/eLife.34282, 2018.
3. Forejt J* (2016) Genetics: Asymmetric breaks in DNA cause sterility. *Nature*, **530**:167-8.
4. Bhattacharyya T, Gregorova S, Mihola O, Anger M., Sebestova J, Denny P, Simecek P, Forejt, J* (2013) Mechanistic basis of male infertility in mouse intersubspecific hybrids. *Proc Natl Acad Sci USA*, **110**:E468-77. doi: 10.1073/pnas.1219126110, 2013.
5. Mihola O, Trachtulec Z, Vlcek C, Schimenti JC, Forejt J* (2009) A mouse speciation gene encodes a meiotic Histone H3 methyltransferase. *Science*, **323**:373-375.

In the picture: 1. Gergelits Václav | 2. Parvanov Emil | 3. Forejt Jiří | 4. Jansa Petr | 5. Mukaj Amisa | 6. Fotopulosová Vladana | 7. Fusek Karel | 8. Lustyk (Wiatrowska) Diana

LABORATORY OF

RNA BIOLOGY

RNA splicing, snRNPs, spliceosome, nuclear structure, retinitis pigmentosa

David Staněk

more information

e-mail

Our DNA encodes information for synthesis of all our proteins. However, this information in DNA is fragmented and genes contain long sequences that need to be removed in a process called RNA splicing. Unused RNA sequences are removed by a large, sophisticated and dynamic molecular machine called the spliceosome, which is the most complex particle in our cells consisting of several non-coding RNAs and dozens of auxiliary proteins. Our long-term goal is to determine how the spliceosome assembles at the right time and place. We also investigate how the nuclear architecture contributes to correct formation of the spliceosome. Finally, we aim to determine why mutations in spliceosomal components cause retinitis pigmentosa, a human genetic disease characterized by photoreceptor cell degeneration.

Formation of spliceosomal complexes *in vivo*

Combing advanced microscopy techniques with molecular biology and biochemistry approaches, we explore where and when the spliceosome components assemble in the cell nucleus. We identified a conserved nuclear compartment, the Cajal body, as the site of assembly and recycling of spliceosomal particles. Recently, we provided evidence that the Cajal body acts as a quality controller that surveillances formation of spliceosomal components and sequesters defective particles, and we determined the molecular mechanism that discriminates between correctly and incorrectly assembled particles.

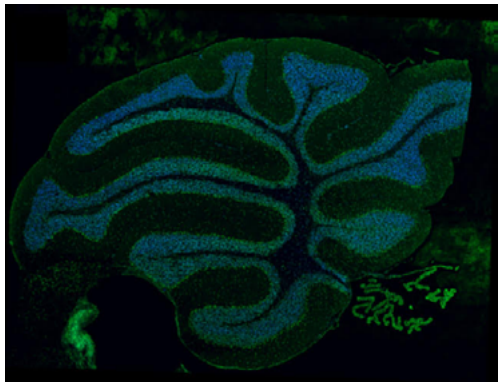

Figure 1. A section of mouse cerebellum immunostained for splicing factor Prpf8 (green). Nuclei counterstained by DAPI (blue).

Spliceosome and retina degeneration

The autosomal dominant disorder retinitis pigmentosa (RP) is characterized by progressive loss of peripheral and night vision, which eventually leads to total blindness. RP is caused by molecular defects in many different proteins, including those found in the spliceosome. Why mutations of ubiquitous spliceosomal components specifically affect retina cells, however, remains elusive. In our research, we combine model organisms, 3D organoids and cell cultures to identify the detrimental effects of RP mutations on RNA splicing in retina cells.

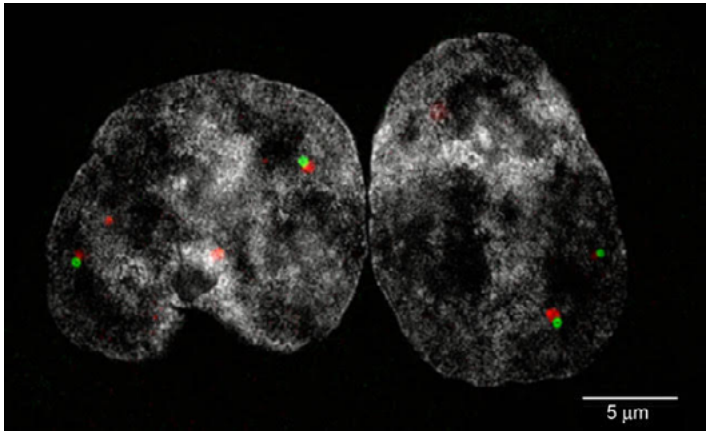

Figure 2. Human cells immunstained for coilin (red) and SMN protein (green). Coilin is a marker of nuclear structures called Cajal bodies, SMN is a marker of nuclear structures called gems. Nuclei counterstained by DAPI (white).

Selected publications:

1. Krchnáková Z, Thakur PK, Krausová M, Bieberstein N, Haberman N, Müller-McNicoll M, Stanek D* (2019) Splicing of long non-coding RNAs primarily depends on polypyrimidine tract and 5′ splice-site sequences due to weak interactions with SR proteins. ***Nucleic Acids Res,* 47**:911-928
2. Roithová A, Klimešová K, Pánek J, Will CL, Lührmann R, Stanek D*, Girard C* (**2018**) The Sm-core mediates the retention of partially-assembled spliceosomal snRNPs in Cajal bodies until their full maturation. ***Nucleic Acids Res,* 46**:3774-3790
3. Malinová A, Cvačková Z, Matějů D, Hořejší Z, Abéza C, Vandermoere F, Bertrand E*, Staněk D*, Verheggen C* (**2017**) Assembly of the U5 snRNP component PRPF8 is controlled by the HSP90/R2TP chaperones. ***J Cell Biol,* 216**:1579-1596
4. Staněk D, Fox A* (**2017**) Nuclear bodies: news insights into structure and function. ***Curr Opin Cell Biol,* 46**:94-101
5. Krausová M, Staněk D* (**2018**) snRNP proteins in health and disease. ***Semin Cell Dev Biol,* 79:92-102.** pii: S1084-9521(17): 30150-7

In the picture: 1. Sýkora Michal | 2. Staněk David | 3. Cvačková Zuzana | 4. Zimmann Felix | 5. Krausová Michaela | 6. Thakur Kumar Prasson | 7. Kuzmenko Darya | 8. Hálová Martina | 9. Petržílková Hana | 10. Machatová Křížová Jana

LABORATORY OF

SIGNAL TRANSDUCTION

Plasma membrane signalosome, immunoreceptor signalling, mast cells, ORM family proteins, tetraspanins

Petr Dráber

more information

e-mail

Our laboratory is focused on understanding the molecular mechanisms governing signal transduction from the plasma membrane receptors to the cytoplasm. High-affinity immunoglobulin E receptor (FcεRI), cKIT, and G protein-coupled receptors (GPCRs) are plasma membrane receptors involved in the degranulation and/or chemotaxis of mast cells, potent immune modulators of the tissue microenvironment. Within minutes of antigen-mediated activation, mast cells release a variety of preformed biologically active compounds, followed by a wave of mediator synthesis and secretion. Increasing evidence suggests an intricate network of inhibitory and activating receptors, specific signalling pathways, and adaptor proteins whose overall signalling balance governs the mast cell responsiveness to particular stimuli. In our recent studies, we focused on understanding the role of plasma membrane signalosomes and selected cytoplasmic proteins during mast cell activation through FcεRI, cKit, and GPCRs. To reach our goal, we used various techniques of molecular biology, immunology, immunochemistry, and immunohistochemistry. Our principal approach lies in production of cells or animals with increased or reduced expression of selected genes and comparison of their properties with wild-type cells or wild-type animals. We found and described new functions of the members of ORM family proteins, tetraspanins, transmembrane adaptor protein PAG, and cytoskeletal protein 4.1R in mast cell activation. Our studies are aimed to deepen the knowledge of the cellular and molecular mechanisms involved in allergic and inflammatory diseases. Our long-term goal is to contribute to the development of new, more potent, anti-allergic and anti-inflammatory drugs.

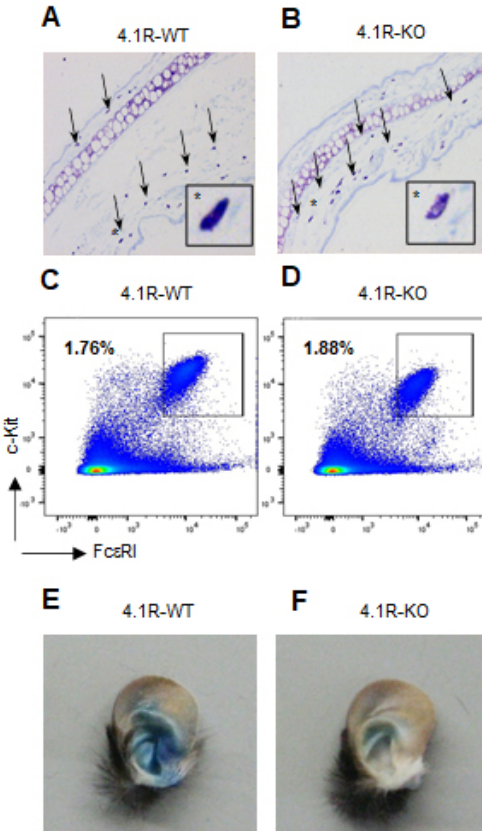

Figure 1. Comparison of wild-type (WT) mice and mice with 4.1R knockout (KO). Although both WT and 4.1R-KO mice express the comparable amount of mast cells in ear tissue (A, B) and peritoneum (C, D), 4.1R-KO mice exhibit reduced passive cutaneous anaphylaxis. Details in Draberova et al., Front. Immunol., 2019.

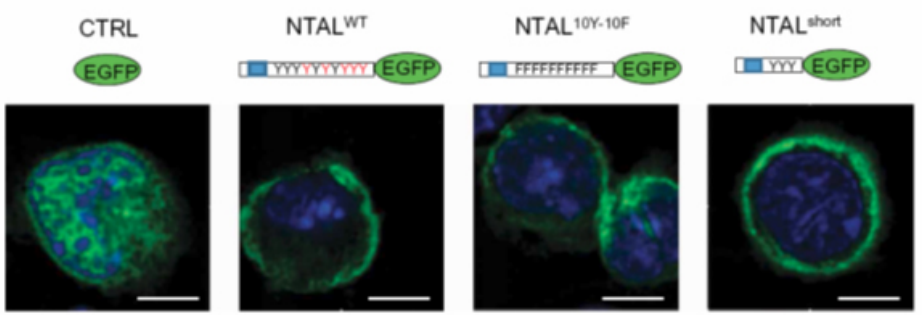

Figure 2. Various vectors used to determine the role of NTAL adaptor protein in prostaglandin E 2 - mediated chemotaxis and localization of the constructs in NTAL knockout bone marrow-derived mast cells. Details in Halova et al., Sci. Signal. 2018. Immunol., 2019.

Selected publications:

1. Draberova L*, Draberova H, Potuckova L, Halova I, Bambouskova M, Mohandas N, Draber P* (2019) Cytoskeletal protein 4.1R is a positive regulator of the FcεRI signaling and chemotaxis in mast cells. *Front* Immunol, doi: 10.3389/fimmu.2019.03068.
2. Halova I*, Bambouskova M, Draberova L, Bugajev V, Draber P* (2018) The transmembrane adaptor protein NTAL limits mast cell chemotaxis toward prostaglandin E_2. *Sci Signal*, **11**:eaao4354.
3. Potuckova L, Draberova L, Halova I, Paulenda T, Draber P* (2018) Positive and negative regulatory roles of C-terminal Src kinase (CSK) in FcεRI-mediated mast cell activation, independent of the transmembrane adaptor PAG/CSK-binding protein. *Front Immunol*, **9**:1771.
4. Halova I, Ronnberg E, Draberova L, Vliagoftis H, Nilsson GP, Draber P* (2018) Changing the threshold-signals and mechanisms of mast cell priming. *Immunol Rev*, **282**:73-86.
5. Bulfone-Paus S, Nilsson G, Draber P, Blank U, Levi-Schaffer F* (2017) Positive and negative signals in mast cell activation. *Trends Immunol*, **38**:657-667.

In the picture: 1. Dráber Petr | 2. Utekal Pavol | 3. Redčenko Oleksij | 4. Mrkáček Michal | 5. Bugajev Viktor | 6. Hálová Ivana | 7. Vávrová Petra | 8. Tůmová Magda | 9. Franková Daniela | 10. Demková Lívia | 11. Dráberová Lubica

LABORATORY OF

STRUCTURAL BIOLOGY

Protein crystallography, human carbonic anhydrase IX, structure-assisted inhibitor design, antibody engineering

Pavlína Maloy Řezáčová

more information

e-mail

The main interests of our group are structural studies of various proteins of biological or medicinal interest using protein crystallography. We use the structural knowledge in understanding the protein function and in some projects also in modulating its function by design of specific inhibitors.

In our structure-based drug discovery project, we target enzymes from pathogenic organisms as well as human enzymes (e.g., human nucleotidases or cancer-specific carbonic anhydrase IX); the knowledge of protein structures provides a platform for the rational design of specific inhibitors.

Our group also focuses on engineering recombinant antibody fragments of potential diagnostic use. We employ several approaches aiming at practical use of recombinant antibody fragments.

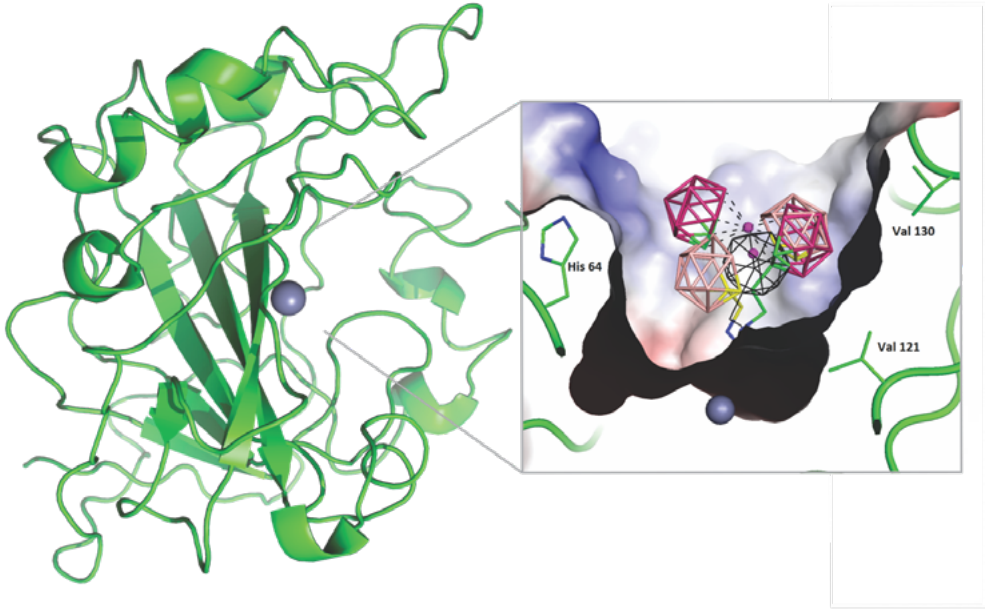

Figure 1. Binding of various carborane-based inhibitors into the active site of cancer-specific carbonic anhydrase IX. High-resolution crystal structures were used in structure-assisted inhibitor design.

Selected publications:

1. Grüner B*, Brynda J, Das V, Šícha V, Štěpánková J, Nekvinda J, Holub J, Pospíšilová K, Fábry M, Pachl P, Král V, Kugler M, Mašek V, Medvedíková M, Matějková S, Nová A, Lišková B, Gurská S, Džubák P, Hajdúch M*, Řezáčová P* (2019) Metallacarborane sulfamides: unconventional, specific, and highly selective inhibitors of carbonic anhydrase IX. *J Med Chem*, **62**:9560-9575.
2. Pola R, Král V, Filippov SK, Kaberov L, Etrych T, Sieglova I, Sedlacek J, Fábry M*, Pechar M* (2019) Polymer cancerostatics targeted by recombinant antibody fragments to GD2-positive tumor cells. *Biomacromolecules*, **20**:412-421.
3. Hnízda A*, Fábry M, Moriyama T, Pachl P, Kugler M, Brinsa V, Ascher DB, Carroll WL, Novák P, Žaliová M, Trka J, Řezáčová P, Yang JJ, Veverka V* (2018) Relapsed acute lymphoblastic leukemia-specific mutations in NT5C2 cluster into hotspots driving intersubunit stimulation. *Leukemia*, **32**:1393-1403.
4. Pachl P, Škerlová J, Šimčíková D, Kotik M, Křenková A, Mader P, Brynda J, Kapešová J, Křen V, Otwinowski Z, Řezáčová P* (2018) Crystal structure of native α-L-rhamnosidase from Aspergillus terreus. *Acta Cryst D*, **74**:1078-1084.
5. Sharma S, Čermáková K, De Rijck J, Demeulemeester J, Fábry M, El Ashkar S, Van Belle S, Lepšík M, Tesina P, Duchoslav V, Novák P, Hubálek M, Srb P, Christ F, Řezáčová P, Hodges HC, Debyser Z, Veverka V* (2018) Affinity switching of the LEDGF/p75 IBD interactome is governed by kinase-dependent phosphorylation. *Proc Natl Acad Sci USA*, **115**:E7053-E7062.

In the picture: 1. Brynda Jiří | 2. Kugler Michael | 3. Sedláček Juraj | 4. Fábry Milan | 5. Hořejší Magdalena | 6. Král Vlastimil | 7. Mrkvičková Věra | 8. Sieglová Irena | 9. Řezáčová (Maloy) Pavlína | 10. Krejčiříková Veronika

LABORATORY OF

TRANSCRIPTIONAL REGULATION

Development, evolution and development, eye, Pax genes

Zbyněk Kozmik

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We are interested in studies of embryonic development and evolution of development (evo-devo). Our focus is on the role of transcription factors and signalling cascades, especially on the role of the Wnt/β-catenin signalling pathway and transcription factors of *Pax* gene family. We utilize several model systems including fish (zebrafish, medaka), invertebrate chordate amphioxus (Branchiostoma sp.), annelid worm (*Platynereis dumerilii*) and cnidarians to study various aspects of evo-devo, especially the evolution of eyes and gene regulatory networks.

Figure 1. Invertebrate chordate amphioxus is a key model organism to understand vertebrate evolution.

Selected publications:

1. Prummel KD, Hess C, Nieuwenhuize S, Parker HJ, Rogers KW, Kozmikova I, Racioppi C, Brombacher EC, Czarkwiani A, Knapp D, Burger S, Chiavacci E, Shah G, Burger A, Huisken J, Yun MH, Christiaen L, Kozmik Z, Müller P, Bronner M, Krumlauf R, Mosimann C (2019) A conserved regulatory program initiates lateral plate mesoderm emergence across chordates. *Nat Commun*, **10**:3857. doi: 10.1038/s41467-019-11561-7.
2. Žídek R, Machoň O, Kozmik Z* (2018) Wnt/β-catenin signalling is necessary for gut differentiation in a marine annelid, Platynereis dumerilii. *Evodevo*, **9**:14. doi: 10.1186/s13227-018-0100-7. eCollection 2018.
3. Pantzartzi CN, Pergner J, Kozmik Z* (2018) The role of transposable elements in functional evolution of amphioxus genome: the case of opsin gene family. *Sci Rep*, **8**:2506. doi: 10.1038/s41598-018-20683-9.
4. Pergner J, Kozmik Z* (2017) Amphioxus photoreceptors – insights into the evolution of vertebrate opsins, vision and circadian rhythmicity. *Int J Dev Biol*, **61**:665-681. doi: 10.1387/ijdb.170230zk.
5. Marlétaz F, Firbas PN, Maeso I, Tena JJ, Bogdanovic O, Perry M, Wyatt CDR, de la Calle-Mustienes E, Bertrand S, Burguera D, Acemel RD, van Heeringen SJ, Naranjo S, Herrera-Ubeda C, Skvortsova K, Jimenez-Gancedo S, Aldea D, Marquez Y, Buono L, Kozmikova I, Permanyer J, Louis A, Albuixech-Crespo B, Le Petillon Y, Leon A, Subirana L, Balwierz PJ, Duckett PE, Farahani E, Aury JM, Mangenot S, Wincker P, Albalat R, Benito-Gutiérrez È, Cañestro C, Castro F, D'Aniello S, Ferrier DEK, Huang S, Laudet V, Marais GAB, Pontarotti P, Schubert M, Seitz H, Somorjai I, Takahashi T, Mirabeau O, Xu A, Yu JK, Carninci P, Martinez-Morales JR, Crollius HR, Kozmik Z, Weirauch MT, Garcia-Fernàndez J, Lister R, Lenhard B, Holland PWH, Escriva H, Gómez-Skarmeta JL, Irimia M (2018) Amphioxus functional genomics and the origins of vertebrate gene regulation. *Nature*, **564**:64-70. doi: 10.1038/s41586-018-0734-6. Epub 2018 Nov 21.

In the picture: 1. Kolková Miroslava | 2. Kozmik Zbyněk | 3. Kozmikova Iryna | 4. Vávrová Anna | 5. Doderović Jovana | 6. Mršťáková Simona | 7. Macháčová Simona | 8. Nosková Veronika

LABORATORY OF

TRANSGENIC MODELS OF DISEASES

Transgenic model, metabolism, craniofacial development, protease, Ub ligase

Radislav Sedláček

BIOCEV

more information

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The work of the laboratory is dedicated to four research areas that are interlinked by technologies used, especially genome editing, and animal models studied to reveal gene functions in the complexity of the whole organism.

In the protease area, we particularly focus on kallikreins, metalloproteinases (MP), and ADAMs (a disintegrin and metalloproteinase). Regarding the kallikreins, we have created a number of mutants for *Klk* genes on the background of SPINK5, the major inhibitor of serine proteases, to reveal their complex network in the skin, especially in the development of the Netherton syndrome.

In the metabolism area, we study the role of CLUH, which is an mRNA-binding protein interacting with more than 400 mRNAs and also regulating mitochondrial functions. We aim to elucidate the importance of CLUH in adipocyte differentiation and mitochondrial biogenesis and cancer.

In the field of ubiquitylation-mediated processes, we have created a number of mutant mice with the aim to understand the role of ubiquitination in regulating the intestinal barrier function, craniofacial development, immunity, and to characterize the links with human inflammatory bowel disease. The work focuses on cullin-RING ubiquitin ligases involved in GIT homeostasis and pathological processes, since the cullin family has been largely associated with different types of cancer in GIT and thus represents a promising pharmacological target. We also study other U3 ligases using (non)-conditional mouse models, among them the role of Btbd3 in the skeleton, Rnf121 in the cardiovascular system, Rnf186 in the lung, Cul4a, Ddb1, Cul3, and others in the gastrointestinal tract. In the area of craniofacial development, we focus on the molecular mechanism driving the craniofacial development and unveiling the molecular regulation of development of mineralized tissues such as teeth and bones. The molecular mechanisms cover the differentiation events of mineral-producing cells, secretion, and maturation of extracellular matrix and finally the crystallization process of hydroxyapatite. We focus on the function of extracellular protein ameloblastin in the regulation of mineralization processes in tooth enamel formation and bone homeostasis process. We also study the function of FAM46A, which is mutated in patients with osteogenesis imperfecta. We generated a Fam46a knockout model to characterize the molecular mechanisms that underlie the observed phenotypic changes.

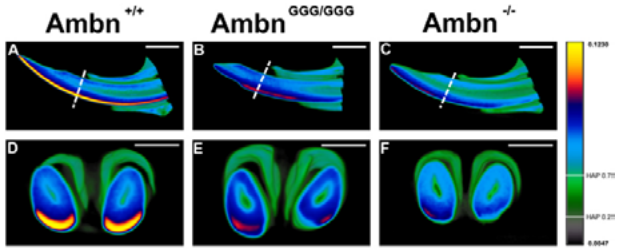

Figure 1. Dominant function of Ambn in formation of structured enamel

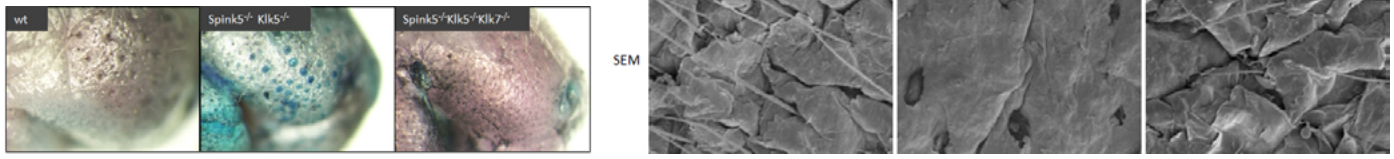

Figure 2. Unregulated activity of KLK7 causes severe epidermal barrier damage in time dependent manner

Selected publications:

1. Kasparek P, Ileninova Z, Zbodakova O, Kanchev I, Benada O, Chalupsky K, Brattsand M, Beck IM, Sedlacek R*(2017) KLK5 and KLK7 ablation fully rescues lethality of Netherton syndrome-like phenotype. *PLoS Genet*, **13**:e1006566.
2. Prochazka J, Prochazkova M, Du W, Spoutil F, Tureckova J, Hoch R, Shimogori T, Sedlacek R, Rubenstein JL, Wittmann T, Klein OD* (2015) Migration of founder epithelial cells drives proper molar tooth positioning and morphogenesis. *Dev Cell*, **35**:713-724.
3. Kaiser K, Gyllborg D, Procházka J, Salašová A, Kompaníková P, Molina FL, Laguna-Goya R, Radaszkiewicz T, Harnoš J, Procházková M, Potěšil D, Barker RA, Casado ÁG, Zdráhal Z, Sedláček R, Arenas E, Villaescusa JC, Bryja V* (2019) WNT5A is transported via lipoprotein particles in the cerebrospinal fluid to regulate hindbrain morphogenesis. *Nat Commun*, **10**:1498.
4. Wald T, Spoutil F, Osickova A, Prochazkova M, Benada O, Kasparek P, Bumba L, Klein OD, Sedlacek R, Sebo P, Prochazka J*, Osicka R*(2017) Intrinsically disordered proteins drive enamel formation via an evolutionarily conserved self-assembly motif. *Proc Natl Acad Sci USA*, **114**:E1641-E1650.
5. Balounová J, Šplíchalová I, Dobešová M, Kolář M, Fišer K, Procházka J, Sedlacek R, Jurisicova A, Sung HK, Kořínek V, Alberich-Jorda M, Godin I, Filipp D* (2019) Toll-like receptor 2 expression on c-kit+ cells tracks the emergence of embryonic definitive hematopoietic progenitors. *Nat Commun*, **10**:5176.

In the picture: 1. Raishbrook Miles Joseph | 2. Kašpar Petr | 3. Szczerkowska Katarzyna | 4. Mrázková Blanka | 5. Michalčíková Tereza | 6. Procházková Michaela | 7. Syding Linn | 8. Šlaufová Marta | 9. Kašpárek Petr | 10. Sedláček Radislav | 11. Turečková Jolana | 12. Sanchez Villalba Alvaro | 13. Slámová Monika | 14. Nováková Rozálie | 15. Buková Ivana | 17. Petrzselyová Silvia | 18. Aranaz Novaliches Goretti | 19. Procházka Jan

LABORATORY OF

VIRAL AND CELLULAR GENETICS

Retrovirus, entry receptor, epigenetics, somatic hypermutation, endogenous retrovirus

Jiří Hejnar

more information

e-mail

Our scientific interests cover the entire field of molecular interactions between retroviruses and their hosts. The retrovirus replication cycle starts by specific binding of retroviral envelope proteins to host cell receptors. After entering host cells, retroviruses integrate into the host chromosomes and use the cell transcription and proteosynthesis machineries to express retroviral proteins and propagate their own progeny. At multiple levels, cellular restriction factors regulate retroviral replication.

Retroviruses broaden their host range by mutations of the env gene, and we identified particular env mutations that activate the receptor-independent virus-cell fusion capacity and could be efficient in retroviral host range extension and cross-species transmission[1]. Vice versa, host cells develop resistance to retroviruses by mutations of genes encoding the specific receptors. We studied the natural polymorphisms in Na+/H+ exchanger (NHE1) in galliform species susceptible or resistant to avian leukosis virus subgroup J (ALV-J), an important pathogen of domestic poultry. Based on this knowledge, we introduced specific mutation of NHE1 into the chicken genome using the CRISPR/Cas9 technology and created an ALV-J-resistant chicken line[2].

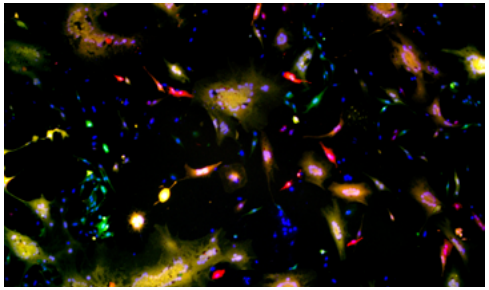

Figure 1. Cell-to-cell fusion induced by human endogenous retrovirus-encoded envelope glycoprotein, syncytin-1, and its receptor, hASCT2. Cells expressing syncytin-1 are marked by red fluorescence (dsRed), hASCT2-positive cells by green fluorescence (GFP). Cell nuclei are stained by Hoechst 33342 (blue). Multinuclear syncytia appear yellow by merging the red and green fluorescence.

An efficient defence mechanism used by the host cells is inactivation of the integrated invaders at the level of transcription via DNA methylation and modifications of adjacent histones. We used the epigenomic approach to retrovirus integration and revealed that transcriptionally active proviruses are preferentially localized close to the transcription starts of targeted genes or in enhancer regions[3]. The epigenomic expertise was used in designing the retroviral vector-based screen of somatic hypermutation (SHM) mistargeting outside the immunoglobulin genes. Our findings showed that topologically associated domains (TAD) of chromatin delineate susceptibility to SHM and that insertion of a strong Ig SHM-targeting element into a cold TAD renders it hot[4].

The last but not least topic in our laboratory are endogenous retroviruses. We described the loss of epigenetic control and the possible role of active DNA demethylation in aberrant expression of endogenous retrovirus HERVWE1 in germ line cancer[5]. By systematic screening of newly published mammalian genomes for endogenous retrovirus copies, we detected the first endogenous deltaretrovirus in the genome of Miniopterus bats[6]. This molecular fossil elucidates the deep evolutionary history of deltaretroviruses.

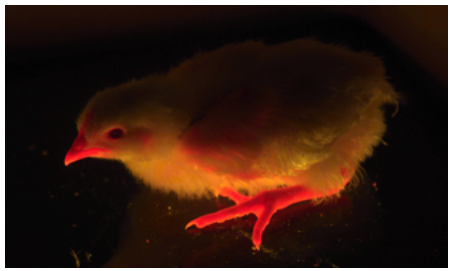

Figure 2. Freshly hatched mCherry-positive chicken. The mCherry reporter gene was introduced into the chicken genome by transposon-driven integration and orthotopic transplantation of primordial germinal cells. This is to document the efficiency of our transgenesis technology used in generation of ALV-J-resistant chicken line by the CRISPR/Cas9 editing.

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1. Lounková A*, Kosla J, Přikryl D, Štafl K, Kučerová D, Svoboda J (2017) Retroviral host range extension is coupled with Env-activating mutations resulting in receptor-independent entry. *Proc Natl Acad Sci USA*, **114**:5148-5157.
2. Koslová A, Trefil P, Mucksová J, Reinišová M, Plachý J, Kalina J, Kučerová D, Geryk J, Krchlíková V, Lejčková B, Hejnar J* (2020) Precise CRISPR/Cas9 editing of the NHE1 gene renders chickens resistant to the J subgroup of avian leukosis virus. *Proc Natl Acad Sci USA*, **117**:2108-2112.
3. Šenigl F, Miklík D, Auxt M, Hejnar J* (2017) Accumulation of long-term transcriptionally active integrated retroviral vectors in active promoters and enhancers. *Nucleic Acids Res*, **45**:12752-12765.
4. Šenigl F*, Maman Y, Dinesh RK, Alinikula J, Seth RB, Pecnová L, Omer AD, Rao SSP, Weisz D, Buerstedde JM, Aiden EL, Casellas R, Hejnar J, Schatz DG* (2019) Topologically associated domains delineate susceptibility to somatic hypermutation. *Cell Rep*, **29**:3902-3915.
5. Benešová M, Trejbalová K, Kovářová D, Vernerová Z, Hron T, Kučerová D, Hejnar J* (2017) DNA hypomethylation and aberrant expression of the human endogenous retrovirus ERVWE1/syncytin-1 in seminomas. *Retrovirology*, **14**:e20.
6. Farkašová H, Hron T, Pačes J, Hulva P, Benda P, Gifford RJ, Elleder D* (2017) Discovery of an endogenous Deltaretrovirus in the genome of long-fingered bats (Chiroptera: Miniopteridae). *Proc Natl Acad Sci USA*, **114**:3145-3150.

In the picture: 1. Karafiát Vít | 2. Kaňka Jakub | 3. Plachý Jiří | 4. Štafl Kryštof | 5. Miklík Dalibor | 6. Elleder Daniel | 7. Geryk Josef | 8. Trávníček Martin | 9. Pečenka Vladimír | 10. Stepanets Volodymyr | 11. Hejnar Jiří | 12. Matoušková Magda | 13. Krchlíková Veronika 14. Trejbalová Kateřina | 15. Slavková Martina | 16. Reinišová Markéta | 17. Hron Tomáš | 18. Gáliková Eliška | 19. Kučerová Dana | 20. Pecnová Ľubomíra

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CZ-OPENSCREEN
Petr Bartůněk

CZ OPENSCREEN
National Infrastructure for Chemical Biology

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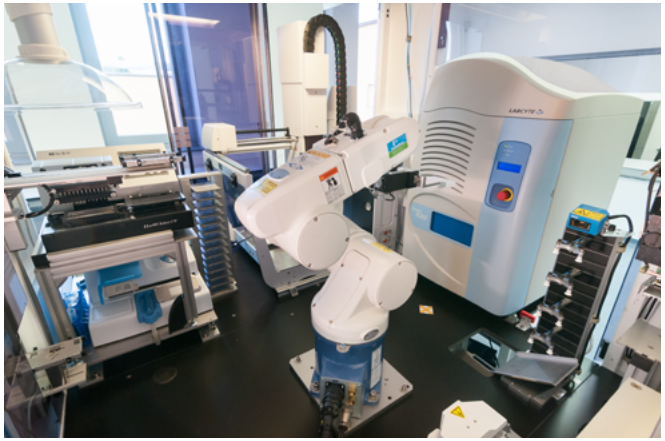
CZ-OPENSCREEN operates the most advanced research infrastructure for basic and applied research in the fields of chemical biology and genetics in the Czech Republic and provides Open Access to its external users. It supports this new interdisciplinary research by bridging traditional nature sciences such as cell biology, molecular and structural biology, biochemistry, organic chemistry and chem/bioinformatics. The main mission of CZ-OPENSCREEN is to identify new molecular probes and to develop new tools for research of chemical compounds as candidates for the development of new potential therapeutics. Unlike commercial platforms, CZ-OPENSCREEN also focuses on non-validated molecular targets, signalling pathways and neglected diseases. To the users from the biological and chemical community, CZ-OPENSCREEN offers standard biological and biochemical assays, consultancy and development of new assays, high-throughput screening (HTS), profiling of chemical compounds on the panel of cell lines, and medicinal chemistry optimization of newly identified biologically active compounds. CZ-OPENSCREEN is systematically building a library of both commercial chemical compounds and compounds synthesized in the Czech Republic. It provides access to this unique library to external users. An integral part of the services is chemiformatics support such as data analysis and storage, development of new analytical tools and database systems. CZ-OPENSCREEN is equipped by state-of-the-art technologies for high-throughput screening of chemical compounds such as integrated robotic HTS stations, robotic station for automatic microscopic analysis and label-free technology, integrated robotic systems for compound storage and sample preparation. Long-term international collaboration of CZ-OPENSCREEN with other European partner institutions contributed to the establishment of the European research Infrastructure Consortium EU-OPENSCREEN ERIC (European Infrastructure of Open Screening Platforms for Chemical Biology). The Czech Republic belongs to the founder states. CZ-OPENSCREEN is its national node and besides other activities, it will host the European Chemical Biology Database (ECBD), where all the data generated by EU-OPENSCREEN ERIC partner sites will be stored.



In the picture: 1. Bartůněk Petr | 2. Hykl Martin | 3. Škuta Ctibor | 4. Voršilák Milan | 5. Bojić Milan | 6. Müller Tomáš | 7. Sedlák David | 8. Bražinová Jana | 9. Franke Kidorová Dita | 10. Šímová Šárka | 11. Králová Jarmila | 12. Schuster Björn | 13. Kolla Jayaprakash Narayana | 14. Popr Martin | 15. Lisová (Marešová) Michaela | 16. Martínková Olga | 17. Kotrbová Zuzana | 18. Langhammer Tomáš | 19. Chawengsaksophak Kallayanee | 20. Epp Allan Trevor

CZECH BIOIMAGING
Pavel Hozák

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Czech-BioImaging is a national research infrastructure for biological and medical imaging. It is a distributed infrastructure of leading imaging facilities in the Czech Republic with IMG as hosting institution and many partners (see Figure 1). The infrastructure, consisting of many nodes, provides an open access to a wide range of imaging technologies and expertise to all scientists in the Czech Republic by a unified and coordinated logistic approach. Two of the nodes are part of EuroBioImaging and provide international services.
The aim of Czech-BioImaging is:

- to enable permanent access to cutting-edge imaging technologies and expertise in imaging to scientists who do not have it available at their own institutions,
- to increase awareness and knowledge of biological and medical imaging,
- to support mutual cooperation of scientists and sharing best practices and knowledge.

Czech-BioImaging is included in the Roadmap of Large Infrastructures for Research, Experimental Development and Innovation of the Czech Republic for the years 2016 - 2022.

Czech-BioImaging is supported from the programme for large research infrastructures of the Ministry of Education, Youth and Sports within the project "National Infrastructure for Biological and Medical Imaging (Czech-BioImaging – LM2018129)".

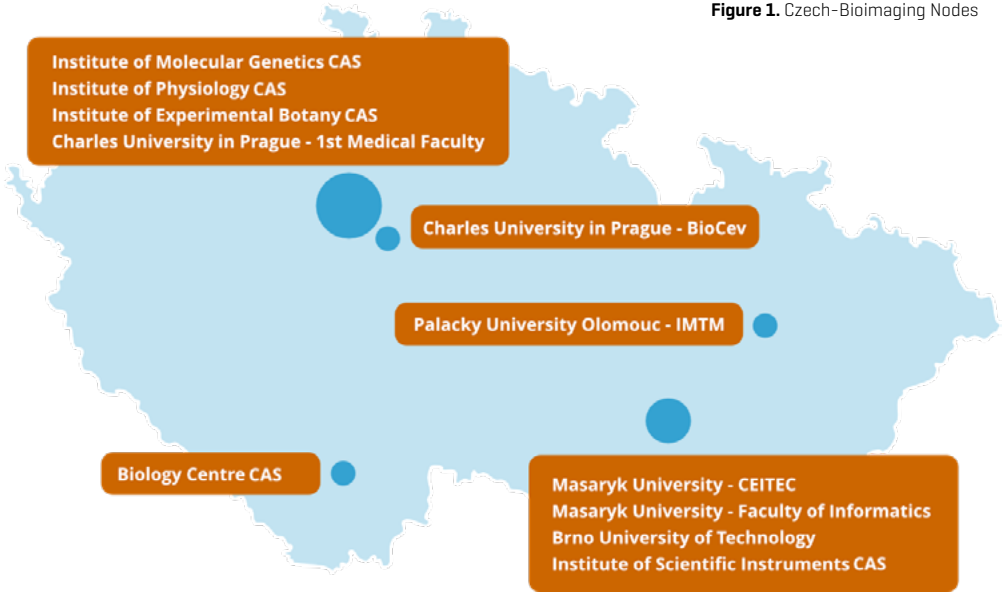

Figure 1. Czech-Bioimaging Nodes

MICROSCOPY CENTRE
Pavel Hozák

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The Microscopy Centre coordinates and provides logistic services to the large research infrastructures Czech-BioImaging and Euro-BioImaging. The Centre mainly serves as the central hub of the Czech-BioImaging infrastructure and as the coordinator of the Prague Node of the Euro-BioImaging ERIC consortium – see below for more information.

With the affiliated microscopy facilities, the Centre offers users "open access" to a wide range of state-of-the-art light and electron microscopy instruments and techniques, consultation services, sample preparation, data acquisition and analysis, image processing tools, and interpretation of the obtained results.

The Centre with the light microscopy and electron microscopy facilities organize training workshops in the field of microscopy. The Centre cooperates on a long-term basis with other members of national microscopy activities, the Czechoslovak Microscopy Society and microscope manufacturers, with focus on new microscopy methods and innovation of the current microscopy instruments.

In the picture: 1. Hozák Pavel | 2. Wernerová Martina | 3. Janoušek Karel | 4. Pišlová Lenka

LIGHT MICROSCOPY CORE FACILITY
Ondrej Horváth

CZECH BIOIMAGING
Imaging principles of life

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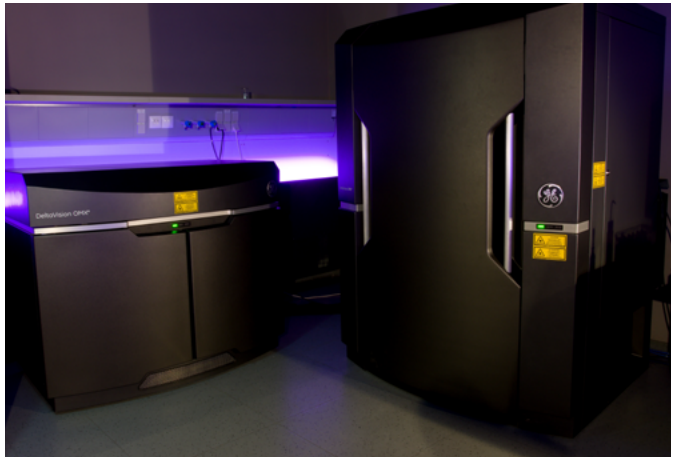
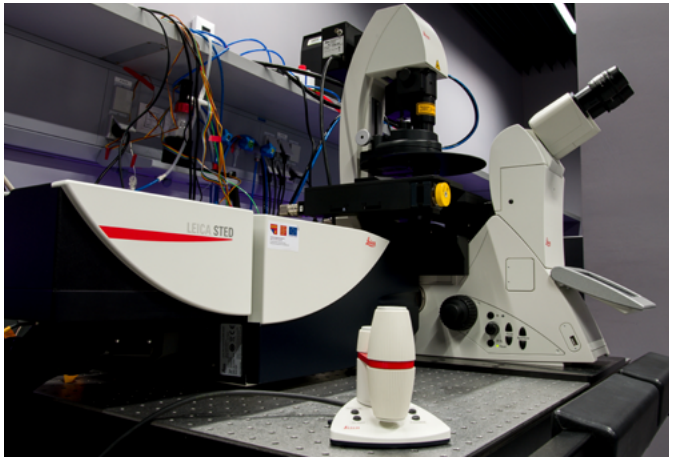
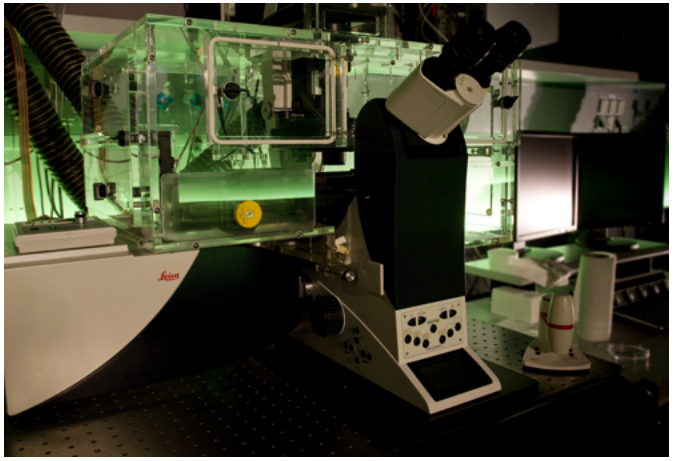
e-mail

The facility provides methodological and instrumentation background for light microscopy techniques. The facility is equipped with a wide range of instruments, ranging from routine fluorescence microscopes, confocal microscopes, up to high-end super-resolution microscopy systems STED, SIM and SMLM; specialized systems dedicated for live cell or live organism imaging, such as confocal spinning disc or lightsheet technology, are also available. The facility provides services for in-house research groups as well as for a wider microscopy community on the open access principle. Most of the instrumentation in the laboratory is available on a self-service basis for trained users. We put big emphasis on user education and training and provide personalized assistance to the users and their projects, not only in the sense of sample preparation and image acquisition, but on data processing, reconstruction and analysis as well. Several offline workstations for data analysis are available (Huygens Pro, Imaris, Arivis, MetaMorph, Fiji - ImageJ, Helicon, MatLab, SoftWorx).

The Light Microscopy Core Facility is involved in the national infrastructure for biological and medical imaging – Czech-Bioimaging. Along with imaging facilities of the Institute of Physiology of the Czech Academy of Sciences, Charles University in Prague (BIOCEV), and Institute of Experimental Botany of the Czech Academy of Sciences we constitute the Prague node of the Czech-Bioimaging infrastructure, which has been promoted as one of the two Czech nodes of the constructed pan-European imaging infrastructure EuroBioimaging (Advanced Light Microscopy Node Prague CZ). The Light Microscopy Core Facility provides the sponsored "Czech-Bioimaging open access" program for both domestic and international academic users.







In the picture: 1. Čapek Martin | 2. Horváth Ondrej | 3. Novotný Ivan | 4. Efenberková Michaela | 5. Chmelová Helena

ELECTRON MICROSCOPY CORE FACILITY
Vlada Filimoněnko

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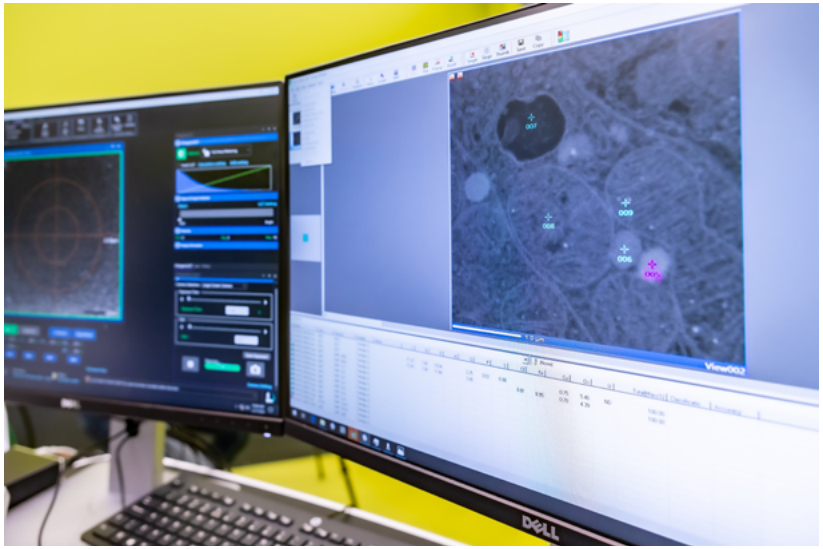
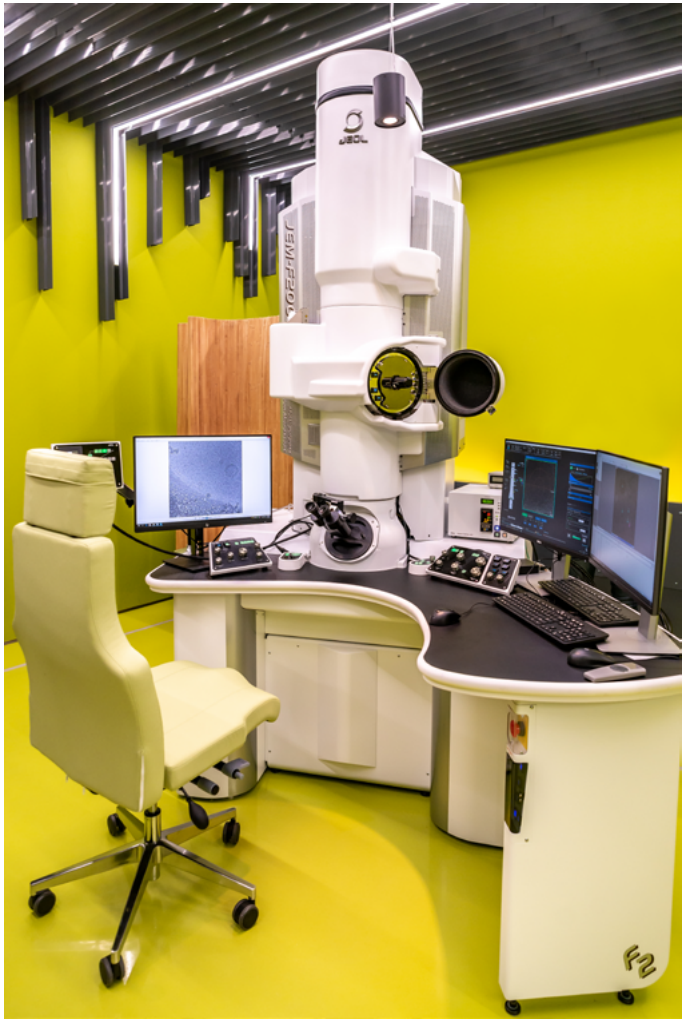
The Electron Microscopy Core Facility provides expertise and cutting edge equipment for a broad range of biological sample preparation and ultrastructural imaging techniques. The core facility deals with various biological samples: human and animal cell cultures, plant and animal tissues, worms, microorganisms, lipid micelles. The sample preparation techniques include routine chemical fixation and resin embedding, cryofixation using high-pressure freezing technique, freeze-substitution, plunge-freezing, cryosectioning, and immunolabelling, including simultaneous detection of multiple targets by our self-developed methods.

High-pressure freezing machines, two automatic freeze-substitution machines, freeze-fracture and replica making device, cryo-ultramicrotomes, Leica EM GP2 for automated plunge-freezing, as well as additional wet lab equipment are available. The core facility is equipped with two transmission electron microscopes (TEM) installed in November 2019 – a standard instrument for routine observation and an advanced 200 kV instrument providing the possibility of high-resolution TEM, STEM, 3D electron tomography, cryo-electron microscopy, and EDS elemental analysis and mapping.
We provide open access to our technologies and expertise via Czech BioImaging and Euro BioImaging infrastructures. As the spectrum of approaches and workflows in electron microscopy is very wide, we help the users to select an appropriate technique and to plan the whole experiment. The sample preparation and image acquisition can be done fully by the facility staff, or we can provide sufficient training and initial support for independent use of the technologies and equipment. We organize a yearly one-week practical course of transmission electron microscopy in life sciences for beginners and intermediate users.



The Electron Microscopy Core Facility associated to the IMG Microscopy Centre is part of the IMG Czech-BioImaging node and Prague Euro-BioImaging node.



In the picture: 1. Vlčák Erik | 2. Pinkas Dominik | 3. Filimoněnko Vláda | 4. Nováková Ivana | 5. Pišlová Lenka

CZECH CENTRE FOR PHENOGENOMICS
Radislav Sedláček

BIOCEV

Czech Centre for Phenogenomics

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The Czech Centre for Phenogenomics (CCP) is a non-distributed biomedical large research infrastructure in the Czech Republic with international significance, providing a unique and complex service portfolio, which on this scale can only be found in few places in the world. The activity of CCP focuses on three main areas, the first being genome editing (mainly in laboratory rodents), which is currently performed primarily using the CRISPR/Cas9 system. CCP belongs to the best centres in the world in this area and offers this service to researchers from around the world, thus facilitating development of animal models to study human diseases. Secondly, CCP focuses on phenotyping, i.e., comprehensive characterization of genetically modified models to describe the functions of the studied gene with an informative mutation. CCP is able to investigate all main physiological systems and reveal how and where the gene functions. As CCP closely cooperates with partners from international consortia, all procedures and technologies are standardized, which improves reproducibility of the results.

CCP is divided into three major modules: i) Transgenic and Archiving Module (TAM), where new animal models are generated, ii) Animal Facility Module (AFM), responsible for housing and breeding, and iii) Phenotyping Module (PM), providing standardized and large-scale phenotyping.

CCP not only develops new technologies for genome editing and for characterization of physiological functions, but provides a service in preclinical research, thus contributing to the development of new therapeutics. This preclinical research represents the third research area, including PDX (Patient-Derived tumour Xenograft) technology, which explores the development of human tumours engrafted into mouse models and their possible therapies. CCP became a new member of the European research consortium - infrastructure EurOPDX.

CCP belongs to the founding members of INFRAFRONTIER (European Research Infrastructure for Phenotyping, Archiving and Distribution of Model Mammalian Genomes) and due to the comprehensive portfolio of its expertise, from generation of mutant models to the knowledge of function of genes and their mutations, it also became a member of worldwide consortia IMPC (International Mouse Phenotyping Consortium). CCP works together with IMPC members on a very ambitious goal, which is the description of function of all mammalian genes.

In the picture [Management CCP]: 1. Rozman Jan | 2. Sedláček Radislav | 3. Koubková Gizela | 4. Červená Lenka | 5. Šroubková Jarmila | 6. Suchanová Šárka | 7. Daněk Libor

TRANSGENIC AND ARCHIVING MODULE

Radislav Sedláček

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Czech Centre for Phenogenomics

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e-mail

The Transgenic and Archiving Module (TAM) is an integral part of the Czech Centre for Phenogenomics (CCP), a national large research infrastructure. This Module provides a broad range of transgenic and archiving services with the aim to create new rodent models to decipher gene functions using full functional ablation or analysing the impact of various mutations, including replication of mutations identified in humans, for instance those that are causative for a disease. The mouse model generation output of CCP-TAM reaches approx. 150 new gene-modified lines a year, thus belonging to the largest centres in Europe. The TAM technology portfolio includes gene/genome targeting using classical technologies or the latest technologies of programmable endonucleases, especially the CRIPR/Cas system, to generate gene/genome-modified mouse and rat models. These activities are complemented by the classic portfolio of services including rederivation/reanimation, and cryo-archiving of mouse and rat strains. In addition, CCP-TAM (partly in cooperation with CCP-AFM) also manages animal import/export, preparation of animal cohorts on demand, genotyping, consultancy support, and administrative support (GMO licenses) and other administrative services connected to genetically modified organisms within the facility. The established comprehensive technology portfolio is fully comparable with any world-class laboratory in this specific area; the technology of "programmable nucleases" such as 'TALEN and CRISPR/Cas9'-assisted gene targeting and genome editing substantially improve the service in the custom-tailored targeting projects, saving costs and time. Besides the services, CCP-TAM also provides education activities to its users and, for instance, organizes an annual "CRISPR course", international workshop dedicated to the genome-editing technologies.

Figure 1. Microinjections

Figure 1. Generation of mutant rat models

In the picture: 1. Krupková Michaela | 2. Tkadlecová Anna | 3. Šolcová Katarzyna Daria | 4. Hroncová Soňa | 5. Ficová Tereza | 6. Králiková Katarína | 7. Doleželová Kateřina | 8. Jeníčková Irena | 9. Sedláček Radislav | 10. Kašpárek Petr | 11. Kopkanová Jana

ANIMAL FACILITY KRČ
Jan Honetschläger

Czech Centre for Phenogenomics

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The IMG animal facility located on the Krč campus provides a superior standard for animal housing and breeding including sufficient experimental space. The facility is fully accredited for breeding both common animal strains and genetically altered animals. The current total capacity is more than 9,000 cages and is split into different separated sections: conventional breeding, quarantine for imported animals and special barrier "specified pathogen-free" breeding operated under the FELASA guidelines. The barriers are equipped with steam sterilizers, vaporised hydrogen peroxide chambers, pass-through boxes and individually ventilated cages to enhance the bioexclusion. The facility delivers its services mainly to IMG users and cooperating institutes within the Krč campus.

In the picture: 1. Kratochvílová Daniela | 2. Hornová Kristýna | 3. Bakešová Zuzana | 4. Smetana Miroslav | 5. Neradil Peter | 6. Herodes Martin | 7. Kaděrková Eva | 8. Honetschläger Jan | 9. Ševčíková Kateřina | 10. Gašpierik Tomáš | 11. Kosmáková Michaela | 12. Dygryn Stanislav | 13. Dušková Nikola | 14. Zukalová Jitka | 15. Matoušková Renata | 16. Indrová Marie | 17. Novotná Monika | 18. Abramová Vera | 19. Vávrová Gabriela | 20. Vorlová Daniela | 21. Mikolášková Markéta | 22. Hviščová Alexandra | 23. Hromušková Jana | 24. Králová Alena | 25. Oros Tetyana | 26. Rynekrová Markéta | 27. Doubravová Romana | 28. Polevičová Lenka | 29. Siváková Ludmila | 30. Vávrová Kateřina | 31. Hájková Emilie

ANIMAL FACILITY BIOCEV

Libor Kopkan | Jan Honetschläger

since 8/2019 | till 8/2019

BIOCEV

Czech Centre for Phenogenomics

more information

e-mail

The Animal Facility Module (AFM) of the Czech Centre for Phenogenomics (CCP) in Vestec is based on the latest advances in housing, breeding and care of laboratory mice and rats to maintain a high standard for animal health and welfare. The CCP AFM Vestec contains four individual, fully separated breeding and experimental barrier areas as well as an autonomous quarantine area. Each barrier includes modern devices to keep a controlled SPF (specific pathogen-free) environment. All animals are housed in individually ventilated cages (IVC) that standardize the animal welfare level.

The CCP AFM services in Vestec, which include rodent colony management with full integration with other CCP modules including Transgenic & Archiving Module and Phenotyping Module, are provided by a team of 35 employees.

Our services: housing and husbandry, animal colony management, technical and experimental service, health monitoring, import and export of animals, quarantine of imported animals, personnel training and project consultancy.

In the picture: 1. Konganbayev Murat | 2. Karbanová Šárka | 3. Žáková Petra | 4. Dušková Kateřina | 5. Hittlová Monika | 6. Balouš David | 7. Balouš David | 8. Vaníková Jana | 9. Cihelková Renáta | 10. Pokorná Pavlína | 11. Kopkan Libor | 12. Ciucur Pavla | 13. Skotnicová Marie | 14. Hradil Sebastien | 15. Javorská Michaela | 16. Krčálová Zuzana | 17. Froňková Jiřina | 18. Kratochvílová Alena | 19. Kameníková Pavla | 20. Babanská Alena | 21. Čermák Antonín | 22. Jína Pavel | 23. Bursa Michal | 24. Lučanová Denisa | 25. Grassingerová Petra | 26. Baloušová Eva | 27. Schwarzová Drahomíra | 28. Závodská Zdeňka | 29. Šustrová Romana | 30. Glosová Svatava | 31. Matoušková Jana

PHENOTYPING MODULE
Radislav Sedláček

BIOCEV

Czech Centre for Phenogenomics

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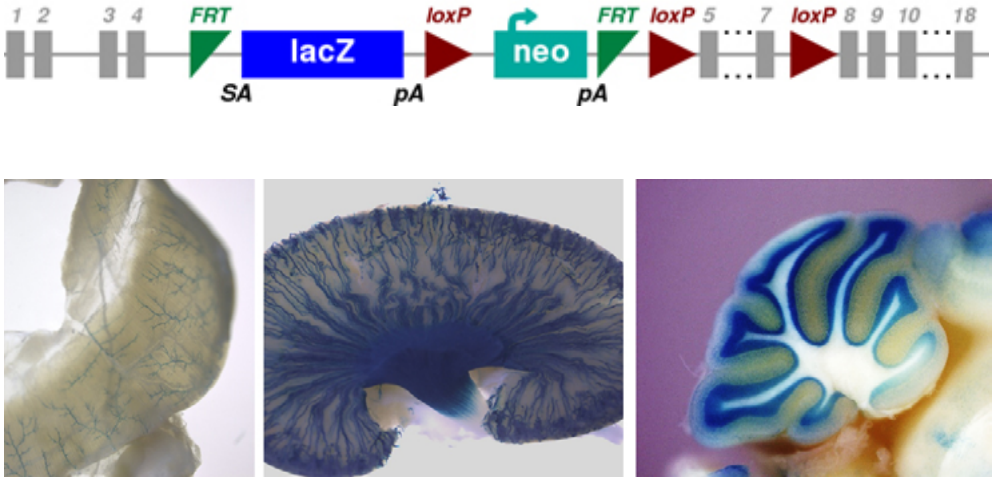
The Phenotyping Module (PM) is an integral part of national large research infrastructure Czech Centre for Phenogenomics (CCP). The Phenotyping Module has been operating since 2016 and comprises several specialized laboratories and a compendium of technologies and expertise for investigating the major physiological systems of the body.

The full list of technologies together with a list of equipment. The technologies accompanying specific services are grouped into units: 1/ histopathology, 2/ immunology, 3/ cardiovascular, 4/ metabolism, 5/ biochemistry, 6/ metabolomics, 7/ bioimaging, 8/ embryology, 9/ lung function, 10/ neurobehavioral, 11/ hearing, 12/ vision, 13/ PDX/cancer models, and 14/ bioinformatics. All these CCP units together with their specific sets of technologies create a unique collection of expertise in a single location.

In total, the available technologies enable collecting more than 700 parameters for each phenotyped animal, and the portfolio of services and parameters is continually developing.

The Units of Metabolism and Clinical Biochemistry build together the Metabolomics platform and intensively interact with histopathology and the newly built MALDI-Imaging and Bioinformatics Unit.

The specialized modules of CCP provide open access-based services to groups and institutions from the entire Czech Republic irrespective of whether they are from the Czech Academy of Sciences or universities. Moreover, CCP also provides free access to international customers from Europe and worldwide, and the number of all these customers is steadily growing.



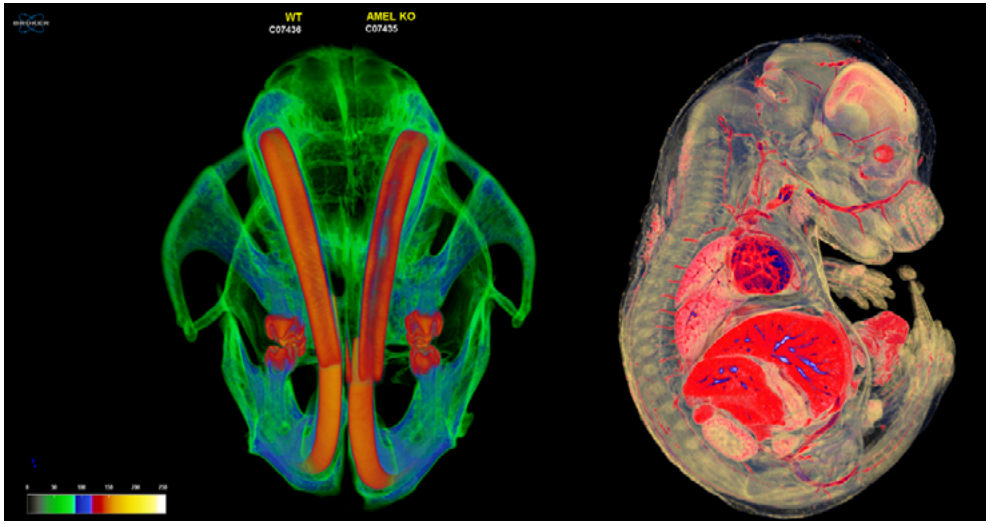


Figure 1. LacZ expression in adult tissues: comprehensive analysis of gene expression pattern

In the picture: 1. Rylová Gabriela | 2. Klíma Kryštof | 3. Malinka František | 4. Pálková Marcela | 5. Raishbrook Miles Joseph | 6. Wu Yu-Chien | 7. Špoutil František | 8. Kučera Lukáš | 9. Žatečka Václav | 10. Pajuelo Reguera David | 11. Majerník Ján | 12. Jana Zima | 13. Makovický Peter | 14. Křížová Kamila | 15. Zareie Ashkan | 16. Valentová Anna | 17. Mrázková Blanka | 18. Michalčíková Tereza | 19. Lindovský Jiří | 20. Procházková Michaela | 21. Fejfarová Karla | 22. Glushchenko Mariya | 23. Štefancová Eva | 24. Duongová Lien | 25. Macek Petr | 26. Kanásová Katarína | 27. Hojná Andrea | 28. Králová Viziová Petra | 29. Bariselli Simone | 30. Symkina Viktoria | 31. Clewell Sarah | 32. Madureira Trufen Carlos Eduardo | 33. Juhasz Atilla | 34. Sain Rajasree | 35. Da Silva Oliviera Ana Rita | 36. Buková Ivana | 37. Nováková Rozálie | 38. Novosadová Vendula | 39. Zudová Dagmar | 40. Petreszelyová Silvia | 41. Barbazza Franceska | 42. Streparola Gaia | 43. Suchanová Šárka | 44. Rozman Jan | 45. Sedláček Radislav | 46. Procházka Jan

ELIXIR CZ
Jan Pačes

more information

e-mail

The Czech ELIXIR Node (part of ELIXIR-EU) represented by the Institute of Molecular Genetics and Institute of Chemistry and Biochemistry of the Czech Academy of Sciences is a national hub for bioinformatics, comprising an advanced computational environment, dedicated data collections and unique tools provided for the life science community. The Node has been created and operated as a distributed infrastructure, currently comprising fourteen organizations. Partner institutions provide tools and databases in an open access regime to Czech scientists and the international research community.

There are three strong areas in which the Node provides a connection between the national and pan-European research structures:

1. The most advanced and developed area belongs to the Structural Bioinformatics field focusing mainly on services and development of specific tools. This field is very tightly connected with Czech IT research infrastructure partners – namely CESNET and CERIT SC – providing not only computational and storage capacity, but also know-how in the networking and use of heterogeneous resources.

2. The second largest area is represented by curated databases in two major areas – specific collections of genomic data on microorganisms and plants and cheminformatics databases, which also serve as an interconnecting element between other biomedical infrastructure projects such as EU-OPENSCREEN and EATRIS.

3. Last but not least, the IT dedicated solutions for the ELIXIR infrastructure are developed by the Node IT partners, and their involvement in other ELIXIR CZ projects represents a common platform for unification and efficiency of the whole process. The Node also serves as a coordination platform of national bioinformatics activities and is responsible for data uniformity, ELIXIR-standard application and for world-scale accessibility in the whole research space within the Czech Republic.

Figure 1. Map of member states within ELIXIR. Each member state establishes "Node" in its country, which is a network of institutes that carry out the scientific and technical work of ELIXIR within that country.

BIOCEV

BIOTECHNOLOGY AND BIOMEDICINE CENTRE
OF THE CZECH ACADEMY OF SCIENCES AND CHARLES UNIVERSITY

Pavel Martásek

BIOCEV

more information

e-mail

The Biotechnology and Biomedicine Centre of the Academy of Sciences and Charles University in Vestec (BIOCEV) was established with essential support from the European Union. The quality of the set scientific programme is reflected by the highest achieved evaluation of the five presented large projects of the Operational Programme Research and Development for Innovations. BIOCEV is a joint project of six Academy institutes (Institute of Molecular Genetics, Institute of Microbiology, Institute of Physiology, Institute of Experimental Medicine, Institute of Biotechnology, and Institute of Macromolecular Chemistry) and Charles University represented by two faculties (Faculty of Sciences and First Faculty of Medicine).

At present, the Centre hosts more than 500 scientists and technical staff. Almost a third of them come from abroad. The end results of the BIOCEV research include drugs specifically targeted to the site of impaired metabolism, polymer vaccines, novel antibiotics, and protein and tissue engineering. The BIOCEV research teams have already published more than 800 scientific outputs including reports in prestigious international journals (e.g., Cell, Molecular Cell, Nature Communication, Gastroenterology, and other).

Besides one National infrastructure – Czech Centre for Phenogenomics, also several IMG research groups (Integrative Biology, Epigenetics of the Cell Nucleus, Eye Biology, Transgenic Models of Diseases, Mouse Molecular Genetics, Cancer Biology and Germ Cell Development groups) and two research services (Cryobank, Media and Washing facility) are located at BIOCEV. At present, 193 IMG employees are located in Vestec, which represents approx. 32 % of total IMG employees (as of year 2019).

In the picture (Administrative team of BIOCEV): 1. Vosátková Lenka | 2. Solil Petr | 3. Žižka David | 4. Horák Filip | 5. Kyselý Richard | 6. Dostál Milan | 7. Sedláček Michal | 8. Martásek Pavel | 9. Polák Martin | 10. Darsa Jana | 11. Paterová Květa

Research Services

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CHICKEN FACILITY KOLEČ
Martina Minariková

more information

e-mail

The chicken breeding facility is located in the village Koleč, north of Prague, about 45 km from IMG. It includes mainly rears genetically defined inbred, congenic and outbred chicken lines. The breeding facility produces eggs, embryos and chickens for several research groups focusing on the chicken model. Chickens are mostly used mainly for virological or immunological projects, currently for the studying of avian leukosis viruses, which, among other things, serves as a model for the study of other retroviruses, such as human immunodeficiency virus. For scientific purposes, we develop genomic editing techniques using the CRISPR /Cas9 system, which is routine in mammals but is only in the basic research phase in birds.

In the picture: 1. Thunová Kamila | 2. Eisensteinová Alena | 3. Dvořáková Jitka | 4. Hrodková Iva | 5. Libovická Zuzana | 6. Skoková Radomíra | 7. Minariková Martina

HISTOLOGICAL LABORATORY
Vladimír Kořínek

more information

e-mail

The laboratory is equipped for preparation of paraffin blocks, tissue sectioning, deparaffination, and antigen retrieval. The laboratory equipment consists of a set of Leica devices that include tissue processor ASP200S, paraffin-embedding station EG1150H, and two fully motorized rotary microtomes RM2255. The tissue processor can process up to two hundred samples in a single run. The paraffin-embedding station provides possibilities for creation of different types of wax blocks. The microtomes are supplied with various types of blades for sectioning different tissue types. The facility is run as a semi-self-service – tissue dehydration and paraffin embedding is handled by the staff; all the other steps are carried out by each researcher individually. The facility is open to all Academy researchers that can use the facility after brief initial training.

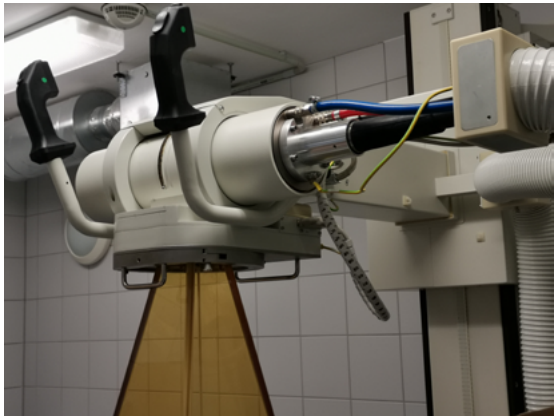
IONIZING RADIATION SOURCE HANDLING CORE FACILITY

Stanislav Pavelka

more information

e-mail

The facility was established in July 2017. However, it provided services already a decade before to support various needs of all the users of ionizing radiation sources at the Institute. Members of research groups at IMG routinely use two very different types of ionizing radiation sources, demanding various methodological and instrumentation background provided by the facility: 1) unsealed radionuclide sources, mainly in the form of radioactively labelled organic compounds, for pharmacological and biochemical studies of metabolism; and 2) X-ray generators in the form of compact cabinet biological irradiators, for regulated X-ray irradiation of small laboratory animals (mice) and samples of cultured cells. The facility offers the following services to users ad 1) handling unsealed radionuclide sources: i) administration of personal monitoring by personal film dosimeters through the company NUVIA dosimetry; ii) counselling in the field of manipulation with radioactive materials; iii) measurements of radioactivity of all kinds of samples; iv) disposal of radioactive waste. For users ad 2) performing routinely regulated X-ray irradiation of samples of biological materials, the core facility is equipped with two X-ray irradiators: i) older (since 2010) orthovoltage X-ray apparatus T-200 (Wolf-Medizintechnik); and ii) since June 2016, a more comfortable Biological Irradiator X-RAD 225XL (PXi Precision X-Ray Inc.). This compact cabinet X-ray-irradiator is equipped with the TouchRAD Panel and a touchscreen computer that hosts the TouchRAD User Interface. This touchscreen interface allows the users, qualified by the facility leader (super-user), to operate all features of the X-RAD Biological Irradiator themselves, at the time according to the IMG reservation system (https://webcalendar.img.cas.cz).



For the Director of the Institute, the facility leader (Assoc Prof S. Pavelka, Ph.D.) acts as a link between the Institute and The State Office for Nuclear Safety (SÚJB), which demands permanent updating of documentation regarding the conditions and working places within the Institute, in compliance with the Act No. 263/2016 Coll. (Atomic Act).

Selected publications:

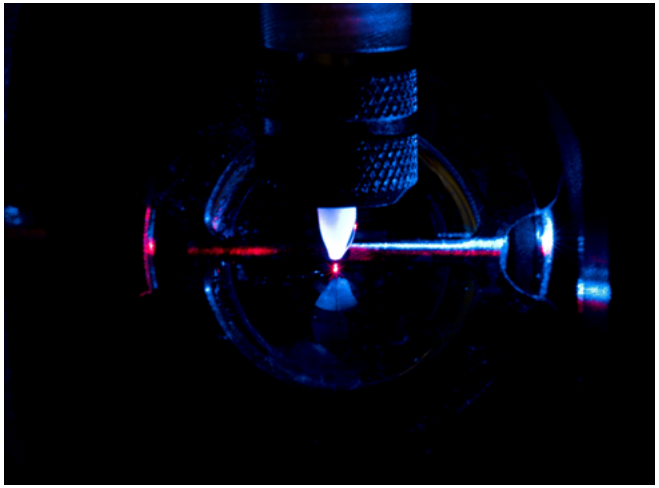
1. Szeiffová Bačová B., Vinczenzová C., Žurmanová J., Kašparová D., Knezl V., Egan Beňová T., Pavelka S, Soukup T., Tribulová N (2017) Altered thyroid status affects myocardial expression of connexin-43 and susceptibility of rat heart to malignant arrhythmias that can be partially normalized by red palm oil intake. *Histochem Cell Biol*, **147:**63-73.
2. Rauchová H, Vokurková M, Pavelka S, Vaněčková I, Tribulová N, Soukup T (2018) Red palm oil supplementation does not increase blood glucose or serum lipids levels in Wistar rats with different thyroid status. *Physiol Res*, **67:**307-315.
3. Sykora M, Szeiffova Bacova B, Egan Benova T, Barancik M, Zurmanova J, Rauchova H, Weismann P, Pavelka S, Kurahara LH, Slezak J, Soukup T, Tribulova N (2019) Cardiac Cx43 and ECM responses to altered thyroid status are blunted in spontaneously hypertensive versus normotensive rats. *Int J Mol Sci*, **20:**3758. doi: 10.3390/ijms20153758.

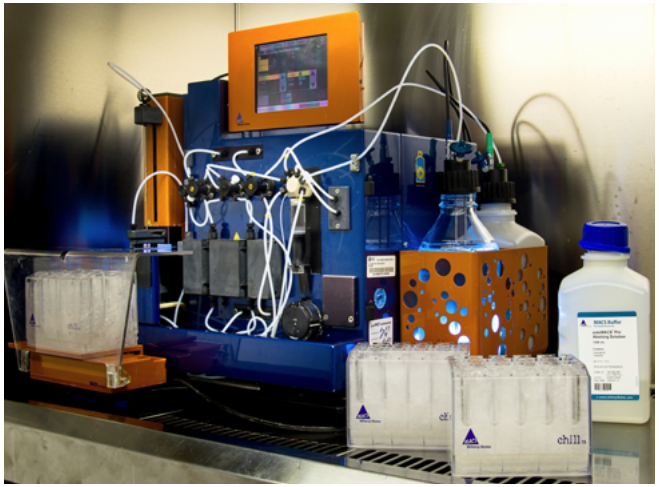
FLOW CYTOMETRY CORE FACILITY
Ondrej Horváth

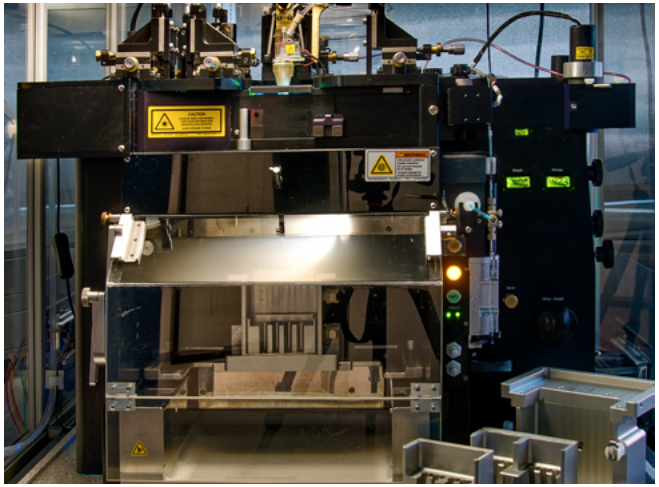
more information

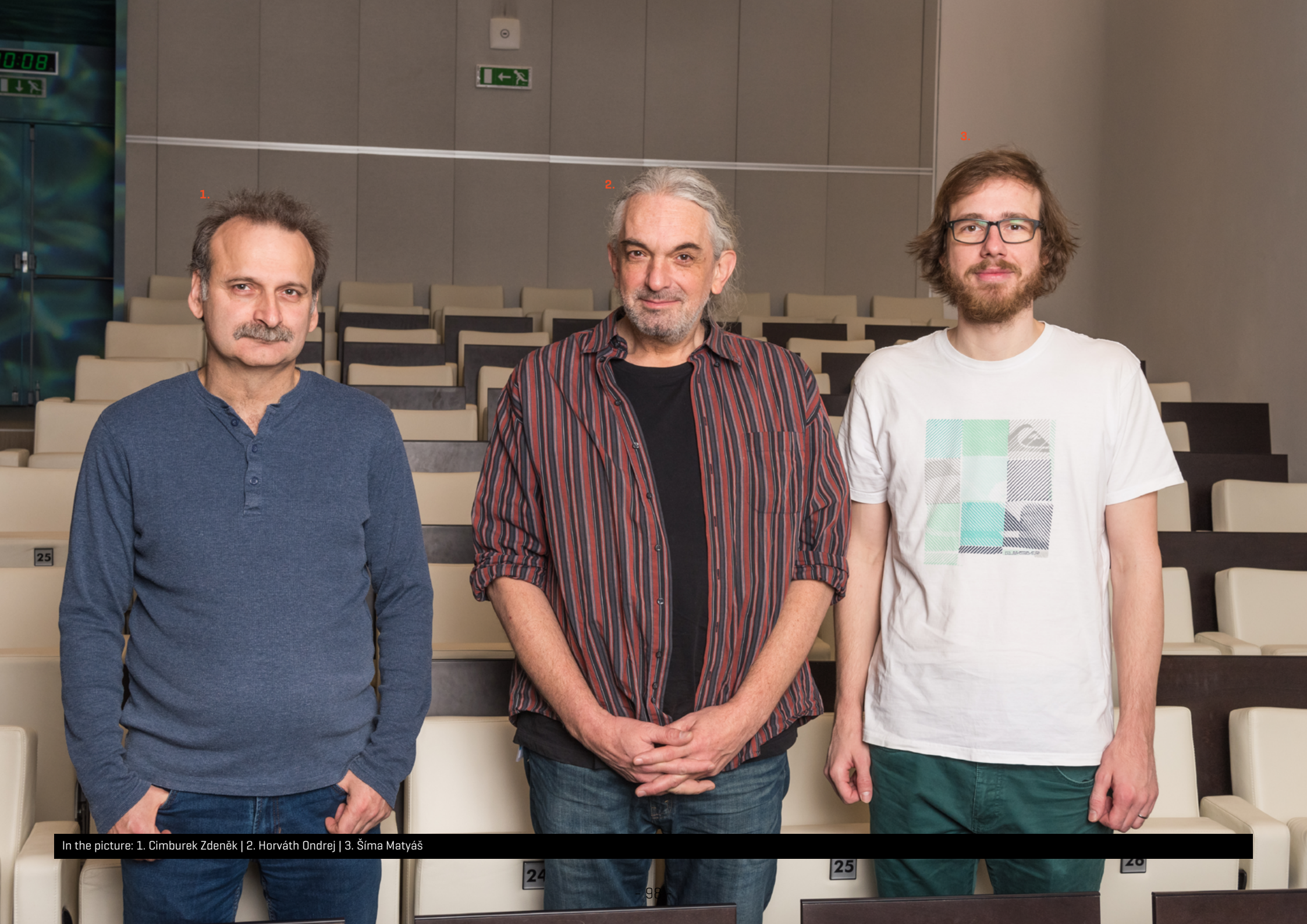
e-mail

The facility provides methodological and instrumentation background for flow cytometry techniques. The facility is equipped with four flow cytometers – two analysers (BD FACSymphony and BD LSRII) and two sorters (BD Influx and BD FACSAria IIu). BD FACSymphony is a high-end cytometer and with six solid-state lasers (355, 405, 445, 488, 561 and 640 nm) and 31 fluorescence detectors is capable to cover most of the flow-cytometry applications. BD LSRII is equipped with four solid-state lasers (405, 488, 561 and 637 nm) and 13 fluorescence detectors. Both analysers are equipped with an HTS loader for high-throughput analysis using 96- or 384-well plates. Polychromatic high-speed jet-in-air cell sorter BD-Influx is equipped with five lasers (355, 405, 488, 561 and 638 nm), 14 fluorescent detectors, small particle option for measuring small particles, and 6-way sorting capability. The BD FACSAria sorter is a cuvette-based polychromatic high-speed cell sorter with five lasers (405, 445, 488, 561 and 637 nm) and 18 fluorescence detectors and 4-way sorting capability. Both sorters have a cloning deposition unit and they are located inside a biological safety cabinet and fully adapted for sterile sorting. The facility is also equipped with an AutoMACS Pro (Miltenyi Biotec) magnetic separator for automatic rapid sorting of cells, as well as cell culture facilities. For analyses, the facility provides access to a powerful analysis tool – FlowJo software. Two working stations with FlowJo are located directly in the facility and 25 FlowJo licences are distributed among the IMG users.









In the picture: 1. Cimburek Zdeněk | 2. Horváth Ondrej | 3. Šíma Matyáš

MEDIA AND WASHING KRČ
Hana Marxová

more information

e-mail

The facility is responsible for distribution of commercial media and FBS, operation of the Supply Centre, preparation of tissue culture media and solutions, preparation of bacteriology media and custom-made antibiotic-containing or non-antibiotic plates. Our greatest speciality is mixing media from components as required by the user. We also offer sterilization of solutions. The washing unit provides washing and sterilization of glass, plastic, and other materials. Another of our tasks is decontamination of GMO waste, its subsequent manipulation, and washing of laboratory clothing.

Hot air sterilization

Steam sterilization solution

In the picture: 1. Fišerová Jana | 2. Borovičková Lenka | 3. Marxová Hana | 4. Alferiová Lenka

MONOCLONAL ANTIBODIES AND CRYOBANK

Dobromila Kumpoštová

more information

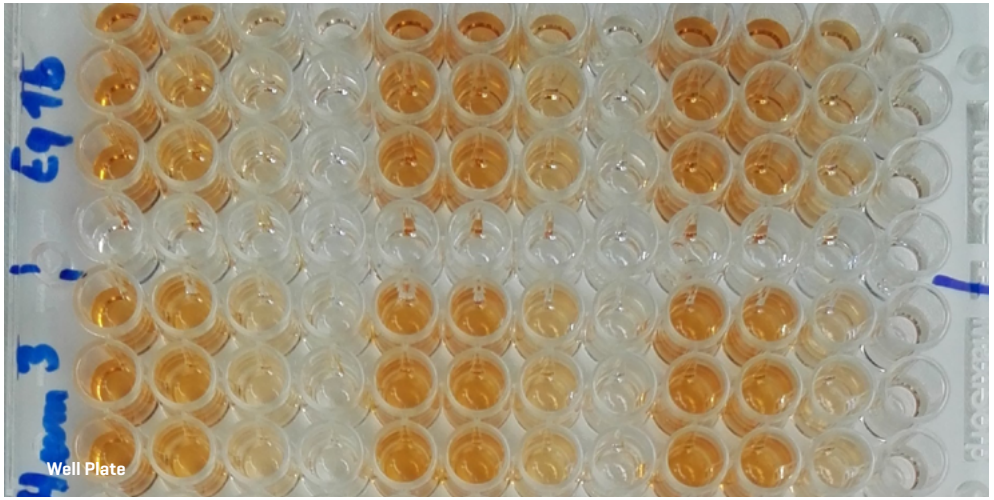
e-mail

Monoclonal Antibody Facility

The facility provides preparation of mouse monoclonal antibodies including immunization using a particular immunization protocol, ELISA testing of production of specific antibodies, cloning of selected samples, freezing of cryobank samples, cultivation of cell culture supernatants, or preparation of ascitic fluid from selected clones and isotype determination of the produced antibody. Further services comprise testing of cell culture supernatants for the presence of mycoplasms and freezing of cell line banks and hybridomas.

Cryobank

The cryobank serves for long-term storage of samples in liquid nitrogen. The current cryobank capacity is 320,000 samples, with further possible extension. The cryobank stores cell lines, hybridomas, mouse sperm and mouse embryos in liquid nitrogen or its vapours. The storage containers (LABS40K – Taylor-Wharton and 24K) are connected to the exterior liquid nitrogen container for 6,000 litres and supplied automatically. The entire cryobank system is secured by a backup energy source in case of power failure. All operations, diagnostics and monitoring of the level of liquid nitrogen in the storage containers are fully automated and controlled. Parameters (temperature, humidity, O2 concentration) and safety both in the cryobank and in the individual storage containers are followed by the monitoring system with GSM and web interface outputs.



Well Plate

GCPII stock solution

In the picture: 1. Borovičková Lenka | 2. Sobotková Ladislava | 3. Kumpoštová Dobromila

CRYOBANK BIOCEV
Dobromila Kumpoštová

BIOCEV

more information

e-mail

The operation of the cryobank for long-term storage of samples in liquid nitrogen started in March 2016 and the cryobank is divided into two parts. The first part is situated in the main building of the BIOCEV Centre and is mainly intended for storage of cell lines and hybridomas. The second part is located in building SO-002 as a component of the Transgenic and Archiving Module. This part of the cryobank mainly serves for preservation of mouse sperm and mouse embryos in liquid nitrogen or its vapours.

The storage containers (LABS40K, LABS80K – Taylor-Wharton and 24K) are connected to an external reservoir for liquid nitrogen with a capacity of 10,000 litres and are refilled automatically. The cryobank also includes four filling sites providing the possibility to draw liquid nitrogen into both pressure and non-pressure containers. The entire cryobank system is connected to a back-up power supply for the cases of power outage. All operations, diagnostics and checking of the liquid nitrogen level in the storage containers are fully automated and controlled. The parameters (temperature, humidity, O2 concentration) and the safety in both the cryobank and the storage containers themselves are controlled by a monitoring system connected to GSM and a web interface.

The cryobank core facility also administers production of dry ice.

Storing of samples in liquid nitrogen

In the picture: 1. Nezbedová Zuzana | 2. Kumpoštová Dobromila

MEDIA AND WASHING BIOCEV
Dobromila Kumpoštová

BIOCEV

more information

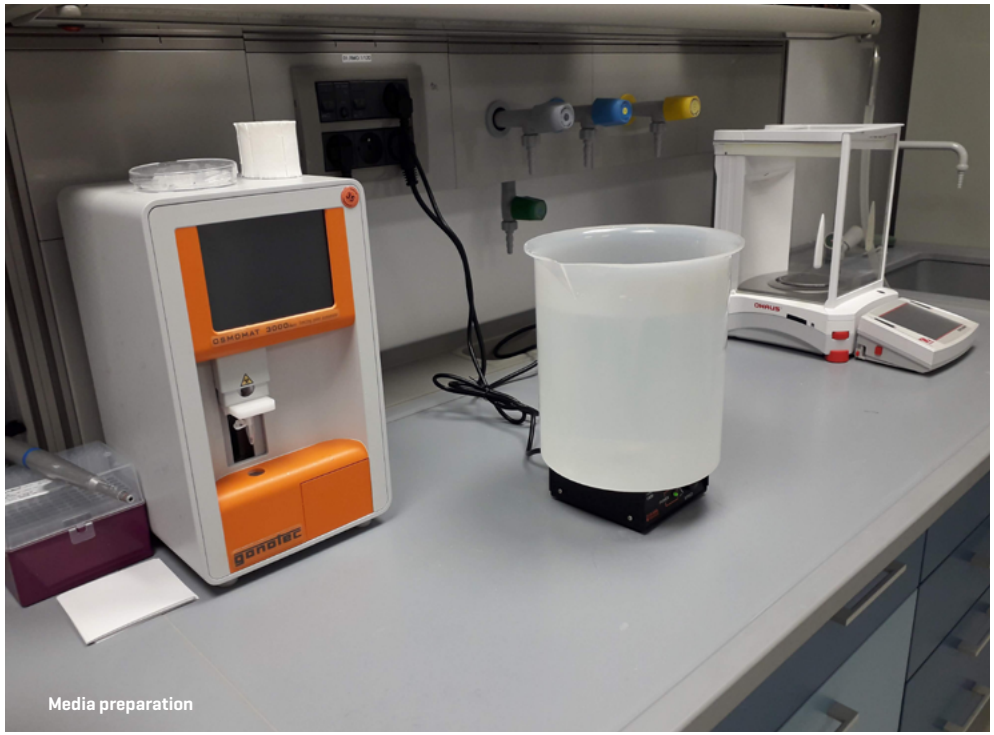
e-mail

The washing unit offers washing of laboratory glass and plastic, provides central washing of working clothing, GMO waste decontamination and elimination of hazardous waste.

The media preparation unit offers preparation of cultivation media and solutions for tissue culture, preparation of bacteriological media and plates, and preparation of "custom-made" solutions. Further, the unit offers vapour sterilization of solutions and vapour or hot-air sterilization of material, as well as dry ice supplies.

Both these units are located on the basement floor of building SO 001. The space is divided into two parts – briefly, to the "dirty" corridor, where dirty glass, clothing and waste for decontamination should be deposited, and the "clean" part, where the washed glass, sterile packed material, clean clothing, etc., is returned to the users.

Washing Facility



Media preparation

In the picture: 1. Zachardová Alena | 2. Nezbedová Zuzana | 3. Petrová Hana | 4. Kumpoštová Dobromila

Administrative Services

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BUILDING MAINTENANCE (Jana Boučková) 111
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ADMINISTRATIVE TEAM
Erik Onoda

more information | e-mail

The Administration Team is one of IMG administration and technical service departments. It provides agendas and tasks in the fields of contract and order processing, maintaining of public Contract register, filing of hard and soft copies of contracts, administration of public procurements, grant projects, technology transfer, and public relations.

In cooperation with the Office of the Director and the Economy Department, the Administration Team is always ready to do its best when supporting the IMG scientific community.

ECONOMY DEPARTMENT
Kamila Dařinová

more information | e-mail

The Economy Department provides support both to the scientific and service groups of our Institute. The major part of our work is devoted to keeping demonstrable accounts and processing wages. Both these activities are of essential importance for maintaining appropriate evidence of the funding allocated to the grant projects.

The colleagues dealing with accounting are ready to process all issued and received invoices, manage the tax issues related to the Institute and take care of setting up the control systems. In accordance with the accounting law, they look after the entire Institute property. They process the travel agenda and manage the major part of small purchases and their distribution into individual groups.

The wage and personnel agenda includes precise processing of salaries and all related documents. The colleague responsible for human resources is one of the first Institute members with whom the new employees come into contact, and he helps them to first orient themselves at IMG.

At the Economy Department, we also participate in preparing the Institute budget. In this area, we contribute to defining the individual partial project or custom budgets and methods of their inspection. We provide cooperation to project managers, namely by processing financial reports.

In the picture: 1. Magazu Radmila | 2. Jonák Jiří | 3. Onoda Erik | 4. Schmoranz Michal | 5. Dvořáková Šárka | 6. Macháčková Eva | 7. Sikorová Šárka | 8. Chvojková Věra

In the picture: 1. Dařinová Kamila | 2. Dlouhá Michaela | 3. Kneifl Robert | 4. Nezbedova Hana | 5. Málková Martina | 6. Peldová Erika | 7. Novák Michal | 8. Dvořáková Edita | 9. Hoferiková Lucie | 10. Nedvědová Irena | 11. Jarošová Barbora | 12. Knížková Klára | 13. Bukovanská Martina | 14. Vašková Vlasta

BUILDING MAINTENANCE
Jana Boučková

more information

e-mail

The IMG Building Maintenance department, which includes six employees, is responsible for operation of seven buildings on the Krč campus with a total floor area of 17,500 m^2. This includes the main building comprising offices and laboratories and the congress hall, the animal facilities, the guest house, and the building housing the kindergarten and the sports facility.

The department provides full operation of technologies in all these buildings, their maintenance and repairs, and adaptation of all spaces including more extensive renovations. This is done in close collaboration with a number of external companies in order to cover all necessary areas of the building operation.

The department is also responsible for renting and administration of 27 apartments in the campus guesthouses, which mostly serve Ph.D. students from abroad. This also includes help with the administrative requirements associated with their stay in the Czech Republic.

Other tasks include record keeping and administration of land lines and mobile phone lines, monitoring of freezing and cooling equipment, administration system for keys, safety at work and fire protection agenda and training, car park, cleaning services, preparation and technical background for scientific seminars and conferences, and last but not least, maintenance and care of 8,100 m2 external spaces including two decorative pools with outside seating, which are in intensive use by the employees for both working and leisure activities.

IMG Kindergarten 'Atomik

Seating area

In the picture: 1. Řezník Roman | 2. Švestka Michal | 3. Boučková Jana | 4. Kasková Marie | 5. Švestková Hana | 6. Novotná Veronika

OFFICE OF THE DIRECTOR
Petr Dráber

more information

e-mail

The Office of the Director is in charge of the organizational and administrative agenda of the Institute Director, prepares documents for the meetings of the Director's Board and takes their minutes. The Office also deals with the entire agenda related to the contacts of the Institute with organs of the Academy of Sciences and grant agencies, organizational and administrative work associated with international contacts of the Institute, updating of internal web pages, recording of Institute publications (ASEP), preparation of documents for regular evaluation of the publication activity of the Institute research groups, processing of annual reports, preparation of documents for evaluation of the Institute, and administrative agenda related to the safety at work, genetically modified organisms and radioisotopes. The Office archives all important Institute documents; it records, processes and sorts out all Institute correspondence, and takes care of the agenda related to keeping files and data box. The Office is also responsible for organizing training of employees, meetings of researchers, annual Institute conferences, open door days, and a number of other intramural and external activities. The Office tasks also include providing legal services, revision of English texts, and translation of both scientific and administrative texts into English.

Boardroom

Director's meeting room

In the picture: 1. Jeglová Jana | 2. Dráber Petr | 3. Polák Martin | 4. Kořínek Vladimír | 5. Štětková Veronika | 6. Marešová Gabriela | 7. Krausová Leona | 8. Takáčová Šárka

INFORMATION TECHNOLOGIES
Petr Divina

more information

e-mail

The IT department provides a wide range of information technology services to support the various needs of the users in the Institute. The main tasks include:

- administration of LAN and wireless network in the img.cas.cz domain
- administration of storage area network (SAN) infrastructure, data backup and archiving
- administration of institutional servers, including e-mail and web administration
- operation of two modern data centres with UPS, air-conditioning, temperature and humidity monitoring, and fire protection system
- technical support for the end-users (PC and Mac platforms, operating system and application installation, configuration) including remote support for the users in the detached sites of the Institute
- printing services
- hardware purchase consultancy
- software purchasing, license management, volume and campus license negotiations

Special support is provided to the Institute facilities and research groups:

- operation of internal databases and information systems (e.g., animal tracking system, booking system)
- development of websites and web applications
- operation of the access control system and the surveillance system
- operation of the audio-visual equipment in the conference hall
- IT assistance for courses and conferences, hardware equipment providing

The IT department aims to deliver innovative services and flexible solutions using the latest technology to support modern scientific research at the Institute as well as its smooth day-to-day operation.

Main data centre room

Audio video control room in the Conference hall

In the picture: 1. Šveňha Jan | 2. Kůs Michal | 3. Ježdík Ondřej | 4. Kopčan Juraj | 5. Žáček Michal | 6. Kohout Vojtěch | 7. Mrázek Miroslav | 8. Růžička Jiří | 9. Rolník Michal | 10. Novotný Michal | 11. Divina Petr | 12. Borovička Martin | 13. Škaroupka Petr | 14. Hurda Jan | 15. Volf Tomáš

Awards and Honours

2019

Václav Hořejší	The Jan Evangelista Purkyně Honorary Medal
Václav Hořejší	The Prize of Society of Arts & Sciences
Veronika Krchlíková	Prize for Young Presenters - Joint Czechoslovak Virology Conference
Kryštof Štafl	Poster Prize - 31st international Workshop on Retroviral Pathology Padova

2018

Václav Hořejší	The Jan Evangelista Purkyně Honorary Medal
Jiří Forejt	The Jan Evangelista Purkyně Honorary Medal
Jiří Hejnar	Praemium Academiae for Extraordinary Scientific Benefit
Petr Svoboda	EMBO membership
Hana Váchová	The Best Presentation Prize – 48th Jírovec's Protozoological Days

2017

Ondřej Ballek	Jaroslav Šterzl Award
Eliška Svobodová	Poster Prize – 22nd Annual Meeting of the RNA Society
Sravya Ganesh	Poster Prize – EMBO/EMBL Symposium
Petr Kašpárek	Neuron Impulse under 33
Jiří Forejt	Memorial Silver Medal of the Senate of the Czech Republic
Václav Hořejší	The Prize of the President of the Czech Academy of Sciences for Promotion or Popularization of Research, Experimental Development and Innovations for 2017
Helena Farkašová	Albert Schweitzer Prize
Peter Dráber	Otto Wichterle Award

Best IMG publications

2019

Balounová J, Šplíchalová I, Dobešová M, Kolář M, Procházka J, Sedlacek R, Kořínek V, Alberich-Jorda M, Filipp D, Balounová J, Šplíchalová I, Dobešová M, Kolář M, Fišer K, Procházka J, Sedlacek R, Jurisicova A, Sung HK, Kořínek V, Alberich-Jorda M, Godin I, Filipp D: Toll-like receptor 2 expression on c-kit cells tracks the emergence of embryonic definitive hematopoietic progenitors. Nat Commun 2019 10(1): 5176. [pubmed] [doi]

2018

Hanzlikova H, Kalasova I, Cihlarova Z, Caldecott KW, Hanzlikova H, Kalasova I, Demin AA, Pennicott LE, Cihlarova Z, Caldecott KW: The Importance of Poly(ADP-Ribose) Polymerase as a Sensor of Unligated Okazaki Fragments during DNA Replication. Mol Cell 2018 71(2): 319-331.e3. [pubmed] [doi]

2017

Skuta C, Popr M, Muller T, Jindrich J, Kahle M, Sedlak D, Svozil D, Bartunek P, Skuta C, Popr M, Muller T, Jindrich J, Kahle M, Sedlak D, Svozil D, Bartunek P: Probes & Drugs Portal: an interactive, open data resource for chemical biology. Nat Methods. 2017 14(8): 759-760. [pubmed] [doi]

Conferences

20. 12. 2019	IMG Annual Conference 2019
25. 09. 2019 - 27. 09. 2019	8th International Symposium on Kallikreins and Kallikrein-Related Peptidases
12. 09. 2019 - 13. 09. 2019	CCP Phenogenomics Conference 2019
24. 05. 2019	12th IMG Ph.D. Conference
15. 05. 2019 - 18. 05. 2019	EMBO Workshop
14. 12. 2018	IMG Annual Conference 2018
20. 09. 2018 - 24. 09. 2018	FEBS Advance Lecture Course and 33rd European Cytoskeletal Forum Meeting
29. 06. 2018	11th IMG Ph.D. Conference
09. 06. 2018 - 13. 06. 2018	The 13th EFIS-EJI Tatra Immunology Conference
03. 05. 2018	Building a Bridge for Science
15. 12. 2017	IMG Annual Conference 2017
27. 08. 2017 - 31. 08. 2017	29th International Workshop on Retroviral Pathology
19. 06. 2017 - 20. 06. 2017	BIOCEV DAYS 2017
02. 06. 2017	10th IMG Ph.D. Conference
28. 05. 2017 - 30. 05. 2017	Hallmarks of Cancer: Focus on RNA – 2017
25. 05. 2017 - 27. 05. 2017	8th EMBRN International Mast Cell and Basophil Meeting
19. 05. 2017	Structural Change for Gender Equality in Research and Innovation: Contextual Factors

Ph.D. programme

The Ph.D. programme at the Institute of Molecular Genetics (IMG) is part of a joint biomedical Ph.D. programme organized by Charles University and several institutes of the Czech Academy of Sciences. Individual Ph.D. programmes focus on specific topics (e.g. immunology, cell biology etc.) and are organized by graduate boards. Currently, there are about 120 Ph.D. students affiliated with the Institute. The Ph.D. programme at the IMG focuses on molecular, cell and developmental biology, immunology, genetics and virology.

The academic year at IMG starts with an Academic Year Opening Meeting led by IMG Director, who also welcomes new Ph.D. students. This is followed in mid-October by IMG Bootcamp, which is dedicated to 1st year Ph.D. students and their induction to the student life at IMG. The IMG Bootcamp is focused on networking, motivation, and elementary skills students need during Ph.D.. This period of time is also used for revising policies and IT support for Ph.D.-related activities. The first half of November is dedicated to Advances in Molecular Biology and Genetics, a two-week seminar course, which most students have as one of their course requirements in study plans. By the end of November, upon announcement of results of grant applications, preparation for selection of new Ph.D. students starts. Once group leaders provide annotations of their open positions, a website is set up with registration of prospective Ph.D. candidates and is made available in January. January and particularly February are dedicated to advertisement of open Ph.D. positions. The deadline for Ph.D. applications for the Interview Day is at the end of February, with the Interview Day taking place usually during the third week in March.

Pedagogical activity

Partial agreements on cooperation with universities

CHARLES UNIVERSITY

Field of study:

- Biochemistry and pathobiochemistry
- Cell biology and pathology
- Immunology
- Developmental and Cell Biology
- Molecular and Cell Biology, Genetics and Virology

UNIVERSITY OF CHEMISTRY AND TECHNOLOGY PRAGUE

Field of study:

- Bioinformatics
- Biochemistry, Bioorganic Chemistry and Microbiology

CTU CZECH TECHNICAL UNIVERSITY IN PRAGUE

Field of study:

- Biomedical and clinical technology

Ph.D. semestral Courses

- Advances in molecular biology and genetics
- Grant application strategy
- Transgenic models in physiology
- Advances in Physiology and Neuroscience
- Protein dynamics in development and in tumors
- Congenital Immunity
- Advances in immunology
- Physiology of aging cellular senescence and carcinogenesis
- Epigenetics
- Transgenic models in physiology
- System biology

Bc./MSc. semestral Courses

- Viral pathogenesis
- Structure and function of RNA
- Molecular biology of cancer I
- Immunology
- Structure and function of cytoskeleton
- Epigenetics, organisms in developomental biology
- Physiology of aging, cellular senescence and carcinogenesis
- Immunology
- Advances in Immunology
- Protein dynamics in development and tumors
- Bioinformatics
- Genomic analysis and algorithms
- Bioinformatics case studies
- Gene expression data analysis
- Systems biology
- Pharmacology
- Congenital Immunity
- Methods of determining three-dimensional structure of macromolecules
- Grant application strategy
- Special chemico-biological fields
- Molecular biology and biochemistry of organisms
- Solution of three-dimensional structure of macromolecules
- Structural cell biology
- Model organisms

Ph.D. semestral Courses

	Charles University		Czech Technical University		University of Chemistry and Technology		South Bohemian University		Palacký University		
	Ph.D.	Bc./MSc.	Ph.D.	Bc./MSc.	Ph.D.	Bc./MSc.	Ph.D.	Bc./MSc.	Ph.D.	Bc./MSc.	TOTAL
2017	14	15	1	3	1	2	1				**37**
2018	15	17	1	3	1	2		1		1	**41**
2019	17	21	1	4	3	2	1	1	1		**51**

Impressum

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